Received: 06 June 2022 / Accepted: 10 October 2022 / Published online: 31 December 2022

DOI 10.34689/SH.2022.24.6.008

UDC 618.15-007.44

A PILOT STUDY OF NEWBORN SCREENING OF INHERITED METABOLIC DISORDERS USING TANDEM MASS SPECTROMETRY IN KAZAKHSTAN

Korlan Z. Saduakassova[1], https://orcid.org/0000-0002-4758-6948

Gulnara S. Svyatova[2], https://orcid.org/0000-0001-5092-3143

Vladislav V. Sklyarov[3],

Gulzhan T. Kassenova[1], https://orcid.org/0000-0003-0815-279X

[1] Al-Farabi Kazakh National University, Higher School of Medicine, Faculty of Medicine and Health care, Almaty, the Republic of Kazakhstan.
[2] Scientific Center of Obstetrics, Gynecology and Perinatology, Republic Medical Genetic Consultation, Almaty, the Republic of Kazakhstan.
[3] Center of Molecular Medicine, Almaty, the Republic of Kazakhstan.

Abstract

Background: Inherited metabolic disorders (IMD) occupy a significant place in human hereditary pathology, occur in all populations, and have severe clinical manifestations. It is known that IMDs are one of the significant causes of childhood morbidity and mortality throughout the world, the indicators of which directly depend on the possibilities of diagnosing and introducing neonatal screening for IMDs in each country. For the first time, the Republic of Kazakhstan expanded neonatal screening by including neonatal selective screening of newborns for 49 IMDs using tandem mass spectrometry (TMS).

The aim of this study was a primary analysis of the frequency of IMD in selective and mass screening, and clarification of the reference standards of the analyzed metabolites in the Kazakhstani population.

Methods: Dry blood drops collected from newborns aged from 0 days to 6 months served as the material for the study (n=1000). The research method was tandem mass spectrometry.

Result: The results of neonatal selective screening for IMD in the Republic of Kazakhstan showed that their preliminary frequency is 16.0 per 1000 newborns, the main share of IMD falls on defects in β-oxidation of fatty acids and lysosomal storage diseases (25.0%), followed by organic aciduria and peroxisomal diseases (18.7%), disorders of the urea cycle and aminoacidopathy - (6.3%).

Conclusion: Early screening and diagnosis with TMS can help reduce mortality and morbidity among children with IMD. Timely treatment, will improve the health of newborns and reduce the incidence of birth defects, as well as reduce the economic burden on patients, families, and society.

Keywords: *Inherited metabolic disorders, tandem mass spectrometry, neonatal selective screening.*

ПИЛОТНОЕ ИССЛЕДОВАНИЕ СКРИНИНГА НОВОРОЖДЕННЫХ НА НАСЛЕДСТВЕННЫЕ БОЛЕЗНИ ОБМЕНА С ИСПОЛЬЗОВАНИЕМ ТАНДЕМНОЙ МАСС-СПЕКТРОМЕТРИИ В КАЗАХСТАНЕ

Корлан З. Садуакасова[1], https://orcid.org/0000-0002-4758-6948

Гульмира С. Святова[2], https://orcid.org/0000-0001-5092-3143

Владислав В. Скляров[3],

Гульжан Т. Касенова[1], https://orcid.org/0000-0003-0815-279X

[1] НАО «Казахский Национальный университет им. аль-Фараби, Высшая школа медицины, Факультет медицины и здравоохранения, г. Алматы, Республика Казахстан;
[2] АО «Научный центр акушерства, гинекологии и перинатологии», Республиканская медико-генетическая консультация, г. Алматы, Республика Казахстан;
[3] ТОО «Центр молекулярной медицины», г. Алматы, Республика Казахстан.

Резюме

Актуальность: Наследственные болезни обмена (НБО) занимают значительное место в наследственной патологии человека, встречаются во всех популяциях и имеют тяжелые клинические проявления. Известно, что НБО являются одной из значимых причин детской заболеваемости и смертности во всем мире, показатели которой напрямую зависят от возможностей диагностики и внедрения неонатального скрининга НБО в каждой стране. Впервые в Республике Казахстан неонатальный скрининг был расширен за счет включения неонатального селективного скрининга новорожденных на 49 НБО с использованием тандемной масс-спектрометрии (ТМС). **Целью**

данного исследования был первичный анализ частоты НБО при выборочном и массовом скрининге, уточнение референтных стандартов анализируемых метаболитов в казахстанской популяции.

Методы. Материалом для исследования послужили сухие капли крови, взятые у новорожденных в возрасте от 0 дней до 6 мес (n=1000). Метод исследования – тандемная масс-спектрометрия.

Результат: Результаты неонатального селективного скрининга НБО в Республике Казахстан показали, что их предварительная частота составляет 16,0 на 1000 новорожденных, основная доля НБО приходится на дефекты β-окисления жирных кислот и лизосомные болезни накопления (25,0%), далее следуют органическая ацидурия и пероксисомальные заболевания (18,7%), нарушения цикла мочевины и аминоацидопатии - (6,3%).

Заключение. Ранний скрининг и диагностика с помощью ТМС могут помочь снизить смертность и заболеваемость среди детей с НБО. Своевременное лечение улучшит здоровье новорожденных и снизит частоту врожденных дефектов, а также снизит экономическую нагрузку на пациентов, семьи и общество.

Ключевые слова: *наследственные болезни обмена, тандемная масс-спектрометрия, неонатальный селективный скрининг.*

Түйіндеме

ҚАЗАҚСТАНДА ТАНДЕМДІК МАСС-СПЕКТРОМЕТРИЯ ҚОЛДАНУЫМЕН ТҰҚЫМ ҚУАЛАЙТЫН МЕТАБОЛИЯЛЫҚ АУРУЛАРДЫҢ НЕОНАТАЛЬДЫ СКРИНИНГІНІҢ ПИЛОТТЫҚ ЗЕРТТЕУІ

Корлан З. Садуакасова[1], https://orcid.org/0000-0002-4758-6948

Гульмира С. Святова[2], https://orcid.org/0000-0001-5092-3143

Владислав В. Скляров[3],

Гульжан Т. Касенова[1], https://orcid.org/0000-0003-0815-279X

[1] КЕАҚ «Әл-Фараби атындағы Қазақ ұлттық университеті», Жоғары медицина мектебі, Медицина және денсаулық сақтау факультеті, Алматы қ., Қазақстан Республикасы.;
[2] АҚ «Акушерлік, гинекология және перинатология ғылыми орталығы, Республикалық медициналық-генетикалық консультация, Алматы қ., Қазақстан Республикасы.;
[3] ЖШС «Молекулярлық медицина орталығы», Алматы қ., Қазақстан Республикасы.

Өзектілігі: Тұқым қуалайтын метаболикалық аурулар (ТМА) адамның тұқым қуалайтын патологиясында маңызды орын алады, барлық популяцияларда кездеседі және ауыр клиникалық көріністерге ие. ТМА дүние жүзінде балалар ауруының және өлімінің маңызды себептерінің бірі болып табылатыны белгілі, оның көрсеткіштері әр елде неонаталдық скринингті диагностикалау және енгізу мүмкіндіктеріне тікелей байланысты. Қазақстан Республикасында алғаш рет неонаталдық скрининг 49 НБО үшін тандемдік масс-спектрометрияны (ТМС) пайдалана отырып, жаңа туған нәрестелерді неонатальды іріктеу скринингін қамтитындай кеңейтілді.

Бұл **зерттеудің мақсаты** селективті және жаппай скринингте ТМА жиілігін бастапқы талдау, қазақстандық популяциядағы талданатын метаболиттердің эталондық стандарттарын нақтылау болды.

Әдістері. Зерттеу материалы ретінде 0 күннен 6 айға дейінгі жаңа туған нәрестелерден алынған құрғақ қан тамшылары (n=1000) болды. Зерттеу әдісі - тандемдік масс-спектрометрия.

Нәтижесі: Қазақстан Республикасындағы ТМА неонатальды селективті скрининг нәтижелері олардың алдын ала жиілігі 1000 жаңа туған нәрестеге шаққанда 16,0 құрайды, ТМА негізгі үлесі май қышқылдарының β-тотығу ақаулары мен лизосомалық жинақтау ауруларына (25,0%) байланысты екенін көрсетті. Одан кейін органикалық ацидурия және пероксисомалық аурулар (18,7%), мочевина циклінің бұзылуы және аминоацидопатия - (6,3%).

Қорытынды. ТМС көмегімен ерте скрининг және диагностика ТМА бар балалар арасындағы өлім мен сырқаттануды азайтуға көмектеседі. Уақытылы емдеу жаңа туған нәрестелердің денсаулығын жақсартуға және туа біткен ақауларды азайтуға, сонымен қатар пациенттерге, отбасыларға және қоғамға экономикалық жүктемені азайтуға мүмкіндік береді.

Түйінді сөздер: *тұқым қуалайтын метаболикалық аурулар, тандемдік масс-спектрометрия, неонатальды селективті скрининг.*

Bibliographic citation:

Saduakassova K.Z., Svyatova G.S., Sklyarov V.V., Kassenova G.T. A pilot study of newborn screening of inherited metabolic disorders using tandem mass spectrometry in Kazakhstan // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2022, (Vol.24) 6, pp. 59-64. doi 10.34689/SH.2022.24.6.008

Садуакасова К.З., Святова Г.С., Скляров В.В., Касенова Г.Т. Пилотное исследование скрининга новорожденных на наследственные болезни обмена с использованием тандемной масс-спектрометрии в Казахстане // Наука и Здравоохранение. 2022. 6(Т.24). С. 59-64. doi 10.34689/SH.2022.24.6.008

Садуакасова К.З., Святова Г.С., Скляров В.В., Касенова Г.Т Қазақстанда тандемдік масс-спектрометрия қолдануымен тұқым қуалайтын метаболиялық аурулардың неонатальды скринингінің пилоттық зерттеуі // Ғылым және Денсаулық сақтау. 2022. 6(Т.24). Б. 59-64. doi 10.34689/SH.2022.24.6.008

Introduction

Inherited metabolic disorders (further in the text IMD) is a class of hereditary monogenic disorders caused by mutations in genes that control the synthesis of enzymes, structural proteins, cell transport proteins, and other polypeptides responsible for complex reactions associated with metabolism. (Britannica. https://www.britannica.com/science/metabolic-disease)

A distinctive feature of IMD is an autosomal recessive type of inheritance in most cases and the presence of highly specific biochemical markers of diseases, on which their laboratory diagnostics is based (biochemical analyzes, determination of the spectrum of amino acids, organic acids in the urine, carnitine, and acylcarnitines in the blood, determination of enzyme activity, molecular-genetic diagnostics) [13]. There is the possibility of metabolic correction for some of this group of diseases.

IMD occupies a prominent place in human hereditary pathology, occurs in all populations, and has severe clinical manifestations. The frequency of individual forms of IMDs in populations is extremely low, 1 per 100,000 newborns, but their total frequency is high. Thus, according to the data of selective screening of newborns in Moscow by tandem mass spectrometry (further in the text TMS), the frequency of all screened orphan IMD was 13.3 per 1000 newborns [18].

It is known that 80% of orphan IMD manifest in early childhood and occupy about 30% of the number of beds in children's hospitals, they are characterized by an acute course and early (up to 3-5 years) death, up to 40% of early childhood mortality is due to IMD [16,21,23,].

Diagnosis and treatment of IMDs are one of the most difficult tasks of clinical genetics, pediatrics, and neurology. Most IMDs are characterized by significant clinical polymorphism and pronounced genetic heterogeneity, which leads to nonspecific clinical manifestations, such as convulsions, coma, muscle weakness, vomiting, hepatosplenomegaly, etc., which make it difficult to make a correct diagnosis on time. Of particular difficulty is the diagnosis of IMD in newborns, when the clinical picture develops early and quickly leads to death. In the neonatal period, approximately 25% of known IMDs manifest themselves, and almost all of them are distinguished by the particular severity of the child's condition. Most children with neonatal forms of IMDs die in the first months of life or are observed for a long time with a variety of inadequate diagnoses (mental retardation, cerebral palsy, epilepsy, "sluggish child" syndrome, etc.).

The only IMD screening method is tandem mass spectrometry, an analytical method that can be used to obtain both qualitative (structure) and quantitative (molecular weight or concentration) information of analyzed molecules after their conversion into ions.

In comparison with the used enzyme immunoassay, immunofluorescent methods, the TMS method has a higher selectivity and specificity, high sensitivity, and a short analysis time. This is the only method that allows different classes of analytes to be combined in a single assay, making it a versatile IMD screening method. TMS makes it possible to analyze a large number of metabolites, which means detecting a large number of IMDs (disturbances in the metabolism of amino acids, organic acids, and defects in mitochondrial b-oxidation of fatty acids, disorders of the urea cycle). The sample of the IMD study is a dry blood drop on filter paper used in the neonatal screening system, the transportation of which does not require compliance with temperature regimes and does not have an expiration date.

Mass and/or selective TMS screening for IMD has been implemented in more than 60 countries of the world, in all developed countries (the USA, EU countries, Canada, Australia, etc.), in several developing countries (China, Malaysia, Singapore, Brazil, Argentina, etc.). etc.) and has proven its high diagnostic value and cost-effectiveness (www.isns-neoscreening.org).

For example, a US cost-benefit analysis found that the total incremental annual cost of TMS screening for 540,000 newborns in California was 5.7 million US $. 83 children with IMD were identified. TMS screening reduced the expected health care costs of sick newborns by $7.2 million, saving $708,000 per lifetime cost at a cost per case detected of $68,000. It has been shown that every dollar invested in TMS screening saved US$9.32 [10].

It is known that IMDs are one of the significant causes of childhood morbidity and mortality throughout the world, the indicators of which directly depend on the possibilities of diagnosing and introducing neonatal screening for IMDs in each country.

A meta-analysis found fluctuations in infant mortality from IMD from 3.2% in North Carolina to 32.7% in Libya [7,14]. Considering that the vast majority of all deaths from IMDs will occur in low-income countries, it has been shown that 33% of the contribution of IMDs to the structure of causes of child mortality represents the lower limit of mortality from IMDs [20,22].

According to WHO, in countries where neonatal or selective screening for IMD is carried out, the mortality and disability of young children have significantly decreased. For example, according to the International Society for Neonatal Screening, www.isns-neoscreening.org, 28 orphan IMDs are screened in Austria, 17 in Denmark, 33 in Italy, 26 in Russia, 19 in Estonia, and 42 in the USA. [2,8,9,19,].

For many IMDs, there is an effective and affordable treatment (in most cases, diet therapy), the cost of which varies. For a few IMDs (about 10) there is an expensive enzyme replacement therapy, the remaining IMDs, in addition to diet therapy, need special vitamins and drugs necessary to detoxify accumulated metabolites, the cost of which is low. During the first year of life, children need intensive treatment, after a year the number of visits and examinations decreases. After 5–7 years of age, the need for specialized therapeutic nutrition usually disappears, and patients are on a low-protein or low-fat diet.

It has become clear that early screening and diagnosis of TMS can help reduce mortality and morbidity among children with IMD. Infant, child mortality, early disability, and other serious consequences of IMD in children can be prevented through early detection and timely treatment, which will improve the health of newborns and reduce the incidence of birth defects, as well as reduce the economic burden on patients, families, and society [1,22].

Currently, TMS screening is performed in developed countries such as the United States, Canada, Germany,

and Spain, as well as in Latin American countries, including Mexico, Brazil, Costa Rica, Germany (2001), Australia (1998), Mainland China and Shanghai (2003). Qatar, Saudi Arabia, and the United Arab Emirates have adopted national expanded newborn screening using TMS [3,11,12,15,17].

The developers of the Roadmap (RM) "Improving the provision of comprehensive care for children with disabilities in the Republic of Kazakhstan for 2021-2023" approved by the Prime Minister of the Republic of Kazakhstan on August 17, 2020, proposed the first time in the Republic of Kazakhstan to expand neonatal screening by including neonatal selective screening of newborns for 49 IMDs using the TMS method.

Material and methods

"Center of Molecular Medicine" (CMM) in Almaty conducted a pilot project to study the prevalence of IMD in the Kazakhstani children's population.

The purpose of the project: primary analysis of the frequency of IMD in selective and mass screening, clarification of the reference standards of the analyzed metabolites in the Kazakhstani population.

The material for the study was dry blood spots, the sampling of which was carried out in 5 cities of the Republic of Kazakhstan: Nur-Sultan - 304 (30.4%), Shymkent - 147 (14.7%), Atyrau - 250 (25%), Almaty - 155 (15.5%), Aktobe - 144 (14.4%). It should be noted that some studies were carried out retrospectively (mortality cases in the neonatal and infantile periods), by examining dry blood spots, which are stored in the archives of medical genetic consultations.

The age distribution is as follows: newborns from 0 to 7 days - 537 (53.7%), from 8 days to 6 months - 154 (15.4%), older than 6 months - 309 (30.9%). Total: 1000 samples (dry blood spots) for TMS analysis, which were delivered to the laboratory of CMM.

The main signs (symptoms) are the sudden onset of a clinical condition after a period of normal child development. In the anamnesis, attention was paid to cases of IMD in several cases, cases of stillbirths, and cases of sudden death syndrome in previous children in the postneonatal period.

Also important were clinical criteria in the form of hepatomegaly (hepatosplenomegaly); metabolic acidosis; multiple fractures. Additional criteria (symptoms): cardiomyopathy; hypoglycemia; thrombocytopenia; increased levels of liver enzymes, bone and joint abnormalities (joint stiffness, chest deformity, rickets-like changes); dystonia, hyperkinesis, that is the already known basic and additional clinical signs of IMD were used [18,21].

In the process of work, it became obvious that simultaneously with the introduction of selective screening for IMD, a coordinated complex system is needed, consisting of training of medical personnel, adherence to a clear screening algorithm, observation of atypical test results, confirmatory testing, diagnosis, treatment and evaluation of the effectiveness of therapy. It also requires the training of neonatologists, pediatricians, and general practitioners to isolate the most appropriate and alert symptoms of IMD in newborns and children.

The research method is tandem mass spectrometry. Equipment used: QSight Perkin Elmer. RU RK-MT -5 No. 018237 dated 12.09.2018. Reagent Kit: NeoBase Non-derivatized MSMS Kit, NeoLSD™ MSMS Kit. Simplicity 3Q analyzer software.

Statistical processing of the obtained data was carried out using the Statistica 6.0 application package, Excel spreadsheets (15.0).

Results

The total number of identified NBOs was 16, of which:

- Organic aciduria - 3 (18.7%): Propionic acidemia - 1, Methylmalonic acidemia - 1, Phenylketonuria – 1;
- Lysosomal storage diseases - 4 (25.0%): Krabbe disease - 2, Gaucher disease - 1, Pompe disease – 1;
- Fatty acid oxidation defects - 4 (25.0%): Primary carnitine deficiency -1, deficiency of short and medium-chain acyl-CoA dehydrogenase - 2, type 2 glutaric aciduria – 1;
- Peroxisomal diseases - 3 (18.7%): Adrenoleukodystrophy - 1, Zellweger's disease - 1, Refsum disease – 1;
- Disorders of the urea cycle - 1 (6.3%): Type I citrullinemia – 1;
- Aminoacidopathy - 1 (6.3%): Non-ketotic hyperglycinemia - 1.

Molecular genetic confirmation was carried out in 5 cases (31.3%). Of these: in two patients with Pompe and Gaucher disease, tests are underway, in a patient with phenylketonuria, a homozygous mutation in the PAH gene and mutations in the ACADM and ACADS genes in the heterozygous state in a patient with a deficiency of short-chain and medium-chain acyl-CoA dehydrogenase.

The control group consisted of 342 clinically healthy newborns (179 girls, 163 boys) aged 3–14 days. As a result of the study of the concentrations of amino acids and acylcarnitines, ketones in the capillary blood of 342 healthy newborns, 0.5 and 99.5 percentiles of the concentrations of the studied metabolites were determined, which were subsequently used as reference values.

The results obtained indicate that selective screening for IMD is more economically justified, but the effectiveness of treatment with a detailed clinical picture is lower. Since some IMDs occur in the form of acute urgent conditions (with the threat of developing a lethargic coma), lethal outcomes and early development of disability with an irreversible loss of function of the central nervous system will be expected in case of untimely diagnosis and treatment.

Our study showed that screening of children with suspected IMD was more effective at the age of up to 6 months since the manifestation of clinical syndromes of many diseases begins after the age of 4 months of life.

A clinical finding deserves special attention when IMDs were detected in children with verified diagnoses from the spectrum of autism spectrum disorder. A logical question arose: are we talking about the comorbidity of autism with some IMDs, or do certain forms of IMDs have an autistic syndrome in their clinical structure? The issue of timely differential diagnosis of mental and speech developmental delays is very relevant since almost all children with IMD have these signs.

Among the studied children, three had a diagnosis of "Children's autism". In one family, twins (sister-brother) showed a decrease in the activity of the enzyme galactocerebrosidase (GALC) - Krabbe's disease, and a 7-

year-old girl - a violation of fatty acid metabolism - a diagnosis of Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type 2).

IMDs were identified in these children when informing medical geneticists in preparation for a pilot project as part of the implementation of the RM. Common to all children from this group of autism spectrum disorders are difficulties in communication, many individual stereotypical movements, and repetitive behaviors - these are the signs, due to overdiagnosis of disorders from the autism spectrum, that make it difficult to timely identify, for example, IMD. These symptoms, as you know, can be not only in autism but also in mental retardation and early childhood schizophrenia. Therefore, the issue of awareness among primary health care professionals and child psychiatrists, and child neurologists about the clinical criteria for IMD and timely differential diagnosis of autism, mental retardation, and other mental and neurological disorders in childhood becomes even more relevant.

Table 1 presents the range of referral diagnoses for TMS screening with identified IMDs.

Table 1. **The spectrum of referral diagnoses for TMS screening with identified IMDs.**

Referral diagnosis for TMS	N	%
Acute encephalitis, sepsis	2	12,6
Metabolic acidosis, coma	7	43,7
Autism, STD	3	18,5
Cerebral palsy	1	6,3
Epilepsy, convulsions resistant to therapy	2	12,6
Bone anomalies	1	6,3
Total:	16	100

As can be seen from Table 1, the most common referral diagnosis was metabolic acidosis, coma in 43.7%, followed by autism - 18.5% and acute encephalitis, sepsis or epilepsy, convulsions resistant to therapy - 12.6% each.

The TMS screening budget to identify IMDs for each country is an important argument in the decision for or against. Our analysis of the available results of the study on the cost-effectiveness of screening (published economic estimates, economic estimates, life expectancy (LY) and QALY, total NBO prevalence) showed that all authors agree that the advantages of TMS are rapid testing, high sensitivity and safety, high throughput and minimal sample volume. There is no data on the shortcomings of the technology. The limitation is the additional costs of the state for the purchase of reagents for analysis [4,5,6,17,23]. This factor is the stumbling block in the decision "to be or not to be" screened by TMS for IMD in each country.

Discussion

Since February 2022, a pilot project has been launched in the Republic of Kazakhstan in all regions of the country for selective screening of newborns using TMS for 49 IMDs to implement paragraph 7 of the Roadmap to improve the provision of comprehensive care to children with disabilities in the Republic of Kazakhstan for 2021-2023. According to the submitted report from the CMM (participant-executor of the pilot project), for the reporting period (February - March 2022), 23 blood samples (dry spots) for TMS at the IMD were received. 3 NBOs (13.0%) were detected - 2 cases of Multiple deficiencies of acyl-CoA dehydrogenase (glutaric aciduria type 2); 1- Deficiency of medium-chain acyl-CoA fatty acid dehydrogenase;

The ultimate goal of the pilot project is whether selective screening of newborns for IMD is needed in the Republic of Kazakhstan or not? When implementing a pilot project, it is very important to notify obstetric and primary health care institutions about this pilot, to assess on-time clinical indications for referral to selective screening for IMD. Even now, when receiving the first results, it became clear that the prevalence of IMD in the Republic of Kazakhstan is likely to be much higher than that detected in the pilot per 1000 newborns. This means that an algorithm should already be developed for accompanying a child from the moment IMD is detected in him - a permanent council of specialists in medical genetics, neonatologists, and pediatricians is needed; if IMD is detected - transfer of data to the obstetric institution or territorial polyclinic at the place of attachment of the child; mandatory medical genetic counseling for families where IMD was detected in a child (molecular genetic analysis to determine the risk of re-birth of a child with IMD), further dispensary observation, provision with the necessary enzymes and development of an appropriate diet, etc.

Conclusion

1. The results of the pilot project of selective screening for IMD in the Republic of Kazakhstan showed that their preliminary frequency is 16.0 per 1000, the main share of NBO falls on defects in β-oxidation of fatty acids and lysosomal storage diseases (25.0%), followed by organic aciduria and peroxisomal diseases (8.7%), disorders of the urea cycle and aminoacidopathy - (6.3%).

2. The main referral diagnosis for TMS analysis in 43.7% were emergency indications such as metabolic acidosis and coma; in older children - autism and delayed psycho-speech development - 18.5%, as well as the presence of therapy-resistant epilepsy and acute encephalitis - 12.6%.

3. All IMD diagnoses were made in the Republic of Kazakhstan for the first time, pathogenetic treatment was not carried out for these children, which led to the death of 7 children (43.7%), which confirms the high social significance of the introduction of neonatal TMS screening for IMD for early diagnosis and timely pathogenetic treatment IMD.

Thus, given the significant economic losses of the state associated with the cost of symptomatic treatment, medical care, life expectancy and lifelong maintenance of disabled children with IMD, early diagnosis of orphan IMD is a necessary condition for reducing infant and child mortality, morbidity and disability in the Republic of Kazakhstan.

Conflict of interest. *None of the authors have any competing interests regarding relevant financial activities outside the submitted work, intellectual property, or any other relationships.*

Author contributions. *Saduakassova K., Svyatova G., Sklyarov V. were involved in the acquisition of data and drafting of the manuscript. Svyatova G., Sklyarov V. was involved in the biochemical analysis of all patients. Saduakassova K., Kassenova G. were involved in the interpretation of data and reviewing and editing the manuscript. All the authors have accepted responsibility for the entire content of this submitted article and approved the submission.*

Data availability statement. *The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.*

Funding *This research received no external funding.*

References:

1. *Cespedes N. et al.* Reference values of amino acids, acylcarnitines and succinylacetone by tandem mass spectrometry for use in newborn screening in southwest Colombia // Colomb. Med. vol.48 no.3 Cali July/Sept. 2017 http://dx.doi.org/10.25100/cm.v48i3.2180 (Дата обращения: 07.02.2022)

2. *Chace D.H., Kalas T.A., Naylor E.W.* The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism // Annu Rev Genomics Hum Genet. 2002. 3:17-45.

3. *Chi-Ju Yang et al.* Diagnosis and therapeutic monitoring of inborn errors of metabolism in 100,077 newborns from Jining city in China // BMC Pediatr. 2018.18(1):110. Published 2018 Mar 13. doi:10.1186/s12887-018-1090-2

4. *Hamers F.F., Rumeau-Pichon C.* Cost-effectiveness analysis of universal newborn screening for medium-chain acyl-CoA dehydrogenase deficiency in France // BMC Pediatr. 2012. 12:60. Published 2012 Jun 8. doi:10.1186/1471-2431- 12-60B.

5. *Josef Bártl* et Simultaneous Determination of Cystathionine, Total Homocysteine, and Methionine in Dried Blood Spots by Liquid Chromatography/Tandem Mass Spectrometry and Its Utility for the Management of Patients With Homocystinuria // Clin Chim Acta. 2014. 437:211-217. doi:10.1016/j.cca.2014.07.028.

6. *Khneisser I. et al.* Cost-benefit analysis: newborn screening for inborn errors of metabolism in Lebanon // J Med Screen. 2015. 22(4):182-186. doi:10.1177/0969141315590675

7. *Lee H.C., Mak C.M., Lam C.W., Yuen Y.P. et al.* Analysis of inborn errors of metabolism: disease spectrum for expanded newborn screening in Hong Kong // Chin Med J (Engl). 2011 Apr. 124(7):983-9.

8. *Lindner M., Abdoh G., Fang-Hoffmann J., Shabeck N.* Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg // J Inherit Metab Dis. 2007 Aug; 30(4):522-9.

9. *Lund A.M., Hougaard D.M., Simonsen H., Andresen B.S., Christensen M., Dunø M., et al*. Biochemical screening of 504,049 newborns in Denmark, the Faroe Islands and Greenland--experience and development of a routine program for expanded newborn screening // Mol Genet Metab. 2012. Nov. 107(3):281-93

10. *Ma S.* Expanded newborn screening for inborn errors of metabolism by tandem mass spectrometry in newborns from Xinxiang city in China // J Clin Lab Anal. 2020. 34(5):e23159. doi:10.1002/jcla.23159

11. *Mak C.M. et al.* Inborn errors of metabolism and expanded newborn screening: review and update // Crit Rev Clin Lab Sci. 2013. 50(6):142-162. doi:10.3109/10408363.2013.847896

12. *Moorthie S.* Systematic review and meta-analysis to estimate the birth prevalence of five inherited metabolic diseases // J Inherit Metab Dis. 2014. 37(6):889-898. doi:10.1007/s10545-014-9729-0

13. *Nguengang Wakap S., Lambert D.M., Olry A. et al.* Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database // Eur J Hum Genet 28, 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0 (Дата обращения: 16.01.2022)

14. *Niu D.M., Chien Y.H., Chiang C.C., Ho H.C., Hwu W.L. et al.* Nationwide survey of extended newborn screening by tandem mass spectrometry in Taiwan // J Inherit Metab Dis. 2010 Oct; 33(Suppl 2):S295-305.

15. *Ozben T.* Expanded newborn screening and confirmatory follow-up testing for inborn errors of metabolism detected by tandem mass spectrometry // Clin Chem Lab Med. 2013. 51(1):157-176. doi:10.1515/cclm-2012-0472.

16. *Pourfarzam Morteza, Fouzieh Zadhoush* "Newborn Screening for inherited metabolic disorders; news and views" // The Official Journal of Isfahan University of Medical Sciences 2013. Vol. 18,9: 801–808.

17. *Shujun Ma et al.* Expanded newborn screening for inborn errors of metabolism by tandem mass spectrometry in newborns from Xinxiang city in China // J Clin Lab Anal. 2020;34(5):e23159. doi:10.1002/jcla.23159

18. *Thiboonboon K. et al.* An Economic Evaluation of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry in Thailand // PLoS ONE. 2015. 10(8): e0134782. https://doi.org/10.1371/journal.pone.0134782 (Дата обращения: 26.01.2022)

19. *Wilcken B., Wiley V., Hammond J., Carpenter K.N.* Screening newborns for inborn errors of metabolism by tandem mass spectrometry // Engl J Med. 2003 Jun 5; 348(23):2304-12.

20. *Yamaguchi S.* Newborn screening in Japan: restructuring for the new era. Ann Acad Med Singap. 2008 Dec; 37(12 Suppl):13-5.

21. *Yang C.J. et al.* Diagnosis and therapeutic monitoring of inborn errors of metabolism in 100,077 newborns from Jining city in China // BMC Pediatr. 2018. 18(1):110. Published 2018 Mar 13. doi:10.1186/s12887-018-1090-2.

22. *Yoon H.R., Lee K.R., Kim H., Kang S., Ha Y., Lee D.H. et al.* Tandem mass spectrometric analysis for disorders in amino, organic and fatty acid metabolism: two year experience in South Korea // Southeast Asian J Trop Med Public Health. 2003. 34 Suppl 3:115-20.

23. *Yunus Z.M., Rahman S.A., Choy Y.S., Keng W.T., Ngu L.H.* Pilot study of newborn screening of inborn error of metabolism using tandem mass spectrometry in Malaysia: outcome and challenges // J Pediatr Endocrinol Metab. 2016 Sep 1. 29(9):1031-9. DOI: 10.1515/jpem-2016-0028. PMID: 27544719.

Автор-корреспондент:
Касенова Гульжан Токтаубековна, старший преподаватель Высшей школы медицины, Факультет медицины и здравоохранения, НАО «Казахский Национальный университет им. аль-Фараби», г. Алматы, Республика Казахстан.
Почтовый адрес: Республика Казахстан, 050000, г.Алматы, ул Айтиева 154/1,
E-mail: gulzhanerdanai@gmail.com
Телефон: +7 708 802 88 83