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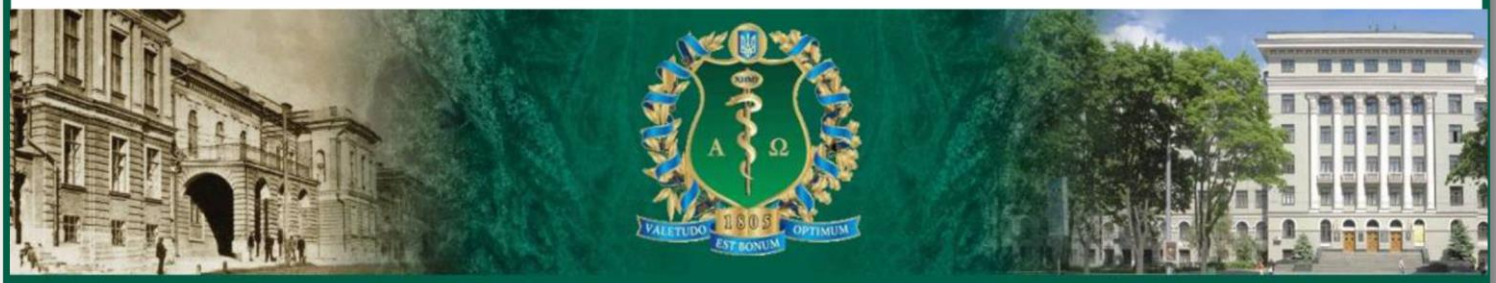

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LEGAL REGULATION OF MEDICAL ACTIVITY IN RUSSIAN EMPIRE BY MEDICAL CHARTER

G.S. Skovoroda Kharkiv National Pedagogical University, Ukraine

Abstract: The article is devoted to the study of legal regulation of county physicians' work in zemstvo medicine. The author determined that the Medical Charter, adopted in 1905, was the first legislative framework regulating medical activities, training, salaries, labour discipline and material responsibility of physicians.

KeyWords: zemstvo medicine, medical activity, physicians, the Medical Charter, legal regulation, duties.

INTRODUCTION

Establishment of healthcare administration (zemstvo medicine) was a significant achievement in the medical field in Russian Empire in the 19th century. The Medical Charter, a codified act in the healthcare sector with three editions (1857, 1892, 1905), was the basic legal document of zemstvo medicine. In turn, the system of zemstvo medicine and the Medical Charters gave a significant place to the so-called medical ranks. Several provisions of the Medical Charters were devoted to legal regulation of working activity of the county physicians. The last edition of the Medical Charter in 1905 was the most complete in this regard.

Conflict of interests

There is no conflict of interests.

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2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of the study was to investigate the provisions of the Medical Charter 1905 in the context of identifying the features of legal regulation of labour in the field of medical activity.

3 RESULTS AND DISCUSSION

First of all, it should be noted that the Medical Charter (1905) was the first document to provide mapping procedure for admission of the medical ranks. Article 43 of the Medical Charter stipulated that "full-time positions shall be appointed to the physicians who were trained at medical faculties of the universities or the Military Medical Academy, or to females, who received the appropriate training" [5, p. 182]. These persons had to possess a certificate (diploma). In the absence of a diploma or in possession of a diploma of foreign countries the candidate's knowledge had to be supported by the certificate of relevant educational institutions of the Russian Empire. Necessary conditions for foreigners to render medical practice also included the ability to speak Russian and taking an oath of allegiance in the prescribed form.

In addition to the conditions for admission to medical activities the Medical Charter regulated the professional duties of medical ranks. Professional duties of physicians

were primarily mentioned in Article 61 of the Medical Charter (1857) which stipulated that "the duties of physicians shall be defined in the relevant institutions and statutes". In 1868 the implementation of the Medical Charter (1857) involved elaboration of service instructions for physicians. According to these instructions county physicians had the following duties: 1) to live in the job area; 2) to manage the hospital, admitting room and pharmacy in medical and economic terms; 3) to receive patients every day in the morning; 4) to be responsible for the storage of potent and poisonous substances; 5) at the first notice of any infectious disease to take immediate measures specified by law, inform the county council and report to the physician; 6) to be under the control and supervision of the elected assembly of healthcare administration [6, p. 12].

Several articles of the Medical Charter expanded job duties of physicians.

Article 54 provided that "every practicing physician shall visit patients who call him in requiring his help" [5, p. 184]. Article 55 contained the following rule: "When a physician is called in by a midwife to a woman in childbirth, he shall come if there are no specific legal reasons hindering him to do so and shall not leave the woman till the end of the childbirth and shall provide all the necessary services" [5, p. 184]. Physicians were obliged to execute medical documentation properly and control selling of medication by the Article 58 of the Medical Charter: "Physicians are obliged to write prescriptions clearly, indicating their rank, name and surname, and observe that the drugs were sold from pharmacies according to their quality and prices determined in the price list. Physicians shall inform the proper authorities on omissions, disorders and abuses of pharmacists, if these omissions and abuses can cause or have actually caused harm to the patient" [5, p. 185].

Fig. 2. "At the physician"
V. Makovskiy (1900)

It should be noted that the Medical Charter described specifics of professional responsibilities of medical ranks. Article 59 of the Medical Charter formulated such a rule: "When healthcare authorities recognize that a doctor has made important errors due to ignorance of his duties, he should be discharged from practice until he passes a new test and gets a certificate to prove his knowledge of the duties" [5, p. 185]. Thus, physicians could be dismissed from practice because of nonobservance of their professional duties.

Article 9 of the Medical Charter provided that "the loss of an instrument shall be recovered by physicians at a specified price; but dulling or damage of an instrument during the operation shall not involve any penalty" [5, p. 177]. So, this provision established the rule regarding physician's responsibility for damage or loss of medical tools.

The order of payment in the field of medical activity was regulated by a number of articles of the Medical Charter. According to the Article 167 of the Medical Charter "medical ranks shall be given salaries and service rights based on the staff scheduling and special provisions" [5, p. 197]. Article 268 of Medical Charter contained the following norm: "Physicians of state-owned establishments, receiving salary, shall be obliged to treat every patient without a fee for medical aid" [5, p. 210]. Article 269 of the Medical Charter contained the following provision on the same subject: "Physicians, receiving salary from the government, are prohibited to demand more payment than defined by law from the poor patients" [5, p. 210]. Article 275 of the Medical Charter determined the amount of payment to physicians "from the poor people" for providing different medical services. According to the Article 277 of the Medical Charter, "a physician who provided medical aid in difficult childbirth, shall take one ruble fifty kopecks as fee for his work from the poor; doctors who receive government salary shall provide medical aid in difficult childbirth to poor women without payment" [5, p. 210-211]. Payment terms from wealthy patients were defined by Article 276 of the Medical Charter: "Physicians are allowed to accept payment exceeding measure, referred to in Article 275 of this Charter, from wealthy people, who want to express their gratitude for medical service" [5, p. 210]. On the one hand, such salary system fixed possibility limits of taking additional fee from the poor; on the other hand, this system did not stimulate physicians to provide quality medical aid to the poor.

It is interesting that the order and payment of shift work were also settled by the Medical Charter. According to the Article 253 of the Medical Charter "county (district) physicians who provide medical aid in regions with shortage of county (district) physicians in addition to their main work shall get a double salary, if they execute their duties for more than a month, and, moreover, with due diligence and serviceability" [5, p. 203]. This provision shows that the reason to attract physicians to work overtime was the lack of staff physicians in the district, and the payment was given for overtime as double salary. Apart from stipulating additional payment for overtime work, Article 262 of the Medical Charter consolidated the right of a county physician for a paid duty journey: "if physician goes outside his official place on the urgent need, he shall be paid by funds in the form of daily allowance and for travel" [5, p. 208]. Article 262 of the Medical Charter specified that "physicians who are on duty journeys shall be paid by the establishments where they work" [5, p. 208].

The Medical Charter 1905 legally settled such important relationships as scientific and practical improvement and promotion of the physicians and other workers in the filed of healthcare. Article 595 of the Medical Charter stated: "Persons willing to receive medical, pharmaceutical or veterinary academic degrees, ranks and assigned rights must pass the test. The tests shall be taken in higher medical and educational institutions authorized by the government" [5, p. 251]. Article 607 of the Medical Charter determined the following "medical degrees and ranks: 1) scientific and practical: a) physician, b) doctor of medicine and surgery; 2) trained for service: district physician; 3)

specially-practical: a) dentist, b) midwife of the first and second rank" [5, p. 252].

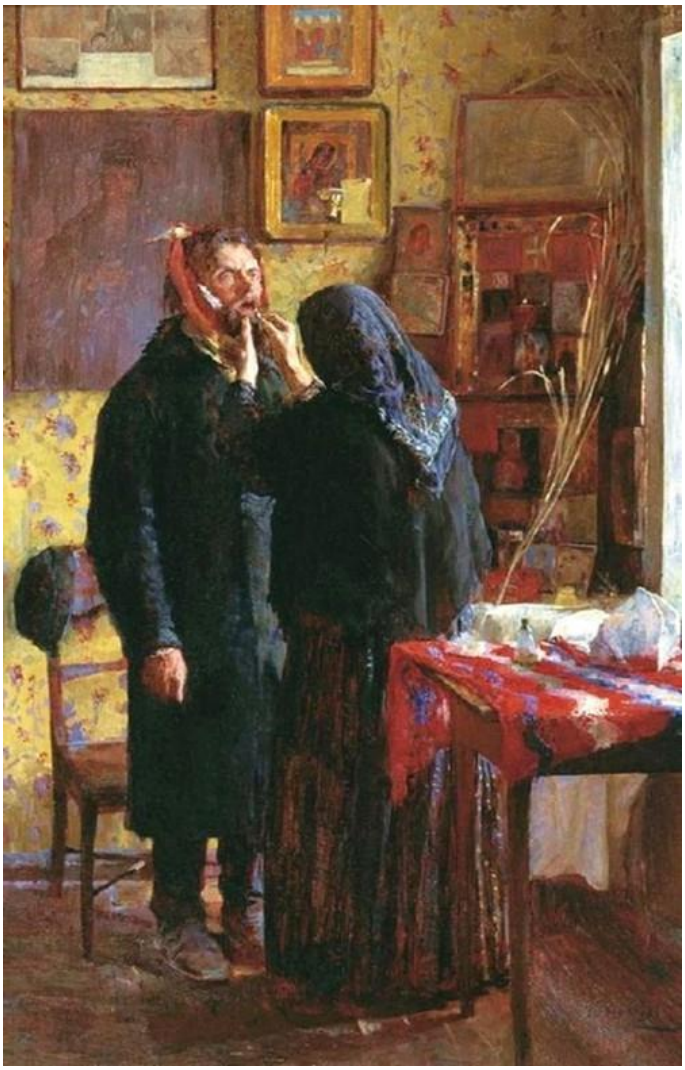

Fig. 2. "At the dentist"
V. Meshkov (1891)

Article 254 of the Medical Charter envisaged an opportunity to get promoted in rank because of high quantity and quality of work, as well as territorial jurisdiction: "County physicians who perform their duties at vacant medical ranks in the same county get additional payment as full salary in Arkhangelsk, Astrakhan, Vologda, Vyatka, Olonets, Orenburg, Ufa, Perm, Caucasus, Siberia and half of the designated salary in other interior provinces" [5, p. 206]. These provisions were aimed at stimulating the development of professional quality of the medical staff.

However, assessing all the positive innovations of the Medical Charter (1905), it should be noted that the legal regulation of labour in the field of medical practice was far from perfect. Problems existed, for example, in standardizing physicians' labour. As M.B. Mirskiy stated, "district hospitals served a certain number of residents in the surrounding restricted area. According to calculations made by county physicians, one hospital is needed for 10 thousand people, and the service radius should not exceed 10 miles" [1, p. 43]. In turn, according to the standards for zemstvo medicine, 2 doctors had to serve 25 thousand residents in Chernihiv [4, p. 300]. In districts the burden on physicians was more uneven. For example, in Konotop district each physician had to provide service to 18 thousand residents with a total area of medical care in the 354 square miles. In Hlukhiv district one physician serviced 60 thousand residents in an area of 1363 square miles [3, p. 122]. As N.M. Pirumova noted, a physician received at least 60 patients a day. During public holidays their number upped to 100 people. The working day lasted at least 12 hours, not counting emergency cases and preparation of drugs [2, p. 106]. Also, the legislature did not consider the impact of special and hazardous working conditions on physicians and other medical personnel. As I.D. Strashun indicated, according to statistics about 60% of county physicians died of typhus [7, p. 114].

Fig. 3. "In the physician's waiting room"
V. Makovskiy (1870)

4 CONCLUSIONS

Thus, Adoption of the Medical Charter in 1905 made a significant development in the legal regulation of labour in the field of medical activity, created the conditions for the improvement of legal support of physicians and established many institutions of labour law in the medical field. The main challenging issues, however, involved improvement of standardization of physicians' work, protection of labour in the medical field, fixation of the duration of working hours and rest time for physicians and other medical personnel.

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CARDIAC SURGERY

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INTRAOPERATIVE TYPE A AORTIC DISSECTION REPAIR (case report)

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Abstract: Iatrogenic aortic dissection (IAD) is a very rare but dangerous complication, which can occur during or after open cardiac surgery, complex percutaneous coronary intervention (PCI), thoracic endovascular aortic aneurysm repair (TEVAR) or transaortic valve replacement (TAVR). Accord-ing to literature, IAD is observed three times more fre-quently during off pump (OPCAB) than conventional coro-nary bypass grafting (CABG). It is also associated with a higher mortality and represents a huge challenge to all cardiovascular professionals including cardiac surgeons who encounter this clinical outcome. Here we present a case of intraoperative Stanford type A aortic dissection during off-pump coronary artery bypass.

KeyWords: Aortic dissection, iatrogenic aortic dissection, type A aortic dissection, Dissection of the thoracic aorta, Stanford classification

CASE STUDY

A 62-year-old hypertensive female underwent triple OPCAB, with saphenous vein grafts to the left anterior descending coronary artery (LAD), first marginal branch of the circumflex coronary artery (Cx) and to the right coronary artery (RCA). The aorta was normal in size and texture. With the use of a partial aortic clamp, we maintained the patient's systolic blood pressure at 90 mmHg during 3 proximal aortovenous anastomoses. Just few minutes after removing the partial clamp, a moderate bleeding from the proximal anastomosis site was observed and the aorta became discolored. Bleeding was stopped by few pledgeted stitches. After transferring the patient to the Intensive care unit (ICU), 4 hours after arrival, acute right leg ischemia was observed and there was suddenly no urine output, despite the diuretics drug therapy. Acute Stanford type A dissection was suspected and the patient was referred to CT-scan (Fig.1).

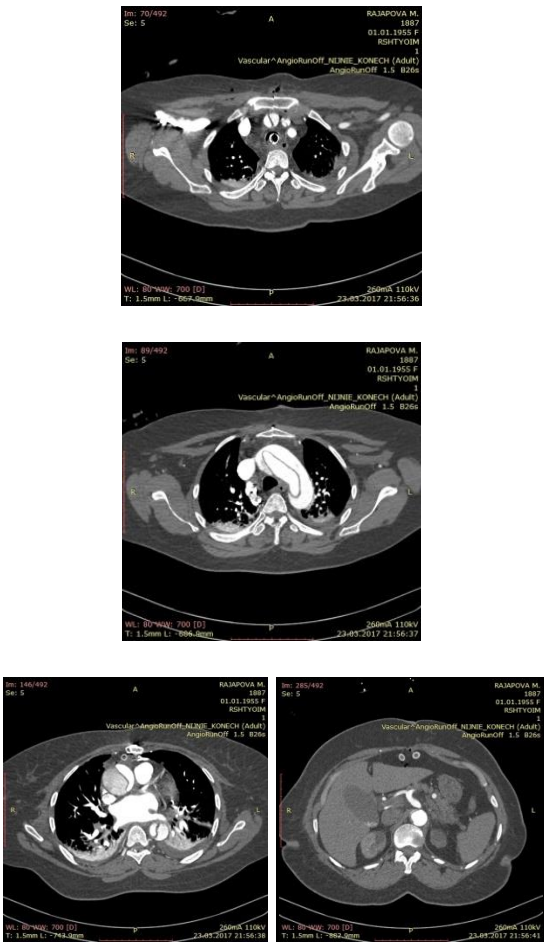

Fig. 1. CT-scan data of 62 y.o. female patient suggestive for type A aortic dissection

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The examination showed a dissection flap that involved the ascending aorta, aortic arch and descending thoracic aorta, with contrast medium filling the true and false lumen—findings that were diagnostic of type A aortic dissection. The patient was urgently transferred in the operating room. The right subclavian artery was canulated using an 8 mm Dacron tube graft and venous return was performed using a two stage canula in the right atrium. The patient's body temperature was cooled down to 18^0C and circulatory arrest with unispheric antegrade selective cerebral perfusion was commended. While opening the aorta, the dissection was localized at the proximal anastomosis of the venous graft to the right coronary artery (RCA) (Fig. 2).

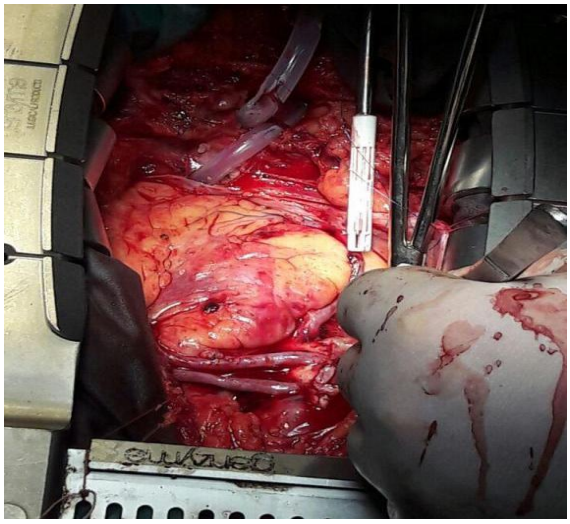

Fig. 2. Aortic dissection at the proximal anastomosis of the venous graft to the RCA

The dissected part of the ascending aorta including all three proximal anastomoses was excised, the surrounding dissected layers of aortic wall were reattached using the "sandwich" technique and first the distal anastomosis using an open anastomosis was performed, to avoid wrong lumen perfusion through the dissected right subclavian artery, the cardiopulmonary bypass was reestablished through the additional side graft of the prosthesis. After the proximal anastomosis using also the "sandwich" technique was finalized, all three venous grafts were then reattached to the Vascutek prosthesis (Fig. 3).

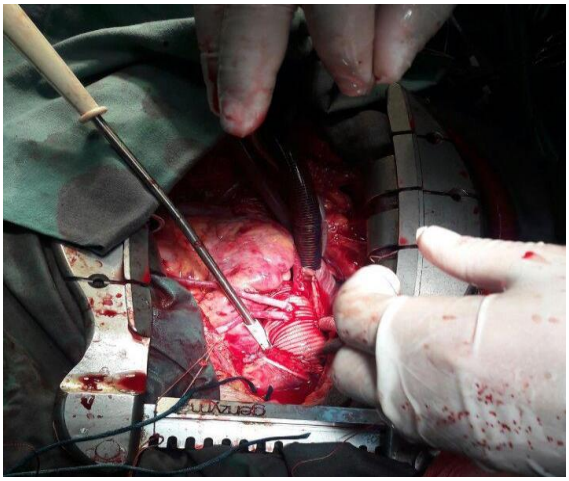

Fig. 3. Completed intraoperative view, ascending aorta is replaced, venous grafts are reattached to the prosthesis

In the postoperative period, the patient developed a coagulation disorder, with a total blood loss of 800 ml. On the third postoperartive day, the patient awoke normally with no signs of brain damage or other organ malperfusion. Unfortunately, on the 11-th postoperative day the patient developed acute respiratory failure and died on the same day.

DISCUSSION

Data Iatrogenic aortic dissection after cardiac surgery is a rare but devastating complication, with higher rate observed intraoperatively than postoperatively [2, 7, 10]. The frequency of aortic dissection is high in patients with severe atherosclerotic disease of the aorta, long-standing hypertension, thin, dilated aortic walls, cystic medial necrosis, and collagen vascular disease [2, 3]. Only immediate recognition and appropriate surgical repair can save the patient. The mortality rate is relatively high and fluctuates between 20% after intraoperative recognition and up to 50% if discovered postoperatively [9]. The risk factors which can lead to this life threatening complication are aortic cannulation, aortic cross-clamps, partial-occlusion clamps, proximal aortic anastomosis, and retrograde dissection from femoral cannulation most of the dissections [6]. Our patient had at least two risk factors: hypertension

and a thinned aorta, which we believe predisposed him to aortic dissection. Other risk factors for dissection include old age and known atherosclerotic disease [2]. Aortic dissection following cardiac surgery can develop intraoperatively, early postoperatively (30 min- 30 days) or late after initial surgery (more than 30 days from cardiac surgery) [11].

Another classification distinguishes late postoperative dissections into acute (patients required intervention within 2 weeks of symptoms) and chronic (late incidentalinding of dissection with no acute symptoms, candidates for elective surgery). Some authors speculated that the use of a partial-occlusion clamp on the pulsating, sometimes diseased aorta could increase the risk of iatrogenic aortic dissection during OPCAB [3, 4]. In 2001, there were publications describing experience with 2 instances of early postoperative aortic dissection and 1 of intraoperative dissection in OPCAB group, and only 1 intraoperative dissection in the on-pump CAB group [2]. According to some data it could be suspected that, in the absence of autopsies, some sudden deaths after OPCAB were also secondary to rupture of unrecognized early postoperative dissection and not to the terminal catastrophic events that are usually invoked [1]. Some authors also stated that the total number of iatrogenic aortic dissections is likely underestimated, and in reality postoperative aortic dissection underlies 3% to 5% of deaths after cardiac surgery [4]. Intraoperative aortic dissection is easily recognized due to the presence of a rapidly expanding hematoma. But sometimes it could be underestimated due to inexperienced team, like in our case. Early dissection after OPCAB is not always easily diagnosed. It may be missed in patients who experience no pain, and it may be confused with more common complications of coronary artery bypass surgery (for example, myocardial infarction, graft occlusion, left ventricular dysfunction,or arrhythmias), leading to crucial delay and possibly to sudden death from rupture of the aorta. Having high level of suspicion (suddenly discolored aorta and bleeding during previous surgery), could help not to lose the time. Among the most ominous signs and symptoms of early dissection after OPCAB are signs of malperfusion, more typical tearing chest and back pain or the sudden loss of peripheral pulses after OPCAB should readily suggest the correct diagnosis.

CT-scan with intravenous contrast is the most important diagnostic option for timely diagnosis of the early postoperative aortic dissection. On CT-scan you can find a typical flap in the ascending aorta that may extend to the aortic arch and the descending thoracic aorta, and contrast medium maybe found in the true and false lumina [8]. These findings are pathognomonic of type A or DeBakey type I acute aortic dissection and should prompt immediate surgical attention.

The dissection can be repaired in fashion similar to acute spontaneous aortic dissection, although with a much higher mortality rate. There are two pattern to repair of dissected aorta by local replacement of the dissected aortic segment with a patch graft or by replacement of the entire ascending aorta with a tube graft, followed by reimplantation of the veins in both cases [13].

Some dissections had specifically associated histologic findings, such as cystic medial necrosis; and inflammation signs and endothelial desquamation others had no specific associations other than aortic layers separated by hematoma [5]. Intraoperative or early postoperative dissection is more prevalent in OPCAB, probably due to a pulsatile pattern of arterial pressure during application of a side-biting clamp and performance of the proximal anastomoses.

Avoidance of cross-clamping or partial clamping the aorta and performing the total arterial revascularization may prevent this complication, but its efficacy is under the question in elderly insulin dependent diabetic patients. Therefore, some authors advice to maintain low systemic pressure (80 mmHg) controlled pharmacologically or by partial clamping the inferior vena cava, during proximal anastomoses formation [12,14].

CONCLUSIONS

Surgical Aortic dissection after cardiac surgery is a rare but extremely dangerous complication, accompanied by a high risk of death. It can be observed at any time, both intraoperatively and at various times after the operation. A

high level of alertness and the presence of characteristic symptoms of malperfusion can help in timely diagnosis. At the same time, the importance of computed tomography with intravenous contrast should not be underestimated. Timely surgical intervention consisting in replacement of the ascending aorta under the circulatory arrest and antegrade perfusion of the brain can save the patient's life.

Conflict of interests

There is no conflict of interests.

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CARDIOLOGY

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METFORMIN AND LEFT VENTRICULAR HYPERTROPHY IN PATIENTS WITH COMORBIDITY

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Abstract: Essential hypertension (EH) remains an important challenge, due to leading positions in morbidity and mortality not only in Ukraine, but also worldwide. Recent studies have suggested that metformin can inhibit cardiomyocyte apoptosis and improve cardiac function. Aim of the study was to investigate metformin influence on left ventricular structure and function in patients with essential hypertension with concomitant type 2 diabetes (T2D). Materials and methods: the study involved 120 patients with essential hypertension (EH), who were divided into three groups according to comorbid state: 60 patients with EH and T2D; 30 with EH with prediabetes; 30 with EH without dysglycemia. Carbohydrate criteria, left ventricle structure and function were analyzed before and after 12 weeks of metformin treatment. Results. Metformin treatment results in fasting glycaemia and insulin resistance diminished by 21.79 % and 26.84 %. Echocardiography in 12 weeks metformin treatment showed a significant decrease in left ventricle myocardium mass by 6.1 % and left ventricle posterior wall thickness by 2.3 %. More pronounced changes in patients with EH and T2D were associated with glucotoxicity, lipotoxicity, a decrease in insulin resistance and pleiotropic metformin effects. Conclusion. Metformin has positive influence on the structure and function of left ventricle, increasing EDV and LV hypertrophy regression. These findings may provide a potential effectiveness for patients with T2D at risk of developing pathological cardiac hypertrophy.

KeyWords: essential hypertension, type 2 diabetes, left ventricle hypertrophy, metformin.

INTRODUCTION

Essential hypertension (EH) remains an important public challenge, because of its leading positions in morbidity and mortality not only in Ukraine, but also worldwide [1]. Hypertension in obese patients in over 60% of cases is associated with glucometabolic disturbances, such as insulin resistance and glucose intolerance [2].

Moreover, diabetes develops in 2 % of treated hypertensive patients every year [3, 4]. Pathological left ventricular hypertrophy is a crucial pathological condition that triggers several serious cardiac events, including arrhythmias, heart failure, and sudden death. Recent studies have suggested that metformin can inhibit cardiomyocyte apoptosis and improve cardiac function [5]. However, whether metformin has an inhibitory effect on cardiac hypertrophy hasn't been clarified.

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2.1 Purpose

Aim of the study was to investigate metformin's influence on left ventricular structure and function in patients with essential hypertension with concomitant type 2 diabetes (T2D).

2.2 Subjects & Methods

The study involved 60 patients with EH and T2D, who were examined according to National and European Recommendations of T2D Treatment [6, 7]. Metformin was prescribed after titration period in average dosage of 1000 – 2000 mg. Comparison group comprised 30 patients with EH and prediabetes. Also 30 patients with EH without accompanied dyglycemia were recruited in the study. Antihypertensive treatment was similar in the groups. Taking into account that metformin is not allowed for prescription to the patients with prediabetes, such patients received life style modification recommendations. The results were analyzed before and in 12 weeks treatment period. The aim of antihypertensive treatment was to achieve the level of arterial pressure of ≤ 140/85. Antiglycemc treatment was consideredsuccessful in case of HbA1c level ≤ 7 %.

Inquiring, inspection and laboratory investigations were provided according to the recommendations of Ukrainian Society of Cardiology and ESC/ESH recommendations [8]. The study was approved by local institutional review board committees, and all participants provided written informed consent. All subjects underwent measurements of height, weight at the baseline visit. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m2). Three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken using a standardized sphygmomanometer on the right arm, after a 15-minute rest in a sitting position; the average of the three measurements was used as subject's blood pressure. A blood specimen was collected after overnight fasting into a tube with further centrifuging and freezing for investigations. Carbohydrate metabolism was evaluated on the basis of plasma glucose, insulin, glycated hemoglobin (HbA1c) that were measured both at fasting, and after 120 min of standard glucose tolerance test (OGTT). For insulin measurements the laboratory set DRG® Insulin (DRG Instruments GmbH, Germany, Marburg) was used.

Echocardiography was rendered to all the patients. M- i B-regimens of echolocation according to Ukrainian and European recommendations were used to estimate the structure and function of the left ventricle. [9]

Statistical representation of the results is mean and standard error of mean (M±SE). The difference between groups was calculated using Kruskal-Wallis test. A p value of less than 0.05 was considered to be statistically significant.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Last decade showed many cardiovascular effects of metformin, which seemed significant in prophylaxis and control of cardiovascular diseases. First UKPDS study showed a 36 % decrease in all deaths, 42 % in T2D, a 39 % decrease in myocardial infarction lethality and 41 % in stroke [10].

Scientific data suggest that cardioprotective effects of metformin are associated with lipid the enhancement of metabolism, improvement of endothelial function and vessel reactivity, control of hemostatic disorders [11 - 13].

As previously shown in our study, metformin treatment resulted in a decrease in fasting glycemia and insulin resistance by 21.79 % and 26.84 % and reduction in abdominal fat deposition by 5.54 %. Improvement of endothelial function in metformin treatment was associated with an increase in endothelial nitric oxide synthase by 8.43%, a decrease in inducible nitric oxide synthase by 20.62 %, with nitric oxide bioavalibility enhancement by 36.6 % by decreasing S-nitrozothiol level. Twelve weeks of metformin treatment showed a positive trend not only in carbohydrate and lipid parameters with insulin sensitivity and endothelial function improvement, but it also resulted in an increase in apelin level by 33.3 %, attenuating of vascular endothelial growth factor by 22.0 %, a decrease in oncostatin M and interleukin-6 by 18 % and 15 %, respectively. [14, 15]. Therefore, assessing the obtained data, we are looking for metformin impact on LV. Table 1 presents criteria of LV structure and function according to dysglycemia level. Linear sizes were found to increase in patients with EH and comorbid state as compared to patients with EH without dysglycemia. LV myocardial wall thickness and LV myocardial mass were significantly higher in case of EH and T2D comorbidity.

Table 1.
Left ventricle structure and function criteria in patients with EH according to comorbid state, Me±SE.

Group / Parameter	Patients with EH	Patients with EH and prediabetes	Patients with EH and T2D	p (Kruskal-Wallis ANOVA)
EDS, cm	4.86±0.05	5.05±0.07	4.91±0.07	>0.05
ESS, cm	3.08±0.05	3.30±0.05	3.14±0.06	>0.05
EDV, ml	112.21±2.8	122.44±4.3	115.70±3.8	>0.05
ESV, ml	38.39±1.48	45.96±3.37	40.82±2.08	>0.05
PWT, cm	1.14±0.01	1.12±0.02	1.18±0.02	<0.05
LVMM, gr	214.51±6.	213.44±8.4	224.96±8.8	<0.05

EDS – end-diastolic size; ESS – end-systolic size; EDV - end-diastolic volume; ESV – end-systolic volume; PWT – posterior wall thickness; LVMM – left ventricle myocardial mass

Echocardiography in 12 weeks of metformin treatment (Table 2) showed a significant decrease in LVMM by 6.1 %, LVT by 2.3 %. Patients with EH with concomitant prediabetes and without comorbidity were not shown to have significant differences in LV EDV, PWT, LVMM. More pronounced

changes in patients with EH and T2D were associated with glucotoxicity, lipotoxicity, a decrease in insulin resistance and pleiotropic metformin effects [16].

Table 2

LV structure and function parameters in patients with EH and T2D after 12 weeks metformin treatment, as compared to patients with EH and prediabetes and ones without comorbid state.

Parameter / Group	EDS, cm	ESS, cm	EDV, ml	ESV, ml	PWT, cm	LVMM, g
Patients with EH	4.66± 0.05	3.04± 0.05	109.9 ±1.95	37.92 ±2.02	1.11± 0.02	211.21 ±5.85
Patients with EH and prediabetes	5.01± 0.02	3.25± 0.05	120.9 ±3.12	45.06 ± 2.65	1.11± 0.02	210.30 ±6.02
Patients with EH and T2D	4.78± 0.05	3.10± 0.02	112.8 ±2.65*	40.78 ±2.01	1.15± 0.02*	211.46 ±5.41*
p (Kruskal-Wallis ANOVA)	>0.05	>0.05	<0.05	>0.05	>0.05	<0.05

*- p <0.001 (Wilcoxon test), comparing to data before treatment; EDS – end-diastolic size; ESS – end-systolic size; EDV - end-diastolic volume; ESV – end-systolic volume; PWT – posterior wall thickness; LVMM – left ventricle myocardial mass

The MET-REMODEL, a double blind, randomized, placebo-controlled trial showed that metformin was effective in regression of the independent cardiac risk factor of LVH in insulin resistant patients with CAD. Positive result may help clinicians identify a new mechanism for LV regression by administering metformin. This may also lead to investigating the mortality benefit of Metformin in patients with CAD and LVH [17].

Metformin is known as an activator of AMP-activated protein kinase (AMPK). Zhang C.X. et al. used cultured cardiomyocytes to examine the effects of metformin on the AMPK-endothelial NO synthase (eNOS) pathway. The findings of the study indicated that long-term treatment with metformin could attenuate ventricular hypertrophy induced by pressure overload via activation of AMPK and a downstream signalling pathway involving eNOS-NO [18]

The investigation of the Yong-nan Fu revealed that long-term administration of metformin may attenuate cardiac hypertrophy induced by pressure overload in nondiabetic mice, and this attenuation is highly dependent on AMPK activation. [19]

Therefore, we speculate that metformin has positive influence on the structure and function of left ventricle with increasing of EDV and LV hypertrophy regress.

4 CONCLUSIONS

Pleiotropic effects of metformin resulted in LV hypertrophy regression by 6.1 % in LVMM, and 2.3 % in LV PWT in patients with EH and T2D. These findings may provide a potential effectiveness for patients with T2D at risk of developing pathological cardiac hypertrophy.

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PEDIATRICS

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MODERN VIEWS OF GERD IN CHILDREN: PROBLEMS AND PERSPECTIVES (review)

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Abstract: Much attention has recently been paid to the upper digestive tract diseases in children, particularly GERD, as it has an impact on quality of life even in children of school age and thereafter in young adults. Scientists came to a consensus that all kinds of examination used in pediatric practice must be maximally available, simple and non-invasive to the extent practical for the child's condition. The question about practicability of performing esophagogastroduodenoscopy for all patients with heartburn and other symptoms of GERD, the question relative to performing ultrasonography of the esophagus for children as an additional method of examination, usage of questionnaire in pediatric practice, formation of disease course prediction algorithm, and identification of preventive measures specific to every patient remains disputable. Therefore, the goal of this research is to provide an overview of modern literature with reference to problematic issues of clinical evidence, risk factors, diagnostics, prediction of gastroesophageal reflux disease course in children of different age (regarding main causative and pathogenic factors, clinical evidence (esophageal and extra-esophageal), diagnostic methods and modern approaches to gastroesophageal reflux disease treatment).

KeyWords: gastroesophageal reflux disease, non-invasive diagnostics, risk factors, prognosis of the course.

Gastroesophageal reflux disease (GERD) is a chronic recurrent disease associated with disorders of motor-evacuation function of gastroesophageal tract which is characterized by established esophageal and extra-esophageal clinical evidence as a result of spontaneous and/or regular backflow of stomach or duodenal content into the esophagus that results in physicochemical damage of the distal segment of the esophagus [1, 2].

GERD is a current problem in modern gastroenterology specified by high disease incidence, a great number and variety of complaints raised by patients, development of severe complications (Barrett esophagus and adenocarcinoma of the esophagus) as well as necessity for long-term therapy [3].

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GERD is one of the most widespread diseases of the digestive system in the Western world with typical symptoms such as heartburn, belching or retrosternal pain and constitute 15% - 20% from overall population. In Asia this number is significantly less and constitutes approximately 5% [4], though over the last years the tendency for morbidity increase is also observed.

GERD incidence in children is uncertain since application of invasive methods of examination (pH measurement and endoscopy) particularly in young children is significantly limited. In the structure of gastroenterological morbidity according to different authors it constitutes 8 to 25% [5, 6].

The significant point is that the risk of digestive system diseases in children is higher than in adults, disease progresses in less time with increasingly frequent and long-lasting recurrence.

The incidence rate of gastroesophageal reflux disease (GERD) has been noted around the world; however, there are significant differences in terms of its frequency in children from 8.7 to 49%. In Ukraine the prevalence rate of GERD (0.83%) and the incidence rate of GERD (0.29%; 2014)

are significantly less than in other countries that may indicate poor education of professionals in the matter [7].

High prevalence of heartburn as a principal symptom of GERD in the world and Ukraine in combination with invasiveness of research, high cost of diagnosis and treatment is a significant social and economic problem of the state health care system. Particularly well-timed screening diagnosis and identification of disease course prediction algorithms and creating specific prophylactic events can prevent development of complications and severe forms of GERD that will significantly reduce costs for long-term treatment and improve the life quality of patients.

Pathologic gastroesophageal reflux onset can be associated with incompetence of cardia, esophagus clearance disorder, and stomach and duodenum motility disorders. Esophagus clearance disorder and gastroduodenal motility disorder are often associated with autonomic nervous system function disorder of different origin. Important favorable factors of GERD development are obesity, non-differential dysplasia of connective tissue, and sliding esophageal hiatal hernia. Contamination and ablation of Helicobacter pylori (Hp) do not play a critical role in GERD genesis [8].

Several meta-analyses showed statistically significant low prevalence of Hp related to GERD [9], as well as Barrett esophagus [8, 10] or esophageal adenocarcinoma [11]. However, ablation of Hp does not affect the course of already present GERD and does not influence the effectiveness of treatment with proton pomp inhibitors (PPI) [12].

Gastroesophageal reflux disease is characterized by a complex of clinical symptoms that occur in response to backflow (reflux) of stomach content into the esophagus and proceeds with occasional recurrences and assumes progressive nature [2, 13, 14].

The symptoms of GERD are quite various and numerous, and can be esophageal and extra-esophageal. Clinical implications significantly depend on the child's age and presence of comorbidity and risk factors.

Esophageal symptoms include the following: heartburn, regurgitation, belching, dysphagia, odynophagia (pain when swallowing) that occurs more frequently in the presence of erosive ulcerated lesions. Nonspecific symptoms for reflux disease that occur more rarely and can be associated with other diseases are as follows: hiccup, vomiting, sensation of a lump in a throat, sensation of excessive amount of liquid in the mouth, throat irritation, burning tongue, etc. Duodenogastroesophageal reflux onset is frequently followed by bitter taste in the mouth, yellow coated tongue [15, 16, 17].

The character of clinical manifestations is influenced by changes in other organs of the digestive system, first of all gastroduodenal pathology which is followed by GERD in a great number of cases. Modern studies showed high frequency of GERD association with functional pathology of organs of the digestive tract particularly with irritable bowel syndrome and functional dyspepsia. Frequent association of GERD with functional disorders of gastrointestinal tract is not accidental and based on their common pathophysiological mechanisms [18].

In addition to significant progression of its incidence and severity, GERD importance is also based on extra-esophageal clinical manifestations and its diagnosis requires extended cycle of laboratory, instrumental methods of examination and collaboration of doctors of different specialties, and in establishing diagnosis they influence the duration and the structure of treatment (Bardhan K.D. et al., 2007, Mayev I.V. and other., 2014).

Children with GERD also complain of belching that is spontaneous backflow of small amounts of food and air or only air into oral cavity. Such belching is a less specific symptom of GERD because firstly it demonstrates an increase in gastric pressure and to a lesser extent depends on presence and activity of GERD [19, 20].

When it comes to heartburn, regurgitation, and belching, attention should be paid to absence of one definition of these terms. It is also necessary to admit that there is no conclusive focus on a regular pattern and frequency of heartburn as a symptom of GERD. Thus, according to Genval Congress recommendations diagnosis of reflux disease can be performed in cases where heartburn occurs twice or more times per week. At Montreal Congress of gastroenterologists international panel 44 specialists from 18 countries

all over the world came to a decision to consider heartburn as a symptom of GERD even if it occurs once a week [17, 20].

More than 60% of children complain of dull pain in epigastric and substernal cavities which appears immediately after meal, increases with trunk bending and reduces after some 1.5-2 hours.

Researchers have recently started paying attention to extraesophageal (atypical) manifestations of gastroesophageal reflux disease because such clinical pattern simulates different diseases. Atypical manifestations of GERD include bronchopulmonary, otolaryngeal, cardiac and dental symptoms. At an early age, the most common are extraesophageal symptoms on the part of the bronchopulmonary system and ENT organs. This association is due to similarity of anatomical relations between the respiratory and digestive systems, and also the same embryological origin [20].

Pathogenesis of GERD is multi-factorial. Comprehension of these factors has recently been sufficiently improved due to understanding of acid pocket and hernia of diaphragm esophageal opening, as well as the interaction between these factors. In spite of recently increased understanding, more investigations should be performed for better comprehension of GERD symptoms, particularly in patients resistant to symptomatic therapy. [17, 21, 22, 23].

By general consent, scientists define GERD as an acid-dependent polysystemic disease because hydrochloric acid is considered to be the main pathogenic factor. The determining risk factors of GERD development in children include disorder of motor-evacuation function of the upper digestive tract, a decrease in resistance of esophageal mucous membrane to hydrochloric acid action, an increase in gastric content aggressiveness, insufficient cardia (absolute or relative), an increase in intragastric and intra-abdominal pressure, a dysfunction of autonomic nervous system, fast growth, heredity, compromised perinatal history, non-differential dysplasia of connective tissues structures and also factors of environment and lifestyle such as: overweight, harmful eating habits, absence of regular physical activity, disproportion of the growth of body and esophagus, consumption of alcohol drinks, smoking in adolescence [15, 16, 24-27].

Duodenogastric reflux is considered to be a complicated factor. In alkaline (biliary) and mixed reflux inflammatory destructive changes of mucous membrane are manifested more than in isolated acid aggression. Presence of both refluxates in esophageal cavity causes risk of columnar epithelium lined lower esophagus (Barrett metaplasia) and esophageal malignancy. In particular, biliary acids increase the activity of COX-2, thereby intensifying proliferation processes [17, 28, 29].

As for probable pathogenic connection between GERD and Helicobacter pylori there are still discussions often expressing polar opinions concerning this issue. HP is considered to be determined mostly in patients in mild diseases while in severe diseases (esophagitis of III-IV stages) it is found only in 16% of patients. R. Heading, a famous gastroenterologist from Great Britain, performed a comparative analysis of conservative treatment results in a great number of patients suffering from GERD depending on their “helicobacter status” which showed that the frequency of clinical and endoscopic remission depends not on the presence or absence of H.pylori but on the evidence of changes in esophageal mucous membrane [10]. There are no precise conclusions concerning H. pylori as a protective factor in respect of GERD occurrence.

GERD diagnosis is based on combination of diagnostic criteria such as: clinical, endoscopic, histologic, roentgenologic, manometric, etc. According to the world experience early diagnosis of GERD dramatically reduces the risk of complications [18, 24, 30-33].

According to international consensus, GERD is a clinical diagnosis; thus, thorough history taking gives a possibility to determine the symptoms associated with gastroesophageal reflux. Basing on national guidelines and clinical recommendations of many countries in Europe and the USA concerning primary diagnosis, this method is the main to identify complications and the onset of treatment at screening stage – qualitative evaluation of clinical symptoms may be more resultant than instrumental methods of diagnosis, which relevance should be estimated by the invasiveness and difficulty of performance in children.

Instrumental methods of investigation are additional or diagnosis confirming [32].

The use of different methods for studying of GERD prevalence has a number of difficulties such as the high cost of large-scale investigations and lack of agreement from great part of people for invasive tests. Therefore, nowadays investigators are studying the opportunity of creation of unified questionnaire which will help to conduct a survey of patients regardless of the country where epidemiology of GERD is studied [34, 35]. Besides, special questionnaire is used to determine specific clinical manifestations associated with GERD in children of early age [2, 6, 7, 16, 32, 36].

Both in Ukraine and in the whole world the main method for clinical diagnosis of GERD is intraesophageal pH-metry which is performed by introducing pH-probe into the distal segments of esophagus and its fixation there for a long time (pH daily monitoring). This method is characterized by high sensitivity in GERD diagnosis and helps to choose individual tactics for the case management. GERD confirmation by pH monitoring is not recommended in the following cases: uncomplicated GERD if test results are not necessary in treatment or prognosis, dysphagia, pain in epigastrium, positive results of other methods of investigation.

Contrast X-ray study is a sufficiently informative method of diagnosis of diaphragm esophageal opening hernia, determination of gastrointestinal tract abnormalities which destroy its motor activity (phrenospasm, diverticula, coarctation, etc.), but this method of diagnosis is rarely used in pediatrics.

Additional methods for determination of GERD risk factors can include the following: diagnosis of reflux-esophagitis in children by echographic investigation of abdominal part of esophagus and cardial section of the stomach which is performed to investigate thickening of esophageal wall, edge roughness of esophageal wall, increase in esophagus diameter after liquid contrasting (not during swallowing), widening of esophageal lumen (not during swallowing); manometry of esophagus – this method helps to register pressure in different parts of esophagus, its ability to relax while swallowing, contracting function of esophagus and also to evaluate the character of peristaltic waves; impedansometry is based on measurement of electric parameters of intraesophageal environment while introducing gastric contents into the esophagus; investigation is performed with the help of intragastric impedance probe and reogastrograph.

Invasiveness of this method in children as in pH-metry limits its application. Due to specialists' interest regarding GERD co-morbidity with other diseases of the digestive, ENT and respiratory organs and also with great attention to the increased atypical and extraesophageal symptoms it is necessary to develop algorithms of additional individualized investigation according to the identified extraesophageal symptoms.

Taking into consideration significant prevalence of GERD, variability of clinical manifestations, severe extraesophageal symptoms, presence (sometimes combination) of risk factors which lead to GERD development or complicate its course in children and teenagers, probability of serious complications and continuous worsening of life quality determine medical and social character of gastroesophageal disease. Its relevance proves the necessity of further search in the study of pathogenesis and clinical manifestations of GERD to improve diagnosis, individualize case management and predict the course of gastroesophageal reflux disease.

Conflict of interests

There is no conflict of interests.

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PEDIATRICS

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PARTICULAR QUALITIES OF THE TREATMENT IN PRE-SCHOOL AGE CHILDREN SENSITIZED TO HOUSE DUST MITES ALLERGEN

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Abstract: *Background.* This study determined the efficacy of sublingual allergen-specific immunotherapy (SLIT) in Ukrainian children younger than 5 years of age with allergic rhinitis and bronchial asthma sensitized to house dust mite allergens. *Methods.* A cohort prospective study was conducted over a two years period with assessment of the sensitization towards inhalant allergens, measured in-vivo by wheal size and number of positive reactions on the standard skin prick test (SPT). SPSS was used to analyse any statistical correlation. *Results.* A total of 125 atopic asthma or/and allergic rhinitis with the mean age of 4.11 ±0.83 who were sensitized to house dust mites Dermatophagoides pteronyssinus and/or Dermatophagoides farina were included. 47 children received two-years SLIT to treat house dust mite allergies using standardized extract of sublingual allergens containing a mixture of house dust mites (Der. pteronyssinus and Der. farinae) in the correlation of 1(0,175 HEP):1(0,175 HEP) (Diater, Spain). These patients were mono-sensitized with Der. pteronyssinus and Der. farinae or were SPT poly-sensitized, but these patients only had house dust mite allergy symptoms. In this group the assessment of clinical efficacy of SLIT showed the significant differences in VAS before treatment and 6 months after its receiving. The symptom "nasal obstruction" was assessed as 2.3±-1.6 points at the beginning of the therapy, and the data reduced almost twice (1.3±-1.1); P <0,05 after 6 months of SLIT; then (12 and 24 months) it decreased to 0.91±0.9 and 0.34±0.5; P <0,01, correspondingly. *Conclusion.* This study has shown that using of SLIT in atopic asthma or/and allergic rhinitis children under 5 year sensitized to house dust mites is an effective and safe treatment method and allows to quickly (over the first 6 months of SLIT) control the symptoms. The data of comparative analysis in the group of patients who didn't receive SLIT has pointed to high frequency of disease symptom occurrence after the end of baseline therapy.

KeyWords: sublingual allergen-specific immunotherapy, children, bronchial asthma, allergic rhinitis, sensitization, allergens, Diater.

INTRODUCTION

High frequency and increasing number of allergic diseases all over the world indicate the necessity for further study of the problem that seems to have been well-studied. The search of new possibilities to diagnose and therapy methods related to them are a strategic task which are determined by WAO for the next decade. A feature of allergic diseases in children is transformation of one form into the other. This process is characterized by relative instability of clinical manifestations of allergy when some symptoms regularly prevail over the other ones in a child [2,7,12,16].

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There are many examples when patients are sensitized to several allergens at the same time. Sensitization to allergenic molecules is one of the main etiological factors in the pathogenesis of development of allergic inflammation. However, in many cases exposure to a particular allergen cannot be completely avoided. Available medical therapies are not always fully effective or well tolerated. [8,14,15]. The efficacy of ASIT in the treatment of allergic diseases of adults and children has been proven and it is represented by the results of numerous randomized double-blind placebo-controlled studies which have resulted in the issuance of the corresponding European and international guidelines [3,11]. But the treatment of children with the use of immunotherapy methods is being discussed [5,9,10,13]. First of all, it is connected to the issues of safety and administration convenience. A wide interest in the new forms of ASIT is also related to the situation of the appearance the symptoms disease which is characteristic for more advanced stages in early-age children. That is why the study

of the issues related to timely prescription of SLIT (as a more comfortable and safe form for children) and the study of its effect on coming to control allergic symptoms and prevention of disease progression can be considered as one of the units of the strategic direction suggested by WAO.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

The aim of this study was to evaluate the effectiveness of SLIT application in children under 5 with allergic rhinitis (AR) and bronchial asthma (BA), sensitized to domestic house dust mite allergens.

2.2 Subjects & Methods

Study population

This cohort prospective study was conducted at the National Children Hospital "OHMATDYT" and Children Outpatient Clinic "OHMATDYT" in Kyiv, Ukraine. This study was performed over a two-year period starting from September 2013. The study involved children with diagnosed bronchial asthma or/and allergic rhinitis who presented to the clinic during this period. Clinical diagnosis AR and/or BA in the intermittent or mild persistent / moderate persistent form – controlled was determined following ICONs criteria (2012).The clinical parameters chosen for assessment of asthma control were: diurnal symptoms, nocturnal symptoms, limitation of activities, need for relievers or rescue medications, presence of exacerbations and measurement of peak expiratory flow (PEF) or forced expiratory volume (FEV1) (according to age) at the clinic visit.

Four hundred and fifty children aged 36 months - 5 years were examined. The inclusion criteria were: severe and/or uncontrolled BA, children who were treated SLIT at the previous stages, children who have contraindications to SLIT. According to inclusion criteria: age from 36 months to 5 years, clinical diagnosis AR and/or BA in the intermittent or mild persistent / moderate persistent form – controlled, determined following ICONs criteria (2012), sensitization to domestic allergens of house dust mites Der. pteronyssinus and/or Der. farinae 125 (27.7%) atopic asthma or/and allergic rhinitis children were selected for further study (according to skin prick tests data).

All children were subjected to the following procedures: diagnostic procedure analysis (allergic history, skin prick test and specific IgE). Clinical monitoring was provided every 6-12-24 months during outpatient clinic visits. Skin prick tests, allergen specific IgE assessments, allergic history assessments (rhino-conjunctivitis symptoms, bronchial asthma episode, skin manifestation) and overall examinations were conducted.

Accordingly, patients were classified into two groups: I. Bronchial asthma or/and allergic rhinitis in children who received a two-year immunotherapy course using sublingual allergens containing a mixture of house dust mites (Der. pteronyssinus and/or Der. farinae) in the correlation of 1 (0,175 HEP):1(0,175 HEP) Diater, Spain

The control group included the children with house dust mite allergies, AR and/or bronchial asthma that only received symptomatic treatments and not SLIT. More detailed data are shown in Table 1.

The study protocol was approved by the Bioethical Commission of the Shupyk National Medical Academy of Postgraduate Education. Informed consent for research was given by the parents of all patients.

Skin prick test

Skin prick test was carried out on the flexor aspect of forearm avoiding the wrist and antecubital fossa. The forearm was coded with a marker pen for the allergens to be tested spacing the tests out at about 3 cm. A drop of the extract was deposited on the indicated position. The skin was then pricked vertically through each drop using a standardized prick test needle (Immunolog). The extract solution was wiped away with a tissue paper. Result was read after 15 to 20 minutes. The following standard inhalant allergens (Diater-Laboratories, Spain) were tested: Der. pteronyssinus, Der. farinae, birch pollen, grass pollen, Artemisia, Ambrosia Alternaria, cat, dog. These extracts were used in all patients at the start of study and during follow up [6]. A solution of histamine hydrochloride in the

concentration of 10mg/ml and, 0.9% saline solution were used as positive and a negative test controls respectively. Skin reaction was assessed after 15 minutes, a specimen where a 3-mm-papule was formed or where papule exceeded the size of the negative test control by more than 3 mm was considered as a positive. These extracts were used in all patients at the start of study and during follow up.

Table 1:

The clinical patient characteristics

Indicator	Group I (n=47)	Control group (n=20)
Sex, n (%)		
Male	33 (70.2)	13(65)
Female	14 (29.8)	7 (35)
Age (M±m), years	4.11 ±0.83	4.3 ±1.2
Age limits	3-5	3-5
Clinical symptoms, n (%)*		
Rhinitis	41 (87.2)	20 (100)
Rhinoconjunctivitis	4 (8.5)	3(15)
Allergic asthma	16 (34.0)	7 (35)
Wheezing	5 (10.6)	-
Upper palate itching	2 (4.2)	-
Cough	41 (87.2)	17 (85)
The results of skin prick test with allergens of house dust mites (average diameter of papule, mm)	8.4±4.1	7.9±3.27
Number of patients with polyvalent sensitization, n (%) – according to the data of skin prick test	21 (44.6)	9 (45)
Monosensitized (%)	30 (63.8)	11 (55)

*- symptom combination is possible

Specific immunotherapy

The study involved 47 children with bronchial asthma or/and allergic rhinitis who received a two-year immunotherapy course using sublingual allergens containing a mixture of house dust mites (Der. pteronyssinus and Der. farinae) in the correlation of 1 (0,175 HEP):1(0,175 HEP) Diater, Spain. Children of the first group (47) received SLIT according to the following treatment protocol: intake of the drug by 1 spraying into the sublingual area on a daily basis; and the initial phase lasted 6 months (the overall dose for a patient was 1,325-1,425 HEP), the maintenance phase lasted for subsequent 18 months (overall allergen dose was on average 3,900 HEP). After the first drug dose of medication was administered the patients stayed in the clinic under the supervision for 40 minutes, for detection and registration of possible adverse effects, and further the drug was administered independently by the parents, control over possible adverse effects was exercised online by the allergologist.

Four visits per year were planned for the patients over the period of observation, and, if necessary – an additional control visit was possible.

The patients of both groups underwent the baseline therapy under the protocols. If necessary, second generation anti-histamine drugs, inhalation beta-agonists, inhalant corticosteroids and leukotriene inhibitor were prescribed to control respiratory symptoms

Measurement of serum r Der p1, r Der p 2 and r Der p10 - specific IgE

The term Allergen component is used for products based on molecular allergens purified from either their natural source (native) or biotechnologically produced as recombinant proteins. By using tests for single allergenic components as a complement to more traditional IgE antibody tests, further clinically relevant information can be gained. Immuno CAP Allergen components are useful tools when investigating and explaining allergic reactions more in detail and to determine if they are caused by cross-reacting IgE antibodies to different allergens.

Molecular diagnostics which used Immuno CAP (Phadia) was performed to identify major (r Der p1, r Der p 2) and minor allergens (r Der p10) of house dust mites [1, 4].

Assessment of clinical findings

The efficacy of SLIT was assessed by a combined visual analogue scale (VAS) including 6 indices of allergic rhinitis and bronchial asthma symptoms, namely: nasal obstruction, rhinorrhea, nasal discharge, sneezing, nasal itch and itch of mucosa in the oral pharynx area and cough. A 5-point gradation of VAS was accepted: 0 points – “0” symp-

toms; 1 point – minimum symptoms; 2 points – mild symptoms; 3 points – moderate symptoms; 4 points – severe symptoms. Graphic images were suggested (different variants of "smiles" as a visualization scale) taking into account the age of the examined patients. Besides that, patients' parents received recommendations on additional intake of symptomatic drugs (if necessary) during the whole examination period. Additional drug intake was recorded in a special diary. The necessity for a daily drug intake was assessed in the following way: 2 points - 1 pill (5mg)/day of anti-histamine drug, 3 points – 2 inhalation of drug (400mkg)/day of nasal inhalant corticosteroids, while 1 pill (4mg / 5mg) of leukotriene inhibitor drug for children with allergic BA was assessed as 5 points. Absence of the necessity to take the drug was evaluated as 0 points.

Statistical analysis

The data that met normal distribution criteria, such as age and disease duration, were analyzed using Student's t-test, for independent variables. Other non-parametric data were compared with the chi-square test. The summary odds ratio, 95% confidence intervals and standard errors using random-effects models were also computed.

Statistical processing of the obtained results was made using the standard statistical package Statistical for Windows 7.0.

For the statistical significance of the results, we used a value of $\alpha=0.05$. The p value of the statistical test is used for accepting or rejection of the hypothesis ($p \geq \alpha$: hypothesis is accepted; $p<\alpha$: hypothesis is rejected). All results were elaborated, documented and presented in absolute and relative numbers and with statistical results by using statistical markers.

Adverse events

Detailed information about adverse events was collected during the study on a form that recorded all events, irrespective of the participants' attitude to the drug medication and of mild, moderate or serious severity.

3 RESULTS AND DISCUSSION

The study showed that 125 children had positive skin prick test results for standard aeroallergens. Dust mites were the most common allergen causing skin test. At the same time most of the patients, 87 (69.6%), were poly-sensitized, and showed different variants of sensitized. According to the positive frequency distribution of the specific aeroallergens, the top five aeroallergens were Der. pteronissinus (92.16%), Der. farinae (86.23%), Alternaria alternate (50.73%), cat (20.32%) and grass pollen (19.4%). Furthermore, 38 (30.4%) children were positive only to D. pteronyssinus and/or D. farina.

In the first group 30 (63.8) children were monosensitized to house dust mite 38 (52.6%). Among the children there were 29 (96.7) cases that showed positive reaction to both D. pteronyssinus and/or D. farina. In the control group 11 (55%) children were sensitized only to D. pteronyssinus and/or D. farina. Average data of the levels sIgE to r Der p1, r Der p2 (major allergenic components) and to r Der p 10 (minor allergenic components) and data SPT are given in Table 2.

In the group of poly-sensitized patients (87 children) molecular diagnostic was made for 21 patients (24.1%). Eighteen children in the group of mono-sensitized and 66 children in the group of poly-sensitized patients refused to undergo because they had indeterminate results. The results of children examination are provided.

The findings of skin prick test and the data of molecular diagnostics in children with allergic rhinitis and allergic bronchial asthma Immunotherapy was administered to 47 children of the first group. After 6 months of therapy, the symptom "nasal obstruction" reduced almost two-fold (1.3±-1.1); $P<0.05$; while 12 and 24 months later SLIT data was 0.91±0.9 and 0.34±0.5; $P<0.01$, correspondingly. Other indices were also characterized by a considerable reduction: cough before the therapy was 2.2±1.5- which was clinically manifested by moderately severe and severe cough symptoms in 60.8% of children, in particular, at night time and early in the morning, while follow-up observation showed a reliable ($P<0.05$) symptom regression to 1.3±1.1 6 months later, 0.7±0.3 12 months later, and 0.2±0.5 24 months later.

Table 2.

Comparison on SPT and sIgE between the groups

Groups of patients	Skin prick tests, average papule diameter in mm	r Der p 1, kUA/L (M±m)	r Der p 2, kUA/L (M±m)	r Der p 10, kUA/L	Skin prick tests, average papule diameter in mm
I group (mono-sensitized) (n-30)	7.4±4.3	13.2±9.8	30.4±12.6	0/01±0.009	0.98/0.92
I group (poly-sensitized children (n-17)	6.1±3.8	8.7±6.3	12.7±8.5	0.02±0.01	0.83/0.72
Control group (mono-sensitized) (n-11)	7.1±3.2	23.2±10.8	13.2±9.8	0.01±0.007	0.87/0.94
Control group (poly-sensitized) (n-9)	6.4±3.7	18.4±8.9	13,.2±9.8	0.01±0.008	0.94/0.91

Thus, 56% had only minimal or mild symptom manifestation in the form of infrequent cough in the morning, without night awakenings by the end of the first year of therapy, and it almost disappeared by the end of the 2nd year of therapy.

Nasal obstruction, rhinorrhea, sneezing, nasal mucosa itching, oral mucosa itching, nasal discharge and cough decreased in all of the patients who underwent immunotherapy (Table 3).

Table 3.

Data on visual analogue scale in children undergoing SLIT and the control group

Symptom, points (0-4)	1st group (n=47)				Control group (n=20)			
	Before treatment	6 months	12 months	24 months	Before treatment	6 months	12 months	24 months
Nasal obstruction	2.3±-1.6**	1.3±-1.1*	0.91±0.9*	0.34±0.5*	2.4±1.4	2.4±1.2	2.2±0.9	2.2±0.8
Rhinorrhea.	2.2±0.9**	0.5±0.5*	0.5±0.6*	0.2±0.4*	1.8±0.9	1.3±0.8	2.5±1.2	2.2±1.1
Sneezing	1.83±1.4**	0.5±0.5*	0.3±0.4*	0.34±0.5*	1.8±1.2	0.9±0.5	0.7±0.4	1.3±0.9
Nasal mucosa itching, oral mucosa itching	0.2±0.9**	0.08±0.9**	0.04±0.2**	0.04±0.2**	0.04±0.2	0.04±0.2	0.04±0.2	0.04±0.2
Nasal discharge	1.8±1.3**	1.3±1.1**	0.6±0.5*	0.4±0.13*	2.2±1.1	1.5±0.7	1.6±0.5	2.2±0.9
Cough	2.2±1.5**	1.3±0.09**	0.7±0.3*	0.2±0.1*	2.6±1.3	1.5±0.7	1.6±0.4	2.3±0.8

Moreover, after 2 years of immunotherapy, patients did not require any further medications. The study showed that there were no significant differences between mono- and poly-sensitized children of the first group ($p > 0.05$).

DISCUSSION

The study showed that SLIT was an effective treatment in children suffering from allergic respiratory diseases such as allergic rhinitis and asthma (less symptoms and less medication intake) in comparison with children treated with symptomatic drugs only. As of the date of the study, patients of both groups had similar indices in VAS symptoms. For example, the same as the symptoms of nasal obstruction and cough described above. Thus, at the beginning of the therapy the "cough" with the control group children amounted for 2.6±1.3 points and did not significantly differ ($P> 0.05$) from that of the first-group children – 2.2±1.5. And at the end of the second year of therapy there was a significant difference in the results between the groups: 0.2±0.1 (1st group) and 2.3±0.8 (control group) ($P <0.01$). Recurrence of some symptoms in the control

group showed the need for SLIT. According to the literature our study showed that the improvement in clinical outcome was observed in both mono-sensitized and poly-sensitized patients [13]. The efficacy of SLIT treatment was not influenced by the patient's age. As of the date of the study, patients of both groups had similar indicators in VAS symptoms.

One of the most important components of SLIT is the possibility of its safe administration which takes into account the risks of possible anaphylactic reactions and its tolerance with children. SLIT tolerance was assessed for the first-group children using a linear scale which was describe above. In particular, 57.4% of patients (and their parents) assessed SLIT tolerance as "good" and 31.9% as "very good". Thus, total result of good and very good tolerance made up 89.3%, which proves high safety of treatment and absence of serious adverse reactions. During the whole period of observation there was no evidence of any severe drug-related allergic/anaphylactic reactions.

Conflict of interests

There is no conflict of interests.

4 CONCLUSIONS

This study has shown that SLIT administration with standardized medical allergens in atopic asthma or/and allergic rhinitis children under 5 year sensitized to domestic allergens of house dust mites is an effective and safe treatment method and allows to quickly (over the first 6 months of SLIT) control the symptoms. The findings of comparative analysis in the group of patients not receiving SLIT indicates high incidence of symptoms after the end of baseline therapy. Quite a number of unsolved issues related to SLIT administration in early-age children require further study of the given therapeutic direction.

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PEDIATRICS

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EVALUATION OF INFANT DEVELOPMENT USING A GUIDE FOR MONITORING CHILD DEVELOPMENT

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Abstract: The purpose of the study was to assess the main domains of child development in healthy infants of Novobavarsky district of Kharkiv (Ukraine) with the use of A GUIDE FOR MONITORING CHILD DEVELOPMENT (GMCD). The development of 100 children aged 0-42 months was evaluated. Developmental delay was assessed in standard deviations in comparison with the indices of the corresponding age. Developmental delay in 1 domain by -2σ was detected in 19 infants, in 2 domains – in 6, in 3 domains – in 1 and in 4 domains – in 1 infant. Developmental delay in 1 domain by -3σ was detected in 3 children. Besides, 2 infants had a considerably delayed development. Children born prematurely were shown to have statistically significant higher incidence rate of developmental delays in impressive language and play. In authors' opinion, the use of the GMCD allows to give medical recommendations on supporting communication skills and emotions development to parents, as well as to refer the families to early intervention service.

KeyWords: development, young children

INTRODUCTION

Pediatrics of development and behavior is one of the most important and perspective fields of pediatrics, dealing with monitoring and studying the child development in cognitive, communicative, socio-emotional, motor and adaptive spheres [1,2]. Pediatrics of development plays a key role in preservation of future population health, which is important from medical, social, and economic perspective, because economics of the country directly depends on the health level of its population [3]. In developed countries, the health care for children of different ages is at a high level; however, the majority of children of the world live in low-income countries, where the conditions of their life, levels of safety and health care do not promote their development. Such factors, as domestic violence, poverty, lack of appropriate attention exert a considerable influence on the child's upbringing [4]. The sooner these deviations are revealed and corrected, the less children will have serious developmental problems in future, when it is too late to correct them.

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2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

The purpose of the study was to assess the development of healthy infants in Novobavarsky district of Kharkiv according to main functional domains using GMCD for referring to early intervention service.

2.2 Subjects & Methods

Assessment of child development of infants aged 0-42 months involved the employment of GMCD [7]. The Guide is a standardized method of assessment, observation and supporting the child development. GMCD has been elaborated for 20 years at the University of Ankara according to the modern theories of child development. The Guide is based on the principles of bioecological theory of child development and the WHO's International Classification of Functioning, Disability and Health (ICF) with the use of family-centered approach.

The Guide consists of three components: 1) assessment of child development; 2) monitoring of the child development in infancy; 3) supporting the child development. The assessed developmental domains are expressive and impressive language, fine and gross motor functions, play, relationship, self-help skills. The GMCD consists of three components: 1) monitoring; 2) supporting

development; and 3) early intervention. Attention is also paid to domestic environment, risks and family decisions.

GMCD includes record data, developmental risks and plan of actions, 10 open-ended questions for parents about developmental domains of their children at the age of 1-2, 3-4, 5-6, 7-8, 9-11, 12-14, 15-17, 18-21, 22-25, 26-29, 30-35, 36-42 months and card for parents support.

During 2016, the development of 100 infants (45 boys and 54 girls) was assessed with GMCD scale. The infants were divided into groups depending on their age: 7 children aged 0-3 months, 6 aged 4-6 months, 27 aged 7-12 months, 18 aged 13-18 months, 7 aged 19-24 months, 12 aged 25-30 months, 13 aged 31-36 months, 10 aged 37-42 months. The parents were interviewed for 10-15 minutes at home, according to the requirements of the questionnaire. The results were assessed by root-mean-square deviation method. According to the methodology of the questionnaire, if a child reached all the indices of the column, corresponding to the child's age interval, the development was defined as standard. If a child reached several indices of the child's own age interval, and all the indices of the previous column (age interval), that was defined as -1σ. If a child was able to reach only the indices of the two age intervals, previous to the child's own one, that was defined as -2σ. If a child was able to complete only the requirements of the age intervals, located 2 and more columns far from the child's own age interval, that was defined as -3σ. If the development forestalls the child's own age interval, the development was assessed as +1σ, +2σ, +3σ.

3 RESULTS AND DISCUSSION

First of all, biological risk factors of development deviations, included in GMCD were detected (anemia (<105 g/l) in 6 infants, premature birth (before full 37 gestation weeks) in 6 infants, low birth weight (<2500g) in 7 infants, perinatal pathology or chronic diseases in 20 infants) among 100 children, whose parents were invited to complete the questionnaire. It should be noted, that 2 infants had very low birth weight (≤1500g). Table 1 presents the distribution of the child development indices by the main domains according to sex.

Table 1:

Absolute values of standard deviations in developmental domains in infants according to sex (n=100)

Developmental domain	-3σ	-2σ	-1σ	Standard	+1σ	+2σ	+3σ
Expressive language	B: 1 G: 2	B: 8 G:5	B:1 G:5	B: 28 G: 30	B: 5 G: 3	B: 3 G: 6	B: - G: 2
Impressive language	B: - G: 2	B: 4 G:2	B:2 G:2	B: 32 G: 38	B: 2 G: 4	B: 6 G: 4	B: - G: 2
Gross motor function	B: - G: -	B: 1 G:4	B:2 G:1	B: 35 G: 36	B: 3 G: 2	B: 5 G:11	B: - G: -
Fine motor function	B: - G: -	B: 1 G:4	B: - G:2	B: 40 G: 40	B: 2 G: 2	B: 3 G: 6	B: - G: -
Relationship	B: - G: -	B:3 G:2	B: - G:1	B: 34 G: 38	B: 4 G: 2	B: 5 G:11	B: - G: -
Play	B: - G: 1	B: 2 G:4	B:1 G:6	B: 33 G: 33	B: 5 G: 4	B: 5 G: 6	B: - G: -
Self-help skills	B: 1 G: -	B:1 G:3	B:1 G:1	B: 34 G: 41	B: 2 G: 1	B: 7 G: 8	B: - G: -

Note: B, boys; G, girls

Thus, development, described as -2σ and -3σ, in speech was ¬¬¬detected in 17% of infants, in language understanding – in 8% of infants, in gross motor function – in 5, in fine motor function – in 5%, in socio-emotional development – in 5%, in play – in 7%, in self-help skills – in 5% of infants. On the whole, developmental delay by -2σ in 1 domain was detected in 19 infants, in 2 domains – in 6, in 3 domains – in 1 and in 4 domains – in 1 infant. The developmental delay by -3σ in 1 domain was detected in 3 infants. Furthermore, 2 infants were found to have considerable developmental delay: one infant delayed development by -2σ in 2 domains and by -3σ in 2 another domains at the same time, and another infant had developmental delay by -2σ in 2 domains and by -3σ in 3 domains. These infants were born prematurely and were reported to have combined perinatal pathology: low birth weight, respiratory disorders and intrauterine growth retardation.

Numerous studies concerning remote effects of development and behavior of the children, born prematurely, detect lots of problems [8, 9, 10]. In total population of children, about 17% aged 0-18 years have developmental disorders; however, only 30% have them diagnosed before school [8]. The children born prematurely are in a special

risk group of developmental disorders; therefore the subsequent thorough surveillance after their discharge from obstetric hospitals and skilled training of specialists may decrease these risks [9]. Very preterm children have an increased incidence rate of cerebral paralysis [10].

In preterm children, 20% of them (p=0.1338) had developmental delay in expressive language by -1σ, 34% had delay in impressive language by -2σ, 17% delayed development in impressive language by -3σ (p=0,0001).

Delay in gross motor function by -2σ (p=0,1511) was detected in 17% of children, 17% delayed development in play domain by -3σ (p=0,073). However, 17% of children of the same group were found to forestall the level of development of their age in expressive and impressive language by +1σ and 17% – by +2σ.

In gross motor function and relationship 50% of children forestalled their age by +2σ. In play and self-help skills 34% of children forestalled their age by +2σ. Table 2 represents the distribution of standard deviations in main developmental domains in full-term child infants.

Table 2

Absolute values of standard deviations in developmental domains in full-term infants according to sex (n=94)

Developmental domain	-3σ	-2σ	-1σ	Standard	+1σ	+2σ	+3σ
Expressive speech, %	3 (3.2)	14 (14.9)	5 (5.3)	55 (58.5)	7 (7.4)	8 (8.5)	2 (2.1)
Impressive speech, %	1 (1.1)	5 (5.3)	4 (4.3)	68 (72.3)	5 (5.3)	9 (9.6)	2 (2.1)
Gross motor function,%	-	4 (4.3)	3 (3.2)	69 (73.4)	5 (5.3)	13 (13.8)	-
Fine motor function,%	-	5 (5.3%)	2 (2.1)	74 (78.7)	4 (4.3)	9 (9.6)	-
Relationship forming, %	-	5 (5.3)	1 (1.1)	69 (73.4)	6 (6.4)	12 (12.8)	-
Play, %	-	6 (6.4)	7 (7.4)	63 (67)	9 (9.6)	9 (9.6)	-
Self-dependence, %	1 (1.1)	4 (4.3)	2 (2.1)	71 (75.5)	3 (3.2)	13 (13.8)	-

Thus, children born prematurely had statistically significant developmental delay rate in impressive language, and that indicates socio-emotional development delay and may be a predictor of autism development in these children. Therefore, parents are offered to make parents' evaluation of developmental status arrangements, such as development of communicational skills and emotions.

Developmental delay in expressive language by -2σ was detected in 17% of children with anemia, as compared with 11.7% of children without anemia. In other domains (play and self-help skills) children with anemia showed either standard developmental levels or even higher ones as compared with their age intervals.

Thus, developmental delays in infants may be detected due to the use of the tool for parents' inquiry – "A Guide for Monitoring Child Development in Low- and Middle-Income Countries". Assessment of child development in developed countries showed 10-20% of infants with one or several developmental problems [5].

In 2005-2006, an investigation concerning the child development in 18 developing countries, showed, that 23% of children (from 3% to 38%, depending on the country) aged 2 to 17 years have developmental deviations [6]. The authors reported, that the assessment of the development of children aged 0-3 years old is the most difficult, however just that very age is the most favorable for the correction of the deviations.

A group of authors has made a universal questionnaire for parents - "A Guide for Monitoring Child Development in Low- and Middle-Income Countries" (GMCD). It is used by doctors and permits to assess the child's development and behavior, regardless of the country the children live in, and to detect the deviations in child development at early stages [7].

4 CONCLUSIONS

1. The use of GMCD allows to diagnose delays in main developmental domains in infants aged 0-42 months.
2. Among 100 infants, 19 delayed development in 1 domain, 6 – in 2 domains, 1 in 3 domains and 1 in 4 domains.
3. Infants born prematurely had statistically significant delay in impressive language and play.
4. The use of GMCD allows to give medical recommendations on supporting communication skills and emotions development to parents, as well as to refer the fami-

lies to the early intervention service.

The perspectives of the further studies should pertain to evaluation of children's development in larger populations.

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PEDIATRICS

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ALAGILLE SYNDROME AS A CHALLENGING CLINICAL CASE IN PEDIATRIC PRACTICE (case report)

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Abstract: Alagille syndrome is a multisystem, highly variable, autosomal dominant disorder, which can be triggered by spontaneous mutation. This disease primarily affects the liver (chronic cholestasis), heart (most often peripheral pulmonary stenosis), eyes (posterior embryotoxon), face (characteristic features), and skeleton (butterfly vertebrae). The paper presents the clinical case of prolonged jaundice with an increased liver enzymes in infant and no final diagnosis for a long time.

KeyWords: Alagille syndrome, chronic cholestasis, ursodeoxycholic acid

INTRODUCTION

Alagille syndrome (ICD-10:Q44.7; ORPHA:52) - autosomal dominant disorder, which is variably characterized by chronic cholestasis due to paucity of intrahepatic bile ducts, peripheral pulmonary artery stenosis, vertebrae segmentation anomalies, characteristic facies, posterior embryotoxon/anterior segment abnormalities, pigmentary retinopathy, and dysplastic kidneys.

The prevalence of Alagille syndrome (AGS) is approximately 1/70,000. AGS is most commonly due to JAG1 (20p12) gene mutations (AGS type 1), encoding a Notch signaling pathway ligand. AGS type 2 is due to NOTCH2 gene mutations (1p12). The diagnosis is based on the clinical picture and liver biopsy revealing chronic cholestasis and paucity of interlobular bile ducts. Imaging (abdominal ultrasonography, cholangiography) helps to identify biliary anatomy. The clinical symptoms are variable and treatment is non-specific, which causes certain clinical difficulties [1]. We would like to provide a clinical case and share our clinical experience in AGS diagnosis and treatment.

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CASE STUDY

On 21st January, 2015 a 1-year and 2-months-old boy was seen by a pediatrician. The child's parents reported that the boy had been examined by different doctors since birth, had been hospitalized twice and had been consulted by medical professionals abroad. The child's liver enzyme levels, particularly alanine transaminase (ALT) and aspartate transaminase (AST) were constantly increased. The patient received multiple medications, however no symptoms improovement and no final diagnosis till the moment of first admission to our clinic.

The patient's parents are first cousins and there is a second child in the family (his elder sister is healthy).

The child is on adapted formula feeding from birth and was not vaccinated (except vaccinations rendered at birth).

Most recent clinical history and findings:

On physical examination his weight was measured to be 8 kg (3 percentile), he did not have fever, was neither able to sit, nor to walk, had no teeth, had a prominent forehead and deep-set eyes. There was maculo-papular itching rash on his skin. Neurological examination did not reveal any abnormalities. Skeletomuscular and ophthalmological findings were within normal range. Throat and oral mucosa had no pathological signs. Lymph nodes were not enlarged. Heart auscultation revealed murmur. Respiratory status was normal. Abdomen was soft with normal bowel sounds. Liver was enlarged by 2 centimeters. He was not found to

have splenomegaly.

In addition, the parents presented the results of previous clinical examinations. The biochemical analysis of blood, taken repeatedly over the year, revealed a steady increase in bilirubin, its fractions, ALT and AST.

Laboratory data on the day of 1-st admission (21st January 2015):

- CBC – slight eosinophilia (4.36), other criteria within normal range;
- CRP, ANA, AMA, total protein, albumin, globulin, calcium – normal.
- Liver enzymes: AST – 202 U/L (Norm – 5-34), ALT – 219 U/L (Norm <55), GGT – 627 U/L (Norm – 12-64);
- Bilirubin: Total - 1.9 mg/dl (RR 0.2-1.2), conjugated bilirubin – 1.2 (RR <0.5), unconjugated bilirubin – 0.7 (RR – 0.2-0.7).
- Echocardiography: pulmonary artery stenosis.

Diagnosing presented certain difficulties. It was obvious that the child had signs of cholestasis with liver parenchyma involvement. The doctor suspected congenital abnormality and its possible association with pulmonary artery stenosis. Following consultations with Professors of Pediatrics from Children's Hospital of Philadelphia and Vienna Medical University, the child was diagnosed with Alagille syndrome (AGS).

This disease was first described by French pediatrician Daniel Alagille in 1969. It is a multisystem, highly variable, autosomal dominant disorder; however the disease can be triggered by spontaneous mutation. The disease is classified as arterio-hepatic dysplasia (disease of the bile duct syndrome) Q 44.7. As a result, lack of the biliary tract in patients causes congenital cholestasis. This disease primarily affects the liver (chronic cholestasis), heart (most often peripheral pulmonary stenosis), eyes (posterior embryotoxon), face (characteristic features), and skeleton (butterfly vertebrae) [2]. AGS has traditionally been diagnosed based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features.

The patient under examination had three of the signs mentioned above: chronic cholestasis, peripheral pulmonary stenosis and characteristic face features, such as prominent forehead and widely set eyes. He was not found to have embryotoxon and skeleton deformation. AGS is caused by mutation in JAG 1 (20th chromosome) (90%), in some cases, mutation in NOTCH 2 (1st chromosome). AGS estimation is 1 in 30 000 [3].

Since it was impossible to conduct genetic examination of the patient, the diagnosis was established clinically and the treatment process began. The patient was administered ursodeoxycholic acid 15 mg/kg/day, vitamin D 3000 U/day and vitamin A 4500 U/day.

After 2.5 months the child was examined once again. He weighed 9 kq (3 percentile) and had 6 teeth. The patient could sit, stand, and walk 2-3 steps without assistance. He had no rash. Itching decreased, but did not disappear.

Laboratory data after 2,5 month of treatment (15th April 2015):

- Liver enzymes: AST – 139 U/L (decreased by 1.5 times), ALT – 102 U/L (decreased by 2 times), GGT – 258 U/L (decreased by 2.4 times),
- Bilirubin did not changed
- Lipids (cholesterol, triglycerides) and prothrombin levels were slightly elevated.
- Vitamin D level was normal.

Subsequently when the child turned 2 years old in January 2016 his condition slightly worsened: pruritus increased and levels of AST, ALT, GGT doubled, so the parents agreed to perform a liver biopsy.

Biopsy showed slight inflammation activity, slight fibrosis, and yellow bile pigment in the cytoplasm of hepatocytes, focal necrosis, and hyperemia of sinusoids, periportal fiber growth and slight fibrotic dilation in portal areas and moderate mononuclear inflammatory infiltration of cells.

Liver biopsy can strongly support the AGS diagnosis if there is bile duct paucity. However, if the individual meets clinical criteria, then a liver biopsy is not mandatory for

diagnostic purposes [4]. The biopsy results of our patient neither confirmed nor denied the diagnosis, since the sample did not include the biliary tract, which is an important step in diagnosing Alagille syndrome.

Medical treatment:

Cholestasis in AGS is commonly profound and manifests clinically with pruritus. Cholestasis typically worsens until school age and then, in some children, it improves or stabilizes. Pruritus observed in AGS is among the most severe of any chronic liver diseases. Unfortunately, there are no known radiological or genetic markers that can predict which children will have progression of their liver disease and in which children it will improve. Pruritus often disturbs sleep, daily activities, and cognitive development [5].

Bile flow may be stimulated by choleretics, and ursodeoxycholic acid, as the most commonly used agent (10-20 mg/kg/day, divided in 2 doses). Bile acid-binding resins, such as cholestyramine, 240 mg/kg/day, divided into 3 doses with maximum dose of 8 g/day, are often effective but not palatable. One of these two medications is a first line therapy for AGS [2].

Patient treatment:

Vitamin D and Vitamin A were no longer required, ursodeoxycholic acid was administered at the same dosage and 4 g/day of Cholestyramine as a bile salt-binding agent and emollients to keep the skin hydrated were additionally introduced into the therapy. As a result, this modified treatment improved pruritus and appetite.

1 year follow-up (April 2016).

- The child turned 2.5 years.
- His appetite was good.
- He weighed 10 kg (3 percentile).
- The patient continued to receive ursodeoxycholic acid, and cholestyramine dosage was increased to 8 mg/day.
- Pruritus still persisted.

Further monitoring of this disease is determined by the degree of cholestasis and possible complications. It is also recommended to check fat-soluble vitamin levels twice a year. According to the textbook, the process might stabilize within the period when the child is 4-10 years old; however in 30 % of cases there is a need for liver transplant [4, 5].

Conflict of interests

There is no conflict of interests.

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DIAGNOSIS AND TREATMENT OF SEPSIS IN AN INFANT WITH CONGENITAL LACTASE INSUFFICIENCY (case report)

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Abstract: The article presents the results of clinical observation of the infant suffering from the sepsis and congenital lactase deficiency. The first symptom of the disease in the first day of life was diarrhea. Lactose insufficiency was diagnosed. Later blood has appeared in the feces. Condition of the child stated to get worse and the child was hospitalized. Condition remained to be grave during 2 weeks, symptoms of intoxication, enlargement of liver were marked, stool was up to 15 – 16 times a day, it contained blood mixed with feces, blood blobs and streaks. Analysis of clinical symptoms and result of laboratory investigations gave motive to diagnose sepsis, congenital lactose insufficiency, anemia, and hypotrophy. The treatment included diet (lactose-free formula), antibiotics, infusion, probiotics, vitamins. Results of investigation normalized. The child was discharged from the hospital in satisfactory condition.

KeyWords: infant, lactose insufficiency, sepsis, therapy

CASE STUDY

A 1.5-months-old Miron K. was admitted to Kharkiv Regional Children Clinical Hospital No.1 (RCCH No.1) with frequent (up to 13-15 times a day) liquid stool with mucus and blood, lethargy, weakness, poor sucking ability, and lack of body weight gain.

According to his medical history he was born from the mother with complicated fourth pregnancy. For three years the woman had been suffering from infertility, then she had three spontaneous abortions. This pregnancy proceeded with gestational toxicosis in the second half of pregnancy, and eclampsia. She gave birth at the term of 37 weeks of gestation by caesarean section due to intrauterine fetal hypoxia.

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The child was born with asphyxia, estimated 3.5 points according to Apgar score. His body weight was 3100 g, height – 50 cm, head circumference – 32 cm, chest circumference – 30 cm. He was breastfed on the second day and was discharged from the hospital on the third day.

On the 5th day of life the child had diarrhea with mucus, stool frequency being up to 15 times a day. The pediatrician referred the child to the City Perinatal Center, where he stayed for 7 days. During that period the child was examined at the specialized Kharkiv Regional Medical Genetic Center where he was diagnosed with primary lactase deficiency. The nutrition was corrected and his diet was changed to lactose-free formula. The child's condition normalized in 8 days and he was discharged home.

On the third day of being at home the child's condition worsened, and stool frequency increased to 15 times a day, the stool contained mucus and blood. The condition was progressively worsening. He was referred to RCCH No.1 by a district doctor. At the Intensive Care Unit of the clinic the child was diagnosed with intestinal bleeding, and he was hospitalized to the Department of Surgery.

At admission the child's condition was severe. The severity of the condition was caused by intoxication, dehydration, neurological disorders. The child was dull and adynamic. His skin was pale, subcutaneous fat got thin, turgor and elasticity of tissues were reduced and neonatal reflexes were weak. He had a reduced muscle tone, puerile breathing in the lungs and respiratory rate of 50 breaths per minute. His heart sounds were muffled, clean, rhythmic; heart beat rate was 152 beats per minute. The abdomen was soft, the liver was palpated 3 cm below the edge of the costal arch and the spleen was 1.5 cm. Stool was liquid, watery and mixed with blood. Urination was normal.

The child was diagnosed with congenital lactase insufficiency, gastroenterocolitis, 1st degree hypotrophy, hypoxic and ischemic lesion of the central nervous system, neurotony depression syndrome and early recovery period. Differential diagnostic included necrotizing enterocolitis of newborns, and surgical pathology, accompanied with intestinal bleeding. The child was transferred to the ward for younger children of RCCH No.1.

Follow-up examination for 15 days showed that his condition remained severe, intoxication symptoms persisted, diarrhea was up to 15-16 times a day and the stool contained blood mixed with feces, as well as blood blobs and streaks.

Laboratory and instrumental findings essential for diagnosis were as follows:

Blood count: (indice fluctuated during the follow-up): Hb – 72 - 102 g/L; erythrocytes– 3.3 – 4.0*1012 /l; Ht – 26 - 28%; platelets– 140-192*109/l; leukocytes– 5.4 – 17.6*109/l; neutrophils – 60 - 82%; stab neutrophils – 1 - 17%.

Urinalysis: microscopy of sediment – 3 and 4 to 57 in sight, leukocytes – 2 - 3 in sight up to ½.

Coprogram: epithelial cells –10-20 in sight, leukocytes – 10-25 in sight, erythrocytes – 50-70 in sight, large amount of iodophilic flora.

The reaction for occult blood was positive.

Bacteriological blood test (twice with an interval of 2 days) revealed Staphylococcus saprophyticus sensitive to Lincomycin, Tetracycline, Vancomycin, Rifampicin, Chloramphenicol.

Bacteriological urine test: Escheriehia coli, Enteroccus faeciane, Klebsiella pneumoniac.

Bacteriological feces test: Staphylococcus saprophyticus sensitive to Rifampicin, Chloramphenicol, Klebsicella, Sensitive to Rifampicin, Tetracycline.

Feces test for dysbacteriosis: Lactobacilli were not found. Conditionally pathogenic enterobacteria – Klebsiella 108 (N – 104).

Ultrasound examination of the brain and internal organs revealed hypoplasia of the thymus, other organs were without abnormalities.

Immune status was checked twice but no pathology was revealed.

Endoscopic examination of the esophagus, stomach, duodenum, sigmoid colon, and rectum revealed no pathology.

Test of calprotectin revealed no pathology.

Findings of investigations performed at Kharkiv Regional Medical Genetic Center:

Biochemical blood test: total cholesterol – 2,52 mmol/l (normal – 2.95 - 5.25 mmol/l), uric acid – 3.06 U/l (normal – 1,37 - 2.98 U/l), calcium – 2.13, ALT, phosphorus, creatinine, creatininase, lactate dehydrogenase, total bilirubin, gammaglutamyl/transferase – within normal range.

Investigation of lactose activity: the patient was found to have lactose activity insufficiency: polymorphism of lactose 13910 C/T gene (LCT) – polymorphism of C/C in homozygous state.

The diagnosis of lactose insuficiency was confirmed by the symptoms, history data, laboratory and instrumental findings. The use of lactose-free formula was recommended. Supplementations containing lactose enzyme (Mamalak, Koliprev, Lactazar) were recommended before taking infant formula according to age.

Due to certain difficulties in the treatment of the patient, poor efficiency of the administered therapy was discussed at the consultation with the specialists – geneticists, pediatricians, surgeons, gastroenterologist, and immunologist.

Findings of the multidisciplinary case management

team: considering the history, presentation, laboratory and instrumental findings which include a diagnosed congenital abnormality – congenital lactase insufficiency, a progressive increase in the severity of the child's condition due to accompanying inflammatory process – hemorrhagic colitis; pyelonephritis, anemia and hypotrophy; bacteremia (presence of Staphylococcus saprophyticus in the blood, Staphylococcus saprophyticus and Klebsiella in the feces, Escheriehia coli, Enteroccus faeciane, Klebsiella pneumoniac in the urine) identified in laboratory investigations; erythrocytes in coprogram, signs of inflammation in the blood test- leukocytosis, neutrophilia; primary lactose deficiency confirmed by the second investigation carried out at the RMGC, the diagnosis should be specified as follows:

Primary diagnosis – congenital lactose insufficiency accompanied by sepsis of septicopyemic type, enterocolitis, pyelonephritis.

Concomitant diagnosis – hypoxic- ischemic encephalopathy, depression syndrome, tonicity disorders, early recovery period.

Complications – 1st degree deficiency anemia, 1st degree hypotrophy.

Laboratory and instrumental findings allowed to exclude immunological failure, and surgical pathology.

The child received the following treatment: nutritional care (a formula of Nutrilon malabsorption, later lactose-free formula (Nestle), infusion therapy – 5% glucose, 0.9% sodium chloride), antimicrobial therapy in accordance with the sensitivity of detected flora, Kreon, Biogaia, Smecta, vitamins B1 and B6.

The child's condition improved: dysfunction of the intestine subsided, stool characteristics returned to normal, laboratory data (blood, urine, feces, bacteriological investigation) normalized. The child's weight started to increase. The child was discharged from the hospital on the 28th day in satisfactory condition. Follow-up examination of the district pediatrician, gastroenterologist, geneticists was advised.

Clinical findings showed a severe course of a combination of lactose insufficiency and infectious process accompanied by the development of hypotrophy and deficiency anemia.

Lactase insufficiency.

Breast milk sugar – lactose is one of the most important components of breast milk. This sugar is found in nature only in the milk of mammals, and its highest concentration is in women's milk. Fetal lactase activity is observed from 10-12 weeks of gestation; it begins to increase from 24 weeks and reaches its maximum to 38-40 weeks, persisting for the first year of a child's life. The disease is triggered by mutation of the structural gene LCT (beta glycosidase complex of lactase- phlorizin hydrolase) of the small intestine, which leads to insufficiency of the enzyme. The gene is mapped on the short arm of the 21st chromosome 2q21 [1].

Lactose provides about 40% of the energy required by the child and is necessary for the brain development. In the small intestine a larger molecule of lactose is broken by lactase into two smaller molecules – glucose and galactose. Glucose is an important source of energy whereas galactose becomes a part of galactolipids necessary for the development of the central nervous system.

Lactose which is not broken down in the small intestine (for example, due to deficiency of lactase) moves further and stimulates the formation of intestinal bacterial colonies of Lactobacillus bifidus. These fermenting bacteria provide the acid medium in the gastrointestinal tract, inhibit pathogenic bacteria, fungi and parasites.

If the activity of lactase (the enzyme that breaks down lactose) is reduced or absent (the condition is called lactase deficiency), lactose becomes the food for bacteria in the small intestine and enters the large intestine in significant quantities. There lactose creates a nutrient medium for reproduction of many microorganisms, resulting in liquefaction of the stool and flatulence, as well as intestinal pain. The extremely acidic stool in its turn can cause further damage of the intestinal walls.

Insufficient activity of lactase may lead to the reduction of extra weight, because, firstly, it cannot break down milk sugar, which is an important source of energy, and, secondly, the damage to the intestine leads to the deterio-

ration of absorption and digestion of the other nutrients of breast milk.

There are two types of lactase deficiency – primary and secondary. It is possible to specify another type of lactase deficiency, in which, due to the individual characteristics of lactation and mother's organization of breast feeding, a child having the enzyme in sufficient quantity, however, experiences the similar symptoms.

Primary lactase insufficiency occurs in case the surface cells of the small intestine (enterocytes) are not damaged, but the activity of lactase is decreased (partial lactase insufficiency, hypolactasia) or absent (complete lactase insufficiency, alactasia).

Secondary lactase deficiency occurs when lactase production is reduced due to the damage of the cells that produce it.

Primary lactase insufficiency can be:

1. congenital – due to genetic disease (it is quite rare)

2. transient – in premature babies and those who are immature by the time of birth

3. of adult type

Secondary lactase insufficiency occurs much more often. Usually, it is caused by any acute or chronic disease, such as intestinal infection, allergic reaction to cow's milk protein, inflammatory processes in the intestine, atrophic changes.

The symptoms of lactase deficiency include liquid (often frothy, with a sour smell) stool, which can be both frequent (more than 8-10 times a day) and rare or absent without stimulation (it is typical for babies having artificial feeding with lactase insufficiency); child anxiety during or after feeding, profuse vomiting; bloating; no weight gain or weight loss.

There are several tests allowing in one way or another confirm lactase deficiency – lactose curve, hydrogen test, stool tests for carbohydrates, analysis of coprogram, but the most reliable way to confirm lactase insufficiency – biopsy of the small intestine [2].

Lactase enzyme is usually used to treat lactase deficiency. The enzyme is given in courses. At the age of 3-4 months, when lactase becomes mature, the treatment is often cancelled. It is also important to choose the right dose. If the dose is too small, the symptoms of lactase insufficiency can still persist, if the dose is too high, the stool can become excessively thick, similar to clay, resulting in constipation. The enzyme is usually given before feeding, dissolved in some breast milk. Usually the doctor recommends to give lactase every 3-4 hours, thus, if necessary, the baby can be fed in the intervals.

The intestinal flora and lining should be restored. In treatment of primary LD the basic treatment is accompanied by correction of intestinal dysbiosis.

In secondary lactase insufficiency (the most common condition) the main attention should be given to treatment of the underlying disease that caused the damage of the walls of the bowel (e.g. gastroenteritis), but reducing the amount of lactose in the diet or lactase fermentation should be considered as a temporary measure, necessary before the recovery of the lining of the intestine. In mild cases, it may be necessary to give lactase for some time, so the bowel will recover without any additional treatment [3-5].

Bacteremia and sepsis.

Bacteremia is a disorder of hematopoietic system caused by bacteria. Sepsis (septicemia) is bacteremia, complicated by clinical manifestations of systemic infection. Sometimes the term "septic syndrome" is used with regard to severe systemic infection in which infectious agents or their toxic products are allegedly circulating in the blood.

Both temporary and permanent bacteremia can lead to metastatic infection. Bacteremia often occurs secondary to other diseases or malnutrition; it is, as a rule, intermittent in nature and associated with opportunistic infection. The primary source of infection is usually located in the genitourinary system, gastrointestinal tract, lungs or on the skin.

Transient bacteremia with a small amount of bacteria in blood is often asymptomatic. Persistent bacteremia with a large amount of bacteria in the blood usually gives the clinical picture of systemic infection, including fever, as well as gastrointestinal symptoms (nausea, vomiting, diar-

rhea). In some cases, the first manifestation of the disease is a septic shock with such characteristic signs as alteration of consciousness, hypotension, disorders of breathing.

The diagnosis is confirmed by rapid progressive severity of the condition. There are complications that can be caused by aerobic bacteria apart from gram-negative microorganisms.

According to some authors, at present, microbial associations with more pronounced pathogenic properties than monoculture play the leading role in the etiology of infectious complications. This is because the virulence of microorganisms may increase in associations of several types in the presence of synergistic action. Asporogenous anaerobic bacteria in association with aerobic species can cause development of more severe forms of a disease. An important role in the interpretation of the results of bacteriological studies is played by the degree of patient's colonization by microorganisms, i.e. it is important not only qualitative but quantitative evaluation of the test results.

The factors contributing to the activation of microflora and subsequent development of infection are reduction of general and local immunity, and use of antibiotics disturbing the natural interaction of microorganisms [6].

Conflict of interests

There is no conflict of interests.

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PEDIATRICS

Grechanina Yu., Bugaeva E., Biletska S.

A CLINICAL CASE OF SUCCESSFUL REHABILITATION OF A CHILD WITH UNDINE SYNDROME (CCHS-CONGENITAL CENTRAL HYPOVENTILATION SYNDROME, ONDINE SYNDROME, OMIM 209880)

Kharkiv National Medical University, Ukraine [1]
Kharkov Interregional Specialized Medical Genetic Center – Center of Rare (Orphan) Diseases, Ukraine [2]

Abstract: The article describes a case of the combination of an orphan monogenic disease (Undine syndrome) with a disruption of methylation cycle (epigenetic status) and mitochondrial dysfunction. Correction of concomitant metabolic disorders has allowed improving the quality of life of the child.

KeyWords: Undine syndrome, synthropy, methylation, mitochondrial dysfunction

INTRODUCTION

Undine syndrome (central hypoventilation syndrome) is a rare orphan disease with an autosomal dominant type of inheritance. According to different authors, the incidence of the syndrome fluctuates [9, 41]. The syndrome was first described in 1962 by Severinghaus and Mitchell in three patients after surgical neurosurgical intervention [18]. Central hypoventilation syndrome is a disease of the respiratory system, which leads to apnea attacks during sleep. It may be congenital or acquired at a later age.

Possible causes include traumatic brain damage, particularly in the trunk. Congenital cases are rare and are associated with autonomous breath control deficiency [9,18]. The diagnosis can not be established immediately due to symptoms similar to pulmonary insufficiency [10].

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Also there might be asymptomatic carriage among family members with a similar mutation. According to different authors, apnea develops mainly in sleep, but in severe cases it was noted during wakefulness.

Syndromes with late onset are very rarely described [13, 21, 40]. The authors do not bound the syndrome to a specific gender [10].

Furthermore, cases of sleep apnea are associated with neuroblastomas (tumors of sympathetic ganglia), Hirschsprung disease (partial agenesis of the enteric nervous system) [8], dysphagia (difficulty swallowing) are also described. Additional symptoms include darkening of the skin color which is associated with lack of oxygen, increased drowsiness, fatigue, headaches, and disturbance of night sleep (inability to sleep at night). Some patients may have sensitivity to sedatives and drugs. Reduced concentration of oxygen in erythrocytes also leads to hypoxia, which is caused by pulmonary vasoconstriction and hypertension, leading to pulmonary spasms [29]. Other symptoms comprise gastroesophageal reflux, ophthalmic disorders, convulsions, relapsing pneumonia, developmental delay, episodes of loss of consciousness and violation of temperature regulation [8].

As a rule, the syndrome results from congenital malfor-

mation of the head or, more rarely, of the spinal cord. But it can also be caused by strokes, tumors, complications of neurosurgical interventions, consequences of neurodegenerative diseases, such as Parkinson's syndrome, multiple sclerosis [38]. Some patients develop the syndrome with impaired auditory potentials secondary to chronic alcoholism [20].

A genetic defect is associated with this syndrome, particularly a mutation in the PHOX2B gene (in 91% of cases) [21, 35], the 4p12 locus; this transcription factor is involved in the development of neurons [14, 15, 16, 19, 34]. This homeobox gene is important for the normal development of the autonomic nervous system. At the moment, the syndrome is characterized as a neurocristopathy or neural crest disease, from which a part of the autonomic nervous system occurs [18, 28].

As described in the literature, children develop episodes of apnea with cyanosis during the first months of life. Damage to the brain may not be present, but hypercapnia and hypoxia are noted. Polysomnography shows that a violation of ventilation is often noted during the slow-sleep phase. In extremely severe cases, the presence in other stages of sleep and wakefulness is described. Patients with Undine syndrome require constant monitoring of breathing, namely tracheostomy and ventilators and also oxygen therapy and agents for stimulating the respiratory system [19]. Recently, surgical correction of implanting the electrode into the diaphragmatic nerve has been carried out. Mortality among patients with this syndrome is high, unless breathing stimulation is used during sleep [40].

The American Thoracic Society established the following criteria for the diagnosis of Undine's syndrome [22]:

■ adequate ventilation during wakefulness and hypoventilation with a normal respiratory rate and shallow breathing (decreased respiratory volume) during sleep, or hypoventilation, both during wakefulness and during sleep;

■ absence or loss of reaction to hypercapnia and / or hypoxemia during wakefulness and sleep;

■ absence of neuromuscular, pulmonary, cardiac diseases, as well as lesions of the brain stem;

■ presence of a mutation in the PHOX2B gene;

■ the presence of symptoms of autonomic nervous system dysregulation (decreased pupillary response to light, esophageal motility disorder, severe constipation even in the absence of Hirschsprung's disease, profuse sweating, lowering of basal body temperature, decreased perception of anxiety, etc.).

Taking into account that any monogenic or chromosomal syndrome is capable of some metabolic correction considering the revealed disorders, we performed a metabolic correction on the example of the presented clinical case and received a positive effect.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

To present a case of successful rehabilitation of a child with Undine's syndrome through normalization of concomitant metabolic disorders.

2.2 Subjects & Methods

The process of the child's examination involved administration of clinical-genealogical, syndromological, biochemical, molecular-genetic and instrumental methods of investigation.

3 RESULTS AND DISCUSSION

Proband N., a 3-year-old girl attended a medical appointment. On examination she was diagnosed with Undine syndrome (confirmed molecularly at 5 months, a mutation in the gene PHOX-2B).

Presentation: delayed psycho-motor and speech development (the child does not speak), weight deficit, episyndrome, alopecia areata, stereotypes (strokes with brushes), atopic dermatitis, lack of attention, does not chew when tired, repeats head movements from side to side and beats her head.

Past history: she has been considered disabled since birth, when she had seizures with a frequency of 5-7 episodes a day and respiratory depression (was on ALV). She was diagnosed with intrauterine infections of unspecified

etiology, perinatal hypoxic-ischemic CNS lesion, oppression syndrome and motor disorders syndrome in the form of muscle hypotension. For a month she was on mechanical ventilation. At the age of 2 months her condition worsened due to respiratory failure, and she again was rendered auxiliary ventilation. During wakefulness breathing was independent, at night on ventilator. EEG was normal. There was an epipresence against the background of the cohitum (her mother also noted an increase in epicasis in the hot season).

Life history: a child from the third pregnancy (complicated by chronic pyelonephritis, ureaplasmosis, anemia), 2ndphysiological birth in gestation period of 40 weeks. Weight at birth was 3380 g, height 51 cm. Apgar score was 5/6 points.

Features of the phenotype: blonde hair, foci of alopecia in the parietal and occipital areas, blue sclera, short filter.

Family history: cases of oncopathology, epilepsy, blindness of unspecified genesis.

On examination:

- biochemical blood assay: moderately reduced level of alpha-amylase, sodium; increased level of direct bilirubin;
- moderate hyperhomocysteinemia in the metabolites of methylation cycle;
- increased level of lactate when assessing metabolites of energy metabolism;
- moderately elevated level of magnesium and reduced level of copper when assessing trace elements in blood;
- hypermethioninemia in the case of nonspecific hypoacidemia when assessing amino acids.

MTHFR 677 T / T mutation was detected in the study of polymorphic variants of the genes of folate-methionine cycle enzymes.

Gas chromatography / mass-spectrometry of urine showed a change in metabolites indicating a violation in the Krebs cycle.

Assessment of presentation, history taking, phenotype features, clinical genealogy, as well as the results of additional diagnostic methods, allowed to establich **final diagnosis:**

Undine Syndrome. Insufficiency of methylene tetrahydrofolate reductase (polymorphism MTHFR 677 T / T). Disruption of the exchange of sulfur-containing amino acids. Moderate hyperhomocysteinemia. Mitochondrial dysfunction.

Metabolic status assessement showed a decrease in the level of amylase in the blood, moderate hyperbilirubinemia indicating a disruption of the gastrointestinal tract function (pancreatopathy, cholestasis), which must be taken into account when choosing therapeutic strategy.

Increased levels of magnesium may indicate its admission to the analysis, as well as a violation of the system of detoxification. The decrease in the level of copper indicates its insufficient intake in the body triggering a disruption of myelination of nerve fibers.

The presence of polymorphism MTHFR 677 T / T (pathological homozygote) in combination with a moderate increase in the level of homocysteine and methionine in the blood indicates a violation of the epigenetic status (disturbance of the methylation process), which, according to E.Ya. Grechanina et al. [2], on the one hand, increases the course of the underlying disease, and on the other hand, determines the possibility of therapeutic correction, including, the appointment of cofactor and diet therapy.

The increase in lactate level in the blood, the presence of disorders in the Krebs cycle (according to gas chromatography / mass-spectrometry of urine) suggests the presence of mitochondrial dysfunction, which requires a course of electro-tropic therapy. Replenishment of amino acids, including alanine (amino acid directly related to mitochondrial activity) makes it possible to regulate the energy capabilities of the body.

Thus, a complex therapy was prescribed, which included the correction of nutrition (hypomethionine diet, enrichment of the diet with foods high in copper, restriction of digestible carbohydrates and the introduction of whole grains cereals), as well as drugs normalizing the level (P-5-P, TMG) and stimulating energy metabolism (L-carnitine, coenzyme Q10, riboflavin, biotin, succinic acid). In the course of treatment within a month the child stopped cramping and reached the talking stage.

4 CONCLUSIONS

This case demonstrates the effect of synthropy, which is a combination of a rare orphan monogenic disease and metabolic disorders. Correction of the association of disrupted methylation cycle and mitochondrial dysfunction improved the quality of life of the child and led to stable positive changes. Thus, diagnosis and correction of metabolic disorders in monogenic and chromosomal syndromes gives a possibility to provide successful rehabilitation of patients.

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PSYCHIATRICS

Strelnikova I. M., Kozhina H. M.

EXPERIENCE OF EXTENDING ANTIPSYCHOTIC AID TO WOMEN WITH EPILEPSY COMPLICATED BY PSYCHOTIC DISORDERS

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Abstract: This research introduces classifications of epileptic psychoses, current views on etiopathogenic mechanisms of epileptic psychoses development, different aspects and types of their course, considers modern recommendation and describes presentation of epileptic psychoses as well as major approaches to their treatment. The article presents the results of Quetiapine administration in the treatment of epileptic psychoses.

KeyWords: Epileptic psychoses, clinical picture, therapy, Quetiapine.

INTRODUCTION

The issue of epileptic psychoses has recently received the deepest attention due to the fact that patients who suffer from this pathology quite often get full-time treatment in psychiatric clinics as well as receiving necessary aid in out-patient psychiatric institutions. According to the WHO data epileptic psychoses vary in different countries within 2.5% to 8% and mostly depend on the prevailing type of psychotic disorder [1]. Most common are epileptic psychoses of transitory (acute) type (64%) and paroxysmal type (24–28%) with chronic epileptic psychoses being observed much more rarely (8–12%).

Developing efficient strategies for correcting and preventing epileptic psychotic disorders remains an urgent issue in clinical practice since the current level of expertise in this pathology does not provide an unanimous understanding of the pathogenesis of these disorders.

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There is also no relevant evidence of efficient prescribing psychotropic drugs to the patients who suffer from this pathology. Implementing the means and methods of epileptic psychoses pharmacopeia is a topical direction in neuropharmacology and psychiatry. It is determined by the significance of epilepsy itself as well as a number of associated psychotic disorders (epileptic personality changes, epileptic dementia, epileptic psychoses), leading to social misadaption, increased full-time clinic periods and disablement of this category of patients.

The majority of epileptic patients have various psychotic disorders, and the probability of their development increases proportionally to the disease duration. Their origin is determined by a variety of factors, such as the patient's age at the beginning of the disease, the form of epilepsy, its type, the disease resistance to pharmacotherapy, the patient's compliance level, anti-epileptic drugs intake in regular and adequate dosage, additional health hazards, accompanying disorders and duration of the disorder.

Significance of epileptic psychoses is preconditioned by both difficulties of differential diagnosis (the difficulty of differential diagnosis of organic and epileptic psychoses is determined by the primary cause of epilepsy onset since epileptic psychoses may as well be regarded as organic ones once the morphological basis is proven) and the present social and economic consequences for the society

since such complications, when improperly treated or prevented, lead to disability as well as developing or intensifying the features of epileptic dementia.

Epileptic psychoses are disorders of mental presentation characterized by obfuscation which means explicit affective disorders, delusion, hallucination and catatonic disorders related to non-obfuscation, which significantly reduce the understanding of what the patient's surroundings, self-awareness and ability to establish adequate contacts with surroundings [1].

Epileptic psychoses are not unique psychopathic disorders of epilepsy; they are a manifestation of the epileptic disease or its complication. They are mostly observed in patients with symptomatic or conventionally-symptomatic (cryptogenic) epilepsy with unfavorable or medium-progredient epilepsy with long duration. Epileptic psychoses develop in pathogenic connection with active paroxysmal epileptic conditions and specific personality changes or epileptic dementia.

It is important to point out that there are a few classifications of epileptic psychoses. The classification by B. A. Kazakovtsev [1] distinguishes transitory, paroxysmal and chronic epileptic psychoses. Transitory psychoses have an acute beginning, last from a few hours to a few days, may be with obfuscation (dreamy state after a series of tonic-clonic seizures, hallucinatory and delusion states, psychomotor agitation, aggression, epileptic delirium, epileptic oneiroid) or without it (acute paranoid, dysphoric psychosis). Paroxysmal epileptic psychoses are more prolonged in time and last up to one month.

These include affective, affectively delusive, delusive, catatonic and catatonic-paranoid psychoses. Chronic epileptic psychoses last a few months or years, develop at the later stages of the disease (10–15 years), are characterized by distinct polymorphism and retained consciousness. Psychiatrists most often deal with paranoid, hallucinatory paranoid syndromes, verbal hallucinosis, Kandinsky-Clérambault syndrome, dementia with delusion-like utterances, schizophrenoidea states. In clinical practice, epileptic psychoses are customarily systematized according to the time of onset as to paroxysm seizures [12] as pre-ictal (appear before seizures and end when those develop); ictal (appear at the time of seizure or as a consequence to the status of non-paroxysmal epileptic seizures); post-ictal (appear immediately after the epileptic seizure or within 12–72 hours after its end, often after a series of complex partial seizures with or without secondary generalization) and inter-ictal (emerge in the inter-seizure period and are not connected with epileptic seizures). Inter-ictal psychoses are mostly acute or chronic.

There is also a separate type of epileptic psychoses, particularly alternating psychosis being regarded to as inter-ictal psychosis also referred to as Landolt syndrome. The development of this kind of psychosis is associated with "forceful normalization" of EEG curve. This kind of psychosis is characterized by the development of psychotic symptomatology secondary to paroxysm activity reduction and a decrease in seizure frequency. This psychosis may last from a few days to a few weeks. Nowadays medically induced psychosis is distinguished as a side effect to anti-epilepsy therapy. This kind of psychosis can be provoked by any kind of drugs which are used to decrease epileptic activity as a response to taking traditional anti-epilepsy drugs as well as a result of taking new generation drugs. Most authors believe this kind of psychosis does not belong to epileptic psychoses, though it should be taken into account when carrying out differential diagnosis with alternating psychosis [5].

Etiological agents triggering epileptic psychoses are the presence of cryptogenic temporal lobe epilepsy with complex partial seizures with or without generalization, with psychic symptoms and automatisms, improper medication treatment when the prescribed anti-epilepsy drug does not correspond to the seizure type, violating the mode of basic anti-epilepsy therapy, interrupting medication intake, increasing the number of seizures before developing a psychotic episode, the presence of a persistent psychotraumatic factor related to the emotions of fear and anxiety [6].

According to various studies, the development of psychoses is determined by epileptic disorders in neuron activity mostly in limbic structures related to emotion and motivation regulation, complex automatic forms of behavior, which is proven by EEG examinations. Specific changes and dynamics of bioelectrical brain activity while developing psychoses are characterized by an increase and expansion of the epileptic system, low-rate low-amplitude diffusion activity in combination with hyporeactivity to external stimuli for spontaneous psychoses formation or a decrease in intensity of epilepsy mechanism of brain functioning with desynchronization phenomena while developing psychotic states with alternative formation mechanism [7]. Epileptic process in the brain itself is the main factor for psychoses development in epilepsy, which is of fire of polyfire character and always involves mediobasal structures, temporal and frontal lobes on both sides, with mostly complete lateralization. Such disorders develop due to prenatal, perinatal or postnatal brain damage as well as an increase in secondary organic process in brain due to neuron collapse during epileptic bursts.

Taking into account the two components of epileptic process development, namely paroxysm and non-paroxysm mechanisms [9, 10], which are the main triggers of epilepsy psychoses and various types of epileptic psychoses at any stages of illness, the therapeutic tactics must be comprehensive and include anti-psychotic therapy, tranquilizers, antidepressants, anti-epileptic drugs, neuro-metabolic therapy, normalizing brain CSF circulation, psychotherapy correction and so on.

The therapy, when rendering help to those patients, with the exception of the ictal epileptic psychosis type, should start with anti-psychotic drugs, which are the basis in this case. All anti-psychotic drugs by the mechanism of action affect productive psychotic disorders thus providing full or partial reduction of these psychopathologic signs. The first generation antipsychotics (neuroleptics) are mostly antagonistic to dopamine receptors and may provoke and increase neuron epileptic activity. Moreover, most neuroleptics even in small doses may provoke side effects in the form of extrapyramidal disorders on account of changes in the state of the extrapyramidal system.

The incidence and clinical significance of these disorders depend on the presence and the intensity of organic encephalopathy in patients with epilepsy. These disorders are undesirable and poorly tolerated by patients. Clinicians should avoid the drugs of major distinct proconvulsive action when prescribing neuroleptic drugs to patients with epileptic psychoses. It is a well-known fact that phenothiazine drugs are most capable of epileptic threshold reduction. The least proconvulsive action belongs to phenyl propyl ketones although their usage significantly increases the risk of extrapyramidal disorders and late dyskinesia. The second generation antipsychotics (atypical antipsychotics) are characterized by a significantly smaller proconvulsive effect, with medium therapeutic doses they rarely cause extrapyramidal disorders and late dyskinesia, most of them cause insignificant rise in blood serum prolactin level, they not only efficiently function for productive symptomatology but also detain the development of negative symptomatology or mitigate and level its manifestation.

Considering the above said we believe that patients with epileptic psychoses should be prescribed atypical antipsychotic drugs which can have a direct impact on most mechanisms of epileptic psychoses development and decrease further destructive effect. According to recommendations by a number of scientists, such as S. Koch-Stoecker [11], L. M. Yurieva, S.G. Nosov [8], A. E. Dubenko, V. I. Korostiy [5] and others, when choosing antipsychotic drugs it is advisable to prescribe those with minimum potential side effects, to take into account side reactions and toxic influence, to prescribe minimum effective doses, to strictly keep to their titration, not to exceed small or medium day doses and the period of antipsychotic drug intake should not exceed the period of psychosis but be minimally sufficient.

Considering the fact that any antipsychotic drugs by their action mechanism may provoke or enhance epileptic activity, practically any research in the field of estimating

the risks of epileptic seizures after taking antipsychotic drugs, has been carried out involving patients with psychic disorders without epilepsy, our own observation and analysis of the recent scientific publications enables us to consider quetiapine as one of the most acceptable drugs for treating epileptic psychoses patients. No difference as to patient seizures has been registered with the patients without epilepsy who received quetiamine or placebo treatment (0.4 and 0.5 respectively) [5].

The advantage of quetiapine lies in the wide clinical and pharmacological spectrum: antipsychotic, antimania, antiaggression, anxiolytic and sedative effects. Besides, quetiapine is capable of forming a rapid clinical effect accompanied by a high safety profile, it has lower spectrum of side effects compared to other antipsychotic drugs (hyperprolactinemia, metabolic and extrapyramidal complications, the anticholinergic effect; it has an insignificant potential as to body mass increase).

Quetiapine and its active metabolite norquetiapine act as antagonists to dopamine D2-receptors with moderate affinity [13, 14], norquetiapine increases the concentration of the pre-frontal dopamine and serotonin [13,15], blocks the presynaptic receptors 5-HT7 [14, 15], which explains its antipsychotic effect and the influence on the wide spectrum of affective and cognitive disorders. Improvement of cognitive functions in patients treated for schizophrenia and other psychoses can be explained by its low relationship and quick dissociation with dopamine D2-receptors [13, 14, 15], in this research patients were given a medium drug dose – 600 mg a day. According to Chang et al., 2012 Dell`Osso et al., 2012, it can improve life quality in any forms of affective disorders. Quetiapine is a pleiotropic drug which can affect a few targets and can be efficient for treating various psychotic disorders [14]. Quetiapine treatment stipulates symptomatic remission and improves the life quality [15]. In the research by Miljevk et al., 2013 quetiapine demonstrated the neuroprotective effect, within the oxidant system, the drug promoted a decrease in superoxide dismutase and prooxidant effects, antioxidant inhibition, induced hydrogen peroxide in vitro [13, 14, 15] and was capable of protecting cell cultures from oxidative stress related to cytotoxicity induced by the ß-amyloid [13, 15]. These data prove the important role of the drug in reducing the level of active intracellular oxygen and calcium forms, which enhances its antioxidant properties [13, 14, 15]. It can also prevent overproduction of intracellular enzymes of superoxide dismutase, catalase, glutathione peroxidase [14, 15]. Other neuroprotective effects of quetiapine include its capability of removing neurogenesis oppression in hippocampus caused by chronic stress [13, 14, 15].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

The aim of the study was to study the quetiapine clinical effectiveness for treating patients with epileptic psychoses.

2.2 Subjects & Methods

The program of research on the clinical effect of quetiapine has been carried out with 19 female patients aged 26 to 59 with various types of epileptic psychoses except those of the ictal type. Of them, 12 patients were diagnosed with post-ictal epipeptic psychosis, 6 patients with inter-ictal epileptic psychosis and 1 patient with alternating psychosis. By ICD-10, all the patients who took part in the research fall into the F 06 category and they took quetiapine in the combination with an anti-epilepsy drug. At the beginning of the research and during the whole period of treatment the patients were subject to clinical psychopathology, laboratory, neurovisual, ECG examination, the glycaemic and lipidic blood serum profiles being under control.

Within the term of research patients were given quetiapine in different therapeutic doses. Titration started at 25 mg a day on the first day of treatment with a gradual dose increase, which did not exceed the existing recommendations and in some cases even did not go as high as 50 mg a day during titration. The maximum daily dose was 600 mg, the minimum efficient one was 200 mg a day in

two takes. Depending on the type of epileptic psychosis the correction of quetiapine doses and intake duration was performed. Basing on current recommendations, the drug was prescribed in minimum efficient doses and for the minimum sufficient period.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

In the process of research, the initial therapeutic effect for most of the patients was observed during the first week of drug titration (52.6% of patients) and was manifested by sleep improvement, reducing the intensity and duration of psychotic affect; the patients had more gentle and moderate attacks and were more responsive to the surroundings. At the end of the second and the beginning of the fourth week of quetiapine treatment positive alterations of the mental state were observed with proven reduction of the major psychotic symptomatology, leveling of affect, normalizing the mood, stabilizing somatic-vegetative status. There was clinical psychopathological evidence of mental state stabilization on the sixth week of therapy in 73.6% of the patients under investigation.

After the reduction of psychotic state for preventing the withdrawal syndrome the drug dose was gradually reduced with continuous control of the patient's mental state until the ultimate stop of quetiapine intake. It is necessary to point out that clinical psychopathological, laboratory and neurovisual examination repeatedly performed during the whole period of study showed a positive effect of the drug intake on cognitive functions of the patients (36.8% of the patients), praxis improvement (26.3%), neurodymanics improvement (42.1%), voluntary regulation and thinking (68.4%). ECG examination showed no signs of cardiotoxic effects of the drug on any of the patients. According to glycemic and lipid profiles, the deviation from standardized parameters was not statistically significant ($p<0.05$). None of the patients was found to have clinical manifestations of extrapyramidal disorders.

The research showed that the majority of the patients (84.2%) gave a positive response to treatment and displayed good therapy endurance. No clinically important side effects as to higher mental functions have been registered. The most common side effects were sedation (42.1% of the patients), drowsiness (47.3%), orthostatic hypotension (26.4%), dyspepsia (15.7%) and headache (21.1%). These side effects were mostly observed at the beginning of treatment depending on the drug dose, reduced with the process of dose correction and slowing the titration speed. Only one patient (5.2%) with epileptic psychosis stopped taking the drug due to a distinct summation of side effects and absence of substantial positive changes in the mental state within 4 weeks of therapy and 600 mg quetiapine intake.

4 CONCLUSIONS

1. While performing differential diagnosis and prescribing antipsychotic drugs to patients with epileptic psychoses, it is necessary to take into account not only the structure and clinical manifestations of a psychotic episode and the epilepsy form but also the presence and manifestation level of epileptic personality changes, affective disorders, cognitive disorders or dementia, organic epileptic encephalopathy.

2. It is necessary to remember about the complex interaction between antipsychotic and anti-epilepsy drugs, the possible potential side effects, side reactions and toxic influences. When providing therapeutic treatment to such patients, it is necessary to be consistent and avoid quick changes in drug dosage and change of drugs. A patient with epileptic psychosis must keep getting the earlier prescribed anti-epilepsy drugs and, if necessary, their dosage may be increased.

3. The brain epileptic activity may affect the structure, duration and time course of psychotic states.

4. The efficiency of quetiapine in patients with various types of epileptic psychoses was confirmed by various clinical and pharmacological antipsychotic, anti-mania,

anti-aggression, anti-depression, anxiolytic and sedative effects.

5. The drug was well-tolerated by patients because of the high safety level and a lower side effects spectrum compared to other antipsychotic drugs (hyperprolactinemia, metabolic and extrapyramidal complications, anticholinergic effect, it has an insignificant potential as to body mass increase). Also, quetiapine can promote a quick clinical effect, which improves the doctor-patient compliance. At the beginning of treatment and during patient's exit from psychosis it is necessary to perform clinical psychopathological, laboratory, neurovisual examination, to control glycemic and lipid profiles.

6. Quetiapine doses must be minimally sufficient, drug intake should stop after the patient's exit from psychosis with gradual canceling the drug on condition of continuous control of the patient's mental state.

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