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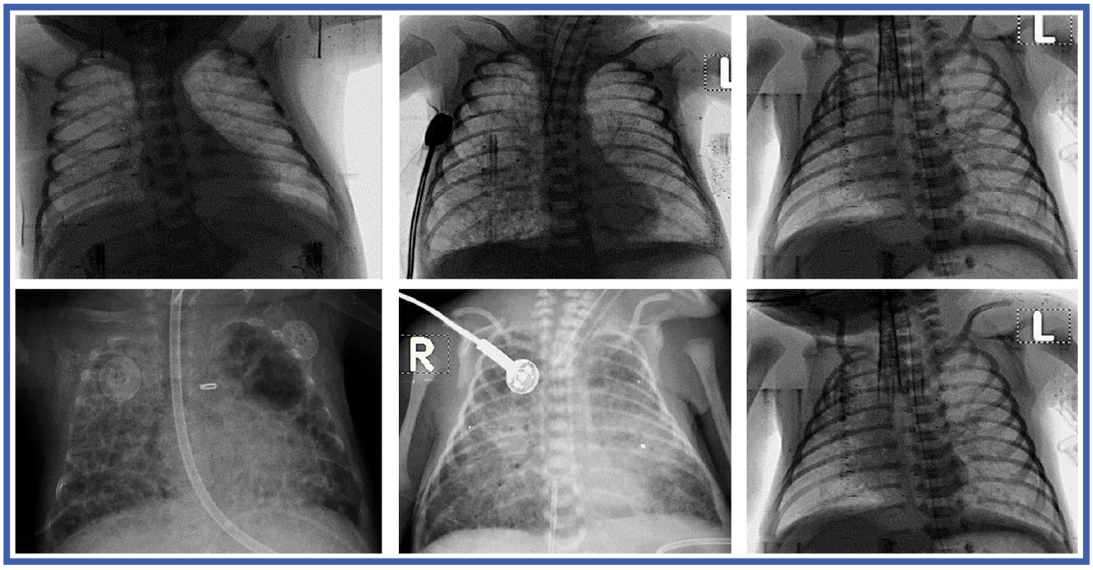
CONTENT HIGHLIGHTS:

Aliona Cotoman, Rodica Selevestru, Svetlana Șciuca
Evaluation of pulmonary imaging data by radiography in children with bronchopulmonary dysplasia



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Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției Medicamentului și Dispozitivelor Medicale (AMDM) http://nomenclator.amdm.gov.md/

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RESEARCH ARTICLE

Parameters predicting non-invasive ventilation failure in COVID-19 patients

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ABSTRACT

Introduction. During COVID-19 pandemic, non-invasive ventilation (NIV) was widely used during COVID-19 Pandemic. The factors predicting NIV failure in COVID-19 patients remain debatable. The goal of this research is to identify the parameters that may correlate NIV failure.

Materials and methods. A retrospective analysis of COVID-19 patients' data, who were admitted to ICU of the Institute of Emergency Medicine, Chisinau, during July-October 2020 and connected to NIV. The study analyzed the demographics, laboratory and respiratory parameters (at admission, at NIV initiation, 24-48h and 72-96h of NIV) and their relation with NIV failure. **.** For continuous variables, the established confidence interval was 95%. The Kruskal-Wallis H test was used for continuous variables and the Fisher's exact test or chi-squared test was used for category data.

Results. In study were included 154 patients. NIV failed in 52 patients. In NIV failure group were registered a higher rate of hypertension (88% vs 74%, p = 0.033), delirium (60% vs 20%, p=0.001) and need for sedation (83% vs 48, p=0.001). The urea levels were lower in NIV success group at admission, at NIV initiation and at 24-48h of NIV. The neutrophil/lymphocyte ratio was higher in NIV failure group at NIV initiation; at 24-48h and 72-96h of NIV. NIV failure group had a higher level of WBC count and C-reactive protein at 24-48h and 72-96h as well as D-dimer at 72-96h of NIV. The ROX index was higher in NIV success group from NIV initiation and through 72h of NIV.

Conclusions. The presence of abnormal values of neutrophil/lymphocyte ratio, urea, lymphocytes, WBC count, C-reactive protein, D-dimer and ROX index during non-invasive ventilation, as well as association of delirium and need for sedation, can be suggestive and informative for high risk of NIV failure in COVID-19 patients. Continuous measurement of these parameters may help the clinicians to decide the optimal timing of conversion to invasive ventilation.

Keywords: non-invasive ventilation, Covid-19, ROX index, failure predictors, hypoxemic respiratory failure.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Currently, there is no consensus about the optimal timing for conversion from non-invasive ventilation to mechanical ventilation in COVID-19 critical ill patients. The identification of the appropriate time of conversion may reduce the morbidity and mortality rate in this category of patients in ICU

The research hypothesis

The demographic, clinical, laboratory and respiratory parameters, closely associated with severity, morbidity and mortality in

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COVID-19 disease, can be associated with non-invasive ventilation failure.

The novelty added by manuscript to the already published scientific literature

Optimization in evaluation of the ricks for non-invasive ventilation failure and improving in respiratory management in COVID-19 patients.

Introduction

The Novel Coronavirus Disease (COVID-19) is an infectious illness that has a pandemic spread since December 2019, infecting over 543,200,000 of the world's population with a 1% of current mortality rate [1].

From the total number of cases, those with asymptomatic, mild, and moderate manifestations represent approximately 80% and the rest of them get severe and critical forms. The rate of Intensive Care Unit (ICU) admission of COVID-19 patients is 11% of the total number of confirmed cases [2]. In patients who have severe and critical manifestation predominates the phenotype of a systemic inflammation, which leads to damage of target organs with tropism for SARS-COV-2 virus (lungs, heart, arterial vascular system, kidneys, ileum and bladder) and The Multiple Organ Dysfunction Syndrome [3, 4].

The Risk factors for severe evolution of COVID-19 are: comorbidities, age older than 65 years, low lymphocytes number, high neutrophil-lymphocyte ratio, high level of D-Dimers, urea, C-Reactive Protein (CRP), ALT, AST and procalcitonin, as well as low PaO2/FiO2 ratio and platelets count etc. [5].

Of the total number of hospitalized COVID-19 non-ICU patients, 33% develop acute respiratory distress syndrome (ARDS), and 26% of them require transfer to ICU. From the total number of COVID-19 ICU-hospitalized patients, 63% are on mechanical ventilation (MV) and approx. 75% are confirmed with ARDS with a mortality rate of up to 93% [6]. This high incidence of ARDS and mortality rate make the pulmonary manifestation of COVID-19 the greatest therapeutic and respiratory support challenge.

The average rate of non-invasive ventilation (NIV) used as respiratory support in COVID-19 is 25.5% [7]. Unfortunately, the predictors of NIV failure as well as clear indications of MV remain debatable. In this context, it is very important to highlight the factors that correlate with NIV failure and would predict the optimal timing for conversion to MV.

Materials and methods

Study population. Was performed the retrospective analysis of COVID-19 patients with acute respiratory failure admitted to the ICU of the Institute of Emergency Medicine, Chisinau, Republic of Moldova, between July 2020 and October 2020 who were connected to NIV. The Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine approved the study and Pharmacy of the Republic of Moldova (minutes No.4 from 07.07.2021).

The inclusion study criteria was need for non-invasive ventilation (BiPAP or PSV) with a duration of more than 24 hours from the initiation. NIV was used more than 20h out of 24h and with application of facemask Criteria for non-invasive ventilation were lack of response to conventional oxygen therapy, absence of tachypnea more than 30-35 respiration/min, absence of severe acidosis or hypercapnia, cooperative patient. Patients in whom non-invasive ventilation was used as a post-extubation support method, or CPAP mode, or were connected to mechanical ventilation in less than 24h after NIV initiation, were excluded from the study. Eligible patients were divided in 2 groups: *NIV success* – patients who were weaned from non-invasive support with respiratory improvement and *NIV failure* – patients who were connected to mechanical ventilation after more than 24h of non-invasive ventilation.

All patients received standard treatment according to the institutional protocol (corticosteroids (methylprednisolone 1mg/kg/day), vitamin therapy, anticoagulants (LMWH or intravenous unfractionated heparin), and antibiotic therapy if necessary. The intubation criteria were based on local institutional practice, including disorder of consciousness, respiratory decompensation (respiratory rate > 30- 35 r/min, participation of auxiliary muscles in the respiratory act) and severe hypoxemia (SpO2 < 85% on maximal non-invasive support).

Data collection. All information was collected from the SiaamS Electronic Medical Record database used in the Institute of Emergency Medicine, Chisinau.

The study was based on the analysis of the following parameters:

Demographic: age, sex, comorbidities (hypertension, diabetes mellitus, obesity), ISARIC (International Acute Respiratory Infection Consortium) score at admission in ICU;

Laboratory: neutrophil-lymphocyte ratio (N/L ratio), lymphocytes count, platelet count, WBC count, urea, creatinine, CRP, D-Dimers level. All parameters were evaluated at admission, at the initiation of NIV, at 24h-48h of NIV and at 72-96h of NIV. In case of multiple samples extraction in these periods, the worse values of these parameters were selected.

Respiratory: the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate (ROX index) was evaluated at the initiation of NIV and then every 12 hours up to 76 hours of NIV.

Outcomes: There were considered as outcomes the duration of NIV, association of delirium (according to the DSM-5 criteria) [8], need for sedation, ICU and hospital length of stay, NIV success or failure, survival.

Statistical analysis. For continuous variables, the established confidence interval was 95%, all other data has been presented as percentage, median and interquartile range. Category variables were reported as number or percentage. Because of non-parametric distribution, The Kruskal-Wallis H test was used for continuous variables and the Fisher's exact test or chi-squared test was used for category data. The diagnostic predictive ability was calculated by statistical analysis of receiver operating curves (ROC). Statistical significance was assigned to the data with a $p < 0.05$. SPSS version 26.0 was used to analyze the data (IBM Corp, Armonk, NY, USA).

Results

A total of 482 patients with severe or critical form of COVID-19 were admitted to ICU, and 154 were enrolled (Figure 1). Demographic and clinical data of the patients are reported in Table 1.

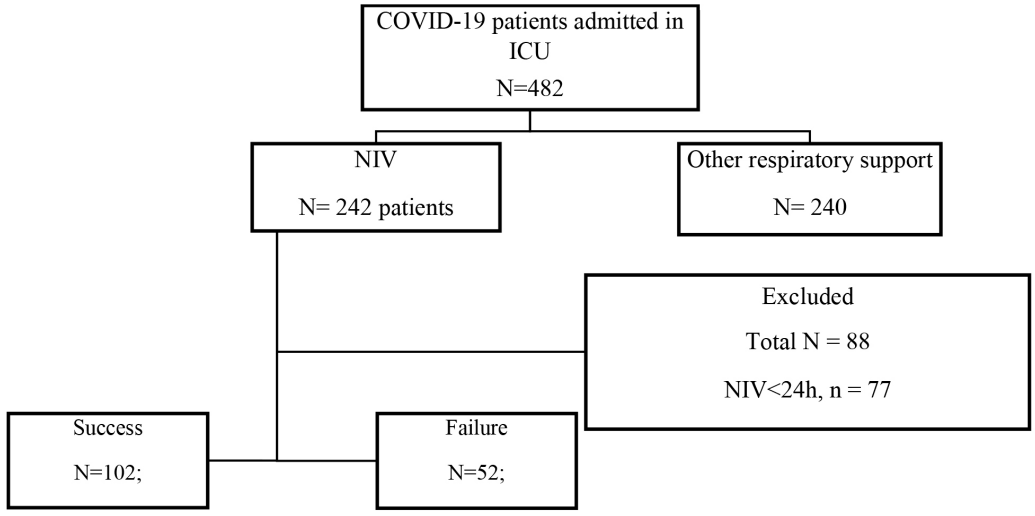

Fig. 1 Study flow chart. ICU - Intensive Care Unit; NIV - non-invasive ventilation; ID - incomplete data.

Table 1. Demographic and clinical data.

Variable	NIV success group (n=102) (66%), Median (IQR)	NIV failure group (n=52) (34%)	*p* value
Age, years	61.5 (54-69.25)	67.5 (60.25-73)	0.02
Male, n (%)	43 (42%)	27 (52 %)	0.25
Hypertension, n (%)	75 (74%)	46 (88%)	0.033
Diabetes mellitus, n (%)	35 (34%)	16 (31%)	0.65
Obesity, n (%)	36 (35%)	21 (40%)	0.53
Day of illness at admission	7 (6-9)	7 (4-9.25)	0.086
ISARIC mortality score points	10 (8-12)	12 (10-14)	0.001
ISARIC mortality score, %	23 (14-33)	33 (23-45)	0.001
ISARIC deterioration score points	615 (544.5-680.5)	673.5 (580-802.5)	0.03
ISARIC deterioration score, %	69 (57.75-78)	77 (63.75-89)	0.03
Outcome			
NIV duration, days	5 (4-7)	6 (4-9)	0.46
Delirium, n (%)	20 (20%)	31 (60%)	<0.001
Need for sedation, n (%)	49 (48%)	43 (83%)	<0.001
ICU stay, days	7 (6-10)	14 (10-17)	<0.001
Hospitalization, days	16.5 (13-23)	14 (10-18.75)	<0.001
In-hospital mortality, n (%)	3 (0.3%)	50 (96%)	<0.001

Note: *ISARIC- International Severe Acute Respiratory Infection Consortium score; ICU - Intensive Care Unit; NIV - non-invasive ventilation. Data are presented as median (interquartile rage IQR)*

Patients in the NIV success group were younger: 61.5 (IQR 54-69.25) vs 67.5 (IQR 60.25-73), (p=0.02). The percentage of male patients was 52% in the NIV failure group vs 42% in the NIV success group (p=0.25). The rate of hypertension was higher in patients who failed the NIV: 88% vs 74% (p=0.033), which represents the risk for NIV failure, OR = 1.203 (CI 95% 1.033-1.401, p=0.0033). The incidence of diabetes mellitus and obesity did not register significant differences between groups. The ISARIC score for deterioration and mortality measured at ICU admission was higher in patients with NIV failure: ISARIC Deterioration score (points/%): 673.5 (77%) vs 615 (69%), (p=0.03) and ISARIC Mortality score (points/%): 12 (33%) vs 10 (23 %), (p=0.001). ICU length of stay (days) was twice shorter in NIV success group, but with longer time of hospitalization. Association of delirium was registered in 20% of cases in NIV success group vs 60% in NIV failure group, (p=0.001). Patients in the NIV success group had less need for sedation 48 % vs 83%, (p=0.001). The presence of delirium and the need for sedation are related to the risk of NIV failure: OR=3.04 (CI 95%, 1.934 - 4.779, p=0.001) for delirium and OR=1.721 (CI 95%, 1.358-2.182 p=0.001) for the need for sedation. Only two patients survived in the NIV failure group, corresponding with 96% of mortality in case of failure. In the NIV success group 3 patients died due to documented pulmonary embolism

after successfully weaning from non-invasive support and discharge from ICU. The Table 2 presents the laboratory parameters of both groups.

Table 2. Patients' baseline laboratory characteristics with statically significance

Variable	NIV success group (n=102) (66%)	NIV failure group (n=52) (34%)	*p* Value
At admission			
Urea, mmol/l	6.7 (5.25-8.3)	8.3 (6.22-11.6)	0.001
At NIV initiation			
N/L ratio	9 (5-13)	10 (6-18.25)	0.047
Urea, mmol/l	6.7 (5.45-8.3)	8.05 (6.37-10.55)	0.003
24-48h of NIV			
N/L ratio	8 (6-15)	15 (8-24)	0.001
Leucocytes, 10^9/l	9.4 (7.5-11.8)	11.3 (8.3-14.9)	0.007
Urea, mmol/l	6.7 (5.45-8.7)	8.25 (6.23-10.9)	0.016
CRP, mg/l	37.7 (18.5-82.7)	69.6 (24-126.25)	0.032
72-96h of NIV			
N/L ratio	11 (5-15)	18 (9-30)	0.001
Lymphocyte,10^9/l	0.86 (0.5-1.38)	0.69 (0.36-0.94)	0.019
Leucocytes, 10^9/l	9.2 (7.4-11.5)	12 (8.8-14.8)	0.001
CRP, mg/l	31.25 (15.32-63.75)	74 (24-138.2)	0.002
D-dimer, mg/l	1.44 (0.58-4.67)	4.4 (1.67-7.62)	0.026

Note: *N/L ratio: neutrophil-lymphocyte ratio; CRP, C-reactive protein; NIV: non-invasive ventilation.*
Data are presented as median (interquartile rage IQR)

The patients with success of NIV, had lower levels of urea (mmol/l) during the hospitalization: at admission to 24-48h of non-invasive ventilation. The neutrophil/lymphocyte ratio recorded statistically significant difference between groups from the start of NIV ventilation and during the 96h of NIV. In the group with NIV failure, the value of C - reactive protein (mg/l) was two-fold higher: 69.6 (IQR 24-126.25) vs 37.7 (IQR 18.5-82.7), p=0.032) at 24-48h and 74 (IQR 24-138.2) vs 31.25 (IQR 15.32-63.75) at 72-96h of NIV. The notable difference between the two groups was found in D-dimer (mg/l) values at 72-96h of NIV: 1.44 (IQR 0.58 - 4.67) *(NIV suc*cess) vs 4.4 (IQR 1.67-7.62) (*NIV failure*), p=0.026 and in lymphocytes number (10^9/l): 0.86 (IQR 0.5-1.38) *(NIV suc*cess) vs 0.69 (IQR 0.36-0.94) (*NIV failure*), p=0.019. WBC count was higher in the NIV failure group at 24-48h and 72-96h of NIV. It was not registered the statistically significant difference in platelets count values during the non-invasive ventilation. Table 3 shows the relationship between different parameters and risk for NIV failure.

The variables that presented the difference in values between the two groups were stratified. Were identified the association between NIV failure and the following parameters: age > 60 years; N/L ratio more than 9.8 at 24-48h and 72-96h of NIV; Leucocytes count > 10x10^9/l at 24-48h, and 72-96h of NIV; Urea > 7.5 mmol/l at admission, NIV initiation and 24h-48h of NIV; D-dimer > 1.5 mg/l at 72-96h of NIV. Values of CRP more than 36 mg/l were correlated with NIV failure only at 72-96h of non-invasive ventilation.

Table 3. Association between demographic characteristics, outcomes, laboratory parameters and risk of NIV failure

Variable	OR (CI 95%)	p-value
Hypertension	1.203 (1.033-1.401)	0.033
Delirium	3.04 (1.934-4.779)	0.0001
Need for sedation	1.721 (1.358-2.182)	0.0001
Age, > 60	1.436 (1.146-1.799)	0.004
N/L ratio, > 9.8 at 24-48h of NIV	1.607 (1.171-2.205)	0.005
N/L ratio, > 9.8 at 72-96h of NIV	1.396 (1.082-1.800)	0.016
Leucocytes, >10x10^9/l at 24-48h of NIV	1.545 (1.130-2.114)	0.009
Leucocytes, >10x10^9/l at 72-96h of NIV	1.667 (1.218-2.280)	0.002
CRP, > 36 mg/l at 24-48h of NIV	1.242 (0.893-1.727)	0.213
CPR, >36 mg/l at 72-96h of NIV	1.512 (1.099-2.082)	0.018
Urea, >7.5 mmol/l at admission	1.527 (1.108-2.104)	0.013
Urea, >7.5 mmol at NIV initiation	1.459 (1.032-2.061)	0.038
Urea, >7.5 mmol/l at 24-48h of NIV	1.471 (1.052-2.058)	0.029
D-dimer, > 1.5 mg/l at 72-96h of NIV	1.545 (1.093-2.185)	0.028

Note*: N/L – neutrophil/lymphocyte ratio; NIV – non-invasive ventilation; CRP – "C" reactive protein.*

Table 4. ROX index values measured dynamically during NIV

Variable	**NIV success group (n=102) (66%)**	**NIV failure group (n=52) (34%)**	***p* Value**
ROX index at NIV initiation	6.03 (5.5-6.5)	5.21 (4.57-6.08)	<0.001
ROX index at 12h of NIV	6.17 (5.65-6.73)	5.48 (4.89-6.13)	<0.001
ROX index at 24h of NIV	6.22 (5.77-6.72)	5.49 (5.01-6.13)	<0.001
ROX index at 36h of NIV	6.23 (5.81-6.78)	5.52 (4.86- 6.07)	<0.001
ROX index at 48h of NIV	6.23 (5.9-6.72)	5.35 (4.85-5.67)	<0.001
ROX index at 60h of NIV	6.23 (5.9-6.72)	5.48 (4.95-5.71)	<0.001
ROX index at 72h of NIV	6.39 (6.02-7.05)	5.41 (4.88-5.71)	<0.001

Note: ROX index: ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate; NIV: non-invasive ventilation.
Data are presented as median (interquartile rage IQR)

The ROX index (Table 4) values was higher in the NIV success group from the NIV initiation until 72h of NIV.

ROC curves of the ROX index predictive model for NIV failure is presented in Table 5. The moderate accuracy in prediction of NIV ventilation failure represents ROX index at NIV initiation (cut-off value: 5.65) with an AUC of 0.696 (p=0.001), sensibility of 70% and specificity of 59.6%. ROX index values from 12 to 36h of NIV demonstrate good accuracy in prediction, with cut-off value of 5.68, AUC 0.708 (p=0.001), a sensibility 74.5% and specificity 59.6% for ROX index at 12h of NIV; cut-off value of 5.86, AUC 0.718 (p=0.001), sensibility 73.5% and specificity 65.4% for ROX index at 24h of NIV and cut-off value 5.68, AUC 0.745 (p=0.001), sensibility 74.5% and specificity 71.1% for ROX index at 36h of NIV. From 48h to 72h of NIV, ROX index

demonstrates a very good predictive model. Its values are: for ROX index at 48h of NIV sensibility 85.3% and specificity 80% at cut-off value 5.71, AUC 0.812, p=0.001, for ROX index at 60h of NIV sensibility 85.3% and specificity 79.2 % at cut-off value 5.74, AUC 0.800, p=0.001 and for ROX index at 72h of NIV sensibility 88.1% and specificity 80% at cut-off value 5.74, AUC 0.841, p=0.001 (Figure 2).

Table 5. ROC curve of the ROX index predictive model for NIV failure.

Variable	Sensitivity (%)	Specificity (%)	Cut-Off Value	AUC (95% CI)	*p*-Value
ROX index at NIV initiation	70	59.6	5.65	0.696 (0.599-0.792)	<0.001
ROX index at 12h of NIV	74.5	59.6	5.68	0.708 (0.612-0.804)	<0.001
ROX index at 24h of NIV	73.5	65.4	5.86	0.718 (0.621-0.815)	<0.001
ROX index at 36h of NIV	74.5	71.2	5.86	0.745 (0.649-0.841)	<0.001
ROX index at 48h of NIV	85.3	80	5.71	0.812 (0.727-0.897)	<0.001
ROX index at 60h of NIV	85.3	79.2	5.74	0.800 (0.713-0.888)	<0.001
ROX index 72h of NIV	88.1	80	5.74	0.841 (0.763-0.919)	<0.001

Note: *AUC - area under the ROC curve; CI - confidence interval; NIV - non-invasive ventilation; ROX index - ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate.*

Discussion

The respiratory support in COVID-19 is dependent on the severity of the disease and can be provided by using nasal cannulas, oxygen masks, high-flow nasal cannulas (HFNC), non-invasive positive pressure ventilation (NIPPV) (CPAP, Bi-PAP, PSV) and MV. During the pandemic, a lot of clinical researches regarding non-invasive support applicability and influence on outcome in COVID-19 patients were performed and different results were registered. More of them encourage the use of non-invasive ventilation support [9].

The successful early NIV was evaluated in the Recovery-RS Clinical Trial, which demonstrated a decrease in mortality when using CPAP therapy as an initial respiratory support strategy compared to conventional oxygen therapy [10].

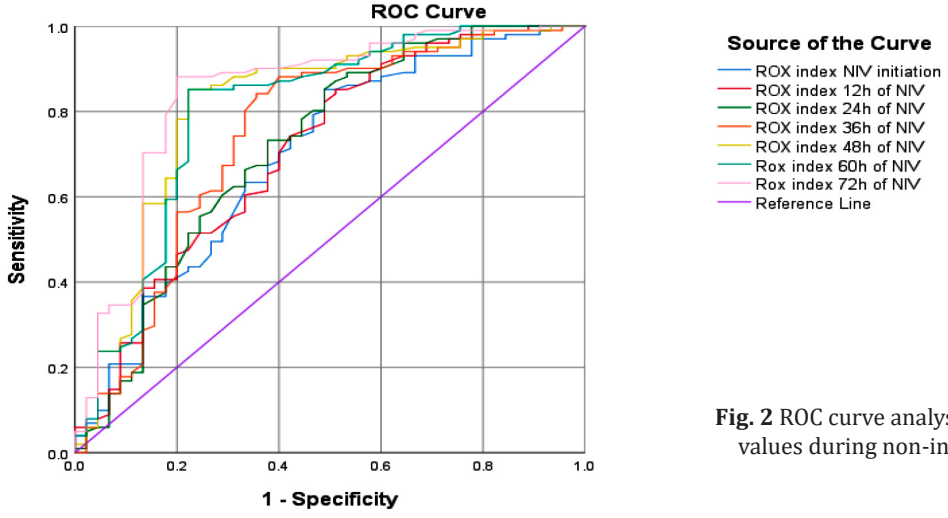

Fig. 2 ROC curve analysis for the ROX index values during non-invasive ventilation.

Overall, the rate of NIV use in COVID 19 patients is 25.5% - 46%, with a failure rate between 30 and 88%. The registered mortality rate in non-success cases is around 59.8% [11-13]. Among the factors that may influence the negative result of non-invasive ventilation are: age > 60 years, comorbidities, low PaO2 / FiO2 ratio, low basal PaO2, CRP value, platelet count, respiratory rate, minute volume, ventilator ratio, D-Dimers level [12]. In this study, the risk for NIV failure was associated with age > 60 years, presence of hypertension, association of delirium and need for sedation during NIV. One of the factors that must be considered in COVID-19 patients at hospital admission is ISARIC score, which was developed, validated, and applied in 9 regions of the United Kingdom. This score evaluates 11 parameters at hospital admission or at first contact with patient. These are the number of comorbidities, age, and sex, presence of pulmonary infiltrates, urea level, respiratory rate, CRP, lymphocyte number, and oxygen saturation [14]. In the presented research, the patients with higher ISARIC mortality and deterioration score were more exposed to NIV failure.

The risk factors and laboratory parameters that influence the result of non-invasive ventilation that have been identified in our study are neutrophil/lymphocyte ratio during non-invasive support, lymphocyte count at 72-96h of NIV, leukocyte count at 24-48h and 72-96h of NIV, urea level during hospitalization, CRP at 24-48h of 72-96h of NIV, D-dimers level at 72-96h of NIV. All these factors, with varying degrees and according to different sources, reflect the clinical evolution, outcome, and prognosis of COVID-19. According to the previous publications, lymphopenia indicates a severe course of COVID-19 disease, due to increased viremia and consumption of immune cells, where the net number of lymphocytes is inversely proportional to the severity of the disease [15].

The previous publication highlighted that the neutrophil-lymphocyte ratio at a value higher than 9.8, indicates the high incidence of ARDS and the need for non-invasive or invasive ventilatory support [16]. The data recorded in this study suggest that neutrophil/lymphocyte ratio (at NIV initiation, at 24-48h of NIV and at 72-96h NIV) and values > 9.8 of N/L ratio represent the risk for NIV failure.

C-reactive protein is the inflammatory marker of the acute phase, and is produced by hepatocytes following stimulation by interleukin-6 and is used as an indicator of the severity of both inflammatory and infectious processes [17]. In the case of patients with COVID-19, it not only directly correlates with the degree and extent of pulmonary damage in the initial stage and the early pulmonary phase [18] but also suggests the possibility of poor prognosis and a four-fold higher rate of negative outcome and respiratory worsening at values more than 10 mg/l [19]. Our data identified increased values of CPR in the NIV failure group at 24-48h and 72-96h and the presence of values > 36mg/l were associated NIV failure.

The presented study showed two-fold values of neutrophil/lymphocyte ratio in dynamics and CRP at 24-48h and 72-96h were identified in the group of patients with NIV failure. This suggests, that increased values of the neutrophil/lymphocyte ratio, CRP and the low number of lymphocytes during NIV indicate the lack of regression of the hyper-inflammatory process, whose evolution is closely correlated with the success of NIV.

The identified high levels of leukocytes in the group of patients with NIV failure suggest an association of bacterial superinfection in this group of patients, which has a rate of 24% in COVID-19 patients, and 41% in case of patients in ICU. The most commonly cultivated germs are Acinetobacter spp. (22.0%), Pseudomonas (10.8%), and Escherichia coli (6.9%) [20]. The presence of bacterial superinfection in patients with COVID-19 disease is an unfavorable prognostic factor, associated with an increased risk of mortality [20].

Because of renal tropism of SARS-COV-2 virus [21], acute kidney injury is recorded at approx. 20% COVID-19 patients, with a mortality rate of approx. 55% in case of its association [22].

Urea values higher than 6.5 mmol/l indicate bad evolution and prognosis and a greater risk of developing the severe and critical form of the illness [23]. The urea values that were related to the risk of NIV failure in this investigation were > 7.5 mmol/l at admission, NIV initiation, and 24-48h of NIV.

Now, there is no consensus on the decision about conversion to mechanical ventilation, this action depends on national or local protocols and tactics, with a lack of global consensus on early or late intubation. These controversies are based on the lack of correlation between the clinical presentation, imaging and the PaO2 / FiO2 ratio used to stratify the severity degree of classic ARDS. For this reason, it has been proposed to manage these patients based on their clinical phenotype [24, 25]. At the same time, the difference in mortality depending on the timing of the intubation has not been proven yet. This justifies the continued application of the wait-and-see approach in some of the clinics [26].

In COVID-19 patients, remain uncertain the criteria and indications for the initiation of mechanical ventilation are. In more of the cases, they are progression of respiratory distress with signs of tissue hypoxia, PaO2 value <50 mmHg, severe acidosis pH <7.25, work of breathing and delirium [27]. Nevertheless, on the other hand, the wait-and-see approach has led to appearance of multiple discussions around the phenomenon of P-SILI (patient self-inflicted long injury) in which lung injury is induced by the patient's own respiratory effort [28].

One of the predictors of non-invasive support techniques failure is ROX Index, which is used for the prediction of the HFNC failure in patients with COVID-19 ARF [29]. Dynamically evaluated every 12 hours, ROX index indicates a high risk of failure of non-invasive ventilation, the need for intubation and mechanical ventilation when its value decrease below 5.99 (more specifically for COVID-19 patients) or 4.88 (in non-covid-19 patients) [30]. The ROX index values that were recorded in this survey were predictive from NIV initiation and during 72h of NIV and may warn about respiratory worsening and the need to discuss the conversion to mechanical ventilation when evaluated in dynamics every 12 hours.

In presented research the reported mortality rate in case of NIV failure was 96%. This may be related to the fact that the study included patients from the first period of the pandemic, this being associated with the lack of experience in medical management and respiratory support.

Conclusions

The abnormal values during continuous measurement of laboratory parameters such as neutrophil/lymphocyte ration, urea level, lymphocyte count, increase in WBC count and maintaining of high values of CPR and D-dimer, as well as association of delirium and need for sedation during NIV, can alert and inform clinicians about the risks of NIV failure in COVID-19 patients with acute respiratory failure. ROX index follow-up every 12h from NIV initiation and through 72h of NIV may predict respiratory worsening in non-invasive ventilated patient. Continuous measurement of these parameters may help the clinicians to decide the optimal timing of conversion to invasive ventilation.

Competing interests

None declared.

Authors' contribution

The authors contributed equally to the research of the scientific literature, the selection of the bibliography, the reading, and analysis of biographical references, the writing of the manuscript and its peer review. All authors have read and approved the final version of the article.

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Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No.4 from 07.07.2021).

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RESEARCH ARTICLE

Manifestations of kidney involvement in COVID-19 patients and progression to chronic kidney disease

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ABSTRACT

Introduction. COVID-19 was initially considered a predominantly respiratory infection, with mortality associated with progression of respiratory failure, but currently is recognized as a multisystem disease with a wide range of manifestations. One of the most common complications of COVID-19 is acute kidney injury (AKI), which predominantly evolved to chronic kidney disease (CKD). The objective of the study was to investigate the types of acute kidney injury and their prognostic value in hospitalized patients with COVID-19 with evolution to chronic kidney disease.

Material and methods. The study utilized a comprehensive database of patients admitted to general department of COVID-19 at *Timofei Moşneaga* Republican Clinical Hospital from 2020 to 2022 years (in total 1000 patients). The first part of the study was a retrospective study, focusing on patients with confirmed COVID-19 and lung injury was diagnosed by computer tomography. The second part was a prospective study assessing the prognostic value of inflammatory markers, renal functional status and kidney injury.

Results. AKI occurs in 29.6% of patients with COVID-19. The risk of AKI and CKD is higher in patients with more comorbidities, a more severe course of disease, elevated levels of ASAT/ALAT > 1.6 and hematuria at admission, which significantly increases the risk of progression to CKD. Patients with a history of CKD, and who had ASAT > 40 U/L, ASAT/ALAT > 1.6 and hematuria, experience the onset of AKI before hospitalization. Independent negative predictors of hospital-developed AKI include hypertension, Charlson Comorbidity Index > 4 points, respiratory failure, ASAT/ALAT > 1.6, D-dimers > 250 ng/ml, and hematuria. Hospital mortality in patients with COVID-19 was 20.8%, compared to 8.5% in patients without AKI, and this rate increased to 50% when AKI developed ($p < 0.001$).

Conclusions. Patients who developed AKI during admission had a higher incidence of negative outcomes compared to those with AKI prior to admission. Independent predictors of in-hospital mortality in COVID-19 patients were increased serum CRP. Death in hospitalized patients with COVID-19 and AKI was independently associated with factors such as age > 75 years, history of CKD, admission to Intensive Care Unit, leukocytosis, and ASAT/ALAT > 1.6.

Keywords: chronic kidney disease, acute kidney injury, COVID-19.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Data on the prevalence of acute kidney injury and chronic kidney disease in COVID-19 patients are contradictory and vary widely (from 0.5% to 80.3%) depending on the severity of disease progression and a lot of different factors which remains unknown till now.

The research hypothesis

Clinical evolution of COVID-19 showed a presence of kidney malfunction, therefor it is important to determine evolution and types

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of acute kidney injury and their prognostic value in hospitalized patients with SARS-CoV2 infection with progression to chronic kidney disease.

The novelty added by the manuscript to the already published scientific literature

The article defines that patients who experienced AKI during the acute phase of COVID-19 are at more than 2.5-fold increased risk of death and *de novo* formation or progression of CKD or within 180 days of discharge.

Introduction

Following an increased incidence of respiratory infections that caused respiratory failure in Wuhan, Hubei province, China, in December 2019, researchers identified a new coronavirus, later named by the World Health Organization (WHO) "severe acute respiratory syndrome caused by coronavirus type 2" (SARS-CoV-2). On March 11, 2020, the spread of the virus was declared a pandemic by the WHO. Despite all the progress in diagnosis and treatment as well as active anti-epidemiological measures, the pandemic with a novel coronavirus (COVID-19) has been one of the most urgent public health problems.

COVID-19 was initially considered a predominantly respiratory infection, with mortality associated with the progression of respiratory failure [1, 2]. Currently, COVID-19 is recognized as a multisystem disease with a wide range of manifestations [1-3]. One of the most common complications of COVID-19 is acute kidney injury (AKI). The frequency of AKI, according to different authors, varies greatly and requires further study, including the number of those who required renal replacement therapies also differs [4]. These epidemiological data are necessary for healthcare planning because renal replacement treatment increases patient care costs [5, 6].

The current data on the prevalence of various AKI phenotypes in COVID-19, along with clinical features and the prognostic significance of changes in urinary sediment, proteinuria, and markers of kidney damage in COVID-19 patients are limited. Retrospective studies report that most patients with AKI were already experiencing impaired kidney function upon hospitalization [2, 4, 7]. However, as for now, the prognostic implications and predictors for the development of different AKI phenotypes remain undefined. The study of the predictive role of changes in urinary sediment, proteinuria and biomarkers in the development of acute renal injury and mortality in real clinical practice may become the basis for developing an improved algorithm for managing patients with COVID-19: stratification of patients at risk of developing AKI, identification of high-risk groups requiring frequent monitoring of clinical and laboratory parameters, and adjusting drug treatments.

AKI is a demonstrated risk factor for a poor prognosis in COVID-19 patients [1, 6, 8]. The data from clinical studies confirm the increased risk of hospital mortality in patients with AKI, which underlines the undoubted relevance of the problem. Despite the large number of publications, the prognostic role of AKI among mortality predictors is not completely elucidated.

The consequences of acute kidney injury, incurred in the acute phase of COVID-19, are less studied. The potential impact of AKI on the risk of re-hospitalization, death, and the development or progression of chronic kidney disease (CKD) after discharge from hospital is less well known. The high prevalence of COVID-19 and associated AKI highlights the need to study long-term and renal outcomes for prognosis and patient care planning.

Data on the prevalence of AKI in COVID-19 patients are contradictory and vary widely (from 0.5% to 80.3%) depending on the severity of disease progression [7, 9, 10]. It has previously been established that AKI is a predictor of poor prognosis in hospitalized patients with COVID-19 [6, 9, 11]. The high prevalence of AKI in the severe COVID-19 group [1, 3, 12] and the increased mortality risk in patients with AKI [4, 13, 14] highlight the need to further explore predictors of kidney damage in this population. Additionally, most studies have investigated the prognosis without considering the timing of kidney failure onset. The purpose of the study is to investigate the types of acute kidney injury and their prognostic value in hospitalized COVID-19 patients who evolve to chronic kidney disease.

Material and methods

The study utilized a comprehensive database of patients admitted to general department of COVID-19 at *Timofei Moşneaga* Republican Clinical Hospital since 2020 to 2022 years, and included 1000 patients. The study consists of two parts. The first part was a retrospective study, which included hospitalized adult patients with confirmed COVID-19 and lung injury according to computer tomography (CT) scan of the chest (favorable opinion of the Research Ethics Committee, minutes №6 from 18.05.2023). Clinical and demographic characteristics of patients are presented in Table 1. The exclusion criteria were: repeated hospitalization, hospitalization less than 48 hours, acute surgical pathology, transfer to another hospital, single measurement of serum creatinine during hospitalization.

Table 1. Clinical and demographic characteristics of patients (n = 1000).

Parameter	Result
Men, (%)	49.2%
Age, years, Me (IQR)	68 (54; 79)
BMI, kg/m^2, M±SD in 828 patients	30±5
Obesity, n (%)	400 (48)
Overweight, n (%)	284 (33)
DM, n (%)	261 (26)
Of them, DM type 2, n (%)	255 (98)
HTA, n (%)	711 (71.1)
From them controlled HTA, n (%)	594 (83)
Anamnesis oncology, n (%)	97 (10)
Of them, relapse at the time of hospitalization, n (%)	46 (47)
Atrial fibrillation, n (%)	153 (15.3)
CKD, n (%)	137 (13.7)
Ischemic heart disease, n (%)	171 (17.1)
Chronic obstructive pulmonary disease, n (%)	67 (6.7)
Cirrhosis, n (%)	12 (1.2)
Charlson Comorbidity Index, CCI, Me (IQR)	3 (2; 5)

***Note**: IQR – interquartile range; Me – median; BMI – body mass index; HTA* – arterial hypertension; CKD – chronic kidney disease; *CCI – Charlson Comorbidity Index; DM – diabetes mellitu*s.

The second part of the paper is a prospective study of the prognostic value of inflammatory markers (CRP), renal function test (serum creatinine) and kidney injury (hematuria, proteinuria) in the development of AKI and hospital mortality, general and renal outcomes in patients who developed AKI in the acute phase of COVID-19.

In all patients, admission physical examination data (saturation O_2 (SpO_2), blood pressure and heart rate) and data on home treatment and therapeutic interventions received during hospitalization were evaluated.

In all patients, a complete blood count was performed (with erythrocyte count, hemoglobin, leukocytes, lymphocytes, platelets), a biochemical analysis of blood with determination of the level of CRP, parameters of renal function (creatinine, electrolytes, GFR estimation using CKD-EPI from 2012), liver function tests (ALAT, ASAT, total bilirubin, albumin), in some patients procalcitonin, lactate dehydrogenase (LDH), ferritin, uric acid, coagulation profile with determination of the level of D-dimer and fibrinogen and urinalysis. Data from laboratory examinations of patients are presented in Table 2. All laboratory parameters were investigated in a local laboratory. Proteinuria was defined as the presence of more than 0.3 g/l of protein in urine. Hematuria was defined as the presence of more than three erythrocytes in the high-power field, leukocyturia - more than four leukocytes in the high-power field.

Assessment of kidney function. Changes in serum creatinine levels according to KDIGO 2012 criteria were used to detect and evaluate the severity of acute kidney injury. Baseline serum creatinine was defined as the lowest serum creatinine value at the time of admission or, if available, the last serum creatinine value within 6 months prior to hospitalization. 2 phenotypes of AKI have been defined – out-of-hospital and hospital acute kidney injury. Patients who were admittedwith AKI or those who developed AKI within the first 48 hours were considered to have out-of-hospital AKI. Hospital AKI was defined as any recorded AKI after 48 hours in hospital. Recovery of baseline renal function was considered positive dynamics of serum creatinine (± 2.5% of normal or baseline) until the end of hospitalization (discharge or death). Transient AKI was considered when AKI resolved within 48 hours, and persistent AKI was considered when it resolved between 48 hours and seven days after onset. Acute kidney injury was defined as an acute malfunction that had not resolved within seven days. A tendency to recover initial renal function was defined as a decrease in serum creatinine by 25% of its maximum value.

Table 2. Laboratory data of COVID-19 patients at admission (n = 1000)

Parameter	Result
Serum creatinine, µmol/L, Me (IQR)	91 (78; 115)
GFR CKD-EPI, ml/min, Me (IQR)	65 (48; 82)
Sodium, mmol/L, Me (IQR)	138 (135; 141)
Potassium, mmol/L, Me (IQR)	4.13 (3.76; 4.57)
CRP, mg/L, Me (IQR)	73 (29; 125)
ASAT, U/L, Me (IQR)	34 (25; 51)
ALAT, U/L, Me (IQR)	24 (16; 41)
ASAT/ALAT, Me (IQR)	1.38 (1,03; 1,86)
Total bilirubin, mmol/L, Me (IQR)	10.2 (7.5; 14)
Serum albumin, g/L, Me (IQR)	34 (30.8; 37)
WBC, 10^9, Me (IQR)	6.1 (4.5; 8.3)
Lymphocytes, 10^9, Me (IQR)	1 (0.7; 1.4)
Hemoglobin, g/L, Me (IQR)	130 (118; 143)
Platelets, 10^9, Me (IQR)	194 (152; 255)
D-Dimers, ng/ml, Me (IQR), available in 814 patients	311 (164; 597)
Hematuria, n (%)	144 (15.5)
Leukocyturia, n (%)	212 (22.8)
Proteinuria, n (%)	279 (30)

***Note**: IQR – interquartile range; Me – median; GFR CKD-EPI – Equations for Glomerular Filtration Rate; WBC* – white blood cell; CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase.*

Assessment of the degree of lung injury by CT of the chest. The degree of lung injury was estimated by CT of the chest: CT-1 lesion from 1 to 25% of the lungs, CT-2 – 26-50%, CT-3 – 51-75% and CT-4 more than 75% of the volume of lung lesion.

Assessment of long-term results. Overall long-term outcomes (death from any cause within 180 days, readmission to hospital within 30 days) were assessed by telephone contact and data were available for 691 (87%) of discharged patients.

Long-term renal outcomes were assessed by analyzing data on mean serum creatinine within 180 days of discharge, which were available in 446 (56%) of discharged patients. The progression of CKD was considered as a change from baseline to more severe in line with current recommendations [2-4].

Statistical analysis of study results. The statistical processing of the obtained data was performed with the help of StatSoft STATISTICA 9.0 application software packages. Distribution verification was performed using

the Shapiro-Wilk W-criterion criterion. The quantitative variables were described as M and SD (for the normal distribution) or as Me and IQR (for the asymmetric distribution). The significance of differences between two groups in quantitative variables was assessed using the Mann–Whitney U criterion. Qualitative variables were represented by absolute (n) and relative (%) values. All variables for which significance of differences between groups was demonstrated were included in multivariate regression analysis, where 95% OR and CI were determined using logistic regression. The thresholds for quantitative predictors were established based on the correlation of marginal probabilities with the selected limit score. Multinomial logistic regression was performed to examine potential predictors of out- and out-of-hospital AKI. Mortality predictors were assessed using multivariate Cox regression and 95% OR and CI were calculated.

Results

Study of prevalence, severity, phenotypes, risk factors and predictors of AKI. In hospitalized patients with COVID-19 and lung injury, AKI was determined in 296 (29.6%) cases. 56% had stage I of AKI, 26% stage II and 18% stage III according to KDIGO 2012 criteria. 61% (n = 182) of patients with kidney dysfunction were admitted to hospital with impaired renal function or developed it within 48 hours of admission. 36% had transient kidney dysfunction and 29% had persistent kidney dysfunction. It was found that 55.7% of kidney dysfunction patients did not recover their initial kidney function by the end of hospitalization. Less than 20% of patients, whose renal function was compromised during admission and did not tend to restore serum creatinine, tended to recover renal function at discharge.

As a result of the study of risk factors for AKI, patients who developed AKI, as opposed to patients without AKI, were found to be older (74 (54; 82) vs 63 (52; 73) years, respectively, p < 0.0001), had more frequent comorbidities: HTA (86% vs 65%, p < 0.001), DM (33% vs 23%, p = 0.001), cardiovascular disease (CVD) (26% vs 14%, p < 0.001), CKD (23% vs 9%, p < 0.001), history of oncological diseases (17% vs 7%, p < 0.001) and Charlson Comorbidity Index, CCI higher (5 (3; 6) vs 3 (1; 4), scores, p < 0.0001), more frequently administered renin-angiotensin-aldosterone system inhibitors (41 % vs 32 %, p = 0.02), loop diuretics (10 % vs 4 %, p < 0.001), statins (14 % vs 10 %, p = 0.006). Inpatient respiratory failure (56% vs 39%, p < 0.001), more severe maximal lung injury were also more frequently observed among patients with AKI (CT-3 39% vs 27%, p < 0.001; CT-4 11 % vs 3.6 %, p < 0.001). Laboratory data of patients with and without AKI are presented in Table 3.

According to multivariate regression analysis, independent predictors of AKI occurrence were DM (OR 1.79, 95% CI 1.13-2.83), HTA (OR 1.98, 95% CI 1.08-3.63), oncology history (OR 2.56, 95% CI 1.27-5.14), Charlson index > 4 points (OR 2.05, 95% CI 1.12-3.74), respiratory failure (OR 2.05, 95% CI 1.34-3.13), lymphopenia (OR 1.65, 95% CI 1.04-2.60), ASAT/ALAT>1.6 (OR 1.88, 95 % CI 1.22-2.89) and hematuria (OR 2.17, 95 % CI 1.24-3.81) on admission.

Table 3. Laboratory data at admission by presence of AKI

Parameter	Without AKI (n = 704)	With AKI (n = 296)	p
Leukocytes in blood, 10^9, Me (IQR)	5.9 (4.5; 7.8)	7 (4.9; 9.8)	<0.0001
Lymphocytes, 10^9, Me (IQR)	1.1 (0.8; 1.4)	0.8 (0.6; 1.2)	<0.0001
Hemoglobin, g/l, Me (IQR)	132 (121; 144)	125 (111; 140)	<0.0001
Platelets, 10^9, Me (IQR)	196 (154; 259)	190 (142; 241)	0.02
Serum creatinine, µmol/L	86 (74; 101)	126 (95; 166)	<0,0001
Potassium, mmol/L	4.12 (3.8; 4.5)	4,2 (3.7; 4.7)	0.3
CRP, mg/L	64 (23; 112)	101 (54; 157)	<0.0001
ASAT, U/L	33 (24; 47)	38 (26; 55)	0.002
ASAT/ALAT	1.29 (0.98; 1.72)	1.64 (1.24; 2.27)	<0.0001
Total bilirubin, µmol/L	10 (7.3; 13)	11 (7.8; 15)	0.04
Albumin, g/L	35 (32; 38)	32 (28; 36)	<0.0001
LDH, U/L*	325 (248; 451)	442 (306; 603)	<0.0001
Ferritin, ng/ml**	459 (209; 657)	604 (389; 703)	0.002
D-Dimers, ng/ml#	262 (144; 477)	480 (250; 1016)	<0.0001
Hematuria, n (%)	68 (10)	76 (26)	<0.001
Leukocyturia, n (%)	126 (18)	86 (29)	<0,001
Proteinuria, n (%)	171 (24)	108 (36)	<0.001

***Note**: IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase, LDH – lactate dehydrogenase; * - available to 378 patients; ** - available to 340 patients; # - available in 814 patients.*

Comparative analysis of clinical characteristics and prognosis of in hospital and out-of-hospital AKI. After comparative analysis of demographic parameters, no significant differences between groups were identified in terms of gender, obesity frequency, diabetes, HTA, atrial fibrillation, CVD and oncological history. Patients with hospital-acquired AKI were older (78 (67; 83) vs 72 (62; 80), years, p = 0.002), although belonging to the same age group, had a higher Charlson index (5 (4; 6) vs 4 (3; 6), scores, p = 0.02). When comparing anamnestic renal function data, there were no differences in the incidence of CKD and mean serum creatinine prior to hospitalization. No significant differences were found when analyzing differences between groups in pre-admission treatment. When comparing clinical data at admission, no statistically significant differences were found in the incidence of respiratory failure and hemodynamic disorders. When studying differences in laboratory data at admission, patients with AKI that occurred out-of-hospital and those that developed AKI during hospitalization, showed no differences in frequency of changes in blood count, levels of inflammatory markers, liver dysfunction and clotting disorders, frequency of changes in urine summary examination. Maximum laboratory mean values during for in-hospital and out-of-hospital AKI are presented in Table 4.

Table 4. Maximum laboratory average values during hospitalization for in- and out-of-hospital AKI.

Parameter, Me (IQR)	Out-of-hospital AKI (n = 182)	Hospital AKI (n = 114)	p
Leukocytes > $10x10^9$, n (%)	99 (54)	86 (75)	<0.001
Lymphocytes min, 10^9	0.6 (0.4; 0.9)	0.4 (0.3; 0.7)	0.0002
Lymphocytes < $1,2x10^9$, n (%)	157 (86)	108 (95)	0.02
Creatinine max, μmol/L	163 (130; 245)	198 (128; 294)	0.1
Potassium max, mmol/L	5 (4.4; 5.8)	5.1 (4.42; 5,9)	0.4
CRP max, mg/L	151 (96; 234)	206 (146; 270)	0.002
ASAT max, U/L	53 (33; 94)	62 (42; 120)	0.04
Total bilirubin max > 21 μmol/L, n (%)	39 (21)	40 (35)	0.01
D-Dimers max, ng/ml	1317 (417; 3396)	2079 (780; 5150)	0.009

***Note**: AKI – acute kidney injury; IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ASAT – aspartate aminotransferase; min – minimum values during hospitalization; max – maximum values during hospitalization*

Maximum lung involvement (8% vs. 7%, p < 0.05) and progression of lung injury volume (39% vs. 26%, p = 0.03) were observed more frequently in patients with hospital AKI compared to developed AKI until hospitalization. Patients who developed AKI during hospitalization were more likely to experience transfer to the intensive care unit (59% and 41%, p < 0.05), initiation of artificial pulmonary ventilation (49% and 33%, p < 0.05), and hospital mortality (73% and 36%, p < 0.001) than those who had acute kidney injury to hospitalization.

Estimation of prognostic value of inflammatory markers, renal functional status and kidney injury for AKI occurrence and death during hospitalization. The incidence of AKI within the group was 24%, 56% had stage I, 25% stage II and 19% stage III. Patients with AKI compared to the group without AKI were found to have higher serum CRP (114 (66; 194) vs 68 (35; 105), mg/L, p = 0.01), serum creatinine (143 (107; 173) vs 85 (76, 100), μmol/L, p < 0.0001), erythrocytes in urine (3.5 (0; 10) vs 0 (0; 1), p = 0.04) and protein in urine (0.3 (0.2; 0.5) vs 0 (0; 0,15), g/L, p = 0,0003). After regression analysis using 7 separate models, proteinuria (p = 0.02), CRP (p = 0.03) and serum creatinine (p = 0.001) showed significant associations with AKI, whereas hematuria was not statistically significant.

After comparing groups of surviving vs. deceased patients, deceased patients had higher levels of proteinuria at admission (0.2 (0.15; 0.5) vs 0.12 (0; 0.25), g/L, p = 0.03) and serum creatinine (136 (86; 167) vs 86 (79; 107), μmol/L, p = 0.05) and CRP (147 (99; 149) vs 65 (35; 105), mg/L, p = 0.0009). After performing regression analysis using 5 separate models for each predictor, CRP and serum creatinine showed significant associations with mortality, whereas proteinuria was not statistically significant. The optimal limit values for the above biomarkers for predicting hospital mortality were determined based on the correlation of marginal probabilities with the selected cut-off score.

Analysis of short-term outcomes and mortality predictors in hospitalized patients with COVID-19. The median duration of hospitalization was 11 (9; 15) days. 248 (24.8%) patients were in intensive care for at least one day, 136 (13.6%) patients underwent invasive ventilatory support, 89 (8.9%) – required vasopressor support. Thromboembolic complications occurred in 6% of patients. Renal replacement therapy was performed in 10 (1%) patients. 208 (20.8%) patients died in hospital. Mortality was higher in intensive care compared to the general profile ward (56 % vs. 9 %, p < 0.001). Mortality was significantly higher in the acute kidney injury group (50% vs 8.5%, p < 0.001).

Patients who died in hospital were found to be older (79 (67; 85) vs 64 (52; 73), years, p < 0.0001), more frequently had comorbidities, were admitted with respiratory failure (58% vs 41%, p < 0.001), were admitted to intensive care (67% vs 14%, p < 0.001) and had AKI (71% vs 19%, p < 0.001). It was established that during hospitalization, patients who died had higher leukocytosis (80% vs 23%, p < 0.001), lymphopenia (96% vs 69%, p < 0.001), hemoglobin below 120 g/l (41% vs 24%, p < 0.001) compared to survivors, platelets below $150x10^9$ (48% vs 28%, p < 0.001), hypoalbuminemia (97% vs 66%, p < 0.001), hematuria (27 % vs 11 %, p < 0.001), leukocyturia (33 % vs 18 %, p < 0.001) and proteinuria (37 % vs 26 %, p < 0.001), had higher CRP levels (210 (146; 285) vs 97 (50; 151), mg/L, p < 0.0001), serum creatinine (174 (112; 276) vs 93 (80; 115), p < 0.0001), ASAT (70 (41; 122) vs 41 (28; 65), U/L, p < 0.0001), ASAT/ALAT (1.91 (1.28, 2.57) vs 1.14 (0.84; 1.57), p < 0.0001), total bilirubin (16.5 (11; 27) vs 12 (9; 16), μmol/L, p < 0.0001), D-Dimers (2664 (907; 7047) vs 271 (187; 780), ng/ml, p < 0,0001). Age over 75 years (OR 2.27, 95% CI 1.58-3.27), Charlson comorbidity index > 5 points (OR 1.78, 95% CI 1.17-2.72), AKI (OR 1.65, 95% CI 1.11-2.46), leukocytosis (OR 2.69, 95% CI 1.80-4.01), lymphopenia (OR 2.44, 95% CI 1.03-5.79), CRP increase > 100 mg/L (OR 2.08, 95 % CI 1.27-3.42) and ASAT/ALAT > 1.6 (OR 2.68, 95 % CI 1.89-3.78) during hospitalization were independent predictors of mortality according to multivariate Cox regression.

Patients who died with AKI more frequently had transient renal impairment (50.5% vs 22%, p < 0.001), more severe renal injury (stage I 37% vs 76%, p < 0.001, stage II 35% vs 21%, p = 0.03, stage III 28% vs 3%, p < 0.001) and less frequently had recovery of baseline renal function by the end of hospitalization (14% vs 74%, p < 0,001).

After comparing discharged and deceased AKI patients, patients in the second group were older (79 (68; 85) vs 70 (61; 78) years, p < 0.0001), more had hypertension (91% vs

82%, p = 0.02) and CVD (28% vs 18%, p = 0.04), more had respiratory failure at admission (62% vs 50%, p = 0.04) and hospitalized in intensive care units (73% vs 23%, p < 0.001). Laboratory maximums during hospitalization were analyzed in relation to hospital mortality in patients with AKI and data are presented in Table 5. Deceased patients with AKI and those who recovered showed no differences in the frequency of changes in urinary sediment, proteinuria at admission.

Table 5. Maximum laboratory values in patients with AKI by mortality rate.

Parameter, Me (IQR)	Survivors with AKI (n = 148)	Deaths with AKI (n = 148)	p
Leukocytes > $10x10^9$, n (%)	62 (46)	123 (83)	<0.001
Lymphocytes < $1.2x10^9$, n (%)	123 (83)	142 (96)	<0.001
Hemoglobin < 120 g/L, n (%)	77 (52)	93 (63)	0.06
Platelets < $150x10^9$, n (%)	53 (36)	74 (50)	0.01
Creatinine max, µmol/L	147 (119; 189)	243 (158; 307)	<0.0001
Sodium min, mmol/L	135 (131; 138)	136 (131; 140)	0.04
Potassium max > 5.1 mmol/L, n (%)	49 (33)	80 (54)	0.001
CRP max, mg/L	124 (84; 187)	227 (152; 296)	<0.0001
ASAT max, U/L	48 (30; 73)	76 (43; 182)	<0.0001
ASAT/ALAT max	1.45 (1.04; 1.93)	1.98 (1.42; 2.69)	<0.0001
Total bilirubin max, µmol/L	13 (10; 21)	16 (11; 28)	0.006
Albumin min, g/L	29 (24; 33)	23 (19; 27)	<0.0001
Procalcitonin max, ng/ml*	0.24 (0.09; 0.7)	1.4 (0.4; 6.8)	0.0002
LDH max, U/L**	404 (273; 571)	660 (440; 967)	<0.0001
D-Dimers max, ng/ml	717 (323; 2521)	2711 (1247; 6085)	<0.0001
Fibrinogen max, g/L	6.9 (5.4; 7.6)	7 (5.5; 7.9)	0.5

***Note**: AKI – acute kidney injury; IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase, LDH – lactate dehydrogenase; * - available in 96 patients; ** - available in 160 patients.*

According to multivariate regression analysis, patients with AKI who were 75 years > years of age (OR 1.93, 95% CI 1.33-2.79), CKD (OR 1.67, 95% CI 1.12-2.49) were admitted to Intensive Care Department (OR 3.34, 95% CI 2.06-5.41), leukocytosis > $10x10^9$ (OR 2.09, 95% CI 1.32-3.30) and AST/ALT > 1.6 (OR 2.21, 95% CI 1.54-3.17) during hospitalization, all of these factors were independent predictors of mortality.

Assessment of the prognostic character of AKI in relation to long-term outcomes. For the analysis of long-term outcomes, 691 patients were evaluated, of which 554 (80%) patients did not have AKI during the acute period of COVID-19 and 137 (20%) had AKI. Patients who sustained acute kidney injury and were discharged were older (71 (62; 78) vs 64 (52; 73) years, p < 0.0001), more had HTA (82.5% vs 66%, p < 0.001), CVD (25% vs 12%, p < 0.001), atrial fibrillation (18% vs 9%, p = 0.008), cancer (17.5% vs 6.7%, p < 0.001) and CKD (18% vs 9%, p = 0.002), Charlson index higher (4 (3 (3; 5) vs. score 3 (1; 4), p < 0.0001), more admitted to intensive care (23% vs. 10%, p < 0.001) and radiologically had CT-3 and CT-4 (38% vs. 25%, p < 0.05). According to the Cox multivariate regression, as predictors of death from any cause within 180 days of discharge, only the Charlson index (OR 1.46, 95% CI 1.19-1.79) and acute kidney injury (OR 2.83, 95% CI 1.28-6.26) sustained in the acute phase of COVID-19 were predictors. At discharge, 792 patients were monitored, 446 (56%) patients had serum creatinine levels examined within 180 days of discharge. Clinical and demographic characteristics of patients are presented in Table 6.

Table 6. Clinical and demographic characteristics of patients who underwent AKI and in whom renal function was assessed after discharge.

Parameter	Patients without AKI (n = 343)	Patients with AKI (n = 103)	p
Men, n (%)	195 (57)	41 (39)	0.002
Age, years, Me (IQR)	65 (56; 73)	71 (61; 76)	0.006
Obesity, n (%)	157/314 (50)	49/89 (55)	0.4
DM, n (%)	90 (26)	34 (32)	0.2
HTA, n (%)	245 (72)	83 (78)	0.09
Angiotensin-converting enzyme inhibitors, n (%)	132 (39)	37 (35)	0.9
CVD, n (%)	51 (15)	26 (25)	0.02
Charlson Index, Points, Me (IQR)	3 (2; 4)	4 (3; 5)	0.0002
Anamnesis oncology, n (%)	26 (8)	18 (17)	0.003
Atrial fibrillation, n (%)	43 (13)	21 (20)	0.05
CT-3 and above, n (%)	78 (23)	38 (36)	0.005
Admission to Intensive Care Department, n (%)	34 (10)	26 (25)	<0.001

***Note:** AKI – acute kidney injury; IQR – interquartile range; CVD – cardiovascular disease*

Data on GFR were divided into two groups, at discharge and over 180 days, and are presented in Table 7.

It was found that in patients who developed AKI during hospitalization, the incidence of a decrease in GFR was higher by more than 10% compared to GFR at discharge (33% vs 18%, p < 0.05), by more than 20% compared to GFR at discharge (22% vs 6%, p < 0.001) and formation of *de novo* chronic kidney disease or progression of pre-existing CKD (35% vs 15%, p < 0.001) 180 days after discharge from hospital.

Table 7. Mean GFR values at discharge and over 180 days of follow-up

Parameter, n (%)	On discharge		During 180 days	
	Discharged without AKI (n = 343)	Discharged with AKI (n = 103)	Discharged without AKI (n = 343)	Discharged with AKI (n = 103)
GFR CKD-EPI > 60 ml/min	272 (79)	60 (58)**	269 (78)	56 (54)**
GFR CKD-EPI from 59 to 45 ml/min	50 (15)	24 (23)*	50 (15)	23 (22)
GRF CKD-EPI from 44 to 30 ml/min	19 (5,5)	10 (10)	21 (6)	18 (17)**
GFR CKD-EPI < 30 ml/min	2 (0,5)	9 (8)**	3 (1)	6 (5)*

***Note**: GFR CKD-EPI – Equations for Glomerular Filtration Rate; *p < 0.05, **p < 0.001 – the significance of differences between patients with AKI*

Similarly, according to multivariate regression analysis, age > 65 years (OR 4.29, 95% CI 1.96-9.38), Charlson index > 4 points (OR 2.44, 95% CI 1.30-4.59) and AKI development (OR 2.54, 95% CI 1.46-4.43) were predictors of *de novo* CKD or its progression within 180 days.

Discussion

Given the heterogeneity of the data, even though there are standardized AKI criteria recognized by the global medical community, the true prevalence of deteriorating kidney function in patients with COVID-19 is not fully understood. Thus, the pathogenesis of kidney damage in SARS-CoV-2 infection is multifactorial. First, SARS-CoV-2 can exert a direct cytopathic effect on the kidney. This is supported by the detection of coronavirus fragments in the urine of SARS-CoV-2-infected patients determined by polymerase chain reaction [1, 3, 15]. As mentioned above, SARS-CoV-2 uses ACE2 to enter the host cell [2]. Therefore, the most common symptom in patients with CKD and COVID-19 was proteinuria, which is the result of direct damage to podocytes due to ACE2 expression [2, 11, 16], a fact also mentioned in our study. Literature data highlight the presence of hematuria in 20% of patients infected with COVID-19 [4, 17], a value comparable to the value in our study. The authors explain the pathogenesis of hematuria as a consequence of endotheliitis leading to coagulopathy and destruction of the filtration barrier in the renal corpuscles [2, 17-19]. Some authors, including ourselves, believe that the occurrence of proteinuria and hematuria in a COVID-19 patient are independent predictors of the development of the critical stage of the disease [6, 13, 20]. Similarly, literature data also indicate that AKI has been diagnosed in patients with COVID-19 more frequently than cardiovascular (23%) and liver (23%) diseases [11-14, 21]. Of the patients who developed AKI due to coronavirus infection, one in four patients required continuous hemodialysis, and 12 (80%) patients died within the first week of admission [2, 5, 9, 22].

In a large study from the UK, more than half (51%) of patients with AKI had stage 1, 13% had stage 2, and 36% had stage 3 AKI [11], similar results to our study. In another trial from the United States, which included more than 9,000 patients, the incidence of AKI was 39.9%, of which 43% had stage 1, 22% had stage 2, and 36% had stage 3 [9, 15]. This differed in terms of comorbidity compared to our study, but overall were similar. In another retrospective analysis from Scotland, which included 554 hospitalized patients with COVID-19, the incidence of AKI was 60.6%, with the majority of AKI cases corresponding to stage 3 (55.8%) [17]. In a meta-analysis of 13 studies that reported the severity of AKI, the majority (44%) of patients with AKI had stage one, 19% had stage two, and 34% had stage three [13]. This suggest a hypothesis of predominance of comorbidities influencing the degree and severity of kidney damage in SARS-CoV2 infection.

A clinical trial based in a hospital in Wuhan (n = 701) showed that 5.1% of patients admitted for antiviral treatment developed acute kidney injury [23]. Among these patients at admission, 43.9% had proteinuria, 26.7% had hematuria, 13-14% had elevated serum creatinine levels, and glomerular filtration rate was less than 60 ml/min. Also, the results of scientific studies conducted by reputable experts clearly demonstrate that SARS-CoV-2 infection can provoke the development of chronic kidney disease [24, 25]. While it is still difficult to assess the long-term effects of the pandemic, these effects are likely to contribute to an increased incidence of chronic kidney disease.

Conclusions

Acute kidney injury occurs in 29.6% of patients hospitalized with COVID-19. In more than half of cases, kidney dysfunction corresponds to the first stage of AKI, begins before hospitalization, and does not recover until discharge. The risk of AKI is higher in patients with more comorbidities and a more severe course of disease. Patients with history of CKD, AKI often starts before hospitalization. Independent negative predictors of hospital-developed AKIs were HTA, Charlson index > 4 points, respiratory failure, ASAT/ALAT > 1.6, D-Dimers > 250 ng/ml, and hematuria on admission. In patients who underwent AKI in the acute phase of COVID-19, the risk of death and either *de novo* formation of CKD, or progression of existing CKD within 180 days of discharge, is more than 2.5 times higher.

Competing interests.

None declared.

Patient consent.

Obtained.

Ethics approval.

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes no.6 from 18.05.2023).

Authors' contribution.

Study conception and design: TR, LG, EC, ER. Data acquisition: TR, ZA, CG. Analysis and interpretation of data: TR, ER, ZA, CG. Drafting of the manuscript: TR, ER, ZA. Significant manuscript review with significant intellectual involvement: LG, EC, ER. All authors approved the final version of the manuscript.

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RESEARCH ARTICLE

The impact of family screening in patients with Wilson's disease from the Republic of Moldova

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ABSTRACT

Introduction. Wilson's disease (WD) is a rare genetic disease with autosomal recessive transmission, thus screening of all family members of newly diagnosed patients is recommended. Therefore, we aimed to analyze the proband's family members to detect asymptomatic cases and early treatment initiation.

Material and methods. There were retrospectively evaluated 12 families, between 2008 - 2023. The Leipzig Scoring System was used to assess the diagnosis. Genetic testing was performed in all cases by the Sanger sequencing method, examining exons with a high and moderate frequency of mutations.

Results. All patients were of Caucasian origin, and originally from Moldova. No patient reported consanguineous relationships. In 9 families, first-degree relatives were tested - parents and siblings, in the other 3 cases only their descendants were evaluated. In 6/12 cases: both parents were healthy carriers; in the other 3 families, one parent was a healthy carrier, but the other parent had not been tested. Among siblings, 4 healthy carriers and 2 healthy siblings were identified. 7 new family members with WD were identified in 5/12 families. 6 patients were asymptomatic, and 1 - was symptomatic. The most frequent mutations detected were p.H1069Q and p.G1341D, both as compound heterozygous and homozygous recessive. A rare mutation has been detected.

Discussions. Genetic counseling is important for the family of the patient with Wilson's disease, as the evaluation of first-degree relatives is recommended by all international guidelines. First-degree relatives include the proband's siblings, as well as the proband's offspring and parents. It is also important to assess distant relatives, especially in more isolated areas. Although it is an autosomal recessive disorder, systemic family screening is recommended, as cases of paradoxical transmission are recorded. The c.2292C>T variant, identified in one patient, represents a rare mutation that, when occurring in combination with another pathogenic mutation or a homozygous state, can cause WD.

Conclusions. Family screening greatly influences identifying asymptomatic members with Wilson's disease. Genetic testing is very important in differentiating healthy carriers from asymptomatic members, especially when deciding treatment tactics.

Keywords: Wilson's disease, family screening, proband, asymptomatic, genetic test.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Although it is a monogenic disorder, Wilson's disease is characterized by genotypic and phenotypic diversity even within the same family. This study analyzes for the first time families with members with Wilson's disease in the Republic of Moldova. In this way, asymptomatic members can be highlighted.

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The research hypothesis

Irreversible tissue damage can be prevented if Wilson's disease is diagnosed and treated early. Relatives of individuals with Wilson's disease are at high risk of developing the disorder, so they must be screened.

The novelty added by the manuscript to the already published scientific literature

As a result of the exhaustive examination of the families of the probands, new family members were diagnosed with Wilson's disease in the asymptomatic phase of the disease, thus initiating early specific therapy.

Introduction

Wilson's disease (WD) is a rare genetic disorder caused by a pathogenic mutation of the ATPase copper transporting beta (ATP7B) gene, which is involved in cellular copper metabolism. Because of this mutation, a defective protein is synthesized, which does not allow the incorporation of copper ions into ceruloplasmin, as well as the excretion of the metal through bile. Thus, the abnormal copper metabolism subsequently leads to the accumulative deposition of copper in the target organs and impairs the normal functions of the affected organs, especially in the liver and brain [1].

The prevalence of WD in the general population is 1:30 000 - 200 000 people [2, 3], but it can vary according to the geographical area, and in socially, economically, culturally, religiously, and geographically isolated communities it can be much lower, especially if marriages between relatives are practiced [4].

A polymorphic clinical picture characterizes WD, and the disease can evolve from asymptomatic forms, isolated non-specific symptoms, to acute liver failure. It must be suspected in all adults or children presenting with unexplained liver disease or/with a movement disorder of uncertain cause, neuropsychiatric disorders, or unexplained hemolytic anemia [5]. Because of its broad spectrum of clinical manifestations that can present in almost any decade of life, a high degree of clinical suspicion is needed for diagnosis (Fig. 1) [6, 7]. Despite some specific changes in investigations, the diagnosis of WD remains a challenge, given that there is no single specific test, but several tests are needed, and genetic testing for ATP7B mutations is an important criterion when routine examinations are not well defined [8].

In 1912, British neurologist Samuel Kinnear Wilson first described WD as "progressive lenticular degeneration", a fatal familial neurological disorder that may be associated with chronic liver disease leading to cirrhosis. In his work he mentioned that "the most curious and remarkable feature of this familial nervous disease is the constant presence of a profound degree of cirrhosis of the liver", but at that time it was considered not to cause clinical problems [9]. In 1916, physician Byrom Bramwell reported a family in which four siblings died of "acute fatal cirrhosis". Between 1925 and 1929, Drs. Barnes and Hurst described a family in which 3 of the eight children had Wilson's disease, but liver lesions preceded neurological symptoms, and the fourth child died of severe liver disease without neurological symptoms [10]. Respectively, the involvement of several members of the same family with this disease is observed, which denotes the importance of screening for the whole family.

WD is an autosomal recessive disorder. Although it is a monogenic disorder, and the inheritance of characters occurs according to Mendelian laws, paradoxical transmissions of the disease, such as pseudo-dominant transmission, have been recorded. Thus, cases of WD have been reported in consecutive generations, but this can occur, particularly when carrier frequencies are as high as in WD [11]. In addition, cases of atypical inheritance have been described, such as the presence of three concurrent mutations in a single patient or segmental uniparental disomy. This change occurs when both homologs of a chromosome come from the same parent [12].

It is important to screen family members of a newly diagnosed patient with WD, because the risk of developing this disease is 25% for siblings, and 0.5% for offspring [3]. Thus, screening first-degree relatives can identify persons affected by WD in the asymptomatic phase, although organ lesions may already be present. In this phase, the evolution of the disease is favorable with the initiation of specific treatment. Therefore, it is essential to identify them as early as possible and start chelator therapy [13]. This also increases disease awareness among family members, allows for close medical surveillance, and differentiates healthy members or healthy carriers who might be potential donors if a sick member requires a liver transplant [14]. At this stage, it is important to differentiate asymptomatic patients from healthy carriers because 15% of carriers show changes in copper parameters [15]. Genetic testing can confirm the diagnosis when biochemical testing is inconclusive and can identify the individual's status as simple heterozygous, compound heterozygous, or homozygous recessive [13].

Taking into account the heredity, phenotypic diversity, and genotypic heterogeneity of the disease, our goal was to evaluate the families of patients diagnosed with WD to initiate appropriate treatment in asymptomatic members.

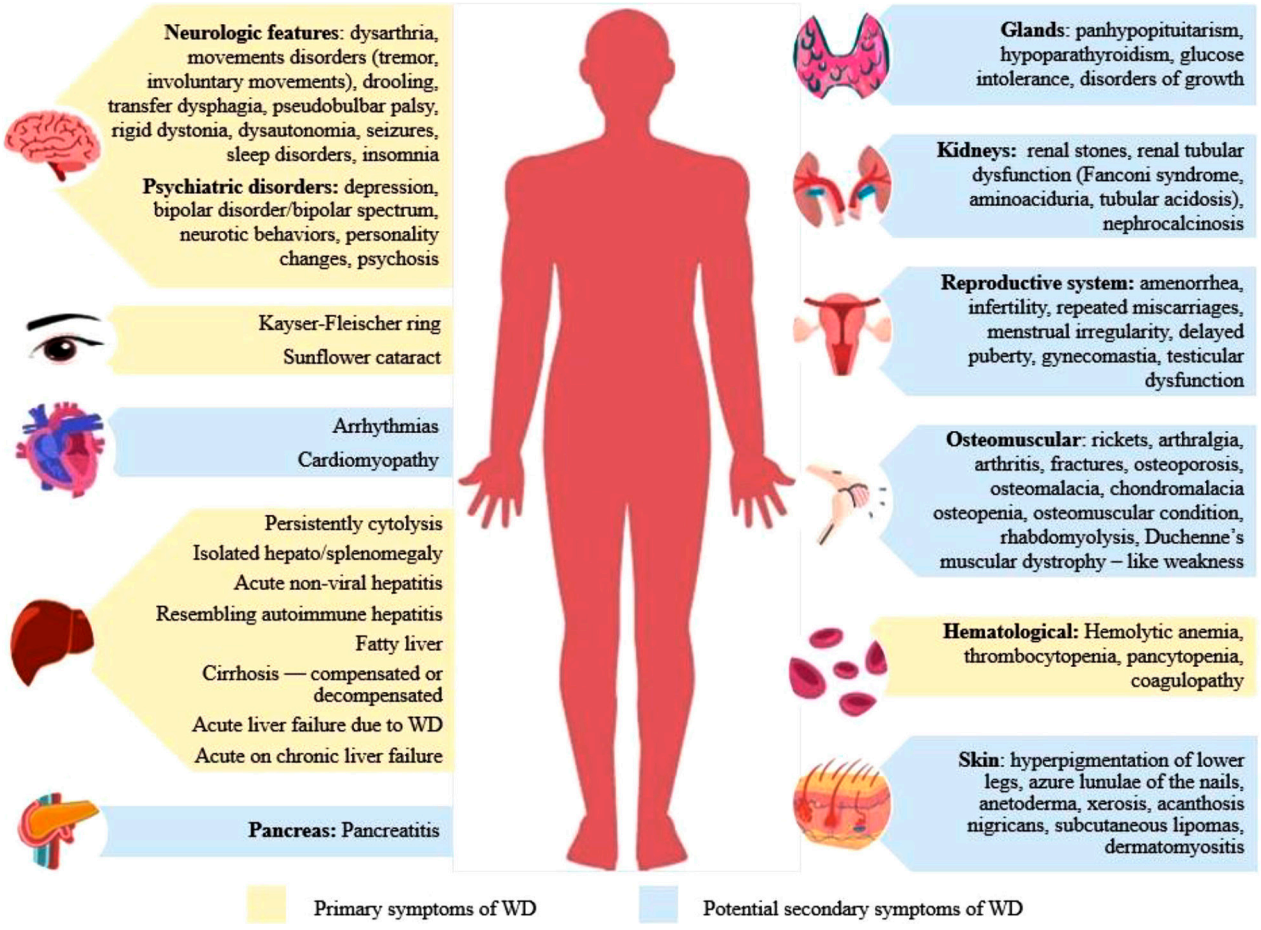

Fig. 1 Clinical Manifestations of Wilson's Disease.

Note: *WD - Wilson's Disease.*

Materials and methods

12 families were evaluated retrospectively and prospectively, between 2008 and 2022 within the Human Molecular Genetics Laboratory and the Gastroenterology Discipline of the *Nicolae Testemiţanu* State University of Medicine and Pharmacy. The given study is part of the research protocol that obtained a favorable opinion from the Research Ethics Committee (minutes No.1 dated 25.05.2021). All study participants (parents of children or patients) signed informed consent forms.

Inclusion criteria:

1. Presence of a sick member with WD;
2. Patients aged ≥ 5 years;
3. Consent of the patient or legal representative to participate in the study.

Exclusion criteria:

1. Absence of family members affected by WD;
2. Patient aged < 5 years;
3. Lack of patient or legal representative consent to participate in the study.

The investigation methods used within the study were:

- *clinical examination* – patients' complaints, medical and family history were collected. Physical examination was performed with recording of anthropometric data and vital signs;
- *laboratory investigations* – complete blood count, liver biochemical profile, coagulation, and copper parameters. Liver biopsy with copper quantification in dry liver tissue was not performed for technical reasons, it is not available in the country.
- *instrumental examinations* – evaluation of Kayser-Fleischer rings of the cornea, abdominal ultrasonography, Fibroscan, and brain magnetic resonance imaging.
- *molecular-genetic analysis* –Sanger sequencing of the ATP7B gene was performed, examining exons with a high and moderate frequency of mutations, at the Human Molecular Genetics Laboratory in Moldova. In certain cases, whole gene sequencing was performed in Germany, Italy, and France.
- *D- Penicillamine test* – The first dose (D-penicillamine 500 mg) is administered at 8:30 a.m., and the next dose (D-penicillamine 500 mg) at 8:30 p.m. (12 hours after the first dose). Urine collection begins after the first dose, in a special "acid-washed" container, so care is required in handling. Collect con-

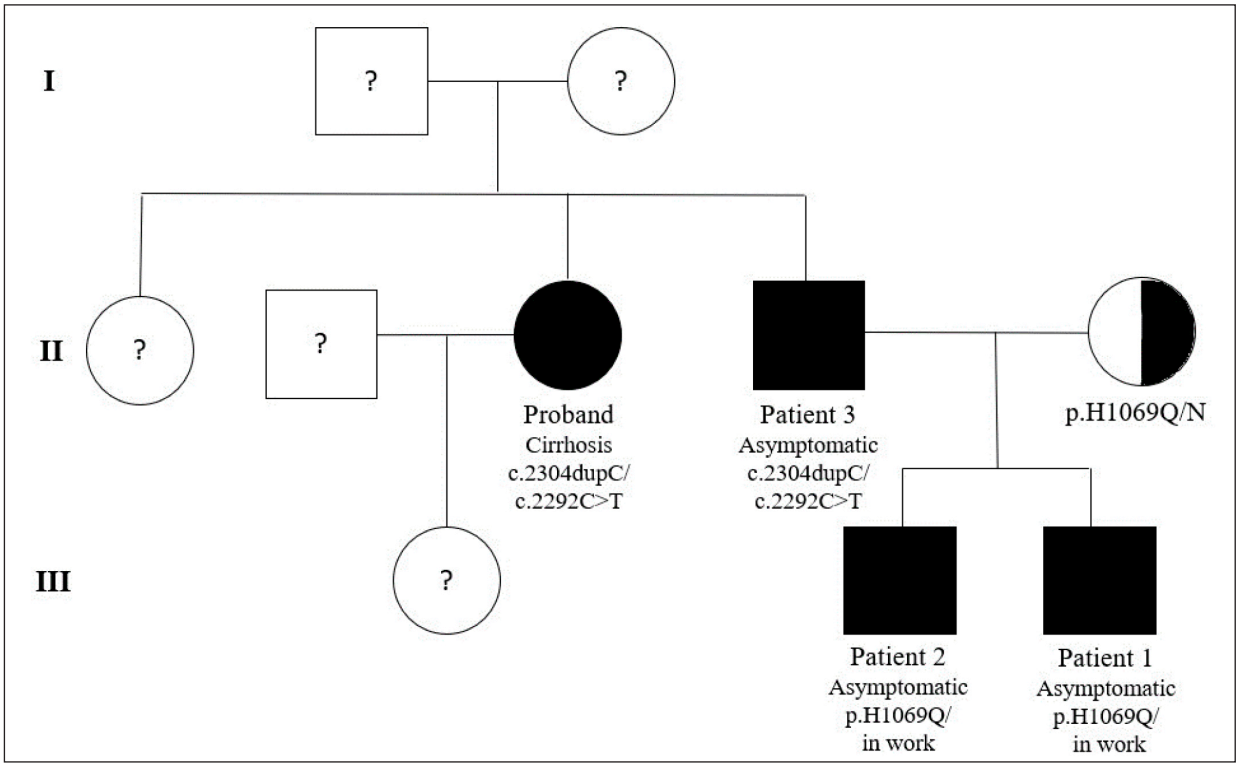

Fig. 2 Pseudo-dominant inheritance.

Note: *The filled shapes - affected individuals. The half-filled shapes - the carrier. c.2304dupC/c.2292C>T - compound heterozygous; p.H1069Q/N – a healthy carrier; p.H1069Q/in work - compound heterozygous, the second mutation is under examination; ? - genetic status unknown.*

tinuously for 24 hours, including night and morning samples.

- *calculation of the Leipzig Scoring System* (2001) for all enrolled subjects; a score ≥ 4 points establishes the diagnosis of WD.
- *mathematical-statistical processing methods* – Microsoft Excel, Epi Info, Student's t-test.
- *creation of the figures* - Canva, PowerPoint.

Results

All individuals included in the study underwent clinical, paraclinical, and genetic examinations. Each patient was of Caucasian origin, and originally from Moldova. Most probands originate from the south of the country (6/12), and 3 probands each originate from the north and the center of the country. No patient reported consanguineous relationships. Hepatic onset was more common in females (4/6, $p < 0.01$), while neurological onset was more prevalent in males (4/6, $p < 0.05$).

In 9 of the families, the 1st-degree relatives were tested - parents and siblings, in the other 3 cases only their descendants were evaluated. In half of the cases (6 out of 12), both parents are healthy carriers; in the other 3 families, one parent is a healthy carrier, but the other parent has not been tested. Among the siblings, 4 were identified as healthy carriers and 2 were healthy (no mutation detected). The most frequent mutations detected were p.H1069Q and p.G1341D, both as homozygous recessive and heterozygous (simple and compound). A rare mutation has been detected - c.2292C>T.

As a result of the evaluation in 5 out of 12 families involved in the study, 7 new members with WD were identified (6 males and 1 female). The mean age was 16 years (range 5-34 years). In 4 cases, there were 1st-degree relatives (siblings), and in 3 cases - 2nd-degree relatives (cousins, nephews). 6 patients were asymptomatic, and 1 had neurological symptoms but were not included in any nosology until the evaluation for WD (Table 1). In the case of one family, a paradoxical transmission of the disease was identified - pseudo-dominant inheritance (Fig. 2). In 3 cases where both parents are healthy carriers, both children were diagnosed with WD, with one diagnosis occurring through family screening (Figure 3). In 6 cases, WD was associated with liver damage, and one case presented with a mixed phenotype. In 2 asymptomatic patients, no changes in copper parameters were observed, only cytolysis with hepatosplenomegaly or only hepatomegaly being highlighted, but after stimulation with D-penicillamine, urinary copper in 24 hours increased more than 5 times the upper limits of the norm. In both cases, the genetic test confirmed the presence of 2 pathogenic mutations. Kayser-Fleischer ring was observed only in a single patient with neurological damage. All patients newly diagnosed with Wilson's disease initiated specific therapy.

Table 1. Results of investigations of new patients with WD identified by family screening.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, y	5	8	34	12	5	23	22
Sex	Male	Male	Male	Female	Male	Male	Male
Relationship with proband	Nephew	Nephew	Brother	Sister	Brother	Brother	Cousin
Clinical symptoms	No	No	No	No	No	No	Yes
Phenotype	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Neurohepatic
Serum ceruloplasmin	10 (15-30mg/dl)	14 (15-30 mg/dl)	5 (15-30 mg/dl)	24 (16-45 mg/dl)	24 (16-45 mg/dl)	6.9 (25-43 mg/dl)	53 (200-600mg/l)
Urinary copper 24 h	72.7 (3-35 µg/24h)	117.95 (10-60 µg/24h)	139.4 (10-60 µg/24h)	41.91 (10-60 µg/24h)	41.91 (10-60 µg/24h)	52.4 (10-60 µg/24h)	189 (<60 ug/24h)
Urinary copper 24 h after D- Penicillamine test	424.9 (10-60 µg/24h)	976.5 (10-60 µg/24h)	484.9 (10-60 µg/24h)	1022 (10-60 µg/24h)	325 (10-60 µg/24h)	1324 (<60 mg/24h)	317 (15-59 µg/24h)
Serum ALT	185 (<36 U/L)	173 (<29 U/L)	38 (<41 U/L)	100 (<30 U/L)	20 (<30 U/L)	58.8 (<35 U/L))	19.9 (<35 U/L)
Serum AST	88.6 (<53 U/L)	104 (<36 U/L)	26 (<37 U/L)	39 (<30 U/L)	15 (<30 U/L)	35 (<31 U/L)	20.2 (<35 U/L)
Kayser-Fleischer ring	Absent	Absent	Absent	Absent	Absent	Absent	Present
Abdominal echography	Normal	H-megaly	HS-megaly	H-megaly	HS-megaly	HS-megaly	S-megaly
Cranial magnetic resonance imaging	Normal	Normal	Normal	Normal	Normal	Not done	diffuse cerebral atrophy in both cerebral and cerebellar hemispheres
ATP7B genotype	p.H1069Q/ in work	p.H1069Q/ in work	c.2304dupC/ c.2292C>T	p.H1069Q/ p.H1069Q	p.H1069Q/ p.Gly1341Asp	p.G1341D / p.G1341D	p.H1069Q/ p.G1341D
Leipzig Score	5p	4p	8p	6p	6p	8p	12 p

Note: *ATP7B - ATPase Copper Transporting Beta; H-megaly – hepatomegaly; HS-megaly – hepatosplenomegaly; S-megaly – splenomegaly; ALT - alanine transaminase; AST - aspartate transaminase, y – years, h – hour.*

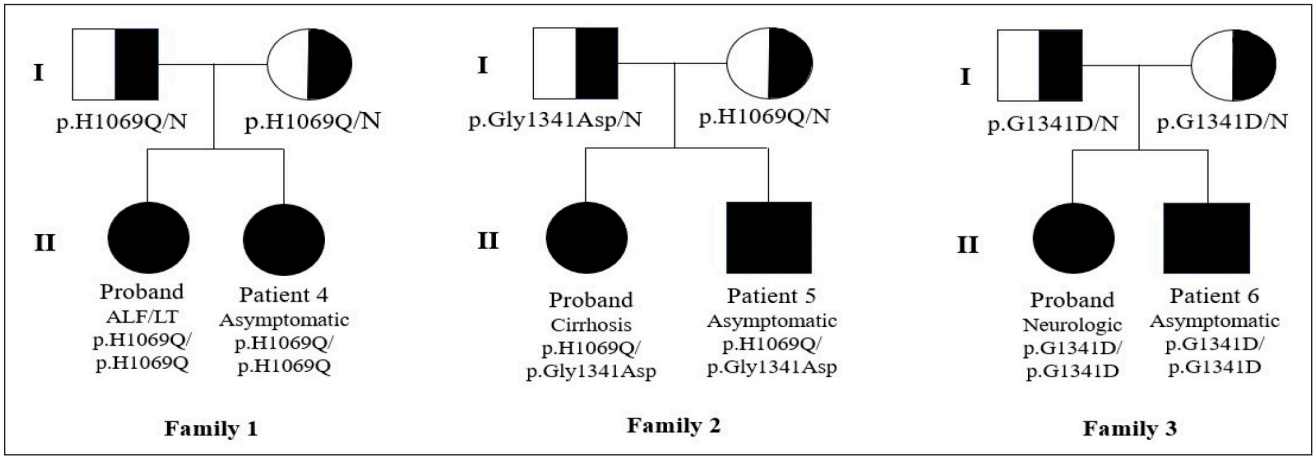

Fig. 3 The pedigree of 3 families with all children affected by WD.

Note: *Filled shapes - affected individuals. Half-filled shapes - a healthy carrier. ALF - acute liver failure; LT - liver transplantation; p.H1069Q/N – a healthy carrier; p.Gly1341Asp/N – a healthy carrier; p.G1341D/N – a healthy carrier; p.H1069Q/p.H1069Q - homozygous recessive; p.H1069Q/p.Gly1341Asp - compound heterozygous; p.G1341D/p.G1341D - homozygous recessive.*

Discussion

Genetic counseling is essential for families of patients with WD, and screening of first-degree relatives is recommended by all international guidelines on diagnosis and treatment of WD [3, 5, 13, 14, 16]. Accurate and timely diagnosis of WD is important for the affected person's relatives, as it enables the most favorable treatment outcomes. [6]. The assessment algorithm includes a comprehensive clinical and biochemical evaluation, as well as an analysis of the ATP7B genotype [16] (Fig. 4).

Newborn screening did not yield the expected results, so the running of national programs is not justified [14].

Screening should be delayed until the age of 2 years, sometimes even later, because WD is rarely symptomatic until 5 years [16]. Occasionally it can be initiated earlier, if there are obvious signs of liver or occult damage (isolated hepatomegaly or splenomegaly, or fatty liver in the absence of changes in biochemical tests) [14]. In special cases, prenatal as well as neonatal testing based on genotype analysis can be performed [5].

WD can be transmitted from affected but asymptomatic parents to their offspring. First-degree relatives do not include only the siblings of a proband, but also the offspring and parents of the proband. Although the risk of developing the disease is higher in siblings, the risk to parents (0.5%) and offspring (0.5%) is underestimated. Despite this, screening of parents and children of a proband is warranted considering the lethal potential of WD [17].

Most commonly, parents are considered healthy carriers. However, there have been reports of patients over 40 years diagnosed with WD. Therefore, considering the possibility of a late onset, clinical and paraclinical exploration of the parents of a newly diagnosed child with WD is indicated [18]. Parents of the proband should contact their siblings to inform them that they may be carriers of Wilson's disease and should be referred for family screening [5]. Also, it should be noted that for patients identified with WD in childhood or adolescence, it is recommended to test their descendants, once they decide to have children [17].

The identification in 2 consecutive generations of WD in apparently unrelated families suggests the advantage of WD screening in the offspring of an affected parent [16]. This was also observed in Patient 1 and Patient 2 in the reported study. Therefore, systemic family screening is recommended despite the autosomal recessive nature of WD transmission [8].

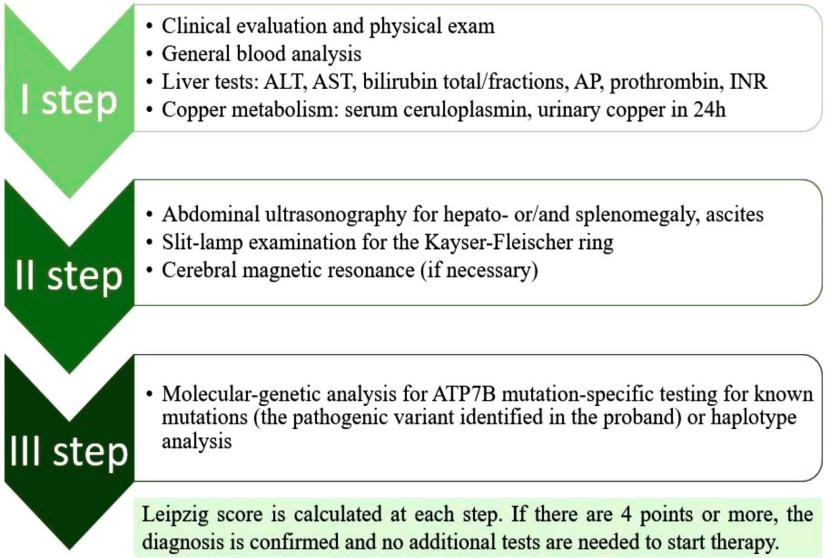

Fig. 4 Diagnostic Approach for Wilson's disease in family screening.

Note: *ALT - alanine transaminase; AST - aspartate transaminase; AP - alkaline phosphatase; INR - international normalized ratio. Adapted from Socha P. et al. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition.* Journal of Pediatric Gastroenterology and Nutrition. *February 2018; 66(2): 334–344.*

WD can present with different clinical symptoms and sometimes different phenotypes in patients with the same genotype, even within the same family [17, 18]. This variability was also observed in our study group, especially in families where both children were affected by WD (Fig. 2 and 3). According to the Mendelian laws of autosomal-recessive transmission, in the case of carrier parents, there is a 25% chance for offspring to develop WD, but in these families, both children were diagnosed with this disorder. This highlights the genetic complexity of the disease, as well as the involvement of potential epigenetic factors.

The probability of nephews and nieces being affected by WD is 1 in 600, and for cousins, the probability is 1 in 800 [19]. In 2 different families in our research with affected members, 2 nephews were identified with WD (Fig. 1) and a cousin (Fig. 5). No consanguineous marriages were reported in these families. The literature describes a case where, after family screening, new WD diagnoses emerged across generations in a single family, including an uncle and two cousins [20]. Such cases highlight the importance of testing distant relatives, especially in more isolated areas.

In our study, it was identified a rare synonymous ATP7B sequence variant c.2292C>T (p.Phe764=) in association with the pathogenic variant c.2304dupC (p.M769Hfs*26) at Patient 3. His sister (proband) has the same mutations. This variant c.2292C>T (p.Phe764=) increases the rate of exon 8 skipping in the canonical ATP7B transcript, predicting an ATP7B protein lacking transmembrane domains 3 and 4 [21]. This mutation accounts for ~0.5% (14 of 2816) of ATP7B alleles evaluated in a study of WD patients [22, 23]. The research of M. Panzer and her colleagues highlighted that the synonymous sequence ATP7B variant c.2292C>T is pathogenic by affecting messenger ribonucleic acid (mRNA) splicing. It is associated with WD being heterozygously compounded with other pathogenic variants or homozygous for this sequence variant [21].

Detection of two pathogenic or probably pathogenic variants on both chromosomes confirms the diagnosis of WD, although, in large studies of Caucasian patients with WD, the

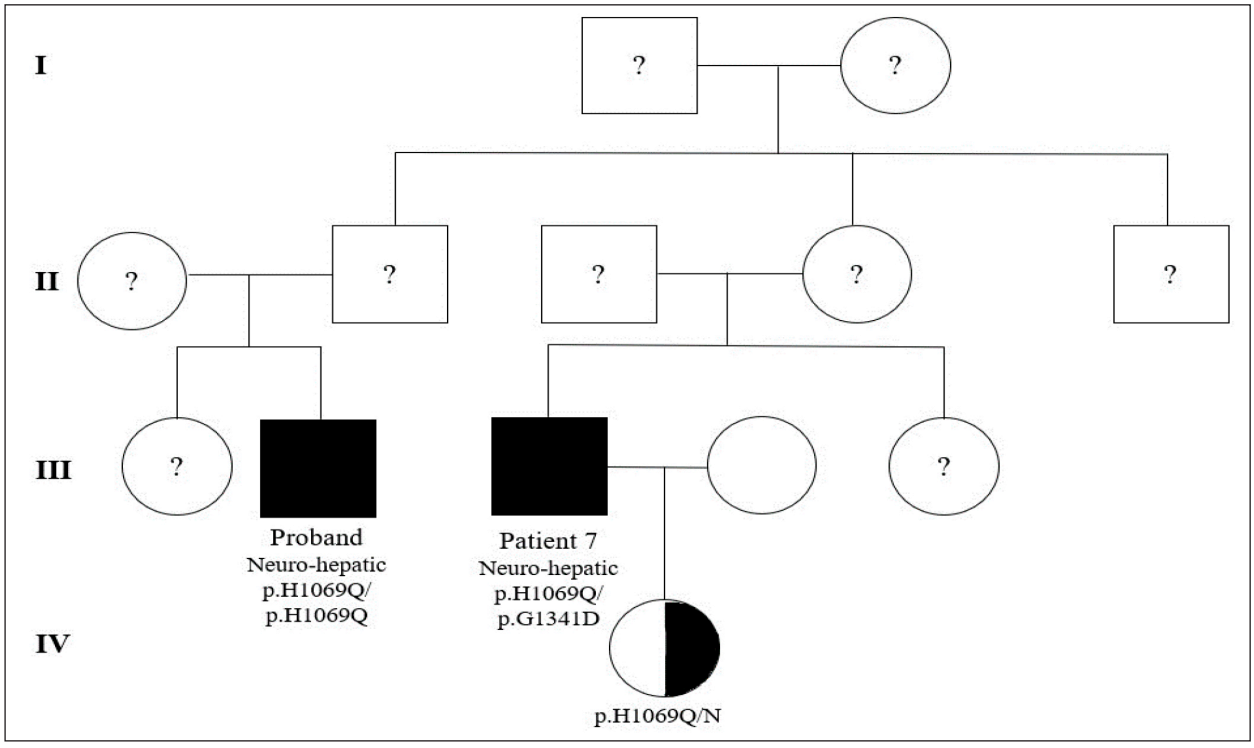

Fig. 5 The pedigree of the Patient 7.

Note: Filled shapes - affected individuals. Half-filled shapes - a healthy carrier. p.H1069Q/ p.H1069Q - homozygous recessive; p.H1069Q/p.G1341D - compound heterozygous; p.H1069Q/N - a healthy carrier; ? - genetic status unknown.

pathogenicity of both ATP7B alleles was associated in approximately 80% of patients tested [22, 23]. Previous studies reported that in 1-21% of cases, no pathogenic variant or only one ATP7B variant was detected. Thus, differentiating between WD patients and healthy carriers is a challenge in the presence of ambiguous symptoms or laboratory tests [12, 22, 23]. A plausible explanation for missing variants in Sanger sequencing of all exons and exon-intron border regions is the presence of genetic deletions/duplications that can only be detected by multiplex ligation-dependent probe amplification (MLPA) or the presence of mutations in untranslated regions, the promoter region or the deep intronic region [24].

Up to 15% of healthy carriers may show mild biochemical changes. Consequently, in such cases, it is difficult to establish the diagnosis of WD or carrier, despite a complex molecular-genetic analysis. In addition, the genetic test is not always available, or the result may be received much later [25]. In some situations, such as biochemical abnormalities and the absence of mutations or the presence of only one, it is recommended to perform a liver biopsy with copper quantification in the dry liver tissue. However, the decision to perform an invasive examination on an asymptomatic person is difficult and uncertain [13]. Thus, there is a need for an accurate, reliable, and non-invasive biological tool for family screening.

Exchangeable copper (CuEXC) is a biochemical marker that estimates free copper overload and provides data on the severity and dissemination of WD. Relative exchangeable copper (percentage of CuEXC to total serum copper) appreciates the toxic fraction of copper in blood and is an excellent biomarker for WD diagnosis with 100% specificity and 100% sensitivity [26]. Research by Dr. Trocello and colleagues showed that REC could be a biomarker that statistically significantly differentiates WD patients from simple heterozygotes (P = 0.016), as well as WD patients from healthy individuals (P = 0.015) so it can be useful for family screening. However further studies are needed to validate this test for family screening [25].

The study had limitations related to the small number of patients examined, therefore to obtain a more accurate result; it is recommended to have evaluated a large sample size. It was also not possible to clinically examine and genetically test all first-degree relatives of the patients.

Conclusions

Our study showed that family screening plays a significant role in identifying asymptomatic members with WD. Genetic testing should be performed to differentiate asymptomatic patients with WD from healthy carriers.

Abbreviations

ATP7B - ATPase Copper Transporting Beta, CuEXC - exchangeable copper, MLPA - multiplex ligation-dependent probe amplification, mRNA - messenger ribonucleic acid, WD - Wilson's disease.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

This study was approved by the Research Ethics Committee of *Nicolae Testemiţanu* State University of Medicine and Pharmacy (minutes no.1, from 25.05.2021).

Authors' contribution

AT conceived the study and participated in the study design. VS conceived the study, performed the genetic tests, and participated in the study design. VC participated in the study design, performed the statistical analysis, and drafted the manuscript. All authors have read and approved the final version of the article.

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RESEARCH ARTICLE

Epidemiology of type 2 diabetes and prediabetes in the adult population of the Republic of Moldova (preliminary data)

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ABSTRACT

Introduction. Type 2 DM accounts for over 95% of all diabetes cases worldwide and represents an important and independent cardio-metabolic risk factor. This is the first national study *(Epidemiological study of widespread endocrine pathologies (diabetes, obesity) in the Republic of Moldova and its management strategy*) that analyzes the prevalence of type 2 diabetes mellitus (DM), prediabetes, obesity, and dyslipidemia in the adult population of Moldova.

Material and methods. This is an epidemiological cross-sectional study with cluster random sampling. A face-to-face interview was conducted with the participants using a pre-tested semi-structured questionnaire. All biochemical tests were performed in a certified laboratory. Statistical analysis used Spearman's correlation test, chi-square, and Wilcoxon tests. The Research Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy (Minutes 3 from December 28 2020) approved this study.

Results. 728 individuals were enrolled, of which 2.5% had unknown DM. Advanced age, obesity, and dyslipidemia were influencing factors for diabetes. 21.4% of participants had prediabetes, with a higher prevalence in men than in women (28.3 % versus 18.9 %). Only 23.2% of men and 30.4% of women had a BMI within the normal range. Abdominal circumference (AC) values greater than 102 cm and 88 cm in men and women, respectively, were determined in 39.4% of men and 53.8% of women.

Conclusions. Our study showed an increased prevalence of carbohydrate metabolism disorders, including prediabetes, as well as a high prevalence of abdominal obesity. Persons with unknown diabetes mellitus have been identified.

Keywords: diabetes mellitus, prediabetes, abdominal obesity, epidemiology.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

There are no data on the prevalence of prediabetes or newly diagnosed cases of diabetes mellitus in the Republic of Moldova, detected through the active investigation of people with and without risk factors.

The research hypothesis

Carbohydrate and lipid metabolism disorders are underdiagnosed in the apparently healthy population of the Republic of Moldova.

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The novelty added by the manuscript to the already published scientific literature.

Data regarding new, actively detected cases of diabetes and prediabetes were obtained.

Introduction

Diabetes mellitus (DM) is a complex and heterogeneous syndrome, induced by the genetic or acquired disorder of insulin secretion and/or the resistance of peripheral cells to insulin action, which induces profound changes in protein, carbohydrate, lipid, and hydro-saline metabolism. The mentioned disorders are the basis for the appearance of a wide spectrum of chronic complications, which can affect all tissues and organs [1]. Type 2 DM accounts for over 95% of all diabetes cases worldwide [2] and represents an important and independent cardio-metabolic risk factor.

Prediabetes is the change in carbohydrate metabolism that includes alterations in fasting glucose and/or glucose tolerance [2]. People with prediabetes have a high risk of developing type 2 DM in the future. Additionally, they have an increased risk of developing diabetes complications and cardiovascular disease.

Diabetes currently has no known single cause, but certain factors such as advanced age, obesity, dyslipidemia, a sedentary lifestyle, and genetic factors are implicated in the development of type 2 DM in most populations [3]. Chronic hyperglycemia is associated with long-term microvascular (neuropathy, retinopathy, and nephropathy) and macrovascular (ischemic heart disease, stroke, peripheral vascular disease) complications. In the absence of early diagnosis and effective treatment, DM complications can advance to severe stages [4]. DM comorbidities lead to a substantial decrease in the quality of life, as well as significant socio-economic consequences [5]. According to the 2019 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimates, diabetes was the 8th leading cause of death and disability in the world in 2019 [6]. In 2019, 6.7 million DM-related deaths were reported, which corresponds to one death every 5 seconds. DM is also a major risk factor for ischemic heart disease and stroke, which were estimated by the GBD in 2019 to be the first and second leading causes of global disease burden, respectively [6, 7]. DM represents a substantial burden on health care systems [8, 9], with estimates from the International Diabetes Federation indicating that 537 million people worldwide had diabetes in 2021, resulting in healthcare costs of 966 billion USD [2]. Globally, it is predicted to reach over 1054 billion USD by 2045 [10, 2]. It is considered that 1 in 2 persons with diabetes is undiagnosed [2].

In 2023, the health system in the Republic of Moldova (RM) had records of 131,550 people with DM. It is estimated that 21% of cases are undiagnosed [11]. Data on the prevalence and incidence of DM and prediabetes are limited due to the lack of studies in this direction.

Material and methods

This is the first cross-sectional epidemiological study *(Epidemiological study of widespread endocrine pathologies (diabetes, obesity) in the Republic of Moldova and management strategy)* that analyzes the prevalence of DM, prediabetes, and dyslipidemia in the population of RM. The data were collected between June 2020 and June 2023 and included 748 people from north, south, and center regions of RM, randomly chosen from the registers of general practitioners (GP). Individuals over 18 years of age who voluntarily expressed their willingness to participate in the study and signed the consent form represented the inclusion criteria. Exclusion criteria were refusal to participate in the study, age up to 18 years, pregnancy, and lactation.

Prior to data collection, written informed consent was obtained from each study participant. Ethical approval was obtained from the Research Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy (Minute 3 from December 28 2020).

The aim of the study was to assess the prevalence of diabetes and obesity in the adult population of RM. The objectives consisted of assessing the spectrum of carbohydrate and lipid metabolism disorders and their association with well-known risk factors for diabetes and obesity, as well as evaluating the nutritional status in the general population of RM.

Social and demographic data (age, sex, marital status, educational level, ethnicity) and behavioral characteristics (smoking, physical activity, nutritional habits), personal or familial history of DM, and comorbidities were collected through face-to-face interviews applying a pre-tested and semi-structured questionnaire.

Anthropometric parameters were measured in each participant using standardized techniques and calibrated equipment. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Obesity, overweight and normal weight were defined as BMI ≥ 30 kg/m^2, 25 – 29.9 kg/m^2 and 18.5 – 24.9 kg/m^2 respectively. Abdominal circumference (AC) was assessed with a centimeter tape at the level of the navel. AC values > 94 cm for men and > 80 cm for women were considered increased, according to WHO [12]. Systolic blood pressure and diastolic blood pressure were measured in a sitting position on the right arm using a calibrated tonometer. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.

Participants were instructed to fast for at least 8 hours prior to laboratory testing. Biological samples of 3–5 ml of venous blood were collected using a simple vacutainer tube.

The blood sample was allowed to clot at room temperature and centrifuged at 3000 rpm for 10 minutes and tested in an accredited laboratory. The fasting blood glucose level was determined using the spectrophotometric method, and the hemoglobin A1c (HbA1c) level was determined using the immunoturbidimetric method.

The diagnosis of DM was established based on the diagnostic criteria of the American Diabetes Association: HbA1c ≥ 6.5%, fasting glucose (FG) ≥ 7 mmol/l, blood glucose 2h after the oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l, or the presence of diabetes history reported by the patient. The diagnostic criteria for prediabetes were: HbA1c value between 5.7 and 6.4%, FG – 5.6 – 6.9 mmol/l, blood glucose 2 hours after OGTT 7.8 – 11 mmol/l.

Data quality was ensured by using a pre-tested semi-structured questionnaire, providing training for the data collector, and active involvement of senior research scientists in the data collection process. The questionnaires were checked for consistency, clarity, and accuracy. Physical measurements were taken twice, and in some cases three times, to minimize observer bias in data measurement and recording.

Statistical analysis was performed using RStudio (R-4.3.2 for Windows. The R-project for statistical computing), an integrated development environment for the R programming language. Descriptive statistics for numerical data included mean and standard deviation, categorical data being presented as absolute and relative frequencies, completed by 95% confidence intervals. Comparative evaluation among the groups for continuous features was performed by Wilcoxon non-parametric test for two independent groups. Spearman's rank correlation test was used as a measure for estimated associations. For all mentioned statistical tests, the type I error rate was considered as 0.05.

Results

So far, 748 people have participated in the study, and 728 people from 7 municipalities and districts of the Republic of Moldova, randomly chosen from the registers of GPs, were included in the data analysis. 20 people (2.7%) were excluded from the study due to incomplete data. Of the 728 people, 198 were men and 530 were women, with an average age of 47.14±12.65 years (Fig. 1).

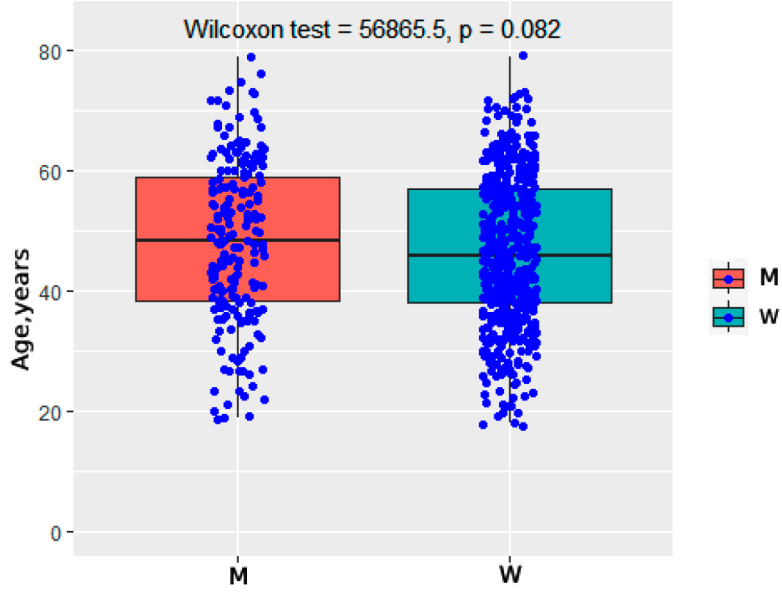

Fig. 1 Age distribution of the studied group.
Boxplot with "jitter".
Note: *Comparative evaluation of age among women and men shows that there is no difference between them (Wilcoxon test = 56865.5, p = 0.082). Abbreviation: M – men, W -women.*

Only 23.2% of men and 30.4% of women had a BMI within the normal range, 41.4% of men and 33.8% of women had a BMI within the range of 25 – 29.9 kg/ m^2, which corresponds to overweight. In the group of people with BMI corresponding to class I obesity (30 – 34.9 kg/ m2), there were 24.7% men and 20.6% women. Class II obesity (BMI 35 – 39.9 kg/m2) was present in 8.6% men and 8.9% women, and BMI > 40 kg/m2, corresponding to class III obesity, was determined in 0.5% men and 2.6% women (Tab. 1).

Table 1. Body mass index in the investigated persons, absolute number (%).

Variable	M, n = 198	95% CI	W, n = 530	95% CI
BMI, kg/m^2				
<18.5	3 (1.5%)	0.39% - 4.7%	20 (3.8%)	2.4% - 5.9%
18.5-24.99	46 (23.2%)	18% - 30%	161 (30.4%)	27% - 35%
25-29.99	82 (41.4%)	35% - 49%	179 (33.8%)	30% - 38%
30-34.99	49 (24.7%)	19% - 31%	109 (20.6%)	17% - 24%
35-39.99	17 (8.6%)	5.2% - 14%	47 (8.9%)	6.7% - 12%
>40	1 (0.5%)	0.03% - 3.2%	14 (2.6%)	1.5% - 4.5%

Note: *BMI – Body mass index, M – Men, W – Women, CI – Confidence Interval.*

AC greater than 94 cm (men) and 80 cm (women) was present in 73.7% of men and 76% of women. AC values greater than 102 cm and 88 cm in men and women, respectively, which correspond to abdominal obesity, were determined in 39.4% of men and 53.8% of women (Tab. 2).

Table 2. Abdominal circumference in the investigated persons, absolute number (%).

Variable	M, n = 198	95% CI	W, n = 530	95% CI
Abdominal circumference, cm				
< 80 cm (W) and < 94 cm (M)	52 (26.3%)	20% - 33%	127 (24.0%)	20% - 28%
80-88 cm (W), 94-102 cm (M)	68 (34.3%)	28% - 41%	118 (22.3%)	19% - 26%
> 88 cm (W), > 102 cm (M)	78 (39.4%)	33% - 47%	285 (53.8%)	49% - 58%

Note: *M – Men, W – Women, CI – Confidence Interval*

A positive correlation was determined between BMI and age (Spearman's rank correlation rho=0.2/0.3, in men/women, $p < 0.01$), as well as between AC and age (Spearman's rank correlation rho=0.44/0.31 in men/women, $p < 0.001$).

The number of DM cases diagnosed for the first time during the study was 2.5% (18 people), with an equal gender distribution, while 21.4% of the participants had prediabetes, with a gender distribution as follows: 28.3% (56) men and 18.9% (100) women. A positive correlation was determined between the increased value of blood glucose and age (Spearman's rank correlation rho=0.33/0.35, men/women, $p < 0.01$) in both sexes.

The risk of developing DM, assessed using the FINDRISC questionnaire, was found to be reduced (<7) in 64 (32.3%) men and 180 (34.0%) women. Slightly increased risk (7-11) was present in 77 (38.9%) men and 172 (32.5%) women. Moderately increased risk (12-14) was present in 30 (15.2%) men and 74 (14.0%) women, and high risk in 20 (10.1%) men and 90 (17.0%) women. 7 (3.5%) men and 14 (2.6%) women fell into the very high risk category (FINDRISC >20).

Discussion

This is the first epidemiological study that analyzes the prevalence of DM, prediabetes, and dyslipidemia in the population of RM. At this stage of the study, 2.5% of new cases of DM were detected. The prevalence of prediabetes was 21.4%, positively correlated with age, being higher in men, similar to the data reported in other studies [13, 14].

The PREDATORR study, led by M. Moța et al., reported similar data regarding the number of new cases of diabetes – 2.4%, and the prevalence of DM – 11.6% [15]. The prevalence of prediabetes was 16.5% in the Romanian population, which is lower compared to the results reported in our study (21.4%). In 2021, the IDF reported a 10 % global prevalence of DM and 6% on average for the European Union (EU). According to the same source, the prevalence of DM in RM is 5.6% [2].

Obesity is a disease with a major negative impact on health. Obesity predisposes to a wide range of diseases that are often interconnected, leading to an increased risk of simple (two comorbid diseases) and complex (four or more comorbid diseases) multimorbidity in these individuals, compared to healthy-weight individuals [16]. Abdominal obesity is one of the main components of metabolic syndrome [17] and is an independent risk factor for various non-communicable diseases, such as cardiovascular disease, type 2 DM, hypertension, and cancer [18, 19]. AC is associated with cardiovascular and all-cause mortality [20]. At the same time, AC is a simple anthropometric measurement that can be easily performed in resource-limited settings and could help screen for cardiometabolic risk [21]. In our study, the prevalence of abdominal obesity was higher among women (76% versus 73.7%) and increased with age, similar to reports from other countries [20, 22].

This study has strengths and limitations. The strengths are the large sample size and the fact that all biochemical analyses were performed in the same certified laboratory. Selection bias is the limitation of the study.

Diabetes mellitus and obesity are a burden on the health system due to the complications of these diseases and associated pathologies, such as major cardiovascular events, debilitating complications, and high costs of hospitalization and treatment. Campaigns aimed at preventing diabetes and obesity must be enforced at the national level alongside general strategies for non-communicable diseases that share similar risk factors. These programs should address key risk factors: promoting healthy eating and physical activity, reducing excess weight, cessation of smoking, and reducing alcohol consumption.

Conclusions

Our study showed an increased prevalence of carbohydrate metabolism disorders, including prediabetes, as well as a high prevalence of abdominal obesity. DM is significantly associated with universally recognized risk factors: overweight, obesity, and dyslipidemia. Persons with unknown diabetes mellitus have been identified. Therefore, targeting strategies to control and prevent modifiable risk factors associated with DM and prediabetes through health promotion measures can contribute to reducing the prevalence and complications of DM. Further studies are needed to appreciate the real extent of the diabetes epidemics.

Competing interests.

None declared.

Patient consent.

Obtained.

Ethics approval.

This study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes 3 from December 28th, 2020).

Authors' contribution.

SV, ID, AS, LV conceived and participated in the work design. SV, ID, VF, SBG, TA, CP drafted the article. OA performed the statistical analysis. SV, AS, OA, LV critically reviewed the article for important intellectual content. All the authors

contributed to the acquisition of data, reviewed the work critically, and approved the final version of the manuscript.

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RESEARCH ARTICLE

Evaluation of pulmonary imaging data by radiography in children with bronchopulmonary dysplasia

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ABSTRACT

Introduction. According to specialized literature, X-rays are also used in the diagnosis and suspicion of chronic bronchopulmonary disease (bronchopulmonary dysplasia (BPD), in premature children.

Material and methods. The study included 105 premature babies who were divided into the study group – premature babies with bronchopulmonary dysplasia (BPD) and the control group – premature babies without BPD. Data were statistically analyzed using Microsoft Excel, MedCalc, SPSS and Contingency Table Analysis as a method of evaluating the performance of a diagnostic test.

Results. Radiological changes of discoidal atelectasis type in subjects with BPD were detected in 49.1% in the basic group versus 13.5% in the control group ($\chi2 = 15.431$; $p < 0.0001$), subsegmental ones 47.2% vs 25.0% ($\chi2 = 5.586$; $p = 0.018$); pulmonary emphysema areas 62.3% vs 5.8% ($\chi2 = 37.182$; $p < 0.0001$), opaque fibrosis sectors 50.9% vs 11.5% ($\chi2 = 18.911$; $p < 0.0001$); signs of pulmonary hypertransparency 47.2% vs 1.9% ($\chi2 = 28.843$; $p < 0.0001$); microcystic formations 41.5% vs 5.8% ($\chi2 = 18.482$; $p < 0.0001$). Depending on the severity degrees of BPD, changes such as discoidal atelectasis were noted, in those with mild grade – 50% medium grade – 38.5%, severe grade – 56.3% ($\chi2 = 16.502$; $p < 0.001$), subsegmental atelectasis 41.7%, vs 38.5% ($\chi2 = 7.956$; $p = 0.047$), pulmonary emphysema areas 58.3%, vs 38.5%, vs 87.5% ($\chi2 = 45.138$; $p < 0.0001$); microcystic formations, 33.3%, vs 53.8%, vs 43.8% ($\chi2 = 20.502$; $p < 0.0001$).

Conclusions. The changes recorded on radiological examination in mild, moderate, and severe cases of BPD in premature babies are of the type discoidal atelectasis, areas of emphysema, opaque sectors of fibrosis, pulmonary hypertransparency, microcystic formations.

Keywords: bronchopulmonary dysplasia, prematurity, radiography.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Bronchopulmonary dysplasia is a multifactorial pathology with multiple associated comorbidities, responsible for the majority of chronic lung disease cases in childhood. The use of imaging examinations, in this particular case - bronchopulmonary radiography, is essential for the objective evaluation of the patients' clinical evolution, the identification of pediatric subjects that require closer follow-up, as well as for the improving communication with the family.

The research hypothesis

Premature infants may develop bronchopulmonary dysplasia with radiological changes, which can affect their health.

The novelty added by the manuscript to the already published scientific literature
Evaluation of imaging data has established a significant increase in premature infants with bronchopulmonary dysplasia.

Introduction

Prematurity remains one of the most important health problems worldwide, which is associated with high morbidity and mortality, high costs of medical care and increased risk of disability. Bronchopulmonary dysplasia (BPD) is considered to be one of the forms of chronic lung damage in newborns, with predilection of preterm infants, which frequently develops as a complication of artificial pulmonary ventilation (APV) [1-3]. It evolves primarily with the primary involvement of the bronchioles and lung parenchyma, with onset of emphysema, fibrosis and/or impairment of alveolar replication and characterized by specificity of radiological changes in the first months of life and regression of clinical and imaging manifestations as the child grows [4-6].

Data on BPD frequency vary considerably worldwide, and the incidence rate is influenced by the used diagnostic criteria ("28 days" or "36 weeks, oxygen dependence"), the mortality of premature newborns, the studied population, the level of technical equipment in neonatal, pulmonology, intensive care units, etc. On average, according to literature data, BPD develops in 30% of newborns who require mechanical ventilation, and about 40% of infants with extremely low birth weight (birth weight of <1000 g) develop DBP [7]. Unlike other causes of morbidity that complicate severe prematurity, the incidence of DBP has not decreased over the past few years [8, 9].

BPD remains a primary cause of chronic respiratory pathology despite advances in neonatal medicine. It is also recognized as a distinct nosological entity among surviving preterm infants, with a frequency among living preemies of 20-40%. Worldwide, it has been estimated that more than 15 million babies are born prematurely. Newborns with severe degrees of prematurity, especially those with BPD, frequently develop respiratory symptoms (usually coughing and wheezing) as well as frequent hospitalizations in the first years of life. Moreover, this clinical entity is associated with increased respiratory morbidity and mortality [9], in particular, during the first two years of life, due to the persistence of respiratory symptoms and the higher number of hospitalizations compared to preterm infants without BPD [10].

In recent years progress has been made in pediatric thoracic imaging, enhancing the diagnostic potential of BPD, facilitating treatment guidance for respiratory distress syndrome (RDS), reducing the likelihood of further progress of BPD and long-term follow-up of chronic pulmonary pathology [1].

First-line radiological examinations, such as pulmonary radiography, are useful in determining the severity of BPD, differentiating it from atelectasis, pneumonia, and air loss syndrome, with changes such as decreased lung volumes, areas of atelectasis and hyperinflation, pulmonary edema and pulmonary interstitial emphysema being noted. The findings on radiological examination range from signs of pulmonary hyperinflation with thickening of the bronchi and atelectasis, to the presence of radiopaque images of pulmonary fibrosis, large airborne cysts, and interstitial emphysema. The trunk of the pulmonary artery may be highlighted due to associated pulmonary hypertension, and in extremely severe cases, cardiomegaly may also be noted [11].

Nevertheless, the recognized major radiological criteria include significant thoracic distension predominantly in the basal areas, opacities with blurred contour, poorly delineated in the middle and upper regions of the lungs, subsegmental atelectasis, fibrotic opaque sectors, areas of emphysema, linear or round opacities [12, 13].

The aim of the research was to evaluate chest x-rays in children with bronchopulmonary dysplasia.

Material and methods

This study represents an analysis of a cohort of 105 premature babies admitted to the Clinic of Pulmonology of the Institute of Mother and Child with a positive history of premature birth and with RDS supported during the neonatal period. Two groups were created: the study group of 53 children (33 boys and 20 girls) with the diagnosis of bronchopulmonary dysplasia and the control group of 52 children (27 boys and 25 girls) who did not develop BPD. The diagnosis of BPD was established based on the analysis of perinatal, history, clinical, laboratory and instrumental data, especially pulmonary imaging, based on international criteria [14]. Radiological examination was performed on all children included in the study. The study complied with the international standards of medical ethics, developed by the Declaration of Helsinki, regarding confidentiality and personal data protection of the participants. The research was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes № 73 from 31.05.2017). The resulting data were disclosed only to the concerned participant; the personal data of each subject were not used and will not be used for any other purpose. The data collected from the primary sources were introduced in the electronic database, whereas the statistical processing was performed using the SPSS (Statistical Package for the Social Sciences) version 20.

Results

Pulmonary radiography was performed on all children included in the research. Thus, the children in the study (Fig. 1) had predominantly radiological changes of atelectasis type, with discoidal changes detected radiologically in 49.1% (n=26) of children with BPD and in 13.5% (n=7) of

children in the control group (χ2=15.431; p<0.0001). Subsegmental changes were reported in 47.2% of children with BPD (n=25) and in 25.0% of children without BPD (n=13) (χ2=5.586; p=0.018). Areas of pulmonary emphysema in the study group were noted in 62.3% (n=33), while in the control group, they were observed in only 5.8% (n=3) (χ2=37.182; p<0.0001). Opaque fibrosis sectors in children with BPD were identified in 50.9% (n=27 cases), and in children without BPD in 11.5% (n=6) (χ2=18.911; p<0.0001). Signs of pulmonary hypertransparency were observed in 47.2% of children with BPD (n=25) compared to single cases (1.9%) in control subjects (χ2=28.843; p<0.0001). Microcystic formations were recorded with a higher share in 41.5% of children with BPD (control group – 5.8% cases) (χ2=18.482; p<0.0001).

The periods of hospitalization resulted in radiological changes with pneumonic foci character (Fig. 1) in 52.8% (n=28) among those in the first group, and in those without BPD in 73.1% (n=38) (χ2=4.609; p=0.032), and bronchoobstructive syndrome was noted in children with BPD in 58.5% (n=31), vs 28.8% (n=15) in the control group (χ2=9.370; p=0.002).

The analysis of radiology results in relation to the severity degrees of BPD (Table 1) noted changes such as discoidal atelectasis (Fig. 2f), present in 50% of those with mild grade (present in every second child, n=12), 38.5% with medium grade (n=5), and 56.3% with severe grade (n=9) (χ2=16.502; p<0.001). Subsegmental atelectasis (Fig. 2b), among those with mild BPD, was recorded in 41.7% (n=10) and in 38.5% with medium grade (n=5) (χ2=7.956; p=0.047). Areas of pulmonary emphysema in children with mild BPD were detected in every second case – 58.3% (n=14), in every third child with average severity (38.5%, n=5), and in most of those with severe grade (87.5%, n=14) (χ2=45.138; p<0.0001).

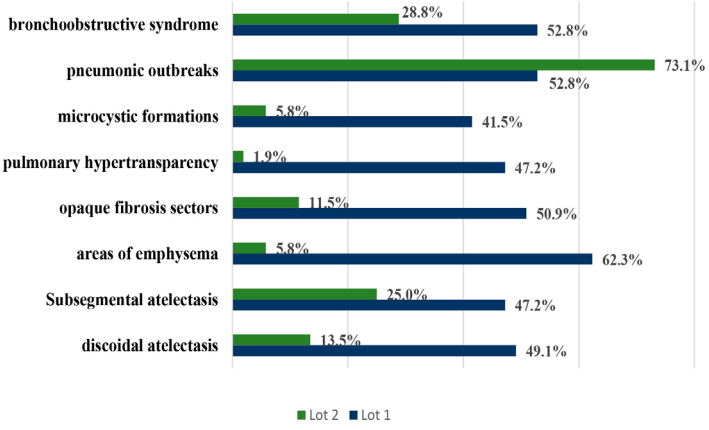

Fig. 1 Imaging changes on pulmonary radiography in children with bronchopulmonary dysplasia

Microcystic formations (Fig. 2d, e), which are often characteristic of pulmonary diseases with obstructive genesis, were present in children with mild BPD degree in 33.3% (n=8), in medium severity – 53.8% (n=7), and in severe grade – 43.8% (n=7) (χ2=20.502; p<0.0001).

Pneumonic foci were also visualized (Fig. 2. a, c, f): in children with mild BPD in 41.7% cases (n=10), in those with medium grade – in 76.9% cases (n=10), and in every second child with severe BPD (n=8) (χ2=9.177; p=0.027).

At the same time, in pediatric subjects with BPD in pulmonary imaging evaluation, bronchoobstructive syndrome was also present (Fig. 2 c, e, f), noted in 62.5% (n=15) in those with mild degree, 5% (n=5) in medium grade, and 68.8% (n=15) in severe grade (χ2=12.329; p=0.006). The imaging expression of broncho-obstructive disorders is also relevant through signs of pulmonary hypertransparency, which in children with mild BPD was found in 45.8% (n=11), in the middle degree – 38.5% (n=5), and in severe degree – 56.3% (n=9), (χ2=30.103; p<0.0001).

Foci of pulmonary fibrosis are mentioned in the literature as imaging signs suggestive of BPD and were recorded in the research performed. Opaque fibrosis sectors (Fig. 5, 6, 7) were identified in 54.2% (n=13) of subjects with a mild degree of BPD, in 46.2 (n=6) of those with medium severity, and in 50.0% (n=8) of those with severe degree (χ2=19.172; p<0.0001).

For the objectification of imaging data characteristic of the evolutionary development of BPD, radiographic images with various modifications are presented (Fig. 2 a-f).

Table 1. Lung imaging changes in varying degrees of severity of BPD

Lung imaging signs	BPD light grade (n=24)		BPD medium grade (n=13)		BPD severe grade (n=16)		p
	Abs	%	Abs	%	Abs	%	
Discoidal atelectasis	12	50,0	5	38,5	9	56,3	0,001
Subsegmental atelectasis	10	41,7	5	38,5	10	62,5	0,047
Areas of emphysema	14	58,3	5	38,5	14	87,5	<0.0001
Microcystic formations	8	33.3	7	53,8	7	43,7	<0.0001
Pneumonic outbreaks	10	41,7	10	76,9	8	50,0	0,027
Broncho-obstructive syndrome	15	62,5	5	38,5	11	68,8	0,006
Opaque fibrosis sectors	13	54,2	6	46,2	8	50,0	<0.0001
Pulmonary hypertransparency	11	48,5	5	38,5	9	56,3	<0.0001

Note: *BPD- bronchopulmonary dysplasia, ABS- absent, n – number, % - percent*

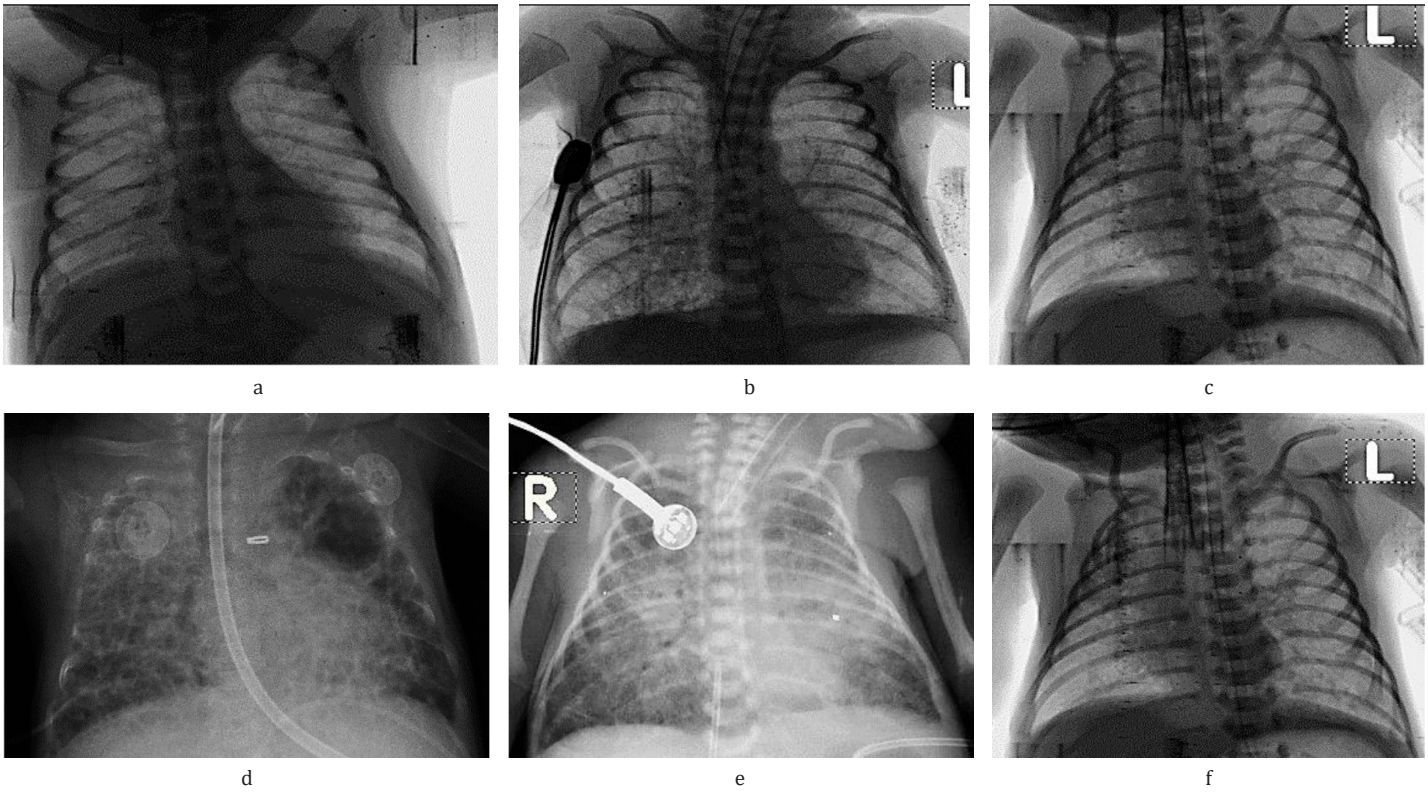

Fig. 2 Various radiographic images with different changes in premature infants with bronchopulmonary dysplasia
a: Segmental pneumonia (S-4,5) on the right, bronchoobstructive syndrome
b: Subsegmental atelectasis, discoidal
c: Pneumonic infiltration, bronchoobstructive syndrome
d: Intensified, fibrotized, deformed lung drawing. Bilateral diffuse microcystic formations (signs of BPD)
e: Hyperaerated lungs, obstructive syndrome. Deformed, fibrotized lung drawing. Bilaterally diffuse microcystic formations. On the right in S2 discoidal atelectasis.
f: Deformed drawing, discoid atelectasis S2, bronchoobstructive syndrome, hyperinflation, pneumonia S7.

Discussion

BPD is a chronic lung disease involving damage to the alveoli and pulmonary vessels due to neonatal lung underdevelopment, oxygen therapy used in the postnatal period, and associated infections [15], which causes delayed lung development, further contributing to insufficient development of the alveoli and pulmonary capillaries. BPD was first described as a chronic lung disease associated with RDS by Northway in 1967.

Clinically, BPD is established as a diagnosis if the newborn requires supplemental oxygen at 28 days after birth and has specific features on chest radiograph at 36 weeks' corrected gestational age. Depending on the characteristics of the lung x-ray images, it is divided into 4 stages, respectively: 1st stage – similar findings in chest x-ray with RDS (1–3 days), 2nd stage – bilateral opacification (4–10 days), 3rd stage – density uneven bilateral lung fields, with bands or irregular shadows (11–30 days), 4th stage – bilateral opacities with lung hyperinflation, atelectasis (30 days).

The survival of extremely premature infants and very low birth weight preterm infants has steadily improved thanks to the use of lung surfactant and various protective ventilation techniques [16]. Approximately 42% of newborns weighing less than 750 g and only 4% of newborns weighing between 1251 and 1500 g develop BPD.

According to a study conducted in China, the incidence of BPD was about 1.28% among preterm infants compared to 19.3% among extremely premature babies (<28 weeks gestation, in 2011) [17, 18]. Factors influencing the severity of BPD among premature babies were also analyzed, demonstrating that birth weight and gestational age correlated with both the incidence and the severity of BPD. Additionally, low birth weight (<1000 g) and low gestational age (<28 weeks) were associated with a higher incidence and severity of BPD [6, 14].

BPD associated with obstructive ventilation impairment and pulmonary emphysema as an end result is recognized as a new type of BPD, which is significantly different from the typical form in terms of clinical and pathological characteristics and outcomes. Consequently, the conventional 4-step radiographic classification for the typical form cannot be applied to the new type.

In the study, chest X-ray images were compared between mild, moderate, and severe forms of BPD, revealing

changes such as discoidal atelectasis, areas of emphysema, opaque fibrosis sectors, pulmonary hypertransparency, and microcystic formations, albeit with varying degrees of prominence. Although chest X-ray is not a definitive tool for assessing the severity of BPD, it still holds a certain predictive value; specifically, the more severe the BPD, the sooner characteristic changes in chest X-ray will manifest. However, it should be noted that chest radiography has somewhat low diagnostic specificity for BPD in children. Therefore, it is used as an auxiliary tool for the diagnosis and staging of this pathology, considering its limitations.

Conclusions

Pulmonary radiography is one of the diagnostic methods for BPD in premature infants and can record discoidal atelectasis, areas of emphysema, opaque sectors of fibrosis, pulmonary hypertransparency, and microcystic formations. The research confirms the importance of evaluating the type and extent of radiological changes in premature infants based on the severity of BPD. It has been demonstrated that this method is effective both in practical clinical settings and scientific work.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

The research was approved by the Research Ethics Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (report no. 73 of 31.05.2017).

Authors' contribution

The authors contributed equally to the research of the scientific literature, the selection of the bibliography, the reading and analysis of biographical references, the writing of the manuscript and its peer review. All authors have read and approved the final version of the article.

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RESEARCH ARTICLE

Visual field evaluation following brain injury in school-aged children

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ABSTRACT

Introduction. Brain injury may affect both afferent and efferent visual pathways. In children it is quite difficult to determine visual disturbances since they are often non cooperative. Visual field examination is an objective evaluation method that can outline visual pathway alteration in the acute period of head trauma.

Materials and methods. Forty-eight patients with persisting visual symptoms after mild traumatic brain injury were examined. A control group of the same size has been evaluated.

Results. Patients in the research group showed an obvious alteration of the fixation capacity of more than 20% in 91.7%-95.8%, while in the control group the fixation capacity was up to 20% in 68.7%-70.8%. The ability to fix false positive points was up to 20% in 43.8%-45.8% patients in the research group and 70.8%-83.3% in the control group. The rate to fix false negative points was within the range of up to 20% for the research group in 93.7%-95.8% and the control group 91.7%-97.9%. The index of localized defects was up to 3dB in 62.5%-70.8% in the research group and predominantly 91.6%-95.8% for the control group. The average elevation index was within the range of < -3dB, 3dB> in 12.5%-20.8% research group and respectively 54.1%-56.2% control group. The graphic interpretation of changes in the visual field revealed a prevalence of the incidence of diffuse retinal depression with relative paracentral scotomas in 64.6%-68.7%.

Conclusions. Based on the results, we can conclude that perimetric examination in the case of brain injured pediatric patients fulfils the requirements of credibility. Perimetric examination could be a landmark in the initial phase of settling post brain injured visual disturbances.

Keywords: visual field, brain injury, children, head trauma.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

There are no reference values for evaluating visual field after brain injury in school-aged children. This obscures the utility of this method during different stages of brain trauma.

The research hypothesis

To determine the utility of visual field evaluation in school-aged children after brain injury.

The novelty added by manuscript to the already published scientific literature

The research outlines features of visual field evaluation after brain injury in the group of children aged 7 to 18 years.

Introduction

Visual field is considered the area perceived by one or both eyes while focusing a stationary point. There are two methods of evaluating the visual field: static perimetry and kinetic perimetry. In our research, static perimetry has been used, based on stationary light stimuli projected on the inside of the dome of various sizes and with variable light intensities. The program represents a predefined number of light stimuli (between 50 and 100) projected in different areas of the visual field (Field) that are projected in different variants (Strategy). The neuroanatomy and neurophysiology of the visual pathway is the key to the clinical understanding of visual field examination. The afferent visual pathway begins at each eyeball and undergoes the perception of visual stimuli to the cortex. Along the pathway, this stimulus will pass through the area of the optic chiasm, the optic tract, the lateral geniculate body and the optic radiation so that at the end the image is projected on the occipital cortical visual center in area 17/V1 (also known as the cerebral retina).

Suchoff I. B. mentions that visual field deficits are quite often observed after a traumatic brain injury (TBI). Usually, their presence signals a severe TBI, but they can be detected in the case of a moderate TBI with the involvement of optic chiasm damage or because of a posttraumatic neuropathy [1].

Ciuffreda K. J. *et al.* attests that visual field defects usually refer to certain sectors, which are missing or appear to be sensory suppressed following the effect of trauma on the primary visual pathways. These areas can range from hemianopsia to small regions of reduced sensitivity. In these cases, the symptoms can vary widely, starting with severe vision difficulties to minor visual effects. Visual field deficits were identified in 35% of patients with visual changes after TBI [2, 3]. Certain patients could benefit from using embedded prisms, such as Fresnel or Peli prisms [2, 4]. The training should include the stimulation with light targets of both the deficient sector and the entire visual field. Some programs are designed to enhance the visual field by stimulating cortical function. They achieve this by training patients to recognize visual field deficits as accurately as possible and even to adjust the orientation of their eyes towards these deficits [2, 5].

The visual pathway consists of a sensory chain made up of types of 4 neurons, three of which originate in various layers of the retina.

The first type of neurons corresponds to the basal layer of photoreceptors: 120 million rods, which predominate in the peripheral retina triggering a person's scotopic vision, and 6.5 million cone cells in the central area for photooptic vision. Most perimeters today use a brightness of 3-10 cd/m, adjusted to the photopic range, which exclusively tests the functional state of the photoreceptor cells.

The second type of neurons corresponds to the middle retinal layer represented by bipolar cells. At the periphery of the retina, a bipolar cell is considered to receive information from several photoreceptor cells, while the one located in the central part transmits information to a single receptor. This is why in neurological lesions, the evaluation of the visual field (VF) in the central 30 degrees is considered much more informative and objective.

The third type of neurons refers to the inner layer of ganglion cells that forms the optic nerve fascicle through its axons.

The fourth type of neurons begins with 4-5 million axons in the lateral geniculate body, joining it after passing through the optic radiation with the occipital cortical visual center [6-11].

The correspondence between the stimulated retinal area and its projection on the area of the visual field is always inverted: the temporal quadrants of the VF correspond to the nasal retina, and the nasal quadrants correspond to the temporal retina. This rule also applies to the lower and upper quadrants.

One of the screening strategies that can be used, according to literature data, is a rapid assessment method that allows for the detection of the presence, position, and size of absolute and relative defects exceeding 6dB depth [12, 13]. It divides all points into three categories:

- Flawless
- Defect (relative scotoma)
- Absolute defect (scotoma).

According to recent studies, the credibility indices do not present a determined value in pediatric population. Thus, the alteration of the fixation capacity (CF) is determined to be: for the age range 5-10 years at 45.5%, ages 11-14 years at 20.18% and for 15-18 years at 31.3%. The evaluation of false positive points (FP) was determined to have the following distribution: for 5-10 years at 11.72%, for ages 11-14 years at 3.82% and for 15-18 years at 5.4%. The evaluation of false negative points (FN) was determined: for 5-10 years at 9.88%, for ages 11-14 years at 5.88% and for 15-18 years at 6.44% [14]. On the other hand, some authors stipulate that these indicators could be referred to less strict values, resulting from the analysis of only high-quality results. Thus, we could use ranges of less than 20% for CF, less than 33% for FP and less than 33% for FN [14]. In our research, three reference intervals were evaluated with the following distribution: results up to 20%, results between 21-60% and respectively 61-100% in order to determine the most credible reference values in pediatric patients after TBI.

Materials and methods

Our research was carried out through the clinical evaluation of 96 patients aged between 7-18, hospitalized in the Department of Neurosurgery of the Mother and Child Institute, *Natalia Gheorghiu* National Scientific-Practical Center for Pediatric Surgery. Patients were evaluated 5-7 days after trauma occurrence, as their general state did not allow performance of the visual field examination. Most of the patients 39.6% revealed a mild traumatic brain injury resulted from a fall from height (54.2%) or a traffic accident (31.2%). Regarding the neurological status, it can be mentioned that 58.3% presented neuropathies, 20.8% coordination prob-

lems and 25% of the patients had tremor in the upper and lower limbs. In addition, children that have been included in the research underwent an ophthalmological evaluation that outlined that 83.3%-89.6% of patients revealed a visual acuity ranged between 0.09-0.5 units for the Snellen chart associated with a slight hyperopia of +3.00D in 93.7% - 95.8%. Upper gaze disturbances have been recorded in 58.3%, stereoscopic function alteration in 20.9% and a clear ophthalmoscopic picture in 45.9% patients.

The evaluation has been performed using the Rodenstock perimeter. The screening strategy was chosen because it is a summary method, providing light stimuli above the expected threshold level at all visual field test points. Patients have been asked to concentrate on the red flash point in the middle of the examination area in order to have a better fixation. All external sound and visual stress factors have been excluded, as the examination has been undergone in partial darkness conditions. The Standard Field Test, encompassing an evaluation of 12 points within a 30-degree field, stimulus color of green at 570 nm and a background of 10 abs with automatic level control. After a period of 4 months, the evaluation was repeated in order to outline changes in the researched parameters. Given that pediatric patients are often poorly cooperative, several breaks were scheduled, in order to avoid possible errors.

In order to achieve research objectives, a cohort study was conducted.

Research inclusion criteria.

L1 batch eligibility criteria:

- School-aged children who present visual disorders after TBI.
- No organic pathology of the visual analyzer.
- Patients without other associated chronic pathology.

L0 batch eligibility criteria:

- School-aged children who present visual disorders with no TBI.
- No organic pathology of the visual analyzer.
- Patients without other associated chronic pathology.

Results

Visual field examination was performed in both groups, revealing some visual field deficits in patients after TBI. The results of this examination indicated a lack of fixation among the patients in the research group. Specifically, for the right eye, in 89.6% (43 patients) the loss of fixation fluctuated between 61-100%, in 8.3% (4 patients) this value was up to 20%, and in 2.1% (1 patient) values ranged between 21%-60%. In the control group, the loss of the fixation of the right eye was observed in 68.7% (33 patients) - in the range of up to 20%, in 23% (11 patients) in the range of 61-100% and in 8.3% (4 patients) in the range of 21-60% ($p < 0.001$).

For the left eye, the results indicated a lack of fixation among patients in the research group: 91.6% (44 patients) experienced a loss of fixation in the range of 61%-100%, and 4.2% in the range of 21%-60% while 4.2% up to 20%, compared to the values for the left eye in the control group: 70.8% (34 patients) in the range of up to 20%, in 25% (12 patients) in the range of 21-60%, and 4.2% (2 patients) in the range of 61%-100% ($p < 0.01$) (tab. 1).

Evaluation of the ability to fixate on false positive points increased indices in both eyes among children in both the research group and in the control group, primarily values up to 20%, with a higher number in the control group. For the right eye 83.3% in the control group versus 45.8% in the research group, and for the left eye, 70.8% in the control group versus 43.8% in the research group ($p < 0.05$).

Table 1. Fixation loss ratio after brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	**%**
Right	Up to 20%	4	8.3	33	68.7
	21%-60%	1	2.1	4	8.3
	61%-100%	43	89.6	11	23
		p < 0.01			
Left	Up to 20%	2	4,2	34	70,8
	21%-60%	2	4,2	12	25
	61%-100%	44	91,6	2	4,2
		p < 0.001			

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

Meanwhile, it should be noted that the ability to fixate false positive points in the patients of the research group for the interval 21-60% was observed in 22.9% versus 12.5% in the control group, and the interval of 61-100% - 31.3% patients in the research group versus 4.2% in the control group (tab. 2) ($p < 0.001$). For the left eye, the range 21-60% was noted with practically the same frequency among both the patients of the research group and the patients of the control group (22.9% versus 20.8%). Moreover, the rate of the ability to fixate false positive points in the range of 61-100% in the left eye noted a slight upward trend among the patients of the research group: 33.3%, compared to 8.3% in the control group ($p < 0.05$).

Table 2. False positive points fixation after brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	**%**
Right	Up to 20%	22	45.8	40	83.3
	21%-60%	11	22.9	6	12.5
	61%-100%	15	31.3	2	4.2
		p < 0.001			
Left	Up to 20%	21	43.8	34	70.8
	21%-60%	11	22.9	10	20.8
	61%-100%	16	33.3	4	8.3
		p < 0.05			

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

The evaluation of the ability to fixate false negative points did not reveal significant statistical differences between the researched groups. Thus, in both the research and the control group, the majority of patients (> 91% of cases) for both

eyes, presented values up to 20%, specifically for the right eye: 95.8% in the research group and91.7% in the control group (p < 0.05), and for the left eye: 93.7% in the research group and 97.9% in the control group (p < 0.05) (tab. 3).

Table 3. False negative points fixation after brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	**%**
Right	Up to 20%	46	95.8	44	91.7
	21%-60%	1	2.1	3	6.2
	61%-100%	1	2.1	1	2.1
	p < 0.05				
Left	Up to 20%	45	93.7	47	97.9
	21%-60%	1	2.1	1	2.1
	61%-100%	2	4.2	0	0
	p < 0.05				

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

The structural defects index (SD) represents numerical values of the elevation levels present in the area of the visual field. This index can only take a positive value, and if it is numerically higher, it indicates the presence of changes in the topography of the visual field. The SD index indicated values between < 0dB, 3dB>, which would signify a smooth visual field without irregularities, in 62.5% (30 patients) - L1 and 91.6% (44 patients) - L0 for the right eye. Levels in the < 3dB, 9dB > range were recorded in 35.4% (17 patients) - L1 and 6.2% (3 patients) - L0 respectively. The maximum range of 9dB> reached equal values for both groups of 2.1% (1 patients) - L1 and 2.1% (1 patients) - L0 (p < 0.001). For the left eye, the following values were determined: the range of < 0dB, 3dB > in 70.8% (34 patients) - L1 and 95.8% (46 patients) - L0. The range < 3dB, 9dB > was attributed to 27.1% (13 patients) - L1 and 4.2% (2 patients) - L0 (p < 0.001). Maximum values of >9dB were determined only in the research group – 2.1% (1 patient) (tab. 4).

Table 4. Structural defect index after brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	%
Right	< 0 dB. 3dB>	30	62.5	44	91.6
	< 3 dB. 9 dB>	17	35.4	3	6.2
	9 dB>	1	2.1	1	2.1
	p < 0.001				
Left	< 0 dB. 3dB>	34	70.8	46	95.8
	< 3 dB. 9 dB>	13	27.1	2	4.2
	9 dB>	1	2.1	0	0
	p < 0.001				

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

Another evaluated criterion would be the index of average defects, which represent the numerical differences from the standard values correlated to age. This index can be positive or negative, where a negative value indicates decreased sensitivity, and a positive value indicates increased sensitivity compared to reference numbers. The distribution of the average elevation demonstrated a more accentuated depressive tendency of the visual field in the research group. For the right eye the reference range was < -6dB, -3dB > 47.9% (23 patients), followed by the range of -6dB> for 39.5% (19 patients) and < -3dB, 3dB > for 12.5% (6 patients). Compared to the control group, these indices were mainly in the range < -3dB, 3dB > for 54.1% (26 patients), followed by the range < -6dB, -3dB > for 34.4% (17 patients) and respectively -6dB> for 10.4% (5 patients) (p < 0.001). For the left eye, the value distribution was very similar to the right eye, with the following values determined for the research group: range < -6dB, -3dB> for 56.2% (27 patients), followed by the range of -6dB> for 22.9% (11 patients) and < -3dB, 3dB > for 20.8% (10 patients) (p < 0.001). Compared to the control group: range < -3dB, 3dB > for 56.2% (27 patients), followed by range < -6dB, -3dB > for 37.5% (18 patients) and respectively -6dB> for 6. 2% (3 patients) (tab. 5).

Table 5. Index of average defect after brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	**%**
Right	< -3 dB. 3dB >	6	12.5	26	54.1
	< -6 dB. -3 dB >	23	47.9	17	34.4
	-6 dB>	19	39.5	5	10.4
Left	< -3 dB. 3dB >	10	20.8	27	56.2
	< -6 dB. -3 dB >	27	56.2	18	37.5
	-6 dB >	11	22.9	3	6.2

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

The Bebi curve graphically displays the summary image of the retinal sensitivity of the visual field. The graphic recording of the Bebi curve in the research group revealed the following changes for the right eye: diffuse depression with relative paracentral scotomas in 64.6% (31 patients), diffuse depression with absolute paracentral scotomas in 14.6% (7 patients), diffuse depression in 14.6% (7 patients) and unchanged sensitivity in 62.5% (3 patients). In contrast, data with reference to the control group showed unchanged sensitivity in 72.9% (35 patients), diffuse depression in 20.8% (10 patients), and diffuse depression with relative paracentral scotomas in 6.2% (3 patients). For the left eye, the distribution for the research group was as follows: diffuse depression with relative paracentral scotomas 68.7% (33 patients), diffuse depression with absolute paracentral scotomas in 20.8% (10 patients), and diffuse depression in 8.3% (4 patients) and unchanged sensitivity in 2.1% (1 patient). Data for the control group were indicated unchanged sensitivity in 58.3% (28 patients), diffuse depression in 35.4% (17 patients), and diffuse depression with relative paracentral scotomas in 6.2% (3 patients) (fig.1).

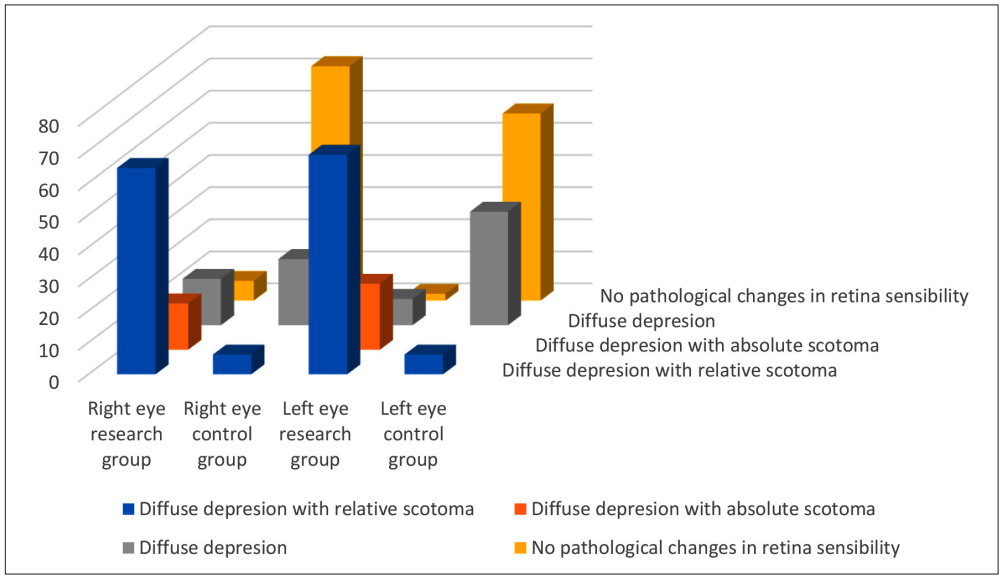

Fig. 1 Bebi curve data after brain injury in children aged between 7-18 years (96 patients).

Visual field examinations were performed 4 months after the trauma in both groups. A lack of fixation was observed among the patients in the research group (tab. 6), with 73% (35 patients) showing values up to 20% for the right eye. In 25% (12 patients) this index was between 21-60%, and 2.1% of cases (1 patient), the index was between 61-100%. In the control group, values for the right eye were determined in 79.1% (38 patients) up to 20%, in 14.6% (7 patients) within the range of 21-60% and 6.3% (3 patients) in the range of 61-100% ($p < 0.001$).

For the left eye, the estimated results revealed a lack of fixation among patients in the research group: in 93.7% of cases (45 patients), the loss of fixation was in the range of up to 20%, and in 4.2% of cases – within the range of 21%-60%. This is compared to the distribution of the fixation values for the left eye in the control group: 97.9% cases (47 patients) - range up to 20%, in 2.1% cases (1 patient) – within the range of 21-60% ($p < 0.001$) (tab. 6).

Table 6. Fixation loss ratio after 4 months of brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	%
Right	Up to 20%	35	73	38	79.1
	21%-60%	12	25	7	14.6
	61%-100%	1	2.1	3	6.3
		p < 0.001			
Left	Up to 20%	45	93.7	47	97.9
	21%-60%	2	4.2	1	2.1
	61%-100%	1	2.1	0	0
		p < 0.001			

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

The evaluation of the ability to fixate the false positive points revealed equal values in both eyes for the interval up to 20%, with 91.7% in the control group, and 91.7% in the research group ($p < 0.001$), and for the left eye 93.7% in the control group, versus 93.7% cases in the research group ($p < 0.001$). Meanwhile, it should be noted that the rate of the ability to fix false positive points in the range of 21-60% for the right eye was revealed in 6.2% patients in the researched group, versus 8.3% in the control group and the range 61-100% - 2.1% patients in the research group (tab.7). For the left eye, the values were as follows: the range of 21-60% - 4.2% patients in the research group, versus 6.3% in the control group and the range 61-100% - 2.1% patients in the research group.

Table 7. False positive points fixation after 4 months of brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	%
Right	Up to 20%	44	91,7	44	91,7
	21%-60%	3	6,2	4	8,3
	61%-100%	1	2,1	0	0
		p < 0.001			
Left	Up to 20%	45	93,7	45	93,7
	21%-60%	2	4,2	3	6,3
	61%-100%	1	2,1	0	0
		p < 0.001			

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

The evaluation of the ability to on fixate false negative points did not reveal significant statistical differences between the groups. Thus, in both the research group and in the control group, most of patients presented values up to 20%, with 93.7% in the research group and 95.8% in the control group ($p < 0.05$), and for the left eye: research group – 89.6% and in the control group – 97.9% ($p < 0.05$) (tab. 8).

Table 8. False negative points fixation after 4 months of brain injury in children aged between 7-18 years (96 patients).

Eye	Values	L1		L0	
		Patients	%	Patients	%
Right	Up to 20%	45	93,7	46	95,8
	21%-60%	2	4,2	0	0
	61%-100%	1	2,1	2	4,2
		p < 0.05			
Left	Up to 20%	43	89,6	47	97.9
	21%-60%	4	8,3	1	2.1
	61%-100%	1	2,1	0	0
		p < 0.05			

Note: L1 – research batch; L0 – control batch; Applied statistical test Fisher's test.

Evaluation of the localized defect indices indicated values between < 0dB, 3dB> in 93.7% (45 patients) - L1 and 97.9% (47 patients) - L0 for the right eye. Levels in the < 3dB, 9dB > range were recorded in 4.2% (2 patients) - L1 and 2.1% (1 patient) - L0. The maximum range of >9dB was recorded for 2.1% (1 patient) of the research group. For the left eye, the following values were determined: the range of < 0dB, 3dB > characteristic for 91.6% (44 patients) - L1 and 100% (48 patients) - L0. The interval < 3dB, 9dB> attributed to 6.3% (3 patients) - L1 and maximum values of 9dB> to 2.1% (1 patient) were determined only in the research group. The distribution of the average elevation in the researched group was as follows for the right eye: the reference range was < -6dB, -3dB > in 12.5% (6 patients), the range of -6dB> in 12.5% (6 patients) and < -3dB, 3dB > in 75% (36 patients). Compared to the control group, these indices were primarily in the range < -3dB, 3dB > in 87.5% (42 patients), followed by the range < -6dB, -3dB > in 12.5% (6 patients). For the left eye, the value distribution was very similar to that of the right eye, with the following determined values for the research group: range < -6dB, -3dB> for 27.1% (13 patients), range of -6dB> for 10.4% (5 patients) and < -3dB, 3dB > for 62.5% (30 patients). Compared to the control group: < -3dB, 3dB > range for 91.7% (44 patients), followed by < -6dB, -3dB > range for 8.3% (4 patients).

The graphic recording of the Bebi curve in the research group revealed the following changes for the right eye: diffuse depression with relative paracentral scotomas in 33.3% (16 patients), diffuse depression with absolute paracentral scotomas in 2.1% (1 patient), diffuse depression in 50% (24 patients) and unchanged sensitivity in 14.6% (7 patients). In contrast, data for the control group showed predominantly unchanged sensitivity in 93.7% (45 patients), diffuse depression in 6.3% (3 patients). For the left eye, the distribution for the research group was as follows: diffuse depression with relative paracentral scotomas in 27.1% (13 patients), diffuse depression with absolute paracentral scotomas in 2.1% (1 patient), diffuse depression in 56.2% (27 patients) and unchanged sensitivity in 14.6% (7 patients). The data for the control group indicated unchanged sensitivity in 79.2% (28 patients), diffuse depression in 20.8% (10 patients) (fig.2).

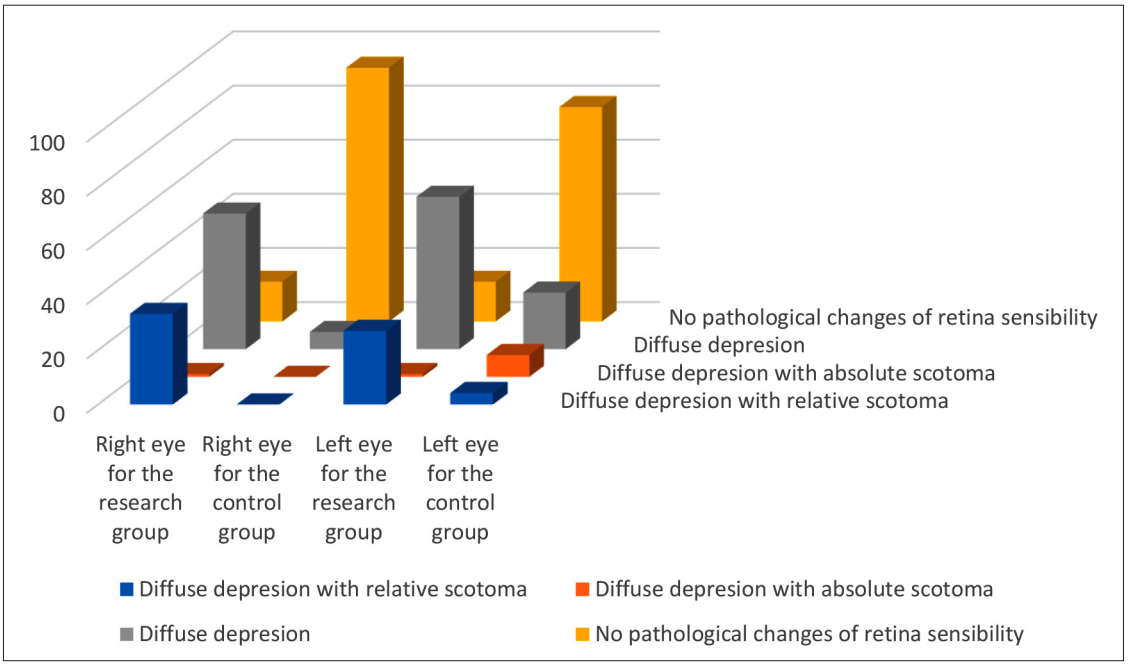

Fig. 2 Bebi curve data after 4 months of brain injury in children aged between 7-18 years (96 patients).

Discussion

Reliability criteria of the visual field assessment were categorized according to previously determined percentage ranges. Patients in the research group exhibited a noticeable disturbance in fixation capacity of more than 20%, while in the control group the fixation capacity was

maintained up to 20%. The rate of the ability to fixate on false positive points was up to 20% patients for both the research and control group. Similarly, the rate of the ability to fixate false negative points was within the range of up to 20% for both the research and control group. These values outline that visual field evaluation in the acute stage of brain injury can be performed, but its results should not be considered fully reliable, as the credibility criteria are not satisfactory met. Subsequent re-evaluation of these indices revealed significant changes. Later, disturbances in the fixation capacity were predominantly for the interval up to 20% for both the research and control group. The ability to fix false positive points was up to 20% in both groups. The ability to fixate on false negative points was within the range of up to 20% for both groups. Thus, perimetric examination could be a significant test in the initial phase of the post-TCB visual disturbances, but it requires repeated evaluation.

One of the aims of our research was to determine whether there are specific intervals for reliability criteria for TBI patients. The difference we found is that the false positive errors and false negative errors may be considered up to 20%, although some authors suggest that this range could extend up to 33% (Salman Dar, 2014). The parameters characterizing the diffuse loss of retinal sensitivity had a distribution with a suppressive tendency for posttraumatic patients. The index of localized defects was up to 3dB in both groups. The average elevation index was within the range of < -3dB, 3dB> in most of the control group. These numbers indicate an obvious alteration of retinal sensitivity after head trauma without a specific scotoma arrangement. The graphic interpretation of changes in the visual field revealed a prevalence of the incidence of diffuse retinal depression with relative paracentral scotomas in the research group, and for the control group unchanged sensitivity was determined. The index of localized defects was up to 3dB in both groups. The average elevation index was within the range of < -3dB, 3dB> in both groups. The graphic interpretation of changes in the visual field over time revealed a shift towards diffuse retinal depression with relative paracentral scotomas, as well as diffuse depression in the case of the research group, and for the control group an unchanged sensitivity was observed. It should be noted that the index of average elevation and localized defects correlates with reliability criteria (Heijl A,2022).

Visual field defects are identified in case of brain trauma in children. One of the goals of the research was to assess if the evaluation method would be sufficiently reliable, considering the fact that children are generally less cooperative. In cases of mild TBI, it is not appropriate to refer to the presence of well-defined visual field defects in the form of hemianopsia and/or quadranopsia. More commonly, relative scotomas are present, scattered in the field of vision, varying in size and intensity, and influenced by the extent of nerve tissue damage. However, we observe a decrease in retinal sensitivity, a fact clearly demonstrated by the Bebi curve, which shows the alteration of the visual stimulus perception by the retina in the immediate post-traumatic period. These changes, however, are compensated as the recovery period progresses, possibly due to the neurostimulatory treatment to which every post-TBI patient is subjected. Most of the research point that TBI may be associated with hemianopia or quadrantopia in the adult population (Saliman N., 2021). According to our research in pediatric population, retinal sensitivity is affected with relative scotomas dispersed without any particular location.

Conclusions

1. Due to the fact that the reliability criteria of visual field assessment, such as fixation loss, false positive and false negative points fixation, do not meet the required credibility values in the acute period of brain injury in school-aged, the determined values should not be taken into consideration. However, they should be recorded and re-evaluated to determine possible organic changes.

2. The reference values for reliability criteria in visual field examinations in school-aged children set the intervals for fixation loss, false positive points fixation and false negative points fixation at up to 20%.

3. Most the school children undergoing TBI exhibit in the acute period, changes of the retinal sensitivity detected on visual field assessment, with values of structural defects ranged between < 3 dB, 9 dB> and index of average defects >-6 dB.

4. Graphical representation of visual field evaluation in school-aged children after TBI does not present delimited visual field defects such as hemianopia and/or quadrantopia, but shows diffuse sensibility alteration in 50% and diffuse sensibility alteration with relative paracentral scotomas in 33.3%.

Competing interests

None declared.

Authors' contribution

VV conceptualized the project and drafted the first manuscript. EB interpreted the data. EB critically revised the manuscript. All authors revised and approved the final version of the manuscript.

Patient consent

Obtained.

Ethical statement and patient consent

The Research Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy approved the study, on 21.05.2018 minutes No.63.

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RESEARCH ARTICLE

Diagnosis of maxillary compression syndrome

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ABSTRACT

Introduction. Upper maxillary compression syndrome is characterized by a deficit in transversal development and is recognized within the classification system of the German school. Regardless of the schools' affiliation according to which this malocclusion is classified, the objective is to determine and select the treatment method with maximum efficiency. Thus, the compression of the upper jaw can also be included as a component in class II subdivision 1 malocclusions, presenting in 2 clinical forms. In addition, the types of palatal suture and their impact on the development of the maxilla in the transverse plane were identified. The purpose of the study was to assess the importance of cone beam computed tomography (CBCT) n providing a comprehensive diagnosis of this malocclusion and formulating an elaborate treatment plan.

Material and methods. After applying the inclusion and exclusion criteria, 165 patients were enrolled in the study. The research included patients with jaw compression syndrome diagnosed orthodontically during the mixed and permanent dentition periods. The patients were divided into 3 groups according to the stages of formation of the medio-palatine suture, correlating with their biological age. The research sample was calculated using ANOVA program: fixed effects, omnibus, one-way Analysis.

Results. Determining the shape and degree of formation of the median palatal suture at the ages studied in the research, favors the selection of modality, type, and speed of expansion. These factors are directly related to the stage of formation of the palatal suture, which may or may not coincide with the patient's biological age. CBCT is the method of choice for assessing this. Furthermore, the range of movement in millimeters that can be achieved after separating the upper jaw can be determined, regardless of the type of expansion.

Conclusions. Based on the analysis of the data, we can appreciate the variety of expansion methods depending on the degree of formation of the medio-palatine suture. Through a comprehensive paraclinical examination and accurate interpretation, we can establish the definitive diagnosis of this clinical entity and create a treatment plan that minimizes the chance of recurrence.

Keywords: palatal suture, CBCT, compression, discrepancy, palate.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Maxillary compression syndrome and its clinical manifestations can be easily diagnosed based on the radiological examination, especially cone beam computed tomography. For accurate diagnosis, it is enough to know the anatomy of the maxilla and the varieties of the palatal suture.

The research hypothesis

The importance of increasing the effectiveness of orthodontic treatment in patients with narrowing and deformation of the up-

per jaw in the period of mixed dentition and permanent dentition based on data analyzed on cone beam computed tomography.

The novelty added by the manuscript to the already published scientific literature

The ability to interpret and analyze computed tomography scans is crucial for identifying malocclusion and establishing definitive diagnosis in orthodontics.

Introduction

Dento-maxillary anomalies are characterized by growth and development disorders, primary or acquired, of the dental system or maxillary bone bases major imbalances in the dento-alveolar and occlusal arches [1].

The form-function correlation throughout the individual's life can play a significant role in the etiological process of occlusal anomalies. If function can influence the growth of the jaws, then a change in function can cause the dento-maxillary anomaly. The growth of the upper and lower jaw in the transverse plane is achieved at a variable rate, with periods of intense activity and relative rest [2]. According to several authors, the activity of the medio-sagittal suture continues up to the age of 9 years, being achieved through the mechanism of apposition and resorption. Boboc G. finds an increase of 0.5 mm/year without a difference between the sexes in the anterior area, though for boys, it is higher in the posterior area [3]. The acceleration of the transverse development process occurs around the age of 4-6 years, manifested by the appearance of spacing in the upper and lower front teeth. After the age of 10, changes in the transverse plane are minimal, and for the maxilla, growth continues up to 16 years for boys and 12-13 years for girls. According to Moyers R., there is an increase of 4 mm in the maxilla. He also states that during tooth eruption, the jaws develop in the transverse plane due to the vertical growth of the alveolar processes [4].

The Pont index assesses the transverse development of the dental arches by relating the arch's dimensions to the size of the teeth, or when normal facial development maintains a certain proportion between the dimension of the arches and the dimension of the face. Currently, the most widely used method for assessing the development of the arches, especially the upper one, is the analysis of the total space (according to Tweed) [5, 6].

The frequency of division 1 of class II is high, ranging between 55 - 70%, depending on the age of the patients, which is significantly higher than division 2, representing only 9% of the total number of malocclusions [7, 8]. The narrowing of the upper jaw is one of the common pathologies, both as an independent malocclusion and as a component element of a basic dentomaxillary anomaly. Snaghina N. G. (1966) reports an incidence of 63.2% in her orthodontic practice. Along with the upper jaw, the upper dental arch usually narrows [9]. In all clinical cases of compression of the upper jaw, it is necessary to perform a biometrical analysis model to assess the degree of compression, both at the premolars and upper molars levels. This facilitates the assessment of an individual treatment plan [10].

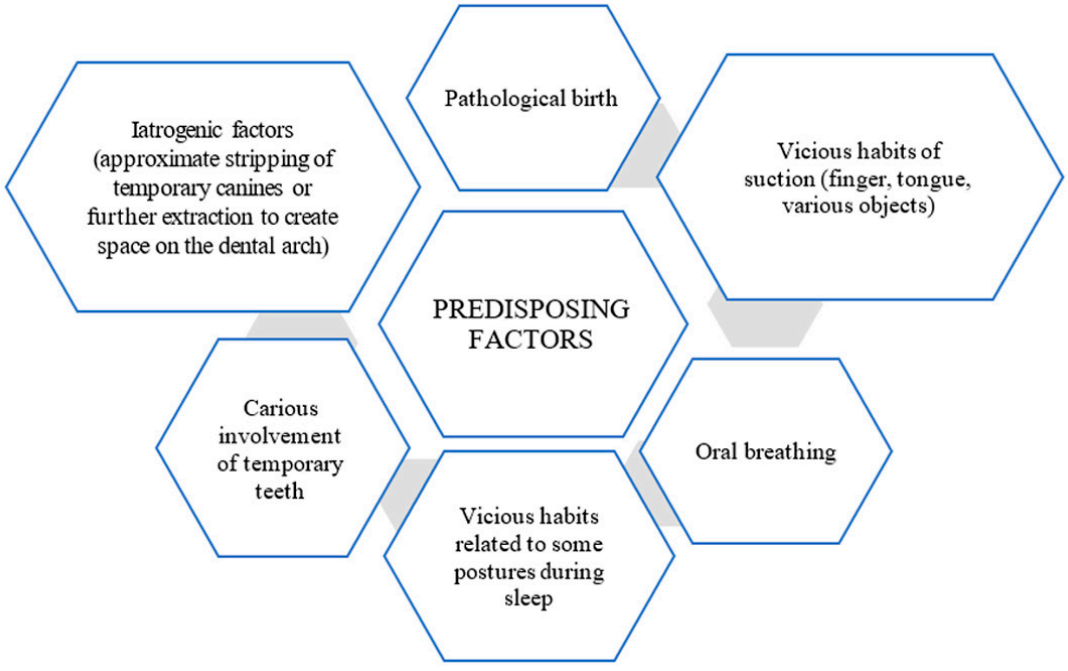

Fig. 1 Predisposing factors in triggering jaw compression syndrome [11].

In addition, the phenomenon of delayed eruption in hypothyroidism can cause developmental disorders with the narrowing of the arches, and the insufficiently developed muscle tissue can have a harmful impact on the development of the jawbones. It is unanimously accepted that the genesis of the deformity is included in the diagnosis and provides important data for it. Jaw narrowing cannot be reduced to a single cause and effect, according to the Cause – Time – Tissue – Results equation (the Dockrell orthodontic equation) [12, 13]. The longitudinal growth study by Bolton and Harris determined the heritable component in skeletal traits. Up to 4 years, certain palatal features show a strong genetic determination, it decreases with age, whereas the heritability of craniofacial features increases, with vertical ones being more influenced by the genotype than the horizontal ones [14-16].

Table 1. Longitudinal growth analysis according to Bolton analysis [17]

Age	Craniofacial parameters	Arch and occlusion parameters
4	0.6	0.5
14	0.9	0.2
20	0.9	0.1

The median palatine suture serves as the growth center for the maxilla. Either inadequate growth in this segment, such as excess or deficiency, causes malocclusions and/or tooth crowding. However, the pattern formation mechanism of palatal sutures, such as the sagittal or median suture, is poorly understood. The palatine suture is the suture between the left and right maxilla and the palatine bone. It is composed of a median palatal suture, present in the middle maxillary region, and a transverse palatal suture that forms the border between the palatine bone and the maxillary bone pictured in figure 2. Most of the surface of the hard palate is made up of the maxilla, so the transverse palatal suture is in the posterior third of the hard palate [18, 19]. The morphology and development of the palatine suture were initially described by direct observation of bone specimens and later by radiographic observations. In forensics, the palatal suture is an age indicator, similar to the calvarial suture [18].

The stages of midpalatal suture fusion were initially described by Angelieri based on standardized cross-sectional cone beam computed tomography (CBCT) images. The radiographic appearance of the midpalatal suture early in life has been noted as a line or area of high density just prior to interdigitation and sutural fusion. The following descriptive stages of the maturation of the middle palatal suture are proposed in figure 3 [19].

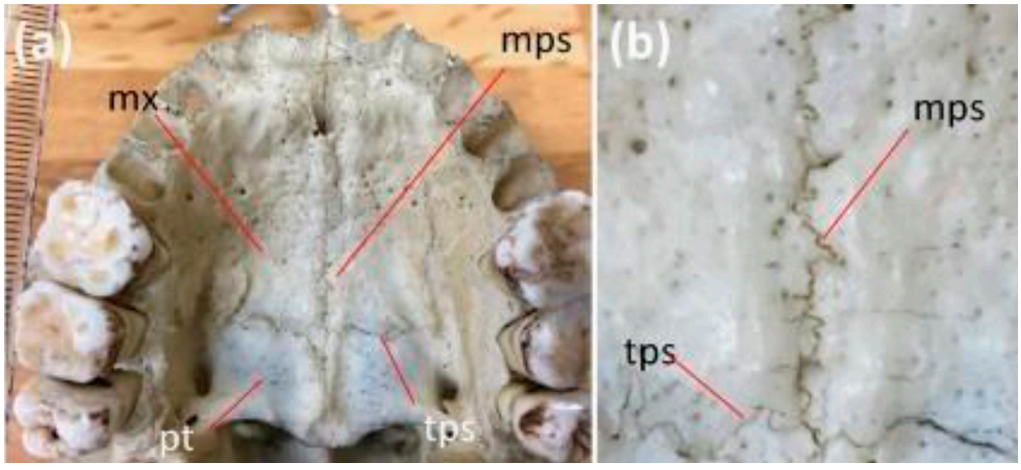

Fig. 2 Anatomy of the palatal suture: association with development and clinical treatment. (a) Palate suture. The median palatal suture is at the midline of the hard palate, while the transverse palatal suture is at the interface between the maxilla and the palate. (b) Magnified view (x24). *mx* – maxilla, *mps* – mid palatal suture, *pt* – palatal bone, *tps* – transverse palatal suture [18].

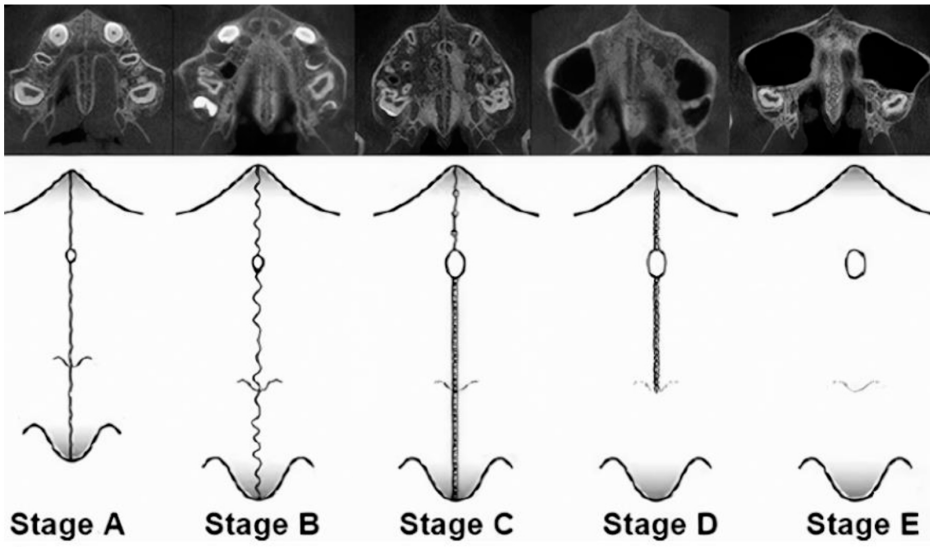

Fig. 3 Maturation stages of the median palatal suture. Modified by Angelieri [19].

In stage A, the palatal suture is almost a straight suture line of high density, with little or no interdigitation. In stage B, the median palatal suture becomes irregular in shape and appears as a scalloped high-density line. Stage B patients may also have some small areas where 2 parallel, scalloped, high-density lines are seen close together and separated by low-density spaces. In stage C, the midpalatal suture appears as 2 parallel, scalloped, high-density lines that are close to each other, separated by small low-density spaces in the maxillary and palatine bones (between the incisive foramen and the maxillary-palatine suture and posterior to the suture palatomaxillary). The suture can be arranged either straight or irregularly. In stage D, fusion of the midpalatal suture has occurred with the palatine bone, with maturation progressing from posterior to anterior. In the palatine bone, the median palatal suture cannot be visualized at this stage and the bone density is increased. In the maxillary portion of the suture, fusion has not yet occurred, and the suture can still be seen as 2 high density lines separated by small low-density spaces. In stage E, fusion of the midpalatal suture in the maxilla has occurred. The actual suture is not visible in at least one portion of the jaw. The bone density is the same as in other regions of the palate [20-22].

Material and methods

The study, conducted at the department of orthodontics and at "Calfa Dent" dental clinic was based on data from clinical and paraclinical examinations, along with diagnostic methods. The study included 165 patients with compression syndrome of the upper jaw aged between 7-18 years, from both rural and urban areas of the country.

Patients were examined paraclinically by CBCT. This diagnostic method is an important complementary test in the diagnosis and planning of orthodontic treatment. In daily practice, the analysis of the dental and alveolar arches is used, but not the analysis of the dentofacial skeletal parameters, as shown in figure 4. The determination of the skeletal parameters of the upper jaw is the basic factor for the selection of the treatment method of patients with endoalveolia of the upper jaw, both for the dento-alveolar form and the skeletal form.

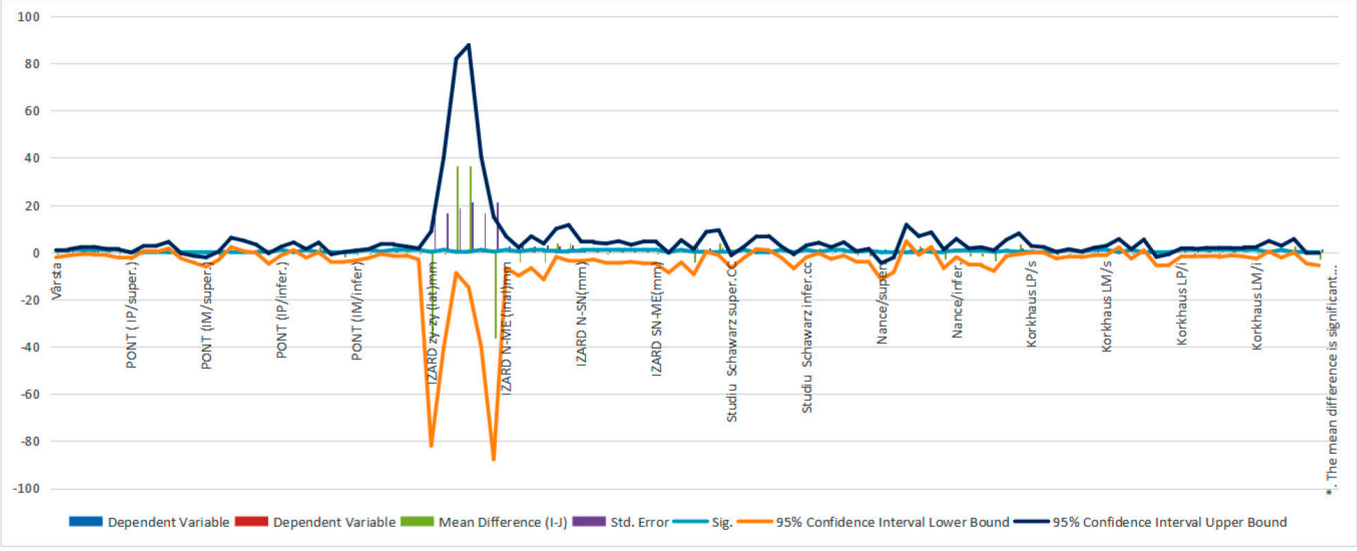

Fig. 4 Biometric indices in maxillary compression, according to multiple means of analysis

The most common modification in the reduction of the transverse dimension is the narrowing of the jaw. The genetic damage to the arches is correlated with the damage to the entire process of growth in width and manifests itself in both arches, sometimes with quite pronounced narrowing. The upper arch is more influenced by external factors; environmental factors have the potential to alter growth and affect normal overall development.

The inclusion criteria for CBCT were constituted by asymmetric deformities of the jaws (maxillary retromicrognathia, retrognathia, inferior promacrognathia), crossed occlusion, developmental deviations of the maxilla from the mandible no more than 5 mm transversely, mesialized occlusion, distalized occlusion, jaw narrowings. Exclusion criteria for CBCT: concomitant pathologies, bone tissue pathologies, unsatisfactory hygiene. The Profile Teleradiography (TRG) analysis determined the degree of narrowing of the upper jaw, the inclination of the group of lateral teeth, the level of formation of the median suture. Based on establishing the differential diagnosis, two clinical forms were highlighted, with protrusion and with crowding. The following variants have been proposed for the form with protrusion: Chase's biproalveolodontia, protrusion characteristic of periodontal disease, endocrine disorders (namely hypothyroidism). For the crowding form: absolute/relative macrodontia and generalized mesioposition.

Results

Radiological analysis of the median suture before and after treatment revealed expansion of the palatal suture, as shown in figure 5. Transverse dento-alveolar arch widening was achieved with a hypercorrection for the subsequent arrangement of the position of the lower lateral teeth and the achievement of multiple fissure-cuspid contacts, creating space for the eruption of upper permanent teeth and removing crowding of upper front teeth. In this work group, the activation speed of the expansion device was insignificant because the median suture was in the initial phase of mineralization and its realization occurred both at the dental and skeletal levels. Some commonly used orthodontic treatment techniques for the upper arch include slow jaw expansion, rapid jaw expansion, and surgically assisted rapid jaw expansion. Slow jaw expansion requires light and steady force, while fast jaw expansion requires high and steady pressure to activate. Surgically assisted rapid maxillary expansion has gradually become popular to correct transverse maxillary hypoplasia. Maxillary expansion has various consequences on the nasomaxillary complex.

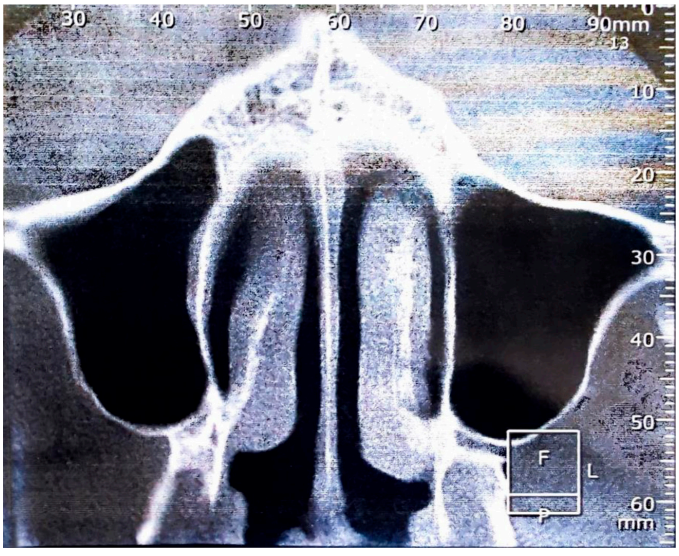

Fig. 5 Methodological schedule of the study

Discussion

There are multiple effects of maxillary expansion on the nasomaxillary complex, particularly having a direct effect on the median palatine suture along with the palate, maxilla, mandible, temporomandibular joint, soft tissue, and maxillary anterior and posterior teeth [23]. The optimal treatment plan is established based on the complementary paraclinical examination (CBCT), namely: the analysis of the palatal suture, the calculation of the transverse offer of the maxilla and the adjacent anatomical reports [24]. At the same time, based on the CBCT, the capacity in millimeters of the movement that can be performed following the disjunction of the upper jaw can be established, regardless of the type of expansion. This is because the teeth subjected to compression have an increased root angulation, a fact that indicates the need to apply a movement preferably of tilting, not of translation as was usual before [25].

Conclusions

Maxillary compression syndrome is a clinical manifestation often encountered in orthodontic practice, whether as stand-alone malocclusion according to German classification or as clinical component of the class II malocclusion by Angle. Only based on a complex paraclinical examination and correct interpretation we can establish the definitive diagnosis of this clinical entity and indicate a correct treatment plan that will minimize recurrence. Therefore, CBCT is the best investigative method in the assessment of upper jaw compression, because it provides complex information across all 3 reference planes and also helps in the correct interpretation of the palatal suture, which is key to therapeutic success in treating this type of malocclusion.

Competing interests

None declared.

Contribution of authors

SC, VT, IS, AMS drafted the manuscript and realized the literature search, VT, SC designed the study and revised the manuscript critically, SC and IS drafted the manuscript and AMS revised the manuscript critically. All authors have read and approved the final version of the article.

Ethical statement and patient consent

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UDC: 616.432-006-089

REVIEW ARTICLE

Surgical approaches in pituitary neuroendocrine tumors

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ABSTRACT

Introduction. Pituitary neuroendocrine tumors account for 3.9-7.4/100.000 of central nervous system tumors in the Western world. They are particularly noteworthy, comprising 10-15% of all cases, with a higher prevalence in the 75-79 age group. In the Republic of Moldova, these tumors account for 34% of cases in postmortem examinations while remain an actual theme of discussion in the ENDO WHO congress and are regarded as a factor, which may influence the quality of life (QOL).

Material and methods. We have critically revised 66 literary sources, which were selected using the PubMed library after introducing the keywords "pituitary adenoma surgical approach".

Results. The main surgical approaches were the transsphenoidal (transnasal, sublabial and endonasal) and transcranial (subfrontal unilateral/bilateral, fronto-lateral, fronto-temporal and median basilar) while the additional surgical approaches were designed for complicated and unusual pituitary neuroendocrine tumors and included combined versions, multiple surgeries or extended approaches. Numerous factors were influential for the selection of a surgical approach concerning the pituitary neuroendocrine tumors. They are not sensible for a type of pituitary neuroendocrine tumor according to the WHO classification while the size of a tumor may dictate its surgical approach.

Conclusion. Each surgical intervention requires a personalized approach and the critical thinking of the surgical team but most of them can be systematically considered before confronting the tumor in an intraoperatory environment because most of the preoperatory investigations are proven unreliable. There is no established superior surgical approach for each surgical intervention.

Keywords: pituitary neuroendocrine tumor, surgical approach, surgical complications.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Unfortunately, there are no universal surgical approaches for each type of pituitary neuroendocrine tumors thus; a surgeon must be experienced in order to manage accurately such a surgical intervention.

The research hypothesis

There are a series of surgical approaches that may be efficient in different particular states of pituitary neuroendocrine tumors depending on their infiltration, size, and stage. The identification of these approaches is imperative.

The novelty added by the manuscript to the already published scientific literature

We have not found any studies in the literature that have integrated all the surgical approaches, both ordinary and unusual ones and have introduced a wider classification.

Introduction

Pituitary neuroendocrine tumors are a group of non-malignant tumors, which affects the central nervous system with a currently rising incidence in the Western world (3.9 to 7.4 cases per 100.000 in Belgium) [1]. They are being regarded as approximately 10-15% of the surgically treatable tumors of the central nervous system with a dominant incidence for the age group of 75-79 years [2]. The rate of this pathoanatomical structure was of 60% in Romania and of 34% in the Republic of Moldova in a study poll collected during necropsy [3]. The weight of a normal pituitary gland is approximately 0.5-1 g and its diameter of up to 1 cm [4].

The nomenclature of this pathological formation along with its classification have undergone significant changes over time. According to the ENDO3 WHO 2004, we could have differentiated the typical adenoma, atypical adenoma, and carcinoma. The ENDO4 WHO 2017 has come with an update on this matter considering only adenoma and carcinoma while the CNS5 WHO 2021 changed the nominal terminology of adenoma for pituitary neuroendocrine tumor remaining with the second type – carcinoma. Finally, the last known conference regarding this scientific question which is ENDO5 WHO 2022 and has agreed with the before mentioned, adopting the terminology of pituitary neuroendocrine tumor and carcinoma [5].

The main clinical classification that is indexed by the World Health Organization (WHO) in 2017 regards the growth factors and the hormones that reside in their target cells [6, 7].

The NR5A1 gene encodes the steroidogenic factor 1 (SF1) which regulates the differentiation of the cells which produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), the POU1F1 gene encodes the pituitary transcription factor 1 (PIT1) which will induce the differentiation of the cells responsible for the growth hormone (GH), prolactin (PRL) and thyroid stimulating hormone (TSH) secretion and the TBX19 gene will encode the T-box transcription factor (TPIT) that will in turn induce the differentiation of the cells that will synthesize adrenocorticotropic hormone (ACTH) [6]. Estrogen receptor α (ER-α) and estrogen receptor β (ER-β) are key regulators of the lactotroph and gonadotroph tumor cells and are responsible for the hormone secretion and gonadotroph cell proliferation and apoptosis [8]. This receptor is notorious in breast cancer pathological mechanisms and has a major clinical value in its diagnosis [9]. Mutations of the transcription factor GATA2 are required for the development of the gonadotroph and thyrotroph pituitary neuroendocrine tumors [10, 11]. The estrogen receptors (ERs) and the GATA2 transcription factor have no tumoral type assigned but they may be involved indirectly in the clinical classification [8, 10].

The following pituitary neuroendocrine tumor types can be considered: somatotroph (PIT1 pathway), lactotroph (PIT1 and ER-α pathways), thyrotroph (PIT1 and GATA2 pathways), corticotroph (TPIT pathway), gonadotroph (SF1, GATA2, ER-α and ER-β pathways), null cell pituitary neuroendocrine tumor (no pathways), plurihormonal types (usually somatotroph, lactotroph and thyrotroph: PIT1 pathway) and double pituitary neuroendocrine tumor (lactotroph and corticotroph: PIT1 and TPIT pathways) [2, 7, 8].

Most of the lactotroph tumors are managed using pharmacological methods while the rest of the tumors need surgical approach [2]. An exception for the aforementioned are the pituitary carcinomas which are metastatic tumors that have no protocols designed for their management and are usually resistant to pharmacologic treatment options [12].

Pituitary neuroendocrine tumors can be classified according to their size. Thus we may mention the microadenomas (<10 mm), macroadenomas (≥10 mm) and gigantic adenomas (≥40 mm) [13]. The proportion of these formations is 60% for microadenomas and 40% for macroadenomas [14].

Internationally, surgical strategies for pituitary neuroendocrine tumors are evaluated both historically and in terms of future perspectives. The aim is to provide neurosurgical patients with the most effective intervention, leading to an improved quality of life postoperatively.

Material and methods

A randomized literature study was conducted on 06.08.2023-22.08.2023 in order to identify randomized clinical trials, meta-analyses and review articles. The search was conducted using the PubMed library.

After introducing the keywords "pituitary adenoma surgical approach" we have selected the first 100 scientific articles from which we considered relevant to the topic only 45 sources. Additional 21 sources were studied independently without applying any search protocol, being collected manually. Overall, there were studied 66 literary sources.

We have studied all the known nomenclature considerations for the classical term of "pituitary adenoma" using the most recent publications in order to avoid a gap of terminology query [5].

The revised sources were selected using the principles that were described in the specialty literature.

Results and discussions

Historical aspects. The literature reports state that the first adenomectomy was realized in 1889 but was reported only in 1906 using the transcranial subfrontal approach [15], while the first documented report of this intervention dates back to 1892 with a transcranial subtemporal approach [16]. Schloffer was the first to use the alternative transsphenoidal approach in order to manage a pituitary neuroendocrine tumor in 1907 and Hirsch extended this method by using a nasal speculum in 1910. Dandy still pioneered the transcranial method in 1918 [15], while Hardy has seen the progressive potential in augmenting the transsphenoidal route in 1960 by adding sophisticated technologies like illumination [17]. The most recent advances included the addition of technologies like intraoperative magnetic resonance imaging [18, 19], optical coherence tomography [20], fluoroscopy [21] and neuronavigation using preoperatory CT or MRI findings [19, 22, 23].

Main surgical approaches. There are two surgical routes – the transcranial and transsphenoidal one (Table 1) [24]. Solari D. *et al* has elaborated in 2014 a more detailed classification of these two according to the instruments that were used or the incisions that has to be made. We differentiate the following transsphenoidal approaches: microsurgical and endoscopic which may have transnasal, sublabial or endonasal incisions. Transcranial approaches may be subfrontal (unilateral or bilateral interhemispheric), fronto-lateral, fronto-temporal [15] or median basilar [21]. The transsphenoidal routes were also considered by McEwen DR *et al.* in 1995 [4].

Table 1. Main surgical approaches in pituitary neuroendocrine tumors.

Transsphenoidal (microsurgical or endoscopic)	Transcranial
Transnasal	Subfrontal (unilateral or bilateral)
Sublabial	Fronto-lateral
Endonasal	Fronto-temporal
	Median basilar

Additional surgical approaches. The following surgical approaches are essentially enhanced versions of the previously discussed methods thus making the interventions more complex, but with an increased rate of success (Table 2). Mehta GU et al. reported a mixed type that implied the usage of both microsurgical and endoscopic methods in 2017 [25]. Combined or multiple surgical interventions can be regarded as a separate entity because they are not routinely performed. We can differentiate the following combined approaches: transcranial / transcranial, transsphenoidal / transcranian and transsphenoidal / transsphenoidal while multiple surgical interventions are similar to the previous mentioned, but they are performed in multiple interventions [26]. Some incisions may be extended in order to give a larger view of the adjacent anatomical and anatomo-pathological structures. The transsphenoidal extensions are anterior (via tuberculum sellae and processus clinoideus [27-29], posterior (subsellar via *diaphragma sellae*) [27, 30], lateral (transoculomotor triangle via sphenoidotomy) [31-33], ethmoidal [34] and combined (anterior and posterior) [32]. The transcranial extensions imply the frontal, temporal, orbito-zygomatic and transcortical transventricular ones [35].

Table 2. Additional surgical approaches in pituitary neuroendocrine tumors.

Combined	Multiple	Extended (transsphenoidal)	Extended (transcranial)
Transcranial / transcranial	Transcranial / transcranial	Anterior	Frontal
Transcranial / transsphenoidal	Transcranial / transsphenoidal	Posterior	Temporal
Transsphenoidal / transsphenoidal	Transsphenoidal / transsphenoidal	Lateral	Obito-zygomatic
		Ethmoidal	Transcortical-transventricular
		Antero-posterior	

Practical considerations. The transnasal transseptal approach can be made bilaterally and is proven to have a better preservation of olfactory mucosa functionality [36] compared to the single-nostril endoscopic transnasal transsphenoidal approach [37]. Conditions like tobacco usage and prior naso-sinusal infections are factors, which may induce a diminished olfactory function in postoperatory settings [37]. The transnasal route includes 3 phases: the endonasal / transsphenoidal, the resection phase, and the skull base reconstruction phase [38].

The sublabial transsphenoidal approach is highly traumatic and has great risks for postoperative complications or unneeded lesions of the nasal septum, gums, and lips along with a nose deformation [39]. The endoscopic endonasal transsphenoidal approach has a better outcome prediction then the endoscopic transnasal transsphenoidal one [40]. Contraindications for the transsphenoidal approach: anterior or medium cranial fossa extensions, lesions with intense vascularization, lesions extended above the sella turcica, recurrent tumors, and the anatomical variability of the internal carotid artery [4].

The Knosp and modified Knosp scale can have a good prognosis for the surgical approaches; while the Hardy-Wilson scale is not statistically significant, [41] and the Knosp scale along with the tumor dimension can be a good prediction factor for the surgical intervention complexity [42]. The only factor, which is reliable to determine recurrence risk, is the presence of the residual tumor after resection, while age, gender, infiltration, Knosp and Hardy-Wilson scales are not statistically adequate for that [16].

The microsurgical methods have a decreased rate of recurrence compared to the endoscopic ones (45% vs 70%) [26], while the invasive tumors require an endoscopic approach in order to have a favorable outcome [43]. If there is any aneurism surrounding the pituitary neuroendocrine tumor, then the combined endoscopic endonasal and bilateral transcranial subfrontal approaches may be of great use [44].

The transcranial approach is associated with significant pituitary dysfunction in the postoperative period and craniopharyngiomas result with diabetes insipidus more often than the pituitary neuroendocrine tumors [21]. Literature data state that this complication has an incidence of 2.5-20% [17]. An infiltration in the posterior cranial fossa is indicative for transcranial surgery [45].

The endoscopic endonasal approach is the most efficient in the excision of the calcium depositions on the capsule surrounding the pituitary neuroendocrine tumor [46] being also the first that is considered in any pituitary neuroendocrine tumor surgical intervention [45]. The tran-

scranial fronto-temporal approach can be dangerous for the lesion of the branches from the *plexus parotideus* [30]. An orbito-zygomatic extended approach may not be necessary when an orbital invasion is compatible [14].

The cerebrospinal fluid (CSF) leakage is diminished in the extended posterior transsphenoidal approach [27]. A nasoseptal flap (Hadad) can be made in order to preserve the tissues and to avoid the cerebrospinal fluid (CSF) leakage [17, 47] along with substitution using adipose tissue, connective tissue from fascia and osseous tissue [17].

In the pediatric population the most efficient approach was the transnasal transsphenoidian one with a marked decompression of the optic chiasm [48] and endoscopic methods are more preferred than the microsurgical ones [49]. The pediatric differential diagnosis is vital because most often they may be confounded with other pathological structures like craniopharyngiomas, Rathke cleft cysts, Langerhans cell histiocytosis, sarcoidosis and dermoid/epidermoid cysts [48, 49], while pituitary neuroendocrine tumors may be associated with more complex conditions like Carney complex, McCune Albright syndrome and multiple endocrine neoplasia type 1 [50]. The optical coherence tomography is a valuable tool for determination of the optic chiasm integrity after the resection of a pituitary neuroendocrine tumor [43]. Magnetic resonance imaging is not proven to be reliable for the determination of the pituitary neuroendocrine tumor consistency [51]. The "chop-sticks" method which implies a 3-instrument and 2-handed operatory technique is proven to reduce the postoperative morbidity [52].

Anatomical and anatomo-pathological considerations. The bones that are involved in the transnasal transsphenoidal approach may be variable in their positions and dimensions. Thus, the nasal septum may have a deviation on the left side in 23.1% cases, bilateral middle turbinate pneumatization in 19.2% cases, bilateral middle turbinate curvature in 7.7% cases, supraposition of the ethmoid sinus above the sphenoid sinus in 3.8% cases, vertical sphenoid fissure in 3.8% cases and internal carotid artery defects in 3.7% cases [53]. One study conducted by researchers from the Republic of Moldova observed a 30% anatomical variability of the Willis circle [54].

The pituitary neuroendocrine tumor may have a capsule that surrounds it from healthy glandular tissue. These capsules can be unique or can be patched in groups. Small tumors usually do not have capsules thus making them more difficult to spot using radiological methods [55]. Cerebral abscesses may coexist with the pituitary neuroendocrine tumors thus requiring their excision and placement of a drainage system [56]. Hemorrhage is not unusual in setting and will require extended versions of the surgical approaches [57]. An aneurysm may be present associated with the arterial branches surrounding the pituitary neuroendocrine tumor [44].

Double pituitary neuroendocrine tumors can require critical thinking in intraoperative settings [58]. The calcifications always adhere to the pituitary neuroendocrine tumor capsule [59].

A mutation in the BRAF gene (V600E) determines the development of a special state of tumor that is intermediary between the pituitary neuroendocrine tumor and craniopharyngioma [60]. Tumors which invade the cavernous sinus can be operated with an extended transsphenoidal approach with posterior ethmoidectomy but will determine transitory postoperatorive double-vision [34].

The gigantic pituitary neuroendocrine tumors have blood vessels originating from the infraclinoidal portion of the internal carotid artery thus making an extended anterior approach risky and determining the necessity to use the transcranial approach [61, 62], while it has been proven that the transnasal transsphenoidal approach is efficient for most of these tumors [63] and they were also usually managed using endoscopic endonasal transsphenoidal approach. An infiltration in the 3rd ventricle was proven to be difficult in surgical management no matter the approach (transcranial or transsphenoidal) [45]. Schwannoma can be misdiagnosed as a pituitary neuroendocrine tumor if it is located adjacent to the sella turcica [64].

Predictions scales. The Knosp scale constitute 5 severity degrees. Grade 0: the tumor is medial to the medial tangential line; Grade 1: the tumor is between the medial tangential line and the intercarotid line; Grade 2: the tumor is between the intercarotid line and the lateral tangential line; Grade 3: the tumor is lateral to the lateral tangential line and Grade 4: the intracavernous portion of the internal carotid artery is completely covered in tumoral tissue. The modified Knosp scale includes Grade 3A: the tumor is above the intracavernous internal carotid artery and Grade 3B: the tumor is below the intracavernous portion of the internal carotid artery [41].

The Hardy-Wilson scale has the A-E severity degrees. Type A: suprasellar mass of <10 mm; type B: the tumoral mass reaches the 3rd ventricle and is 10-20 mm; type C: the tumoral mass is inside the 3rd ventricle and is 20-30 mm; type D: the tumoral mass extends above the Monro foramen and is >30 mm and type E: the tumoral mass is extending laterally [38].

Conclusions

The surgical approaches in pituitary neuroendocrine tumors have a historical continuity with regard of the constant improvements that are made in this field. Different conditions require a personalized approach and the skills of a trained neurosurgeon in order to choose the right surgical strategy. Preoperatory clinical instruments are not always reliable thus requiring decisions that are made intraoperatively according to the previous experiences of the neurosurgical team. Most of the complications can be avoided if preventive measures are taken adequately. There is no proven superior surgical approach for each surgical intervention.

Competing interests

None declared.

Contribution of authors

DC drafted the manuscript and realized the literature search, VA designed the study and revised the manuscript

critically, SV drafted the manuscript and revised the manuscript critically, AD revised the manuscript critically.

Ethical statement

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REVIEW ARTICLE

Oral lichen planus – an oral potentially malignant disorder (OPMD) of the oral cavity

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ABSTRACT

Introduction. Oral lichen planus is a chronic inflammatory disease of unknown etiology, characterized by recurrent lesions, presenting as reticular lesions, sometimes accompanied by atrophic, erosive, and/or ulcerative areas. Despite being one of the most common conditions affecting the oral mucosa, oral lichen planus remains an ailment with undefined etiology and unclear pathogenesis, imprecise management, and uncertain premalignant potential.

Materials and methods. A narrative literature review study was conducted. A bibliographic search was carried out in databases such as PubMed, Hinari, SpringerLink, the National Center of Biotechnology Information, and Medline. Articles published from 1990 to 2023 were selected using various combinations of keywords: "oral lichen planus," and "epidemiology," "etiology," "pathogenesis," "symptoms," "management," "histopathology," and "malignant transformation." After processing the data from these databases, 475 full articles were found. The final bibliography comprised 50 relevant sources, considered representative of the materials published on the topic of this synthesis article.

Results. Oral lichen planus is an inflammatory condition associated with T-cell-mediated immune dysfunction. Triggers include autoimmune responses to local antigens, microorganisms, and stress. The disease results from a complex interplay of host factors, lifestyle, and environmental factors leading to T-cell-mediated immune dysregulation. Diagnosis of oral lichen planus is based on clinical features (multiple, bilateral, symmetrically distributed lesions, occurring most commonly on the buccal mucosa, dorsal tongue surface, and gingiva), histopathological findings (predominantly lymphocytic band-like infiltrate in the lamina propria, presence of apoptotic cells in the basal cell layer, absence of epithelial dysplasia), and immune-related changes (deposition of fibrinogen along the basement membrane zone, presence of granular fluorescent deposits containing IgA, IgG, and IgM in colloid bodies).

Conclusions. Oral lichen planus is a chronic inflammatory condition mediated by T-cells in response to various extrinsic antigens, modified autoantigens, or superantigens, with periods of remission and relapse and the potential for malignant transformation. The etiology and pathogenesis of this condition are complex, diagnosis relies on clinical features, histopathological findings, and immunological data, patient treatment is symptomatic, and the potential for malignant transformation varies. Nevertheless, prospective studies with large sample sizes, adequate treatment duration, and long-term follow-up are needed.

Keywords: oral lichen planus, epidemiology, etiology, pathogenesis, symptoms, histopathology, treatment, malignant transformation.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Despite numerous studies conducted, the epidemiology, etiology, and pathogenesis of oral lichen planus (OLP) are complex and incompletely understood. The therapy administered is often unsatisfactory and is associated with a series of adverse effects. Although

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OLP is considered an oral potential malignant disorder, its potential for malignant transformation is still contradictory.

The research hypothesis

The analysis and overview of the severity of oral lichen planus lesions correlate with an increased risk of malignant transformation, suggesting it is a potential predictive marker for assessing malignant potential in affected individuals.

The novelty added by manuscript to the already published scientific literature

This article summarizes a synthesis of the most recent international publications on etiological factors and pathogenetic theories, clinical forms, diagnostic methods, therapeutic approaches, and the risk of malignant transformation of oral lichen planus.

Introduction

Oral lichen planus (OLP) is an autoimmune, chronic, inflammatory disease that affects the stratified squamous epithelium of the oral mucosa. Despite being one of the most common conditions of the oral mucosa, the etiology and pathogenesis of OLP remain uncertain. However, scientists consider OLP to be a multifactorial process involving genetic, psychological, and infectious factors, characterized by immune-mediated damage of basal epithelial cells by T lymphocytes [1-3]. The prevalence of the disease in the general population ranges from 0.1% to 4%, most commonly affecting middle-aged patients in the 30-60 age group, with women being more predisposed than men at a ratio of 1.4:1. OLP is rarely diagnosed in children and young adults [1-3]. The condition presents with white reticular lesions (often bilateral), sometimes accompanied by atrophic, erosive, and ulcerative areas, with distinct relapses and remissions. The buccal mucosa, tongue, and gingiva are the most commonly affected areas. Treatment of OLP patients is symptomatic but often yields a limited response. Although the potential for malignant transformation is uncertain, and the degree of associated risk varies, the World Health Organization (WHO) has classified OLP as a potentially malignant disorder [1, 3].

In light of the above, the purpose of this article was to provide a synthesis of the most recent data to update the understanding of the etiology, pathogenesis, epidemiology, clinical presentation, diagnosis, management, and the potential for malignant transformation of OLP.

Materials and methods

To achieve the set objective, an initial search for specialized scientific publications was conducted, and relevant articles were identified using the Google Search engine and from databases including PubMed, Hinari, SpringerLink, National Center of Biotechnology Information, and Medline. The criteria for selecting the articles included contemporary data on OLP using the following keywords: "oral lichen planus," "epidemiology," "etiology," "pathogenesis," "symptoms," "management," "histopathology," "malignant transformation," which were used in various combinations to maximize search yield.

For advanced selection of bibliographic sources, the following filters were applied: full-text articles, articles in the English language, articles published between 1990 and 2023. After a preliminary analysis of titles, original articles, editorials, narrative synthesis, systematic reviews, and meta-analyses were selected, containing relevant information and contemporary concepts regarding the etiology, pathogenesis, epidemiology, clinical presentation, diagnosis, management, and the potential for malignant transformation of OLP. Additionally, a search was conducted in the reference lists of the identified sources to highlight additional relevant publications that were not found during the initial database search.

The information from the publications included in the bibliography was collected, classified, evaluated, and synthesized, highlighting the key aspects of the contemporary understanding of OLP. To minimize the risk of systematic errors (bias) in the study, a thorough search was conducted in the databases to identify a maximum number of relevant publications for the study's purpose. Only studies meeting validity criteria were considered, and secure exclusion criteria were used to remove articles from the study. Both studies showing positive and negative results were analyzed.

When necessary, additional sources of information were consulted to clarify certain concepts. Duplicate publications, articles that did not align with the study's purpose, and those that were inaccessible for full viewing were excluded from the list of publications generated by the search engine.

Results

After processing the information identified through the Google Search engine and from the databases PubMed, Hinari, SpringerLink, National Center of Biotechnology Information, and Medline, following the search criteria, a total of 475 articles related to the topic of ozone therapy were found. After a primary analysis of the titles, 59 articles were potentially relevant for the synthesis. Upon repeated review of these sources, a final selection of 50 relevant publications was made, ultimately included in the bibliography of this work. These 50 articles were consid-

ered representative of the materials published on the subject of this synthesis article.

Publications whose content did not align with the addressed theme, even if selected by the search program, as well as articles that were not accessible for free viewing and not available through HINARI (Health Internet Work Access to Research Initiative) or in the scientific medical library of the Public Institution "Nicolae Testemițanu" State University of Medicine and Pharmacy, were subsequently excluded from the list.

Definition. Oral lichen planus (OLP) is an inflammatory condition characterized by immune-mediated T-cell dysfunction, which can manifest with varying appearances from keratotic to erythematous and ulcerative. OLP is a chronic immune-mediated disease marked by recurrent and repeated relapses and remissions, resistance to treatment, and a potential for malignancy [4-10].

The etiology of OLP is not fully elucidated and is considered multifactorial, remaining controversial. Numerous potential triggering factors are involved in the pathogenesis of OLP, including local and systemic factors related to delayed T-cell-mediated hypersensitivity [1, 4-9, 11-13].

Studies have implicated stress, anxiety, depression, genetic predisposition, pharmaceutical products, dental materials, systemic conditions, and viruses (including hepatitis type C virus - HCV and hepatitis type B virus - HBV) as causal agents, influencing the onset, development, exacerbation, or recurrence of OLP. However, the most notable risk factor is considered to be HCV infection [1, 7, 8, 11-16].

Pathogenesis. Previous studies have found that OLP is an autoimmune, localized disease induced by the dysfunction of T cells with an unknown internal or external predisposing factor. Activated cytotoxic T lymphocytes accumulate in the superficial *lamina propria*, as a band-like infiltrate and release a large quantity of inflammatory mediators, initiating the apoptosis of basal keratinocytes and their vacuolar degeneration. Over time, this leads to basal membrane disturbances and chronicization of the disease. Likely, OLP is a cell-mediated immune cytotoxic reaction to a variety of extrinsic antigens, modified autoantigens, or superantigens [1, 5, 8-10, 12, 17-20].

The pathogenesis of OLP may involve both antigen-specific and non-specific mechanisms. Antigen-specific mechanisms in OLP include antigen presentation by basal keratinocytes and the destruction of antigen-specific keratinocytes by cytotoxic T cells. Superantigens are considered antigens that mediate excessive, non-specific activation of T cells [9].

Accumulated data support the vital role of immunological mechanisms in the pathogenesis of OLP, particularly in the massive production of various cells and inflammatory mediators. It is conceived that the disease results from the complex interaction of host factors, lifestyle, and environmental factors, leading to T cell-mediated immune dysregulation [9, 19, 20].

Epidemiology. OLP most commonly develops in middle-aged and elderly adults of both sexes, with a predominance in women (1.4:1-2.0:1) [1, 4, 5, 14, 16-18, 21]. The exact prevalence and incidence of OLP are not well known and vary significantly. Due to the lack of clear diagnostic criteria, the use of a common methodology in epidemiological studies, and a consensus on the true prevalence of OLP, it remains challenging to determine accurate figures. According to epidemiological studies, the average global prevalence ranges from 1.01% to 1.27%, with variations based on the studied geographical area, ranging from 0.35% to 2.6% [1, 4, 5, 15, 17, 22]. The prevalence also varies from 0.1% to 5.0% in the general population and differs between genders – 0.96% among men and 1.57% among women [4, 11, 17, 23].

In two recent systematic reviews and meta-analyses published in 2020 and 2021, OLP had a global prevalence of 0.89-1.01% among the general population and 0.98% among patients. However, this indicator exhibited significant geographical differences ($p<0.001$). A higher prevalence of OLP was observed in non-Asian countries, among women, and among individuals aged 40 and older [6, 24, 25].

Clinical Presentation. The symptoms of OLP vary depending on the clinical type and the severity of the lesions. Approximately 82% of OLP patients are either asymptomatic or report nonspecific symptoms in the oral cavity, such as roughness, burning or pain, discomfort, irritation, xerostomia, bleeding, and dysgeusia. Symptoms are particularly pronounced when consuming hot or spicy foods, leading to difficulties in chewing, swallowing, and speaking. Over time, red or white patches appear on the oral mucosa, which gradually progress to erosions and ulcers, intensifying the symptoms and causing higher levels of anxiety, depression, and a reduced quality of life [1, 3, 14, 16, 26].

The clinical manifestations of OLP are diverse and polymorphic and can appear in various clinical forms, often associated with each other. This complexity can pose a diagnostic and therapeutic challenge due to its refractory and recurrent nature [4, 8, 16]. The characteristic clinical features of OLP present as white papules that enlarge and coalesce to form a reticular, annular, or plaque-like pattern with or without atrophy or erosion [1, 6, 8, 14, 16, 17, 22, 27].

From a clinical perspective, six distinct types of OLP are emphasized:

• Reticular or typical keratotic form (30% of cases): This is the most common form, characterized by numerous keratotic lines or slightly raised grayish-white streaks that intersect (the so-called Wickham striae), creating a lace-like or reticular pattern. These striae are usually located bilaterally and symmetrically on the buccal mucosa, but they can also be observed on the tongue, less frequently on the gums and lips. This form typically does not cause clinical symptoms and is often detected during routine examinations.

• Plaque form: This form is characterized by homogeneous white patches and may clinically resemble leukoplakia but has a multifocal distribution. The plaques typically have a slightly elevated or smooth, flat surface and are most commonly found on the dorsal surface of the tongue and the buccal mucosa.

• Atrophic (erythematous) or exudative-hyperemic form: This type features the appearance of red patches with very fine white streaks. It can be associated with the erosive or reticular form. The proportion of atrophic and keratinized areas typically varies throughout the affected area. The attached gingiva is most commonly affected with an irregular distribution in quadrants. Clinical symptoms include a burning sensation in the oral cavity, sensitivity, and discomfort.

• Erosive (ulcerative) form: This form may present ulcers at the center of the lesion. The ulcer is typically covered with a white, fibrinous membrane and is surrounded by erythematous mucosa. The disease's progression is dynamic, involving new areas from week to week. White streaks are observed around the ulcer on clinical examination.

• Papular form: This is a rare form that contains small, white, raised, pinpoint-sized papules and may generate fine lace-like patterns.

• Bullous form: This is a rare form; it involves blisters that can range from a few millimeters to several centimeters in diameter. They are present for a short duration, after which they rupture, leaving painful ulcers. These lesions are more commonly found in the area of the third molars. They can also occur, though less frequently, on the tongue, gums, and lip mucosa. The bullous form is typically associated with the reticular form [3, 6, 8, 10, 13, 16, 20, 26-28].

The reticular, papular, and plaque forms of OLP, known as "non-erosive lesions" or "predominantly white forms," are often asymptomatic and are frequently detected incidentally by a dentist [1, 3, 5, 13, 16]. On the other hand, the atrophic/erosive, ulcerative, and bullous lesions, referred to as "erosive lesions" or "predominantly red forms," cause severe symptoms, primarily pain and a burning sensation, limiting food intake and oral hygiene. These symptoms significantly affect oral health-related quality of life, with a substantial impact on overall health, regardless of age and gender. The erosive form is the most severe and recurrent clinical variant, and erosive and bullous forms can transform into ulcerative forms [1, 5, 13, 16, 21, 29].

OLP lesions are typically multiple, bilateral (less commonly unilateral), more or less symmetrical, and can appear solitarily or simultaneously in various combinations, involving the oral mucosa (60-70% of cases), the dorsal surface of the tongue, gums, lower lip mucosa, and palate. According to the results of several studies, the first three locations, which are prone to trauma, are the most common (80-90% of cases), while the floor of the mouth, hard palate, and lip mucosa are rarely affected [2, 3, 8, 10, 20, 26, 28, 30].

OLP is often accompanied by skin lesions or involves other squamous mucous membranes. Approximately 15-20% of OLP patients develop skin lesions, and around 20% have concurrent genital lesions. Among patients with cutaneous lichen planus, OLP lesions occur in up to 60-70% of cases [9, 11, 15-17, 20, 27, 31].

Diagnostics. Because OLP is a condition with malignant potential, early and accurate diagnosis is crucial, allowing for timely and appropriate management and improving the patient's quality of life [1, 16, 29, 32]. However, the diverse clinical presentation and the asymptomatic nature of the most common subtype of OLP make the disease an underdiagnosed health problem [1, 16, 29, 32].

Currently, there are no widely accepted diagnostic criteria for OLP. Diagnosis is based on clinical and histological criteria and includes: (1) detailed medical history and a comprehensive mucocutaneous clinical examination; (2) cytological examination; (3) hematological examination; and (4) biopsy with histopathological and immunofluorescence examination [1, 4, 10, 11, 16, 20, 27, 33]. However, classic OLP lesions (bilateral, reticular, with Wickham striae) can be diagnosed based on clinical appearance alone. The clinical presentation of rarer forms can be significantly different from classic OLP and, therefore, may be challenging to diagnose based solely on clinical examination [1, 16, 20, 27, 33].

Significant changes have been made over the years regarding the diagnosis of OLP. In 1978, the World Health Organization (WHO) developed a set of clinical and histopathological criteria for the diagnosis of this condition. These criteria were typical but nonspecific, and they were not able to distinguish between OLP and oral lichenoid lesions (OLL). In 2003, van der Meij and van der Waal made modifications to these criteria, confirming the absence of epithelial dysplasia in the diagnosis of OLP. The most recent diagnostic approach for OLP was published in 2016 [11]. The authors compared the criteria established by the WHO with those modified by van der Meij and van der Waal. They reported mild to moderate clinicopathological correlation in the definitive diagnosis of OLP and recommended associating clinical and histopathological features for a definitive diagnosis. The latest modified classification is that of the American Academy of Oral and Maxillofacial Pathology (2016), which includes clinical and histopathological characteristics capable of correctly distinguishing OLP from OLL:

• Clinical Criteria: (a) symmetrical multifocal distribution; (b) white and red lesions presenting one or more of the following forms: reticular/papular, atrophic (erythematous), erosive (ulcerative), plaque-like, vesicular; (c) lesions are not exclusively located in places where smokeless tobacco products are placed; adjacent and in contact with dental restorations; (d) the onset of lesions does not correlate with the initiation of treatment with a medication or the use of products containing cinnamon.

• Histopathological Criteria: (a) predominantly lymphocytic infiltrate in a band-like or irregular pattern in the *lamina propria* limited to the epithelium - *lamina propria* interface; (b) hydropic degeneration of basal cells; (c) lymphocytic exocytosis; (d) absence of epithelial dysplasia; (e) absence of architectural changes in the verrucous epithelium [10-12, 16, 22].

Therefore, marginal tissue biopsy, including both lesions and areas with a normal appearance, is considered the "gold standard" for diagnosing OLP. The histopathological features of OLP are characteristic and consist of epithelial

hyperkeratosis, hydropic or vacuolar degeneration of basal epithelial cells, atrophy, or "sawtooth" acanthosis of spinous epithelial cells, a homogenous eosinophilic deposit at the junction between connective tissue and epithelium, band-like lymphocytic infiltrate in the superficial *lamina propria*, apoptotic keratinocytes in the lower epithelial layer with the formation of colloid or civatte bodies [1, 8, 9, 11, 12, 17, 20, 27, 34-36].

Direct immunofluorescence examination of tissue in cases of OLP demonstrates the deposition of fibrinogen along the basal membrane zone (at the mucosa-submucosa interface) in 90-100% of cases. At the level of civatte bodies, the method highlights the presence of granular fluorescent deposits containing IgA, IgG, and IgM. Indirect immunofluorescence examination detects anti-basal cell antibodies [1, 11, 12, 20, 24, 35, 36].

So, the diagnosis of OLP is based on clinical characteristics, histopathological findings, and immunological data [8, 33, 37]. The most widely accepted histopathological features of OLP are three, which should be present concurrently:

• Chronic cellular inflammatory subepithelial infiltration, limited to the surface of the connective tissue, in a dense and well-defined "band-like" pattern, predominantly composed of lymphocytes.

• Hydropic degeneration of the basal layer of keratinocytes (basal epithelium), forming colloid bodies (Civatte).

• Absence of dysplasia in the epithelial layer [1, 5, 8, 9, 20, 26, 27, 30, 37].

The differential diagnosis of reticular OLP includes leukoplakia, oral lichenoid lesions (OLL), and discoid lupus. The differential diagnosis of erosive OLP includes the following conditions in the oral cavity: cheek chewing or biting (*morsicatio buccarum*), hypersensitivity mucositis, OLL, chronic oral candidiasis, oral squamous cell carcinoma (OSCC), benign pemphigus, pemphigus vulgaris, and systemic diseases (discoid lupus erythematosus, erythema multiforme). Differential diagnosis of OLP from other diseases is particularly challenging in non-reticular forms, which often require biopsy with histopathological examination and immunofluorescence testing. [1, 8, 33, 34, 38, 39].

Management. In patients with non-erosive lesions (reticular, papular, or plaque-like) with typical clinical manifestations (bilateral and symmetrical lesions), a biopsy to confirm the clinical diagnosis is not obligatory. In the case of erosive lesions (atrophy/erosion, ulcerative, or bullous), a biopsy is necessary, especially for lesions with suspected dysplastic changes or malignant transformation.

The management of OLP includes: (1) Establishing the diagnosis based on medical history, clinical examination, and comprehensive tests – histopathological examination, direct and indirect immunofluorescence tests; (2) Informing the patient about the condition – a chronic, recurrent disease with periods of exacerbation and remission; (3) Treatment; (4) Long-term periodic monitoring to detect early dysplastic and malignant transformation changes.

Currently, a wide range of therapeutic options is available for the management of OLP, but none of them are curative [1, 6, 10, 19, 20, 33, 40-42]. Due to the unknown etiology, the therapeutic approach to OLP is symptomatic, depending on the type of lesion, associated symptoms, clinical presentation, the extent of the disease, and potential side effects of medications. The primary goals of OLP treatment are to alleviate discomfort and stress through patient education and oral hygiene measures, eliminate local irritating or aggravating factors in the oral cavity, alleviate distressing symptoms, reduce inflammation, expedite and extend periods of remission, and decrease the risk of malignant transformation [1, 2, 10-12, 17, 20, 27, 33, 35, 41-43].

Patients with asymptomatic non-erosive lesions do not require immediate treatment unless they become inflamed, ulcerated, or painful, but regular monitoring is necessary. Patients with symptomatic erosive forms require immediate and effective drug treatment to alleviate the clinical picture and improve the quality of life of the patients. According to the data in the literature, up to 20% of OLP lesions can spontaneously regress without treatment [1, 2, 10-12, 17, 20, 27, 35, 41-44]. Since OLP is an immunologically mediated condition, the drugs of choice for treatment are corticosteroids, administered topically, intralesionally, or systemically, followed by topical calcineurin inhibitors, and, if necessary or prophylactically, antifungal agents. Resistant lesions require systemic therapy with corticosteroids or immunosuppressants [1, 4-6, 8, 10, 11, 17, 19, 20, 23, 27, 30, 35, 36, 41, 45].

The management of OLP includes: (1) Pharmacological treatment: inflammatory/symptomatic therapy with topical, intralesional, or systemic corticosteroids; topical calcineurin inhibitors (immunosuppressants); topical or systemic retinoids (immunomodulators); immunosuppressants like azathioprine and methotrexate, and lycopene (an antioxidant); (2) non-pharmacological treatment: this may involve phototherapy with ultraviolet rays, photodynamic therapy, and laser therapy; (3) surgical excision: this is recommended for patients with isolated, persistent, or treatment-resistant erosions. However, it's important to note that therapeutic outcomes are often disappointing [1, 2, 6, 10, 12, 19, 20, 27, 30, 33, 35, 41, 43, 45].

Eliminating predisposing factors and maintaining meticulous oral hygiene are necessary to prevent recurrences. Additionally, continuous clinical monitoring of patients with OLP is required to assess therapeutic responses and any changes in the appearance of lesions [11, 12, 30].

Prognosis. One of the most significant concerns regarding OLP is its increased potential for malignant transformation into OSCC [22, 32]. Previous studies have found that if there is a risk, it is very difficult to quantify it, possibly so low that it's challenging to determine if OLP is genuinely associated with a significant risk of malignant transformation [22, 32]. Regardless of the incidence of malignant transformation, in 1978, the WHO defined OLP as a "potentially malignant disorder," representing a generalized condition with a significantly increased risk of OSCC [22, 28, 32].

The hypothesis for the relationship between OLP and OSCC is chronic inflammation, which over time contributes

to the formation of critical DNA lesions leading to the development of OSCC [46].

Previous prospective and retrospective studies have found a potential for malignant transformation of OLP ranging from 0.07% to 6.5% over observation periods ranging from 0.5 to 22 years [3, 5, 22, 28]. According to WHO data, this figure varies from 0.4% to 12.5%, with an average rate of 1.09% [11, 15, 16, 23, 27, 30, 34, 47].

According to the results of a systematic literature review published in 2016, which evaluated data from 38 studies between 1995 and 2014 with a total of 16,032 cases of OLP, the rate of malignant transformation of the condition varied from 0% to 5.8% [48]. According to the results of six recent systematic reviews and meta-analyses and a study published in 2023, which evaluated data from eight systematic reviews published between 2014 and 2023, the rate of malignant transformation of OLP ranged from 0.44% to 1.4% [22, 49, 50]. A meta-analysis based on 10 high-quality studies highlighted a higher proportion of malignant transformation (2.28%) [49]. The highest prevalence of malignant transformation was reported in the erosive, atrophic, and ulcerative subtypes of OLP, which involve the hard palate, tongue, labial mucosa, and gingiva [1, 5, 6, 16, 22, 46]. Given the consistent evidence of the risk of oral malignancy, patients with OLP should be carefully monitored for the early development of OSCC [32, 49].

Therefore, OLP is a potentially malignant condition with a rate of malignant transformation ranging from 0% to 12.5% depending on the follow-up period. Studies have listed the following risk factors for the malignant transformation of OLP: lesion localization on the tongue, the red type (atrophic or erosive form), tobacco and alcohol consumption, and HCV [22, 46, 47]. The wide range of OLP malignant transformation rates obtained in these analyses can be attributed to differences in the diagnostic criteria used, the average follow-up periods, and the number of cases evaluated [48].

Conclusions

1. OLP is a chronic inflammatory condition with periods of remission and relapse, harboring a malignant potential, and most likely being a result of a cell-mediated reaction to a variety of extrinsic antigens, modified autoantigens, or superantigens. Both the etiology and pathogenesis of this disease are complex and incompletely understood, necessitating further research, especially due to the risk of malignant transformation.

2. The diagnosis of OLP is based on clinical characteristics, histopathological results, and immunological data:

- Clinical criteria: (a) multifocal symmetric distribution; (b) white and red lesions that exhibit one or more of the following forms: reticular/papular, atrophic (erythematous), erosive (ulcerative), plaque-like, bullous; (c) lesions are not exclusively localized in the sites of smokeless tobacco placement; adjacent to and in contact with dental restorations; (d) the onset of lesions does not correlate with the initiation of treatment with a drug or the use of products containing cinnamon.
- Histopathological criteria: (a) predominantly band-like or irregular lymphocytic infiltrate in the *lamina propria* limited to the epithelium - *lamina propria* interface; (b) hydropic degeneration of basal cells; (c) lymphocytic exocytosis; (d) absence of epithelial dysplasia; (e) absence of architectural changes in verrucous epithelium.

3. The management of OLP includes: (1) pharmacological treatment: anti-inflammatory/symptomatic therapy (topical, intralesional, or systemic corticosteroids), topical calcineurin inhibitors (immunosuppressants), topical or systemic retinoids (immunomodulators), immunosuppressants (azathioprine, methotrexate), lycopene (antioxidant); (2) non-pharmacological treatment: ultraviolet phototherapy, photodynamic therapy, and laser therapy; (3) surgical excision, recommended for patients with isolated and persistent OLP erosions resistant to conservative treatment.

4. The elimination of predisposing factors and maintaining meticulous oral hygiene are necessary for preventing relapses, and continuous clinical monitoring of patients with OLP is required to monitor therapeutic responses and any changes in lesion appearance.

Competing interests

None declared.

Ethical statement

No approval was required for this study.

Authors' contribution

The authors contributed equally to the research of the scientific literature, the selection of the bibliography, the reading, and analysis of biographical references, the writing of the manuscript and its peer review. All authors have read and approved the final version of the article.

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CASE STUDY

Obstetrical anesthesia for a patient with multiple sclerosis: case report and literature review

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ABSTRACT

Introduction. Multiple sclerosis is an autoimmune disease characterized by chronic inflammation with progressive demyelination and axonal dysfunction. The disease affects about 1 million young adults, 2/3 of which are women of childbearing age, with all patients develop irreversible neurological dysfunction. There is observed a stagnation of the disease during pregnancy, with the return of exacerbations in the postpartum period. Contemporary specialty textbooks neither confirm nor deny the safety of neuraxial anesthesia in patients with central nervous system diseases.

Clinical case. We present the clinical case of a 25-year-old nullipara pregnant (36 weeks and 6 days gestation age), known with relapsing-remitting multiple sclerosis and epilepsy. The woman has relapsing multiple sclerosis symptoms during last 6 days, reason why is urgently consulted by the anesthesiologist for cesarean delivery.

Management and outcome. The article describes the technique of epidural anesthesia for the obstetrical patient with multiple sclerosis and the course of the perianesthetic evolution, including 1-year follow-up after cesarean section.

Discussions. With the aim of avoiding potential influences on the evolution and progression of the disease, clinical judgment and the choice of anesthetic technique (general vs. neuraxial) depends on several factors: vaginal delivery or caesarean section, the presence of contextual clinical modifiers (native or drug-induced coagulopathy, infection), the urgency of the intervention, and the patient's cooperation. In case of parturients with multiple sclerosis, all the risks should be rigorously evaluated: on one hand - the additional risk of general anesthesia (risk of aspiration, potential loss of airway control, critical desaturations) and on the other hand - the risk of hypothetical local anesthetic toxicity in the case of neuraxial techniques.

Conclusion. Neuraxial epidural anesthesia is a safe technique in obstetric patients with multiple sclerosis.

Keywords: multiple sclerosis, epidural anesthesia, cesarian delivery, high-risk pregnancy.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Given the fact that multiple sclerosis is a rare disease, there are limited studies describing anesthetic techniques for the obstetric patient with this illness. Also, of special interest is the interrelation between the type of anesthesia and episodes of postpartum recurrences.

The research hypothesis

Using epidural analgesia and anesthesia at the minimum effective concentration can minimize any potential risks of local anesthetic to cross into the cerebrospinal fluid, linked to potential worsening of multiple sclerosis.

The novelty added by the manuscript to the already published scientific literature

The article provides anesthesiology and intensive care specialists with an up-to-date literature review of the perianesthetic management in obstetrical patient with multiple sclerosis, following a case of epidural anesthesia for cesarean section delivery in a patient with multiple sclerosis, providing prospectively the evolution of the disease up to 1 year post-anesthesia.

Introduction

Multiple sclerosis (MS) is a chronic multifocal inflammatory autoimmune disease of the central nervous system, which, through demyelination of the white matter, can lead to considerable disability. It is the most common cause of neurological disability in young adults worldwide, with half of those affected living in Europe [1-3].

According to a national neuroepidemiological study, the prevalence of multiple sclerosis in the Republic of Moldova is 21 cases per 100,000 inhabitants, of which 63.5% are female (average age 42.1±11.9 years old) and 36.5% male (average age 40.8±12.8 years old) [2]. The latest data from the Multiple Sclerosis International Federation Atlas (MSIF) reports an increase in the number of people diagnosed with MS as follows: 2.1 million in 2008, 2.3 million in 2013 and 2.8 million in 2020, with an increased prevalence in women, featuring a female/male ratio of 2:1 [4]. The disease onset could happen at any age, but it often occurs in the second or third decade of life, affecting those of reproductive age [1, 5].

The etiology of MS is multifactorial, involving targeting of the genetic predisposition by a series of environmental (temperate zone) and occupational factors. Thus, a six times higher prevalence of MS was found in monozygotic twins compared to dizygotic twins [1, 5]. Indeed, the human leukocyte antigen (HLA) gene cluster, located on chromosome 6p21, has been identified as the most likely locus of genetic predisposition to MS [2].

The clinical course of MS is marked by periodic subacute symptoms (vague or specific), with exacerbations and remissions, with 4 distinguished patterns of disease evolution: relapsing-remitting, secondary progressive, primary progressive, progressive relapsing [1, 3]. The frequency of MS exacerbations is variable, with an average of 0.4 attacks per year. In general, relapses consist of reinstatement of previously observed neurological deficits (bulbar, cerebellar, and pyramidal) [1].

The pathophysiology of MS involves a functional autoimmune imbalance between CD4+ lymphocytes, known as T-helper type 1 (Th1) and T-helper type 2 (Th2). Thus, an exaggerated response of Th1, which secretes pro-inflammatory cytokines (IFN-gamma, IL 2 and TNF-alpha), and an attenuated response of Th2 lymphocytes, responsible for the production of anti-inflammatory cytokines (IL 4, 5, 10, 13) [1]. Penetration of the blood-brain barrier by activated T-helpers leads to edema and chronic inflammation, with demyelination and axonal dysfunction. During pregnancy, humoral immunity takes over cellular immunity, so that in the MS patient, pregnancy can temporarily correct the autoimmune imbalance between Th1 and Th2. In the postpartum period, with the reversal of hormonal changes, there is a return to the autoimmune balance existing before conception, with the exacerbation of the Th1 immune response and the decrease of the Th2 mediated immune response [1].

Over time, there have always been precautions regarding subarachnoid anesthesia in patients with MS, due to the exposure of demyelinated areas of the spinal cord to local anesthetics, with potential neurotoxic effects [1, 6].

Currently, the specialty literature neither confirms nor refutes the safety of neuraxial anesthesia in patients with central nervous system diseases, nor is the relative safety of spinal anesthesia versus epidural anesthesia/analgesia in patients with MS defined [1, 7, 8].

The purpose of the article is to present the perianesthetic management of the parturient with MS for cesarean delivery and an updated literature review.

Clinical case

Patients' description. Nullipara (first pregnancy, occurred spontaneously, 36 weeks and 6 days gestation age), 25 years old (1.57 m, 85 kg, weight gain during pregnancy 15 kg) is referred by the obstetrician-gynecologist to the preanesthetic consultation for urgent cesarean delivery.

Disease history. At 24 weeks gestational age, the nullipara patient (amenorrhea since 04.05.2022) registers for pregnancy monitoring and childbirth at Medpark International Hospital. The patient was consulted and added to the hospital records, assigned as a"high-risk pregnancy". In recent years, the pregnant woman has been in the records of many other medical specialists: epileptologist, neurologist, ophthalmologist, and traumatologist.

The patient was definitively, clinically, through imaging, diagnosed with relapsing-remitting MS, with a patient disability score of 2.0 points (The Expanded Disability Status Scale, EDSS), and has been registered in the official records of the neurologist since 2015. MS relapses were documented in 2018 and in February and June of 2021, when specific treatments were initiated. At the same time, since 2015 the primipara has been known to have idiopathic epilepsy (chronic treatment with Depakin Chrono® 250 mg in the morning and 500 mg in the evening), the last episode of seizures occurring 2 years ago.

At the 12-week gestational period, she is consulted by an epileptologist, who recommends continuing the anticonvulsant treatment and re-evaluation at the 32-week gestational age. Additionally, the patient is being monitored by the ophthalmologist for astigmatism, partial atrophy of the optic nerve on the right, decreased bilaterally visual acuity, bilateral amblyopia (more on the right side). The trauma-

tologist-orthopedic doctor monitors the patient for grade I-II scoliosis. Patient denies any family history of MS. Occupation: housewife. Balanced diet. Predominantly sedentary lifestyle.

The patient presents to the consultation of the obstetrician-gynecologist at the 30-week gestational age, showing a physiological progression of the pregnancy, all together with remission of the primary disease. At this term, the ophthalmologist documents the decrease of visual distance acuity (RE > LE). Biomicroscopy and fundus examination: normal.

Later, at 36 weeks gestational age the patient complains of left face paresthesias, with an insidious onset over a few days, accompanied by burning left periocular pain, paresthesias of the upper and lower limb on the left. The neurologist indicates the administration of corticosteroids (dexamethasone 4 mg/1 ml once a day) for 7 days, with improvement of symptoms. Thus, the patient is admitted for the completion of the pregnancy related to the exacerbation of MS.

The neurological examination on the day of the caesarean section revealed hypoesthesia of the left hemiface, with trigeminal neuralgia on the left. Overall, the neurological examination was normal: round symmetrical photoreactive pupils (R = L), bilaterally preserved convergence, absent nystagmus. Symmetrical face, Marinescu symptom absent bilaterally, tongue located medially. Weber test without lateralization. Vivid palatal and pharyngeal veil reflexes. Negative Chwosteck sign. Normal symmetrical upper limbs osteotendinous reflexes (R = L); of the lower limbs, normal patellar and Achilles reflexes (R = L). Negative stretch marks. Negative meningeal signs. Absent pathological signs. Normotonus. Deep sensitivity preserved. Cerebellar tests done right. Stable Romberg position, heel-knee test within normal limits. Muscle strength 5/5. It is recommended to continue the antiepileptic treatment and monitor the neurological symptoms, and in case of clinical worsening of MS, quantified as deterioration by 0.5 points according to the EDSS, the initiation of pulse therapy with methylprednisolone.

Given that the ongoing pregnancy on the background of MS exacerbation may have the potential to cause fetal distress, the decision was made to deliver the baby by caesarean section, requesting the urgent consultation of the anesthesiologist doctor.

The paraclinical examination. The ultrasound examination in the third trimester of pregnancy (17.01.23) reveals an ongoing monofetal pregnancy, which sonographically corresponds to 38 weeks and 0 days of amenorrhea, with fetal morphology and functional status within normal limits. Posterior-fundal placenta, nonprevia, normal volume of amniotic fluid for the given gestational age. Estimated weight of the fetus 3319±200 gr.

Complete blood count and coagulations tests (17.01.23) within reference range for the patient in the third trimester of pregnancy. Blood group A (II) positive, Kell negative.

Hemodynamics: blood pressure (BP) 110/96 mmHg, sinus rhythm with heart rate (HR) at 81 b/min. Monitoring parameters of the fetal heartbeats within normal limits.

The challenge was determined by the choice of the type of anesthesia for the given clinical case of MS evolution, in an effort to avoid the contribution of the chosen anesthetic technique to a probable deepening of MS relapse. Although few, there are clinical trials describing the safety of both general anesthesia and neuraxial anesthetic techniques for patients with MS [1, 6, 7].

At pre-anesthetic consultation, the patient was categorized as a "patient with a full stomach and potential risk of aspiration" (she had lunch only 3 hours ago), with necessity of a waiting time of 8 hours from the last meal, in order to evacuate the gastric content. However, the caution that the obstetric patient is considered *a priori* "full stomach patients" persisted throughout the perioperative period. According to the American Society of Anesthesiologists (ASA), the patient was assigned with ASA III-E risk, without predictive signs for difficult airways (mouth opening 4 cm; thyro-mentionary distance 6.5 cm; Mallampati II, no nuchal stiffness or limitations of movements in the temporomandibular or cervical flexion-extension joint), without known drug allergy. Overall, a favorable prognosis was issued.

In a sitting position, using sterile technique and under the protection of local anesthesia (infiltration of the skin with lidocaine 2%/ 2 ml), the epidural space was approached at L3-L4 level (one attempt, G 18 Tuohy), median line, by the technique of loss of resistance to 0.9% saline solution. Epidural space located at a distance of 4.0 cm from the skin. Catheter advanced without technical difficulties, secured to the skin at the 9.0 cm mark. Negative aspiration test for reflux of cerebrospinal fluid. Negative test dose (lidocaine 2%/ 3ml + adrenaline 1:200000), absent motor block. Sterile dressing applied. Dorsal recumbence with tilting to the left.

An 11 ml volume of mixture (10 ml ropivacaine 0.75% 10 ml with 1 ml fentanyl 50 mcg) was initially administered, incrementally (in boluses of 5.5 ml each). It was evaluated a symmetric Th10 level (iliac cristae) thermal sensitive block at 9 minutes after administration, with stable hemodynamics (BP 107/ 53 mmHg). For the decompression of the inferior vena cava, the patient was placed on left-lateral tilt of 15º by placing a roll under the right lower back. Later, 3 ml of ropivacaine 0.75% were added in the epidural space, with thermal sensitive block up to Th7 after 5 minutes. At the pain sensitivity test in the presumed area of the incision – patient complained of discomfort, with the decision to add 2 ml of ropivacaine 0.75% and the request from the obstetrical operative team for a waiting time of at least 5 more minutes for the onset of effective epidural anesthesia. Bromage 4 motor block. The incision was made 19 minutes after the administration of the first epidural bolus, with no complaints of pain (numerical rating score (NRS) 0/10) or discomfort.

The patient presented to the operating room with BP 121/52 mmHg and HR 100 b/min. After epidural placement and incremental epidural administration of local anesthetic, there was a tendency to hypotension associated with sympatholysis. The lowest BP value was 103/46 mmHg (at total

epidural volume: 13 ml ropivacaine 0.75% + 1 ml fentanyl 50 mcg, 14 minutes after the first bolus), with a mean BP ≥ 65 mmHg and no maternal bradycardia. Intraanesthetic maternal HR varied between 100 and 87 b/min. The patient's highest blood pressure values were recorded upon admission to the operating room and at the time of first cry of the baby (BP 122/53 mmHg). Overall, no vasoactive support was required to maintain hemodynamics. On transfer from operating room to recovery room, BP 116/66 mmHg with HR 86 b/min. In the recovery room, multiparametric monitoring was initiated (including uterine tone and vaginal secretions) for 2 hours. The epidural catheter was removed before discharge from the recovery room to ward. The anticoagulant (enoxaparin 4000U) was administered 8 hours later.

The sensory and motor sensitivity of the right lower limb was restored at 2.5 hours postanesthesia, of the left lower limb restored at 4 hours postanesthesia. NRS was monitored at 2, 6, 12 and 24 hours postoperatively, with variations between 0-3/10 (maximum intensities associated with mobilization).

Discussions

MS symptomatology include vague (headache, fatigue, depression) or specific symptoms: sensory (paresthesias, numbness of the limbs) or motor (partial paralysis of the lower limbs, certain proof of anterior spinal cord horn lesion). Decreased visual acuity, diplopia, nystagmus, and optic nerve papilla abnormalities reflect cranial nerve involvement [7]. MS is a clinical diagnosis, and nuclear magnetic resonance not only assesses disease progression, but can definitively confirm the clinical diagnosis [1, 3, 7], detecting multifocal demyelination even when it is clinically silent [7]. Lumbar puncture and cerebrospinal fluid sampling demonstrate the production of intrathecal immunoglobulins [7, 9]. At the same time, a series of other diseases can coexist with MS or, until the definitive diagnosis of MS; infections, vitamin B12 deficiency, sarcoidosis, vasculitis, spinocerebellar degeneration, or leukodystrophy must be excluded [1]. The patient in current clinical case had a confirmed diagnosis (clinical and imaging), including lumbar puncture, being in the records of the neurologist.

Although there is no specific treatment for MS, there are a number of treatments that modify the course of the disease, slowing down its progression. For example, destructive antibodies detected during periods of exacerbation can be removed by plasmapheresis. In addition, the administration of corticosteroids accelerates recovery [5, 9]. Glatiramer acetate and interferons-beta have the ability to block antigen presentation, reducing relapses. Antineoplastic medication (mitoxantrone) reduces the number of lymphocytes, with the idea of delaying the progression towards the secondary degenerative phase of the disease [5, 9]. From the moment of MS diagnosis establishing, the presented patient has needed to continuously administer anticonvulsant (Depakin) and intermittent corticosteroids at the occurrence of recurrences (4 recurrences during 7 years, pregnancy inclusively).

Regarding the choice of anesthetic technique for obstetrical patients with MS, a rigorous documentation of pre-existing neurological deficits is necessary. Particular attention will be paid to the implications of the respiratory system: the ability to cough, expectorate secretions, and ensure sufficient respiratory volumes [1, 5, 7, 10]. Reduced motor tone, with involvement of the cervical spinal cord can be associated with diaphragmatic paralysis and the necessity of functional respiratory tests [10].

From the point of view of general anesthesia as an option for the patient with MS, the patient has preserved ability to protect her airway through the cough reflex and expectoration of secretions, as well as the achievement of a forced breathing, were analyzed, confirmed, and documented. The exclusion of bulbar involvement was imperative, given the fact that the presented patient had involvement of the cranial nerves (optic (II), trigeminal (V)). At the same time, a difficult airway was not anticipated.

Regardless of the type of anesthesia selected, it is important to mention that the patient with advanced MS may present autonomic nervous system dysfunction, with the need for rigorous monitoring and control of perioperative hemodynamics [1, 11], with poor responsiveness to volume repletion and vasopressors [10].

The patient's chronic medication was also analyzed. Thus, long-term corticosteroid therapy or recent high doses of corticosteroids may require the administration of an additional stress dose of steroids [1, 7, 10]. In the clinical case presented by our team, this was not necessary, postoperatively only 8 mg of dexamethasone (diluted with 0.9% saline solution up to a volume of 20 ml) was administered slowly intravenously, to prolong the analgesic effect of the echo-guided block of transverse abdominal plane. At the same time, long-term corticosteroids' administration may be associated with muscle exhaustion and osteoporosis, which imply increased risks of injuries related to positioning on the operating table [10].

During the preanesthetic clinical examination, our patient did not present spasticity and denied taking baclofen in the past. Baclofen treatment is known to be associated with prolonged muscle weakness after the administration of muscle relaxants used for induction in general anesthesia [1, 7]. At the same time, the presence of spasticity would have required the avoidance of the depolarizing muscle relaxant (succinylcholine) during orotracheal intubation, due to the potential of inducing severe hyperkalemia with lethal risk [1].

Over time, the optimal anesthesia technique for delivery in pregnant women with MS has been a controversial topic. Initially, general anesthesia was considered the safest method [1, 7, 12], with no preference for the molecule (inhaled vs. intravenous), except for nitrous oxide, which, due to vitamin B12 inhibition and potential for myopathy, is avoided [10]. On the contrary, succinylcholine is contraindicated, due to the denervation zones, with increased population of acetylcholine receptors and risk of hyperkalemia. At the same time, the upregulation of acetylcholine recep-

tors creates conditions for resistance to non-depolarizing muscle relaxants, requiring titration of increased doses and mandatory neuromuscular block monitoring. Locoregional techniques were avoided because of the potential neurotoxic effect of local anesthetics linked with perineural administration, neuronal ischemia, or presumed direct trauma [1, 13]. However, neuraxial anesthesia gives the mother the opportunity to see the baby immediately after the delivery and to benefit from clearly superior pain control in the immediate postoperative period.

The literature reports clinical cases where parturient with MS benefited from spinal anesthesia, without MS exacerbation [11, 13]. At the same time, MS can be exacerbated by emotional stress, trauma, surgery, fluid-electrolyte imbalance, fever, or infection [12]. Above all, in order to avoid litigation, in case of finding the pre-existing neurological deficit in a parturient with MS, there still exists a tendency to prioritize general anesthesia [6]. The 2014 consensus recommends that the decision to practice spinal anesthesia for pregnant women with MS should be an individualized decision within the limits of the given contextual clinical case [14].

Regarding neuraxial techniques, the patient was warned about hypothetical technical difficulties related to the presence of grade I-II scoliosis. Taking into account the patient's normosthenic constitution, after lumbar spine inspection and palpation, the degree of suspicion for possible technical difficulties associated with neuraxial approach was reduced, but these, however, could not be totally excluded. Several clinical contextual modifiers were in favor of neuraxial anesthesia: the absence of native coagulopathy, the absence of drug-induced hypocoagulation, the absence of infection at the puncture site, the patient's psychoemotional stability, and cooperation, as well as the "delayed emergency" status of the intervention. In order to avoid the theoretical risk of local anesthetics neurotoxicity on the demyelinated regions of the nerves (located in the subarachnoid space) during spinal anesthesia, epidural anesthesia was chosen. In addition, in the case of epidural anesthesia, the hemodynamic response is milder compared to spinal anesthesia.

To avoid hypothermia, a temperature of 26ºC is maintained in the cesarean operating room, with monitoring of patients' temperature. In case of MS, hyperpyrexia, including an increase in body temperature by only 0.5ºC may contribute to temporary deterioration of neurological function [10]. Infusions were administered at room temperature, and 1 g of acetaminophen, a drug also known as an antipyretic, was administered intravenously every 6 hours as part of multimodal analgesia.

Regarding the initially asymmetrical restoration of the lower limbs sensitivity, it could be due to the potentially demyelinated sectors on the left hand (the patient previously described an episode of recurrence on the left). On the other hand, the explanation could lie in the lateralization of the epidural catheter.

All pregnant women benefit from mechanical and pharmacological prophylaxis of deep vein thrombosis. Due to muscle weakness and the prolonged time until first mobilization, pregnant women with MS may have additional risk for deep vein thrombosis. Although the patient from our case had no motor deficit, given the nocturnal intervention, she was assisted out of bed only in the morning.

Pasto's study found no correlation between epidural analgesia or cesarean delivery and postpartum MS recurrences [15]. Therefore, these procedures can be safely applied to MS patients. The same study reports the relationship between postpartum recurrences and significant remote disability, which necessitates the need for postpartum preventive therapies. Moreover, women who reported recurrences of MS also had a higher disability score preconception, as well as episodes of exacerbations in the year preceding the conception of the child.

The PRIMS (Pregnancy and Multiple Sclerosis) European multicenter study monitored 254 women with MS from the gestational period up to 1 year after delivery. Of the 42 women who received epidural analgesia for vaginal childbirth, compared with 180 women with MS who delivered vaginal without analgesia, no differences were found in the prevalence of MS exacerbation [16].

Contacted 1 year after childbirth, our patient reported no recurrence episodes. However, on the recommendation of the neurologist, starting with 3 months after delivery she doubled the anticonvulsant doses.

According to studies, the prevalence of complications in pregnant women with MS does not exceed that observed in healthy obstetrical population. This statement is also valid regarding for the prevalence of complications in newborns, which shows no additional risks such as low birth weight, premature birth, malformations or sudden death of the newborn [1, 13, 17, 18]. Pregnant women with MS need to be rigorously monitored postpartum, having a slightly longer hospital stay, which is not necessarily associated with an increased prevalence of cesarean sections [18]. In addition, a prospective study of 201 women reports modest protective effects of breastfeeding against MS postpartum relapses [19].

Conclusions

The pregnant woman with MS needs multidisciplinary approach: obstetrician, neurologist, anesthesiologist and intensive care specialists.

The preanesthetic examination of the patient with MS should include thorough documentation of preexisting neurological deficits, assessment of respiratory system involvement, autonomic nervous system dysfunction, and analysis of potential MS chronic medication interactions.

The clinical judgment regarding the anesthetic tactics and selection of the drug molecules for delivery will be made through the prism of risks and benefits for each individual parturient, depending on the neurological examination, the clinical background, the anesthesiologist's experience, but also the patient's preference.

Beyond routine monitoring, intraoperative neuromuscular and body temperature monitoring are mandatory for the MS patient.

MS recurrences in the postpartum period do not depend on the anesthetic technique selected or the method of pregnancy solving, correlating more with recurrences in the immediate preconception year.

Authors' contribution

All listed authors have provided a significant contribution to the collecting of material and writing this article. All authors approved the final version of the manuscript.

Informed consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

None declared.

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CASE STUDY

Single visit indirect pulp capping with Biodentine: clinical case report

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ABSTRACT

Introduction. Dental caries is the most widespread dental disease worldwide; it affects population of different ages. If not treated promptly or addressed improperly, dental caries progresses in a deep cavity, with potential signs of pulp inflammation. The minimal invasive principles of treatment of deep carious lesions provide guidelines for the preservation of the dental pulp, techniques known as vital pulp therapies. Among these techniques, indirect pulp capping is a method that has shown high clinical rates of success over time, if performed properly. The applied bioactive dental material plays an important role. The aim of this clinical case report is to describe a clinical case of single-visit indirect pulp capping with Biodentine, along with the algorithm of diagnosis of the pulp health status and treatment used in deep caries lesion in a permanent tooth.

Materials and methods. Description of a clinical case of a permanent upper molar with a deep carious lesion, treated by single-visit indirect pulp capping with Biodentine. Clinical and radiological methods of investigations were used; the patient was assessed after 3 and 6 months after the applied treatment.

Results. The main complaint of sensitivity to sweet stimuli presented by the patient attenuated shortly after receiving the treatment. After 3 and 6 months, the tooth is asymptomatic; the clinical and radiological findings show no evidence of pulp inflammation.

Conclusions. Biodentine showed successful results when used as a bioactive dental material for indirect pulp capping.

Keywords: deep carious lesion, indirect pulp capping, pulp-dentine complex, Biodentine.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Indirect pulp capping in permanent teeth affected by caries is a method of election when trying to keep the tooth's vitality. The dilemma of whether to completely remove the affected dentine or to keep a thin layer over the pulp is still debated among researchers and clinicians.

The research hypothesis

Keeping a thin layer of affected dentine over the pulp in deep carious lesions, along with the placement of a bioactive material over it, can improve the clinical success of the indirect pulp capping technique.

The novelty added by the manuscript to the scientific literature

A case involving a moderately deep caries in a permanent upper molar is presented, detailing its clinical and radiological manifestations, as well as the modified treatment protocol with Biodentine.

Introduction

Indirect pulp capping (IPC) is defined as a biological treatment method, which consists of the application of a bioactive material over a thin layer of remaining dentine after the excavation of carious tissues, without exposing the pulp. This treatment method aims primarily to protect the odontoblasts of the dental pulp and to promote the formation of reactive dentine at the pulp-dentinal junction [1]. It is also the most conservative method within the concept of vital pulp therapy (VPT), a series of treatment methods that aims to preserve and maintain pulp tissue in a healthy state that has been compromised but not destroyed by caries, trauma, or restorative procedures [2]. In our case report we used the technique of indirect pulp capping, a method that involves placing a bioactive dental material – Biodentine, onto a thin layer of affected dentine, without exposure of the pulp.

Biodentine (Septodont, France) is a calcium silicate hydraulic cement created as a dentine replacement material and specifically designed for vital dental pulp therapy. It has been commercially available since 2009 and it is based on tricalcium silicate. Its aqueous component includes reaction accelerators; thus, it classifies into type 4 hydraulic cements, according to the Camilleri classification [3]. Biodentine's form of presentation consists of a powder in a capsule and a liquid in an ampoule, as shown in figure 1. The manufacturer recommends adding 5 drops of liquid from the ampoule to the powder in the capsule prior to mixing. Then, the capsule is inserted in the amalgamator and mixed at 4500 rpm for 30 seconds in order to obtain a homogeneous texture, which is immediately inserted into the prepared cavity [3].

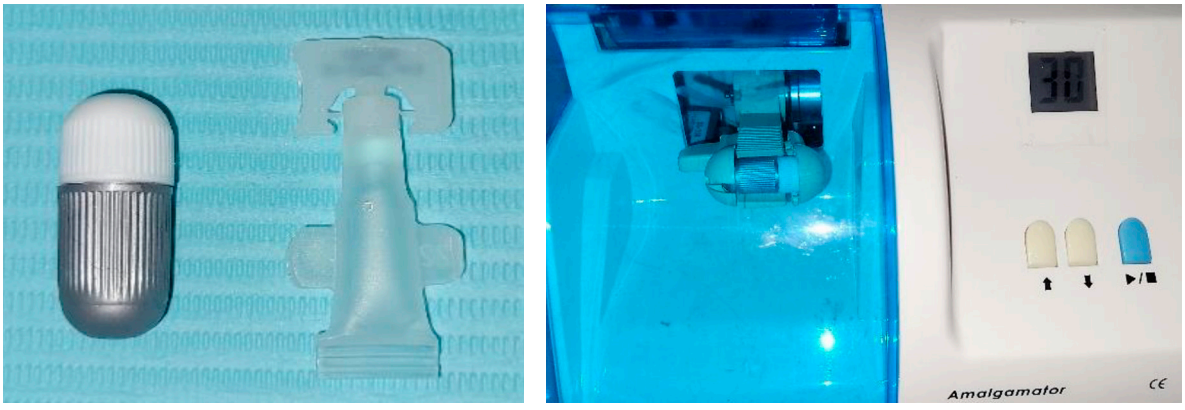

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Fig. 1 Biodentine.
a. form of presentation. b. the capsule in the amalgamator.

Biodentine's chemical composition is based on tricalcium silicate which represents 80% of the powder. Zirconium oxide is included as a radiopacifier, is an inert material and does not participate in the hydration reaction unlike bismuth oxide in MTA, and does not cause color changes in dental tissues. Calcium carbonate represents 15% of the powder, and is a reaction modifier, which allows the early release of calcium ions in solution in larger quantities than unmodified tricalcium silicate. A water-soluble polymer and calcium chloride are incorporated into the liquid component. Calcium chloride reduces setting time. The water-soluble polymer in the liquid has a double role: first, it allows a reduced water-to-powder ratio and results in increased material strength; secondly, it increases the viscosity of the material and improves its handling. The end product of tricalcium silicate hydration is calcium silicate hydrate and calcium hydroxide. The initial setting time declared by the manufacturer is 12 minutes [4].

The antimicrobial potential of Biodentine has been evaluated in numerous studies and compared to other pulp capping materials. Freshly mixed Biodentine was tested against *Streptococcus mutans*, *Enterococcus faecalis*, *Escherichia coli* and *Candida albicans*, and showed a greater antibacterial effect ($p < 0.05$) than mineral trioxide aggregate (ProRoot® MTA, Dentsply) and a glass ionomer cement [5]. The hydroxyl ions released during the hydration of Biodentine create an alkaline pH in the environment that has antimicrobial effects. The alkaline pH is also produced by other pulp capping materials such as mineral trioxide aggregate or calcium hydroxide, so the antibacterial mechanism of these materials is similar [6].

In case of injury to the pulp-dentine complex, the pulp's response can vary from an increase in the synthetic activity of the odontoblast in cases of mild/moderate damage, to the differentiation of odontoblast cells from pulp stem cells in the event of pulp exposure, which leads to the secretion of tertiary dentine. In both cases, the tertiary dentine will serve as protection for the pulp, and the rate of its deposition will largely depend on the severity of the traumatic or carious lesion, the degree of pulpal inflammation, the pulp capping material used and its sealing ability. The regeneration of the pulp-dentine complex is a well-orchestrated process that following the use of Biodentine, consists of the following steps:

1. Resolution of the inflammation: following the application of Biodentine to the exposed/unexposed pulp, there is a recruitment of inflammatory THP-1 cells, including their adhesion to activated endothelial cells, as well as their migration and activation in macrophage-like cells. This leads to a decrease in the expression of cyclooxygenase-1 and cyclooxygenase-2 - two enzymes involved in the initial phase of inflammation. It also significantly decreases the secretion of two mediators of inflammation: prostaglandin E2 and thromboxane B2.

2. Neoangiogenesis: stimulation of the expression and secretion of the following factors involved in neoangiogenesis: vascular-endothelial growth factor from pulp stem cells, fibroblast growth factor 2, platelet-derived growth factor, and transforming growth factor β1.

3. Stimulation of pulpal fibroblasts proliferation: This results from increased secretion of fibroblast growth factor 2 and transforming growth factor β1.

4. Proliferation and migration of dental pulp stem cells: is orchestrated by growth factors such as transforming growth factor β1, known to stimulate odontoblastic differentiation and the secretion of fibroblast growth factor 2, which induces stem cell proliferation.

5. Differentiation of stem cells into odontoblast-like cells that will synthesize reparative dentine, with its subsequent mineralization: mesenchymal progenitor cells migrate to the wound area and differentiate into a phenotype with mineralizing capabilities, also known as secondary odontoblasts. These cells deposit hard tissue at the covering site and create a biological closure of the defect, termed a "dentine bridge". The newly formed mineralized tissue is classified as tertiary dentine and is called reparative or reactive dentine [4].

Materials and methods

This article reports a clinical case study of a 22-year-old male who requested dental care with the chief complaint of sensitivity to sweet stimuli in the upper right molar region. The patient underwent clinical and radiological examination. Inspection, probing, percussion, and tests to assess pulp vitality, including cold and electrical sensitivity tests, were performed.

Results

Clinical examination revealed a deep carious cavity in tooth 17. Dental probing was not painful; the dentine had a soft consistency; axial percussion was negative. For cold testing, a cotton pellet soaked in Endo-Frost spray was used, and the response indicated a vital pulp. Additionally, electrical pulp testing was performed with a DigiTest device, recording a value of 16 μA. On the orthopantomography, an extended radiolucency was detected in tooth 17 without communication with the pulp chamber. No pathological periapical findings were found. The final diagnosis was a deep chronic carious lesion, class I cavity by Black.

According to the enhanced treatment protocol proposed by Bjørndal in 2018 [7], a single visit indirect pulp capping of tooth 17 was performed, following these subsequent steps:

1. Loco-regional anesthesia with Septanest 1:100.000;
2. Isolation of the working field with rubber dam;
3. Selective carious cavity preparation – a thin layer of affected dentine was kept;
4. Cavity disinfection with sodium hypochlorite 5.25% for 10 sec.;
5. Application of a thin layer of Biodentine on the bottom of the cavity;
6. Bonding with VI-th generation adhesive system;
7. Application of a permanent restoration with light curing composite.

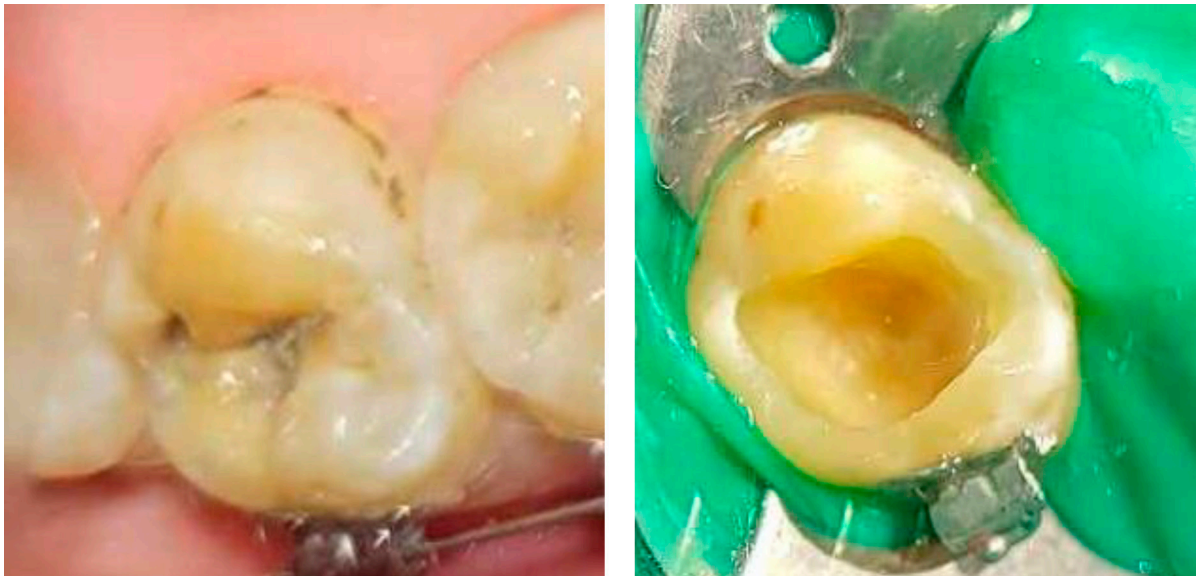

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Fig. 2 Deep carious lesion tooth 17, cavity class I by Black.
a. intraoral initial status; b. final preparation of the cavity.

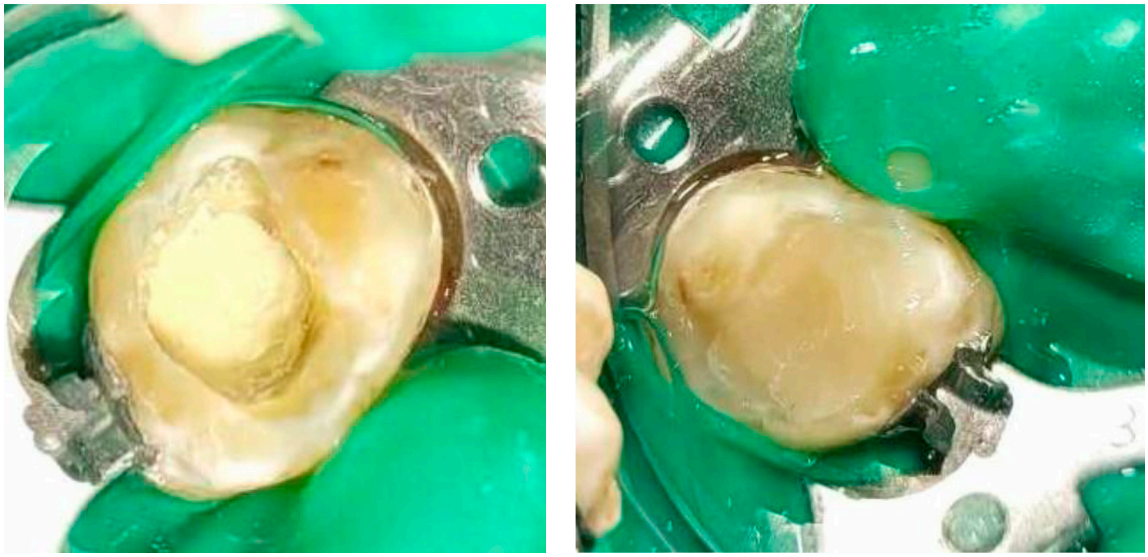

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Fig. 3 Indirect pulp capping of tooth 17 with Biodentine.
a. a 2 mm layer of Biodentine covering the bottom of the cavity; b. permanent restoration from light curing composite.

Discussions

This clinical case study describes the procedure of indirect pulp capping, which involves the application of a thin layer of bioactive dental material over a thin layer of affected dentine. It is considered that a layer of 0.5 – 1 mm of dentine has an increased number of large dentinal tubules that communicate with the dental pulp, allowing the diffusion of active components of dental materials into the pulp [8]. At the same time, since the pulp was not exposed, it has a very high chance of regeneration if proper treatment is applied.

According to Bjørndal, cases with deep carious lesions require a modified treatment algorithm that includes the removal only of the infected carious tissue, the use of optical magnification, disinfection, and hemostasis with 5.25% sodium hypochlorite, and the use of a hydraulic calcium silicate cement as pulp capping agent [7]. Exactly this algorithm was applied in our clinical case study.

Researchers have shown high rates (95-100%) of clinical success of Biodentine when applied as an indirect or direct pulp-capping agent [9]. This is due to the advantages of the material: appropriate setting time of approximately 12 minutes, easy manipulation, no staining of hard dental tissues, good adhesion to dentine, no dissolution over time, high sealing capacity, high pH, antimicrobial activity, and stimulation of pulp-dentine regeneration process.

The patient was examined at 3 and 6 months after the applied treatment. He no longer presented sensitivity to any irritants. Vitality pulp tests (electrical and cold) confirmed the healthy status of the pulp. On the orthopantomography, a thin layer of newly created tertiary dentine was depicted, and no periapical pathological modifications were found. Our findings correlate with different studies that have shown high success rates of calcium silicate cements in VPT, including Biodentine [9, 10].

Factors contributing to the success of indirect pulp capping could include: establishing the correct pulpal health status before selecting the treatment; proper patient selection – age under 35 and good general health condition; selection of appropriate dental materials for pulp capping and permanent filling; absolute isolation of the tooth with rubber dam from the oral cavity – an environment with a high bacterial load; use of optical magnification and proper disinfection of the prepared cavity, etc.

Conclusions

The indirect pulp capping with Biodentine was considered a success because the main complaint - the sensitivity from sweet stimuli disappeared after the treatment was applied. Also, at the follow-up visits at 3 and 6 months, the cold vitality tests indicated a vital pulp, the electrical pulp testing recorded decreasing values (14 μA and 11 μA respectively), and no pathological periapical radiological modifications were found. In conclusion, we can say that Biodentine exhibited very good handling properties, confirming its status as a promising pulp-capping agent for teeth affected by deep caries.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

No approval was required for this study.

Authors' contribution

Both authors contributed equally to the writing of manuscript. The authors read and approved the final version of the manuscript.

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ANNIVERSARY

Ion Ababii - a life dedicated to medicine

Emil Ceban

Rector, MD, PhD, Professor, corresponding member of the Academy of Sciences of Moldova, *Nicolae Testemiţanu* State University of Medicine and Pharmacy, Chişinău, Republic of Moldova

Ion Ababii, doctor habilitatus in medical sciences, university professor, academician of the Academy of Sciences of Moldova (ASM), former head of the Department of Otorhinolaryngology and rector of the *Nicolae Testemiţanu* State University of Medicine and Pharmacy from the Republic of Moldova (*Nicolae Testemiţanu* SUMPh), former Minister of Health and Social Protection of the Republic of Moldova, Knight of the Order of the Republic, has reached the honorable age of 80.

Born on February 11, 1944, in the village of Ochiul-Alb, located in the Drochia district, Ion Ababii comes from a family of farmers deeply rooted in local traditions. His journey through life and career has been remarkable and noteworthy.

Education started in his native village with the 7-grade school, the general education secondary school in Baraboi commune and the State Institute of Medicine in Chisinau (SIMC), which he graduated with honors in 1966. The foundational education laid a solid groundwork for his remarkable ascent through the professional ranks, demonstrating a blend of clinical excellence and academic prowess. Beginning as an internist and otorhinolaryngologist specialist at the Straseni District Hospital from 1966 to 1969, he then pursued a doctorate at the Children's Clinic of the Institute of Scientific Research in Otorhinolaryngology in Moscow, Russian Federation. This rigorous academic pursuit culminated in the defense of his thesis and the award of a Doctor of Medical Sciences degree in 1973. Afterwards, Ion Ababii completed his post-doctorate at the same institution, defending his doctoral habilitation thesis in 1986. His academic and professional milestones continued with his appointment as the head of the Department of Otorhinolaryngology from 1988 to 2019, earning the title of university professor in 1989. He served as Vice-Chancellor for Clinical Medicine from 1989 to 1994, was named a corresponding member of the Academy of Sciences of Moldova (ASM) in 1993, and assumed the prestigious post of rector at *Nicolae Testemiţanu* SUMPh from 1994 to 2019. His recognition within the academic community was further solidified by his induction as a full member of the ASM in 2000. Ion Ababii's contributions extended beyond academia into public service, where he held the position of Minister of Health and Social Protection from 2005 to 2008. Currently, he serves as a consultant professor at the Department of Otorhinolaryngology, continuing his lifelong dedication to clinical, scientific, pedagogical, and managerial excellence. This illustrious career is not merely a collection of titles and positions but a testament to Ion Ababii's profound impact on the medical field and his unwavering commitment to improving health care and education.

At the beginning of his career, Ion Ababii seamlessly merged his clinical duties as a top-tier pediatric otorhinolaryngologist with his academic and research pursuits. He progressed through various educational roles, starting as an assistant in 1972, advancing to associate professor by 1985, and then assuming the role of head of the Otorhinolaryngology Department at the State Institute of Medicine in Chisinau (later known as *Nicolae Testemiţanu* SUMPh) from 1988. Since October 2019, he has been imparting his vast knowledge and experience as a consultant professor in the same department.

As a distinguished otorhinolaryngologist, Professor Ion Ababii spearheaded the introduction and implementation of innovative treatments for children suffering from acute stenotic and recurrent laryngotracheitis. His pioneering work led to the establishment of a new research direction within otorhinolaryngology focused on developing prognostic indices. These indices are crucial for assessing the

risk levels associated with the recurrence of ENT diseases and their progression to chronic conditions in children. The significance of these prognostic indicators cannot be overstated. They play a vital role in preventing the chronicity of ENT diseases, thereby enhancing the overall health and quality of life for children. Through his innovative research and dedication to clinical excellence, Professor Ion Ababii has significantly contributed to the field of pediatric otorhinolaryngology, laying the groundwork for future advancements in the treatment and prevention of ENT diseases in children.

Ion Ababii, a scientist of international renown, has made significant strides in the field of otorhinolaryngology, focusing his research on the diagnosis and treatment of complex diseases. His work spans a broad array of areas, including recurrent inflammatory diseases of the ear and upper respiratory tract in children, assessment of the auditory organ in premature and underweight infants, and the management of latent otitis and otoantritis in young children. His expertise also extends to auricular suppurations, the intersection of immunology and otorhinolaryngology, pediatric audiology, the application of laser therapy in ENT, and the utilization of functional endoscopic surgery for the nose and paranasal sinuses, as well as microsurgery for the ear and upper respiratory tract, and tackling chronic tonsillitis in children, among others.

Ion Ababii's contributions have not only been theoretical but also practical, especially in terms of advancing medical technology within the clinic. Under his guidance, the clinic was outfitted with the latest medical equipment and technologies, enabling the introduction of new diagnostic and therapeutic methodologies. These innovations include computerized audiometry, tympanometry, endoscopic functional surgery, endolaryngeal microsurgery, optical endoscopy, laser technology, and investigations into immune status, significantly broadening the scope and efficacy of treatments available to patients. Furthermore, at the behest of Professor Ion Ababii, the Laboratory of Pathology in ENT for premature children was established. This facility is dedicated to exploring various aspects of the pathogenesis, diagnosis, and treatment of inflammatory diseases affecting the nose, throat, and ear in young children. Through this initiative, Ion Ababii has provided a valuable resource for the advancement of pediatric otorhinolaryngology, underlining his commitment to improving health outcomes for children suffering from these conditions. His work epitomizes the blend of innovative research and practical application, setting a benchmark for excellence in the medical field.

He is the author of over 540 scientific works, including 450 scientific articles, 11 monographs, 10 manuals, over 30 methodical guidelines, and about 35 patents for inventions and innovations. He actively participated in numerous national and international scientific forums. Under the scientific leadership of Professor Ion Ababii, 16 doctoral and postdoctoral theses were defended in medical sciences – this accomplishment signifies the establishment of a veritable scientific school under Ion Ababii's guidance, emphasizing his influence as a mentor and leader in his field.

Since 1994, university professor Ion Ababii holds the post of rector of the *Nicolae Testemițanu* State University of Medicine in the Republic of Moldova.

At the initiative and under the leadership of rector Ion Ababii, the *Concept of university training, postgraduate residency and continuous medical education* was developed, the application of which allowed the creation of an effective training system for medical specialists and pharmacists for the Republic of Moldova and for other states at the high-level of that time, according to the standards of the World Federation for Medical Education.

Alma Mater's strategic development directions and objectives were reflected in the University's Development Strategy for the period 2011-2020, developed under the leadership of Rector Ion Ababii. Taking into consideration that we live in the age of digitization, when information technologies are implemented in all fields of activity, under the leadership of rector Ion Ababii, the university's computerization strategy was also developed in the period 2012-2015. The implementation of this strategy was completed with the creation of the University Management Information System (SIMU) – a functional and transparent software. These two documents were the basis of the essential transformations that took place at the university in all areas: human resources, education, research, clinical activity, management, international relations, and social activity.

Under the leadership of Rector Ion Ababii, human resources and the remuneration of teaching staff were prioritized areas, reflecting his commitment to creating a vibrant and conducive educational environment. Recognizing the importance of globalization in education, Ababii spearheaded initiatives to attract talented young professionals to the university's departments and other subdivisions. A key criterion for these new hires was proficiency in internationally recognized languages, particularly English, coupled with adeptness in information technology. This strategic focus not only enriched the university's talent pool but also aligned with the broader goal of enhancing its global standing.

During Ion's Ababii tenure as rector, efforts were made to provide both teaching and academic staff with opportunities to enhance their English language proficiency and computer literacy. These efforts were instrumental in fostering an inclusive and versatile academic environment, enabling the university to offer educational programs in four languages: Romanian, Russian, French, and English. Such linguistic diversity significantly contributed to the internationalization of the educational process, attracting foreign students and facilitating a multicultural learning experience.

In addition to his focus on innovation and inclusivity, Rector Ion Ababii also demonstrated a profound respect for the contributions of the university's senior members,

who brought invaluable academic, scientific, and clinical expertise. Recognizing the importance of preserving this wealth of knowledge, he initiated the establishment of the consultant professor position by governmental order. This role was designed to ensure a seamless generational exchange of knowledge and experience, thereby maintaining continuity in the university's academic excellence and institutional memory. Through these measures, Ion Ababii not only enhanced the educational landscape within the university but also set a precedent for nurturing both emerging talents and seasoned experts, ensuring the institution's ongoing development and relevance in the global academic community.

Guiding the university under Ion Ababii's stewardship was a commitment to the enhancement and structuring of the educational and didactic process. A particular focus was addressing the gaps in pre-university education encountered by first-year students in key foundational subjects. The response involved a concerted effort from the faculty within relevant departments to provide additional instruction, aiming to equip students with the foundational knowledge needed for their subsequent studies.

Drawing inspiration from the practices of European medical schools, Ion Ababii championed the early engagement of students in practical settings such as hospitals, polyclinics, dental offices, and pharmacies right from their first year. This initiative was designed to provide hands-on experience early in their academic journey, fostering a deeper understanding of their future professional roles.

In a strategic move towards enhancing the quality of education and facilitating student mobility, the European Credit Transfer and Accumulation System was adopted during the academic year 2001-2002. This was complemented by the development of educational standards across various profiles, specialties, specializations, and disciplines. Such measures laid the groundwork for inter-university partnerships, ensuring that students' coursework and achievements were recognized across institutions. These reforms not only aligned with international best practices but also positioned the university as a forward-thinking institution, committed to providing a comprehensive and globally compatible education.

The educational strategy at the university experienced significant enhancements under the guidance of rector Ion Ababii, with a shift towards incorporating modern educational technologies. This evolution included the adoption of interactive teaching methods, problem-based learning through clinical cases, the principles of evidence-based medicine, and the use of virtual programs. The institution also embraced distance learning and leveraged contemporary information technologies to enrich the educational experience.

Aiming to bolster the integrity and transparency of the evaluation process, the university introduced the Test-Corector system in the academic year 2002-2003. This development was followed by the implementation of a new assessment method in 2016, the computer-assisted evaluation in SIMU. These initiatives were complemented by the inauguration of the Academic Evaluation Center, which aimed to minimize subjective bias in the evaluation process by removing the human factor.

Starting in 1995, Ion Ababii initiated a transformative approach to postgraduate residency training, ranging from 2 to 5 years, designed to prepare medical specialists and pharmacists. This program marked a significant advancement in higher medical education, focusing on the comprehensive training of healthcare professionals.

Aligned with the Concept of training medical and pharmaceutical personnel in the Republic of Moldova, the university has established stringent quality and performance standards for professional practice. Since 2016, medical specialists and pharmacists are required to continuously update their professional competencies through the Faculty of Continuing Medical Training. This ongoing education process is coordinated by the Department of Continuing Medical Education (DEMC), ensuring that professionals remain at the forefront of their fields, equipped with the latest knowledge and skills to meet the evolving demands of healthcare.

The policy promoted by Rector Ion Ababii was aimed at fostering a symbiotic relationship between education, training, scientific research, and innovation, aligning with the global trends in science development. This vision was encapsulated in the Development Strategy of *Nicolae Testemițanu* SUMPh for 2011-2020, which set forth critical objectives for the institution's research activities. These objectives included enhancing the management of scientific research, elevating the quality and competitiveness of the research output, effectively utilizing, promoting, and disseminating scientific findings, and nurturing the human potential within the scientific research domain.

Under Ion Ababii's leadership, *Nicolae Testemițanu* SUMPh took pioneering steps to bolster the research infrastructure by initiating the formation of a consortium among Moldova's former medical doctoral organizing institutions. This effort culminated in the establishment of the Doctoral School in the field of Medical Sciences, a significant milestone in the country's academic landscape.

Nicolae Testemițanu SUMPh distinguished itself as the first institution in the country to introduce a procedure for assessing the quality of scientific research to ensure academic integrity. This included the ethical review of projects to align with international best practices in research. Efforts were made to expand research collaborations with specialists from clinics and universities around the world, enhancing the global reach and impact of the institution's scientific endeavors. A particular focus was placed on the dissemination of research findings through publications in international journals with an impact factor (IF), underscoring the institution's commitment to contributing to the global scientific community. This strategy not only bolstered the visibility and credibility of the research conducted under the auspices of *Nicolae Testemițanu* SUMPh but also positioned the institution as a leader in medical

science education and research on the international stage.

In 2005, the University's commitment to innovation was recognized on an international level when it was awarded the World Intellectual Property Organization Trophy. This accolade highlighted the institution's contributions to intellectual property and innovation. Further demonstrating its dedication to research excellence and ethical standards, *Nicolae Testemiţanu* SUMPh became a signatory to the European Charter of Researchers and the Code of Conduct for the Recruitment of Researchers in 2014. In a significant acknowledgment of its research capabilities, the University's scientific research activity was accredited by the National Accreditation and Attestation Council of the Republic of Moldova in 2016 for seven research profiles, earning the distinction "Organization with international recognition" (category A).

An integral part of the University's scientific community is the annual scientific conference for students, PhD students, and medical residents held during the University Days. This event plays a crucial role in fostering a vibrant scientific atmosphere. From their first year of study, students engage in research activities through the student scientific circles of various departments, underlining the University's commitment to early research involvement. A notable highlight under Ion Ababii's patronage was the inauguration of the International Congress of Students and Young Doctors - *MedEspera*, in May 2006. This event, which marked its 10th edition this year, stands as a testament to the ongoing efforts to integrate students and young professionals into the global scientific community.

The training of medical specialists and pharmacists at the university has always emphasized the balance between theoretical knowledge and practical skills. The quality and effectiveness of clinical training have been significantly enhanced by collaborative efforts among professors, lecturers, university assistants, resident doctors, and the skilled personnel of hospital departments.

Throughout his tenure, Rector Ion Ababii initiated several measures aimed at improving the conditions for clinical training and continuous professional development of students, resident doctors, medical specialists, and pharmacists. These efforts ensured that the university not only maintained high standards of education and training but also fostered an environment conducive to practical learning and professional growth.

The University Clinic of Primary Nursing, inaugurated in 2003 through Rector Ion Ababii's direct involvement, holds a pivotal role in the clinical activities of *Nicolae Testemiţanu* SUMPh. This significant development came as a result of the partnership within the American International Health Alliance between the Eastern Virginia School of Medicine in Norfolk/Portsmouth, USA, and *Nicolae Testemiţanu* SUMPh. Coinciding with this, the Center for Training and Testing Practical Skills on Standardized Patients was launched, which evolved into the University Center for Simulation in Medical Training (CUSIM). This center offers students, medical residents, and trainee doctors the chance to engage with high-fidelity simulators, enhancing their practical abilities and patient communication skills. The diverse and educationally rich training methods employed within CUSIM are particularly notable for their effectiveness.

For many years, the clinical training for the Faculty of Stomatology was primarily conducted at the University Dental Clinic. The establishment of the University Dental Service in 2011, later renamed the University Dental Center in 2015, marked a significant improvement in training facilities. This upgrade greatly enhanced access to treatment rooms for students and medical residents, fostering optimal conditions for the development of practical skills in line with contemporary demands. Additionally, it expanded the capacity for providing dental treatments to patients within the community. The university administration has undertaken considerable efforts to augment and reinforce the technical and material foundation of the Center.

Furthermore, the *Vasile Procopişin* University Pharmaceutical Center and the Bardar Scientific Center for the Cultivation of Medicinal Plants are instrumental in the practical training of students and the academic staff of the Faculty of Pharmacy. These facilities provide essential resources for hands-on learning and application of pharmaceutical sciences, ensuring that students and staff are well-equipped with the necessary practical skills for their professional development.

In 2018, significant strides were made to update the main normative acts that govern clinical activity, with a particular focus on enhancing the legal and operational framework of clinical practices associated with the *Nicolae Testemiţanu* SUMPh. This initiative led to the revision of the Government Decision №. 42 of January 12, 2006, which pertains to the clinics of the *Nicolae Testemiţanu* State University of Medicine and Pharmacy. Additionally, the Ministry of Health, Labor, and Social Protection issued an order regarding the clinical bases and university clinics of the *Nicolae Testemiţanu* SUMPh departments, further solidifying the structure and governance of clinical activities within the university.

Rector Ion Ababii placed a strong emphasis on international collaboration, which over the years has been directed towards fostering cooperative relations, identifying funding and opportunities for research, mobility, and institutional development projects, and offering services to international citizens in integrated medical, residency, postgraduate, and research studies. One of the earliest collaborative efforts involved establishing relationships with all the universities of medicine and pharmacy in Romania, facilitating academic mobility, participation in scientific events and training, as well as engaging in scientific research and joint projects.

The establishment of the university agency of Francophonie at the Faculty of Medicine in 1998 laid the groundwork for productive collaboration with Francophone higher education institutions from France, Canada, Bulgaria,

and Romania. These partnerships continue to thrive, with academic and research mobilities with universities in France and Belgium now considered a tradition.

The cooperation with the United States of America has been fruitful and enduring. For over 25 years, a collaborative relationship has existed between the *Nicolae Testemițanu* SUMPh and medical education institutions in the state of North Carolina, USA, as part of a cooperation plan approved by the Republic of Moldova - North Carolina Bilateral Committee. This partnership has yielded remarkable outcomes in various domains, including virtual training, pharmacy, dentistry, and primary health care. Notably, the collaboration extended to the Medical Scientific Library of *Nicolae Testemițanu* SUMPh and 12 medical libraries in North Carolina, which provided the university library with access to extensive medical databases, including thousands of monographs, manuals, and scientific journals. Moreover, American doctors have contributed to dental care for children in orphanages, showcasing the tangible benefits of these international collaborations on healthcare and education.

Under the leadership of Rector Ion Ababii, the University forged significant collaborative relationships with German medical institutions, supported by the German Federal Ministry of Health. Notable partnerships were established with the Medical University of Lübeck through the "Reach-for-Moldova" project and the Borstel Scientific Center. These collaborations aimed to enhance practical training opportunities for students and provide research scholarships, fostering a robust exchange of knowledge and expertise.

Furthermore, a productive partnership was initiated with the University of Leipzig, focusing on modernizing the university curriculum and introducing innovative training methods, including simulation. This cooperation extended to fields such as otorhinolaryngology, hearing pathologies, medical assistance for patients with rheumatological diseases, and knowledge exchange in rehabilitation, enriching the academic and clinical experiences of both institutions' communities.

The University also established and continuously developed fruitful relations with the Lithuanian University of Health Sciences in Kaunas, focusing on advancing capacities in endoscopic cardiology among other critical medical fields. Thanks to its high-performing University Hospital, the Lithuanian institution welcomed young specialists from Moldova for training in various medical disciplines. This initiative aimed at adopting new methods and approaches in Moldova, aligning with contemporary European medical practices, thereby enhancing the quality of healthcare provision and medical education in the region.

The collaboration with the Medical University of Poznan, Poland, stands as a testament to the university's commitment to fostering international partnerships. This relationship is characterized by mutual academic mobility involving clinicians, final-year pharmacy students during their summer internships, and faculty members, particularly in the realm of applying simulation methods in medical training.

Moreover, the university has seen fruitful cooperation with medical and academic institutions from the European Union, Russia, Kazakhstan, and notably with medical universities in Ukraine, including Chernivtsi, Odesa, Vinnytsia, and Ternopil. These partnerships have facilitated a productive exchange of knowledge and expertise, significantly enriching the educational and research environment.

The university has benefited from projects financed by governments of countries with advanced economies, including Norway's support for optometry training and oral pathology research and Estonia's funding for sports medicine development. Additionally, Switzerland contributed to strengthening education and doctoral studies in bioethics. These initiatives reflect a broad international support base aiming to enhance the University's educational and research capacities.

Projects financed by European funds such as ERASMUS MUNDUS, ERASMUS+, and TEMPUS have played a crucial role in modernizing higher medical education, enhancing quality assurance, reforming university management, and updating services. These collaborations have been instrumental in aligning the university's practices with international standards.

Rector Ion Ababii's tenure was marked by a keen focus on improving the technical material and informational support for the University's educational and scientific activities. Initiatives under his guidance from 1994 to 2019 include the establishment of the University Center for Medical Rehabilitation, the Scientific Center for the Cultivation of Medicinal Plants, the University Sports Complex, the University Sociocultural Complex, the Alley of Scholars and Illustrious Doctors, and the Driving School, among others. These efforts have significantly enhanced the University's infrastructure and resources.

Ion Ababii also prioritized creating conducive working and study conditions for the university community. This included ensuring comfortable living conditions in the student dormitories, which were regularly renovated and equipped with necessary amenities.

In 2010, the *Nicolae Testemițanu* Residential Complex's construction began, a project initiated by Ion Ababii through a public-private partnership. Completed in 2013, this complex provides accommodation for university employees and specialists from other public medical and health institutions, further demonstrating Ion Ababii's commitment to the well-being of the academic and medical community.

Under Rector Ion Ababii's leadership, *Nicolae Testemițanu* SUMPh underwent significant developments, achieving National Council for Accreditation and Attestation accreditation in 2001 and 2007. These milestones reflect the University's enduring dedication to excellence in medical education and research.

Since July 2009, *Nicolae Testemițanu* SUMPh has been at the forefront of institutional quality assurance, implementing the Quality Management System in alignment

with the ISO 9001:2008 international standard. This initiative underscores the University's commitment to maintaining high standards of education, research, and administration. In a significant step forward, September 2016 saw the university being certified according to the updated requirements of the ISO 9001:2015 standard, marking it as the first higher education institution to achieve this distinction. This certification, which is annually confirmed, attests to the university's continuous efforts to enhance its quality management processes, ensuring that its operations meet the highest international standards.

Since 2011, *Nicolae Testemiţanu* SUMPh has progressively joined prominent international associations, marking its commitment to global engagement and excellence in medical education. The university's memberships include the Association of Medical Schools in Europe from 2011, the Association of International Universities since 2012, and the Association for Medical Education in Europe starting in 2013. These affiliations underscore the institution's dedication to aligning with the highest standards of medical education and research worldwide.

The university's practices and achievements have been recognized on multiple occasions. Notably, during 2013-2014, an evaluation by representatives from the Association of Medical Schools in Europe and the World Federation for Medical Education hailed *Nicolae Testemiţanu* SUMPh as a beacon of good practices in the region, including countries from the former Soviet Union and the Black Sea basin. This commendation highlights the university's role as a model institution in medical education and research.

In recognition of its contributions to the field and on the occasion of its 70th anniversary in 2015, the university was awarded the highest state honor, the Order of the Republic. This prestigious award reflects the university's significant impact on medical education, healthcare, and society in the Republic of Moldova.

The year 2017 saw the approval of a new nomenclature of specialties, leading to the introduction of two undergraduate study programs: Optometry and General Medical Assistance. These programs, designed to run over four years with the accumulation of 240 ECTS credits, signify the University's ongoing efforts to diversify and modernize its educational offerings.

In 2018, the Faculty of Dentistry's Integrated Higher Education Program received accreditation from the Dental Council of California, USA, for five years, with the International Dental Professional Education Program accredited for two years. Furthermore, the institutional accreditation of study programs in Medicine, Dentistry, and Pharmacy by ANACEC for a five-year period highlights the University's adherence to national standards.

The spring of 2019 marked another significant milestone when the university achieved international accreditation for a five-year term from an external commission of experts from Romania, Russia, Lithuania, and Kazakhstan of the Independent Accreditation and Rating Agency (IAAR), according to World Federation for Medical Education standards. This accreditation is a testament to the university's commitment to excellence and its standing in the global medical education community.

During the period from 2005 to 2008, Professor Ion Ababii held the esteemed position of Minister of Health of the Republic of Moldova, making significant contributions to the development and fortification of the national health system as well as advancements in medical education. While we cannot comprehensively list all of the achievements of the university under the guidance of Rector Ion Ababii within these pages, they undoubtedly form a substantial part of the university's legacy.

In addition to his roles in teaching, scientific research, medical practice, and management, Professor Ion Ababii undertook remarkable responsibilities, serving as:

- President of the Scientific and Practical Association of Otorhinolaryngologists in Moldova; Vice-President of the Commission addressing issues in science and sustainable societal development under the President of the Republic of Moldova; Member of the Higher Attestation Commission of the Republic of Moldova; Member of the College and the Presidium of the Council of Experts of the Ministry of Health of the Republic of Moldova; Member of the specialized Scientific Council for defending doctoral theses.
- President of the *Nicolae Testemiţanu* SUMPh Senate; Head of the specialists from the Ministry of Health of the Republic of Moldova; Editor-in-chief of the annual magazine "Anale ştiinţifice ale USMF „Nicolae Testemiţanu", and member of the editorial boards of several other esteemed publications, including "Curierul medical" "Arta Medica", "Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe medicale", "Sănătate Publică, Economie şi Management în Medicină", "Cercetări experimentale medico-chirurgicale".

Professor Ion Ababii's international recognition for his exceptional merits is evident from his roles as: Honorary Member of the Academies of Sciences in Poland and Finland; Honorary Member of the American Biographical Institute; Member of the US Academy of ENT; Coordinator from the Republic of Moldova for the USAID Partnership Program in Norfolk, Virginia, USA, and Chisinau, Republic of Moldova, implemented by AIHA; Member of the Executive Committee at WHO; Member of the editorial boards of various international journals, including: "Folia otorinolaringologica", "ORL.ro", "Cercetări experimentale medico-chirurgicale" (Romania), "Журнал Вушних, Носових і Горлових Хвороби", "Журнал Гродненского Государственного Медицинского Университета" (Ukraine).

The prodigious multilateral activities, high professionalism, and contributions of Professor Ion Ababii to the organization and restructuring of higher medical education and the national health system have been widely appreciated both in the country and abroad. For his exceptional merits in scientific, didactic, and public activities, he has

been honored with several prestigious awards and decorations, including the "Friendship of Peoples" Order (1981), the "Order of the Republic" (2004), and the "Bogdan Întemeietorul" Order (2019). He was also awarded the title of Emeritus of the Republic of Moldova (1995) and has received numerous medals and honors such as the Gold Medal (1997), the Great Albert Schweitzer Gold Medal (2001), the P. Erlich Gold Medal (2002), the "Robert Koch" Medal (2004), the "The Name in Science" Medal from Oxford (2010), the Gold Medal of the International Society "Health of Society" in Kyiv, Ukraine (2016), the Socrates International Distinction in Oxford, UK (2006), a Certificate of Appreciation from the California State Senate (2018), and a Diploma for outstanding performance and contributions to the medical system (2018).

In recognition of his outstanding contributions to medicine, he has been bestowed with the honorary title of Doctor Honoris Causa by various esteemed institutions such as UMF *Carol Davila* in Bucharest, Romania (2006), the International University of Vienna (2007), the University of Medicine and Pharmacy in Târgu Mureș, Romania (2007), the University of Medicine in Craiova, Romania (2008), and the *Victor Babeș* University of Medicine and Pharmacy in Timișoara, Romania (2014). Additionally, he has received numerous awards, diplomas of honor and excellence, certificates of appreciation, and medals at international research, innovation, and invention events.

Throughout his various roles and positions, Professor Ion Ababii has consistently demonstrated maximum responsibility, foresight, professional competence, discipline, principledness, exactingness, collegiality, humanity, and respect. As a scientist, educator, and manager, he has significantly impacted Moldovan education, leaving a lasting legacy on generations of students, medical residents, trainee doctors, and Alma Mater graduates. His commitment to nurturing studious youth through the promotion of work ethic, love for knowledge, respect for humanity, and the pursuit of honor, dignity, and justice has been exemplary.

Professor Ion Ababii's career has been characterized by intelligence, effort, devotion to his cause, civic courage, non-conformism, and steadfastness in his convictions. He is a true patriot, deeply rooted in his love for his country's culture, language, and history, which he continuously instills in younger generations. Even in his venerable age, Professor Ion Ababii remains a model of correctness, honesty, and discipline in all his endeavors.

We sincerely hope that current and future generations will have the privilege of encountering such exemplary figures in their professional and spiritual journeys and recognizing and appreciating the complexities of personalities like Professor Ion Ababii. On the occasion of his special anniversary, we extend our warmest congratulations to Dear Professor, Academician Ion Ababii, on behalf of the university community. We wish him good health, energy, and strength to continue his noble work, and we express our heartfelt gratitude for his dedicated and sacrificial contributions to the development of *Nicolae Testemițanu* SUMPh and the national health system.

Happy Birthday, Distinguished Professor,
Rector Ion Ababii!

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REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

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[Revised May, 2023]

GUIDE FOR AUTHORS

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• The manuscripts should be written in **English**;
• Each manuscript must be accompanied by *Authors statement for publication form* signed by all authors;
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TITLE PAGE	> Article title / Short title > Authors information (full names, academic titles, ORCIDs, affiliations) > Corresponding author's contact details > Authors' contributions > Acknowledgments and funding > Conflict of interest > Article highlights > Word count (for Main text and Abstract)
ABSTRACT AND KEYWORDS	> Structured abstract > Keywords > Clinical trial registration information
MAIN TEXT AND REFERENCES	> Introduction > Materials and methods > Results > Discussion > Conclusions > References
TABLES AND FIGURES	> Tables are inserted immediately after the first paragraph in which they are cited > Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figures should be submitted also as separate files.

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Each author's full name, academic titles, the ORCID iD and the affiliation (the full name of department, institution, city and country) should be provided.

Example:

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> Materials and methods

The *Materials and methods* section should present in sufficient details all carried out procedures. Here should be described protocols and supporting information on the used methods. It will include study design, subjects' recruitment procedure, clear description of all interventions and comparisons and applied statistics (*Selection and Description of Participants, Technical Information, Statistics*). The Methods section should be sufficiently detailed such that others with access to the data would be able to reproduce the results. For studies on humans or animals a statement about ethical approval and informed consent of study subjects should be include. Please specify date and number of Ethics Committee (EC) decision, chair of the EC as well as institution within EC is organized.

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Authors must present results logically using text, tables, and figures, giving the main or most important findings first. Results should be explained (not justified or compared in this section) and include fundamental statements related to hypothesis behind the study.

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The data should be interpreted concisely without repeating materials already presented in the *Results* section. Describe the impact, relevance and significance of the obtained results for the field. The results are compared with those from previous publications and

draw potential future research directions. Discussions should include important interpretations of the findings and results compared with previous studies. In addition, study limitations and potential bias should be mentioned.

> Conclusions

This section should conclude laconically entire study, and highlight the added-value brought on the studied issue. The conclusions should not provide new information or double (repeat) those presented in the *Results* section.

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In-text reference citations should be numbered consecutively, identified by Arabic numerals in square brackets [ ]. References should be listed at the end of the manuscript and numbered in the order in which they are first mentioned in the text. Every reference cited in the text is also present in the reference list (and vice versa). Journals titles should be abbreviated according to the Index Medicus.

It may be cited only articles or abstracts that have been published and are available through public servers. Personal communications, manuscripts in preparation, and other unpublished data should not be included in the reference list, but may be mentioned in parentheses in the text as "unpublished data" or "unpublished observations", indicating the involved researchers. It is of manuscript authors' responsibility to obtain the permission to refer to unpublished data.

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Examples of references

Journal article

Belîi A, Cobâleţchi S, Casian V, Belîi N, Severin G, Chesov I, Bubulici E. Les aspects pharmacoéconomiques dans la gestion de la douleur périopératoire [Pharmaco-economic aspects of perioperative pain management]. Ann Fr Anesth Reanim. 2012;31(1):60-6. French. doi: 10.1016/j.annfar.2011.09.008.

Book

Razin MP, Minaev SV, Turabov IA. Detskaia khirurgiia [Pediatric surgery]. 2nd ed. Moscow: Geotar-Media; 2020. 696 p. Russian.

Chapter in a book

Steiber AL, Chazot C, Kopple JD. Vitamin and trace element needs in chronic kidney disease. In: Burrowes J, Kovesdy C, Byham-Gray L, editors. Nutrition in kidney disease. 3rd ed. Cham: Humana Press; 2020. p. 607-623.

Conference paper

Ojovan V. Medical rehabilitation of children with type 1 diabetes: medical bioethical and psychosocial aspects. In: MedEspera: 9th International Medical Congress for Students and Young Doctors, 12-14 May 2022, Chisinau, Republic of Moldova: Abstract book. Chișinău; 2022. p. 77.

Website reference

World Health Organization (WHO). Therapeutics for Ebola virus disease [Internet]. Geneva: WHO; 2022 [cited 2022 Sep 5]. Available from: https://www.who.int/publications/i/item/9789240055742

TABLES AND FIGURES

Tables should be numbered consecutively with Arabic numerals, and be cited in text. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Tables must be submited as editable text and not as images. Each table should be completely informative in itself, and the data presented in it do not duplicate the results described elsewhere in the article.

The label "Table 1" and a short descriptive title should be provided above the table. Legends, notes, and any abbreviations used in the table should be explained below the table in a footnote. Applied statistical tests and the type of presented data should be also mentioned. Please follow the example:

Table 1. Intra-anesthetic and immediately post-extubation adverse events

	Experimental Cohort (n=100)	Control Cohort (n=100)	p
Dysrhythmia	6.0%	30%	0.49
Hemodynamic instability	7.0%	1.0%	0.034
Prolonged awakening*	11.0%	4.0%	0.19
PONV post-intubation	8.0%	27.0%	0.007
Strong pain on awakening	17.0%	19.0%	1.0

Note: *Unusually slow awaking, after that cerebral concentration of the anesthetic reach the under hypnotic level.
Used statistical analysis: Fisher's exact test.

Figures (photographs or radiographs, drawings, graphs, bar charts, flow charts, and pathways) should be submitted in a suitable format for print publication. Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. Figures' quality should assure the visibility of details. The following file formats are accepted: ".jpeg", ".tiff", ".eps" (preferred format for diagrams), ".ppt", ".pptx" (figures should be of the size of a single slide), with a resolution of at least 300 dpi.
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As stated in the guidelines of the International Committee of Medical Journal Editors (ICJME), all persons listed as authors in the manuscript must meet **ALL of the following criteria** for authorship:

1. substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. drafting the work or reviewing it critically for important intellectual content; AND
3. final approval of the version to be published; AND
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Acknowledgements and funding

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- SAGER guidelines for reporting of sex and gender information in study design, data analyses, results and interpretation of findings.

Ethical approval and Informed consent

If the research project involves human subjects or animals, authors must state in the manuscript that the study was approved by the Ethics Committee of the institution within which the research work was undertaken (the protocol number and the date of evaluation should be provided). Patients' identifying information should not be published in written descriptions and photographs, unless the information is essential for scientific purposes and the patient gave written informed consent for publication. The authors must include a statement confirming that informed consent was obtained from all identifiable study participants (or that no informed consent was required).

Clinical trial registration

The *Moldovan Journal of Health Sciences* follows the trials registration policy of the ICMJE (www.icmje.org) and considers only trials that have been appropriately registered in a public registry prior to submission. Any research that deals with a clinical trial should be registered with a primary national clinical trial registration site, or other primary national registry sites accredited by the World Health Organization (https://www.who.int/ictrp/network/primary/en/). The clinical trial registration number should be provided at the end of the Abstract.

Data access and responsibility

The corresponding author should indicate that he or she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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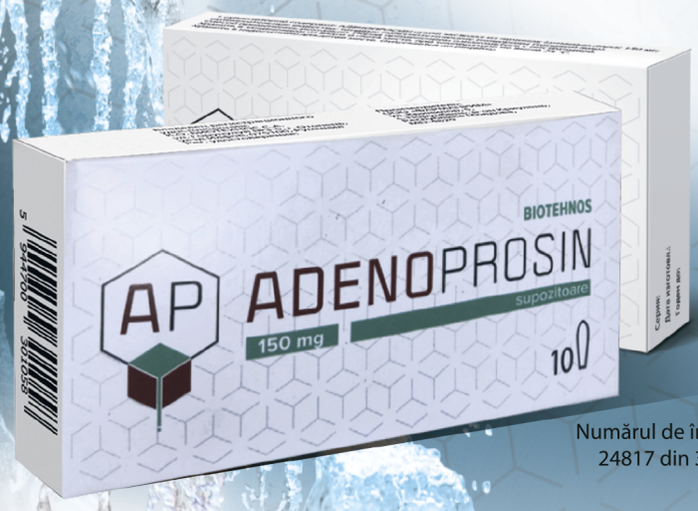

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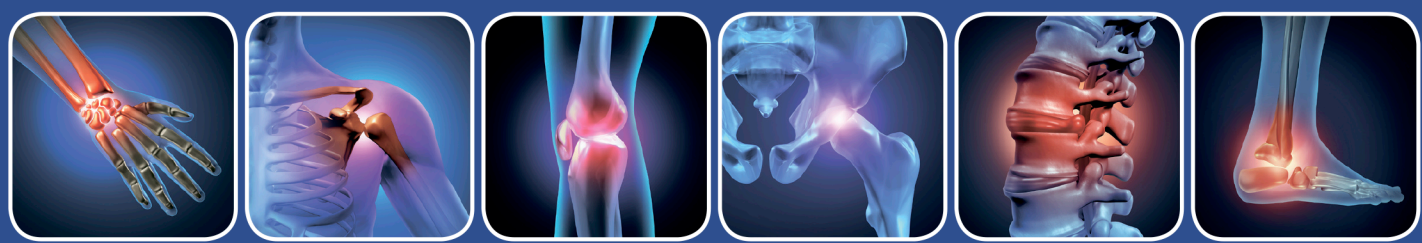
DE DURATĂ



DENUMIREA COMERCIALĂ A MEDICAMENTULUI: AIRTAL 100 mg comprimate filmate. **COMPOZIȚIA CALITATIVĂ ȘI CANTITATIVĂ:** Fiecare comprimat filmat conține aceclofenac 100 mg. **FORMA FARMACEUTICĂ:** Comprimate filmate. **INDICAȚII TERAPEUTICE:** În caz de osteoartrită, artrita reumatoidă și spondilita anchilozantă, precum și alte sindroame dureroase ale aparatului locomotor (de exemplu, periartrita scapulo-humerală și reumatism extraarticular). Pentru tratamentul stărilor dureroase (inclusiv dureri lombare sau dentare și dismenoree primară). **DOZE ȘI MOD DE ADMINISTRARE:** AIRTAL 100 mg comprimate filmate se administrează pe cale orală și trebuie înghițite cu o cantitate suficientă de lichid. Airtal 100 mg comprimate filmate pot fi administrate în timpul meselor. Adulți: Doza maximă recomandată este de 200 mg pe zi, administrată în două prize separate de 100 mg (un comprimat dimineața și unul seara). **CONTRAINDICAȚII:** Aceclofenacul este contraindicat în următoarele situații: Hipersensibilitate la substanța activă sau la oricare dintre excipienți; La pacienții la care administrarea substanțelor cu acțiune similară (de exemplu, acid acetilsalicilic sau alte AINS) precipită crizele de astm bronșic, bronhospasmul, rinita acută sau urticaria sau hipersensibilitate la aceste substanțe; Pacienți cu antecedente de sângerare sau perforație gastrointestinală legate de tratamentul anterior cu AINS. Ulcer peptic/hemoragie active sau recidivante în antecedente (două sau mai multe episoade distincte de ulcerație sau sângerare dovedită); Pacienți cu sângerare activă sau tulburări de sângerare sau tulburări de coagulare (hemofilie); Pacienți cu insuficiență cardiacă congestivă diagnosticată (clasa II-IV NYHA), boală cardiacă ischemică, arteriopatie periferică și/sau boală cerebrovasculară; Pacienți cu deteriorare severă a funcției hepatice sau renale; Sarcină, în special în al treilea trimestru de sarcină, doar dacă sunt motive care să impună acest lucru. **ATENȚIONĂRI ȘI PRECAUȚII SPECIALE:** Utilizarea Airtal concomitent cu alte AINS, inclusiv inhibitorii selectivi de ciclooxigenază-2, trebuie evitată. Reacțiile adverse pot fi reduse la minimum prin utilizarea celei mai mici doze eficace pentru cea mai scurtă perioadă necesară controlării simptomelor. Riscul de sângerare gastrointestinală, ulcerație sau perforație este mai mare la creșterea dozelor de AINS la pacienții cu antecedente de ulcer, în special cei complicați cu hemoragie sau perforație. La pacienții cu antecedente de hipertensiune arterială și/sau insuficiență cardiacă congestivă ușoară până la moderată, sunt necesare monitorizare și recomandări adecvate, deoarece au fost raportate retenție lichidiană și edem în legătură cu tratamentul cu AINS. **REACȚII ADVERSE:** Tulburări gastrointestinale: reacțiile adverse cel mai frecvent observate sunt cele de natură gastrointestinală. Ulcere peptice, perforație sau sângerare GI uneori fatală, mai ales la vârstnici, pot apărea în utilizarea AINS. Pe parcursul administrării de AINS, au fost raportate grețuri, vărsături, diaree, flatulență, constipație, dispepsie, durere abdominală, melenă, hematemeză, stomatită ulcerativă, exacerbare a colitei și boală Crohn. A fost observată mai puțin frecvent gastrita. Reacțiile adverse raportate în asociere cu tratamentul cu AINS au fost edemul, hipertensiunea arterială și insuficiența cardiac. Alte reacții adverse raportate legate de administrarea AINS sunt: Foarte rare (<1/10.000): Tulburări renale și ale căilor urinare: nefrită interstițială. Afecțiuni cutanate și ale țesutului cutanat: reacții buloase, inclusiv sindromul Stevens-Johnson și necroliza epidermică toxică. Clasificare: Grupul II: Acest medicament se eliberează pe bază de prescripție medicală. **DETINATORUL CERTIFICATULUI DE ÎNREGISTRARE:** Gedeon Richter Plc. Gyömrői út 19-21. 1103 Budapest, Ungaria. **NUMĂRUL CERTIFICATULUI DE ÎNREGISTRARE:** 25086. **DATA AUTORIZĂRII:** 29.10.2018. **DATA REVIZUIRII TEXTULUI:** August 2021. ***Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției http://nomenclator.amdm.gov.md/***

DENUMIREA COMERCIALĂ A MEDICAMENTULUI: AIRTAL 15 mg/g cremă. COMPOZIȚIA CALITATIVĂ ȘI CANTITATIVĂ: Un gram de cremă conține aceclofenac 15 mg. **FORMA FARMACEUTICĂ:** Cremă albă. **INDICAȚII TERAPEUTICE:** Tratamentul local al tuturor tipurilor de dureri și inflamații cu diferite cauze locomotorii, incluzând leziuni traumatice. Medicamentul poate fi utilizat pentru ameliorarea inflamațiilor tendoanelor, ligamentelor, mușchilor și articulațiilor, în cazul luxațiilor, entorselor sau contuziei, precum și în tratamentul lumbago, torticolisului și periartritei. **DOZE ȘI MOD DE ADMINISTRARE:** Airtal cremă trebuie aplicat de trei ori pe zi, prin masare ușoară pe zona afectată. Doza aplicată depinde de dimensiunea zonei afectate: 1,5-2g Airtal cremă (aproximativ 5-7 cm). Atenționați pacienții că durata tratamentului fără prescripție medicală în cazul leziunilor musculare și articulare (luxații, entorse, contuzii) și în cazul tendinitelor nu trebuie să depășească 2 săptămâni. Tratamentul fără prescripție medicală în cazul artritei poate fi continuat pentru o perioadă de până la 3 săptămâni. Dacă simptomele se agravează sau nu se ameliorează după 7 zile, pacientul trebuie să se adreseze unui medic pentru o evaluare mai detaliată. Administrare cutanată: Acest medicament este destinat exclusiv uzului extern și nu trebuie utilizat în bandaje ocluzive. După aplicare este necesară spălarea mâinilor, cu excepția cazului când zona tratată este la nivelul mâinilor. Trebuie manifestată prudență astfel încât crema să nu intre în ochi sau în gură. Airtal cremă trebuie utilizat doar pe piele intactă. **CONTRAINDICAȚII:** Hipersensibilitate la substanța activă sau la oricare dintre excipienți. Nu trebuie administrat la pacienții care au prezentat hipersensibilitate la alte AINS. Deși nu a fost stabilită posibila hipersensibilitate încrucișată cu diclofenacul, nu se recomandă aplicarea la acei pacienți care au prezentat hipersensibilitate la diclofenac. Similar altor medicamente antiinflamatoare, aceclofenacul este contraindicat la pacienții la care acidul acetilsalicilic sau alte medicamente antiinflamatoare nesteroidiene produc crize de astm bronșic, urticarie sau rinită acută. **ATENȚIONĂRI ȘI PRECAUȚII SPECIALE:** Dacă utilizarea Airtal cremă produce simptome de iritație locală, administrarea trebuie întreruptă și trebuie inițiat un tratament corespunzător. Nu trebuie utilizat pentru tratamentul plăgilor deschise, mucoaselor sau a pielii iritate (cu eczeme) sau în situații în care zona de aplicare cuprinde orice altă afecțiune cutanată. Trebuie evitată expunerea fără protecție a zonei tratate la radiații solare puternice, pentru a preveni reacțiile de fotosensibilitate. **REACȚII ADVERSE:** Airtal cremă a demonstrat o toleranță locală bună. În anumite cazuri au fost observate iritații locale ușoare sau moderate, însoțite de înroșire a pielii și prurit, aceste simptome dispărând odată cu întreruperea tratamentului. În mod excepțional, în cazul varicelei a fost raportată apariția de complicații infecțioase grave la nivelul pielii și țesuturilor moi în legătură cu utilizarea AINS. Au fost raportări ocazionale de reacții de fotosensibilitate (≥1/1.000 și <1/100) atunci când zona de piele tratată a fost expusă fără protecție adecvată la radiații solare puternice. **DEȚINĂTORUL CERTIFICATULUI DE ÎNREGISTRARE:** Gedeon Richter Plc., Gyömrői út 19-21. 1103 Budapest, Ungaria. **NUMĂRUL CERTIFICATULUI DE ÎNREGISTRARE:** 27870 din 27.05.2022. **DATA REVIZUIRII TEXTULUI:** Mai 2022. **STATUT LEGAL:** Se eliberează fără prescripția medicului. ***Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției http://nomenclator.amdm.gov.md/***

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