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BIOCHEMICAL DISORDERS IN CHILDREN WITH RARE DISEASES

BIOHEMIJSKI POREMEĆAJI KOD DECE SA RETKIM BOLESTIMA

Ljiljana Jovanović[1], Janko Pejović[1], Bogdan Bošković[2]

[1] Institute of Medical Biochemistry, Military Medical Academy, Belgrade, Serbia
[2] Centre for Clinical Pharmacology, Military Medical Academy, Belgrade, Serbia

Correspondence to:

Ljiljana Jovanović, Mr Ph.
Institute of Medical Biochemistry
Military Medical Academy, Belgrade, Serbia
Crnotravska 17, 11000 Belgrade, Serbia
Phone: +381643551460
e-mail: biohemicar@ymail.com

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Abstract

The efforts of international organizations such as the World Health Organization (WHO) and The United Nations Children's Fund (UNICEF), as well as many other national government organizations and non-governmental ones, are constantly improving health standards worldwide and universal health care is becoming a reality. The European Union Council Recommendation on Rare Diseases identified rare diseases as life-threatening or chronically debilitating condition affecting not more than five in 10000 persons in the community. In Serbia, there are about 500 000 people with a rare disease. So, biochemical genetic testing and newborn screening tests are essential for early recognition of and properly intervention for these disorders to reduce morbidity and mortality rates and improve health outcomes. The classes of inborn errors of metabolism (IEMs) including those of amino acids, fats and carbochydrates, and majority of them have autosomal recessive inheritance. Beside those IEMs with intoxication effect or energy deficiency, there is very important group of disorders which result from defects in the synthesis or catabolism of complex molecules (lysosomal disorders, peroxisomal disorders and disorders of intracellular trafficking and processing). Therapy for IEMs is combination of dietary measures and medications. Very important fact that should be highlighted is that many of the medications used for the treatment of IEMs are, in general, of high cost. Advances in therapeutic interventions for IEMs are constantly increasing the importance of newborn (neonatal) screening (by tandem mass spectrometry and traditional screening methods like enzyme assays, immunoassays, electrophoresis). Finally, by recent ratification of the Zoja's law, Serbia made first steps towards adoption of series of legislative acts, construction of newborn (neonatal) screening program and cooperation with developed countries related to faster diagnosis and the medical treatment of children with rare diseases.

BIOCHEMICAL DISORDERS IN CHILDREN WITH RARE DISEASES

In order to follow it up more easily, paper is divided to the following parts:

1. History and definition
2. Biochemical disorders
3. Clinical findings
4. Treatment
   a. Dietary measures
   b. Medications
5. Newborn (neonatal) screening (NBS)
6. Conclusion

1. HISTORY AND DEFINITION

The efforts of international organizations such as the World Health Organization (WHO) and The United Nations Children's Fund (UNICEF), as well as many other national government organizations and non-governmental ones, are constantly improving health standards worldwide and universal health care is becoming a reality [(1)]. But, at the same time there are many challenges, ethical difficulties , and major issues related to health policies and strategies that still need to be addressed and resolved globally, including the treatment of patients in developing countries and patients worldwide with rare diseases [(2, 3)].

In April 1999, the European Parliament and the Council of the European Union adopted a program of community action on rare diseases. The main target of this program was to improve the quality of life for affected individuals, facilitating access to information for the patients and their families and supporting international cooperation between voluntary and professional support groups [4]. In September of 2003, the focus on rare diseases was established as a public health priority with adoption of new six-year community action program [5]. In October 2007, a second five-year program was constituted to reduce the occurrence of rare diseases and two years later, rare diseases were recognized as a public health priority [6-8]. The EU has focused on improving access and quality of patients care and the information and social services provided for the affected individuals, through several projects such as the Rare Disease Patient Solidarity Project (RAPSODY) or „Rare! Together" created by the European Organization for Rare Diseases (EURORDIS) [9,10].

Lately, Law on prevention and diagnosis of genetic diseases, genetically determined abnormalities and rare diseases called „Zoja's Law", was adopted on 23 January 2015 in the Assembly of the Republic of Serbia. The law implies further examination abroad if the disease can not be diagnosed within six months. This research would be sponsored by the newly formed Fund for treatment of children. Once the diagnosis is established, the state would finance the treatment abroad. Also, „Zoja's law" obliges the Republic of Serbia to create a registry of patients suffering from rare diseases for a period of one year.

The European Union Council Recommendation on Rare Diseases (9 June 2009) identified rare diseases as life-threatening or chronically debilitating condition affecting not more than five in 10000 persons in the community [11, 12]. A disease is considered rare when it affects less than one in 2,000 people in Europe [13]. While, each individual disease affects a small part of the population, the aggregate number of affected individuals sums up to 8% of the population, affecting nearly 30 million in Europe [13,14]. In Serbia, there are about 500 000 people with a rare disease [15]. It is estimated that there are about 7000 orphan diseases [16].

A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare disease, the condition itself being referred to as „orphan disease". It may be defined as drugs that are not developed by the pharmaceutical industry for economic profits but which respond to public health need. In the EU, an orphan medicinal product is intended for the diagnosis, prevention and treatment of an orphan disease with a prevalence of less than 5 affected per 10000 persons [16].

The spiraling cost of drug development in accordance with strict regulations, coupled with the low return on investment, often tends to discourage pharmaceutical innovators from developing products for extremely small percentage of the population. But, incentives for drug development provided by governments, as well as support from the FDA and EU Commission in special protocols, are a further boost for the companies developing orphan drugs [17]. That support takes three forms: tax credits and research aids, simplification of marketing authorization procedures, and extended market exclusivity [18].

In the EU, companies with an orphan designation for a medicinal product are given the marketing authorization for 10-year marketing exclusivity. They are given financial incentives in terms of fee reductions (100% reduction for protocol assistance, 100% reduction for preauthorization inspections; 50% reduction for new applications for marketing authorization; 50% reduction for postauthorization activities) or exemptions and national incentives, in the first year after grant of a marketing authorization [17, 18].

2. BIOCHEMICAL DISORDERS

An inborn error of metabolism (IEM) is a genetically determined biochemical disorder that affects an individual's ability to convert nutrients or to use them for energy production. IEMs are caused by impaired activity of enzymes, transpoters, or cofactors and result in accumulation of abnormal metabolites (substrates proximal to the metabolic block and byproducts built by alternative pathways) or by lack of necessary products[19].

However, since nearly 50 to 75 percent of rare diseases begin in childhood, these pediatric disorders deserve special priority [20]. So, biochemical genetic testing and newborn screening tests are essential for early recognition of and properly intervention for these disorders to reduce morbidity and mortality rates and improve health outcomes[21].

According to the American College of Medical Genetics (ACMG) report, newborn screening programs in each state should include at least five fatty acid oxidation disorders, nine organic acidemias, six acidipathies (e.g., phenylketonuria (PKU) and maple syrup urine disease (MSUD), three hemoglobinopathies, and six other disorders(Table1). The classes of inborn errors of metabolism (IEMs) including those of amino acids, fats and carbochydrates, and majority of them have autosomal recessive inheritance [19].(***Table*** 1).

Aminoacidopathies are a group of rare disorders, caused by the deficiency of an enzyme or transporter involved in amino acid metabolism [22]. Inborn errors of amino acid metabolism or aminoacidopathies in total affecting about 1 in 1000 humans worldwide. These disorders can be subdivided in aminoacidopathies (PKU, MSUD, etc.), urea cycle defects (transport defects of urea cycle intermediates) and organic acidurias [23].

Phenylketonuria (PKU, OMIM261600) is a rare inherited disorder that affects around 1 in 10,000 children born in Europe [24]. The metabolic disorder underlying PKU is a mutation in the gene coding for the enzyme, phenylalanine hydroxylase (PAH), which is responsible for the ‚conversion of phenylalanine into tyrosine[25].

Maple syrup urine disease (MSUD, OMIM 248600) is an autosomal recessive genetic disorder, with incidence of 1:185,000 [26]. MSUD is caused by deficient activity of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC). Deficiency of this enzyme complex leads to high levels of the branched-chain amino acids (BCAA) leucine, valine, and isoleucine [27].

Urea cycle disorders (UCDs) and organic acidemias (OA) are inborn errors of protein metabolism [28]. UCDs (OMIM 311250) are inborn errors of ammonia detoxification/arginine synthesis due to defects affecting the catalysts of the Krebs-Henseleit cycle (five core enzymes, one activating enzyme and one mitochondrial ornithine/citrulline antiporter) and it's worldwide incidence is approximately 1:8.000[29].

An example for organic academia is glutaric aciduria type I (GA-I). GA-I is inherited rare genetic disorder with incidence of 1:100,000 worldwide [30]. GA-I (OMIM 231670) is caused by deficiency of the mitochondrial enzyme glutaryl-CoA dehydrogenase (GCDH) which is involved in the final degradation of the amino acids L-lysine, L-hydroxylysine and L-tryptophan [31].

Medium-Chain Acyl-CoA dehydrogenase deficiency (MCADD,OMIM 201450) is the most frequent metabolic disorder of mitochondrial fatty acid oxidation [32]. It's affecting about 1:15000 newborns. The production of the MCAD enzyme is absent or reduced and the β-oxidation of the fatty acids C4 and higher fails. They become useless as an energy source[33].

The group of disorders of carbohydrate metabolism includes the glycogen storage diseases, glucose-G-phosphate dehydrogenase and galactose-1-phosphate uridyl transferase deficiency (GALT). Lack of GALT is the most important to neonates and leads to the inability to metabolize galactose to glucose, resulting in „classic''galactosemia (OMIM 230400) [34]. Galactosemia due to GALT-deficiency is the most common of the galactosemia disorders, with a prevalence of 1:60000 in Caucasians [35].

Beside those IEMs with intoxication effect or energy deficiency, there is very important group of disorders which result from defects in the synthesis or catabolism of complex molecules. The metabolism of complex molecules is altered in all 1) lysosomal disorders, 2) peroxisomal disorders and 3) disorders of intracellular trafficking and processing [36]. Although individual lisosomal storage disorders are rare, the aggregate number of affected individuals sums up to 1:2315 live births. LSDs include Pompe disease (glycogen storage disease type II, caused by acid α-glucosidase (GAA) deficiency), Fabry disease (α-galactosidase (GLA) deficiency), Hunter disease (mucopolysaccharidosis type II, iduronate-2-sulfatase (IDS) deficiency), Gaucher disease (glucocerebrosidase (GBA) deficiency), and Hurler disease (mucopolysaccharidosis type I, α-iduronidase (IDU) deficiency)[37].

3. CLINICAL FINDINGS

Impairment of PAH activity in PKU causes increased levels of phenylalanine that if untreated leads to devastating damage to the brain, with severe mental disability, reduced IQ, seizures and tremors, impaired executive function, psychological and behavioural issues and social difficulties(25). Although intellectual development is near normal with implementation of the adequate diet shortly after birth, there is evidence of suboptimal health outcomes in PKU which

Table 1. *Disorders That Should Be Included in All Screening Programs as recommended by the ACMG Newborn Screening Expert Group*

Organic Acid Disorders	Fatty Acid Oxidation Disorders	Amino Acid Disorders	Hemoglobinopathies	Other Disorders
Isovaleric acidemia (IVA)	Medium-chain acyl-CoA dehydrogenase deficiency(MCAD)	Phenylketonuria (PKU)	Sickle cell anemia (Hb SS)	Congenital hypothyroidism (CH)
Glutaric acidemia type I (GAI)	Very long-chain acyl-CoA dehydrogenase deficiency (VLCHAD)	Maple syrup (urine) disease (MSUD)	Hb S/ β-thalassemia (Hb S/ β-Th)	Biotinidase deficiency (BIOT)
3-Hidroxy 3-methyl glutaric aciduria (HMG)	Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)	Homocystinuria (HCY)	Hb S/C disease (Hb S/C)	Congenital adrenal hyperplasia (CAH)
Multiple carboxylase deficiency (MCD)	Trifunctional protein deficiency (TRF)	Citrulinemia (CIT)		Galaktosemia (GALT)
Methylmalonic acidemia (mutase deficiency) (MUT)	Carnitine uptake defect (CUD)	Argininosuccinic acidimia(ASA)		Hearing loss (HEAR)
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)		Tyrosinemia type I (TYR I)		Cystic fibrosis (CF)
Methylmalonic acidemia (Cbl A,B)				
Propionic acidemia (PROP)				
β-Ketothiolase deficiency (βKT)				

Modified from: Newborn Screening: Toward Uniform panel System, htp//www.acmg/resources/policies/NBS/NBS-sections.htm (accesssed January 18,2007).

include neurocognitive impairments such as poor executive function skills and psychiatric problems, skeletal fragility , and impaired renal function[38,39].

In the classical form of MSUD (less than 3% residual enzyme activity), symptoms first occur in the first week of life, and often include respiratory changes, encephalopathy, a characteristic odor and seizures. In the untreated newborn, deepening encephalopathy manifesting as lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as „fencing" and „bicy-cling" by 4–5 days. Between 7th and 10th day of life coma and central respiratory failure may occur [26-27,40].

Untreated patients in UCDs, develop hyperammonemia which strongly correlates with brain damage, either shortly after birth (~50%) or, later at any age, leading to death or to severe neurological handicap in many survivors[29].

The majority of neonates with GA-I are asymptomatic, except for macrocephaly and transient neurological symptoms such as axial hypotonia and asymmetric posturing. Irreversible neurological symptoms generally occur between the age of three months and three years [31]. The symptoms worsen in the absence of supporting care and can proceed to coma or death [41].

The MCADD-patient shows symptoms similar to Reye's syndrome with hepatomegaly and stupor associated with hypoketonemia, hypoglycemia, hypocarnitinemia, increased alanine and aspartate transaminsase and mild hyperammonemia. In unscreened populations up to quarter of patients with MCADD have died in their first crisis. Sudden unexpected death in infancy (SUDI) may be caused by undiagnosed MCADD and early recognition of this metabolic disease reduces mortality and improves the outcome [33, 42].

GALT-deficiency is a potentially lethal disease in newborns with symptoms occurring within the first weeks of life. Untreated the neonate can develope symptoms such as weight loss, vomiting and diarrhea, lethargy and hypotonia to jaundice, cataracts, hepatomegaly, prolonged bleeding time, and septicemia leading to neonatal death[35]. All these disorders may result in some neurocognitive problems and metabolic decompensations which may result in high morbidity with severe neurological deficits, and may cause death[43].

As a group LSDs manifest during infancy or early childhood and can lead to fatal consequences if untreated, including infant mortality. But, recent improvements in treatment, including enzyme replacement therapy, for certain lysosomal storage diseases have caused renewed interest in newborn screening for individual LSDs [37].

4. TREATMENT

Although IEMs are individually rare, they are collectively common (incidence of 1:1000). As new concepts and techniques become available for identifying biochemical phenotypes, more than 500 human diseases due to IEM are now recognised, and this number is continuously growing. The treatment of these disorders has seen significant advances over the past decade [44].

Therapy for IEMs is combination of dietary measures and medications. The most important measures in treatment of inborn errors are restriction of substrate build–up by means of diet or enzymatic inhibition, removal of toxic products, stimulation of residual enzyme activity, replacement of the deficient product. Although for some diseases treatment options are still limited, special medications together with older, but effective, techniques of special diets and cofactor supplementation, have meant that nowadays many IEM are treatable conditions [45].

a. Dietary measures

Dietary approaches in PKU include better and more palatable phenylalanine-free foods, glycomacropeptide (a natural protein free of phenylalanine), large and neutral amino acids.[23] MSUD treatment usually consists of dietary BCAA restriction[27]. Also, GA-I includes a low lysine diet[30]. Dietary measures in UCD represent severely restricted natural protein intake and routine supplementation with essential amino acids (AA). Protein rich foods are severely restricted or completely prohibited, and foods moderate in protein content (amount of proteins depends on an individual basis according to the severity of the condition, age, growth rate and metabolic control). In AA disorders, adjustment of natural protein is titrated repeatedly against frequent plasma concentrations of precursor AA to maintain them within target ranges and avoid essential AA deficiency[43]. With a diet high in carbohydrates and low in fats and fasting periods shorter than 6 h, the prognosis for the MCADD patient is very well[33]. Dietary galactose restriction has been the backbone of treatment in classic galactosemia and patients are advised to restrict galactose and dairy intake upon diagnosis. This limitation was made by switching infants to an alternative formula, generally soy-based, although an elemental formula was prescribed in some cases [46].

b. Medications

The use of sodium benzoate, phenylacetate or sodium phenylbutyrate represents adjunctive therapy. In urea cycle defects or MSUD they provokes increased excretion of nitrogenated compounds and reducing the accumulation of ammonia. Replacement of arginine or citrullin can reverse ammonia intoxication. Also there is treatment with cofactors which stimulates increased enzyme activity like in UCD (pyridoxine), MSUD (thiamine) or GAI (riboflavin)[45].

A pharmacologic treatment option in PKU is sapropterin (decrease the need for phenylalanine restriction in the diet). Other potential approaches in the future include phenylalanine-ammonia lyase (PAL, an injectable enzyme that metabolises phenylalanine), conjugation with polyethylene glycol of PAL (PEG-PAL, has been successful to decrease the immune response) and for the longer term – gene therapy treatment [23, 45]. In MSUD, beside dietary measures and adjunctive therapy, liver transplantation is a good alternative [27, 47].

In UCD disorders such as N-acetyl-glutamate synthase (NAGS) deficiency recently specific treatment is carglumic acid, a structural analog of NAG has been used as it has been shown to activate carbamyl-phosphate-synthetase-I (CPSI) and restore ureagenesis [48].

Treatment for GA-I include carnitine supplementation and metabolic emergency treatment during episodes likely to induce catabolism can significantly reduce mortality and morbidity rates in early diagnosed patients[30, 45].

Early diagnosis of MCADD, special diet and supplementation of acylcarnitine prevent development of the disease and mortality during derailment reduces to zero. Also, the neurological rest lesions (epilepsy, paralysis, behavioral disorders, developmental disorders) after decompensation are halved. MCADD patients should be followed by the general practitioner in the first 5–7 years of life to avoid decompensation [33].

The care of patients with an LSD requires a multidisciplinary approach; the most of current treatment possibilities do not represent a cure. Symptomatic treatment remains the only strategy for most LSDs. Anti-platelet agents and lipid lowering medications, in conjunction with enzyme replacement therapy (ERT) in Fabry disease (agalsidaseα, agalsidaseβ) may reduce the risk for cerebrovascular events [49, 50]. Disorders caused by a deficiency of an enzyme or soluble protein may be modifiable by cellular; i.e., hematopoietic stem cells transplantation (HSCT) or protein recombinant enzyme replacement therapy [51].

ERT has been shown to alter disease course in divers LSDs, but not modify ultimate neurologic prognosis in severe subtypes in Hunter syndrome (idursulfase), neuropathic Gaucher disease. The best response profile has been noticed in patients with GD type 1 (alglucerase, imiglucerase, velagluceraseα) with resultant hematopoietic reconstitution, reduction of hepatosplenemoagly and prevention of bone disease [49, 52, 53]. In patients with infantile Pompe disease, ERT (alglucosidaseα) enables the resolution of cardiomyopathy and enhance survival, except for those with high antibody titers in whom prognosis remained scarce [54]. ERT-treated patients can produce antibodies against recombinant enzymes that might nullify the activity of the infused protein or interfere with its cellular uptake. Longterm studies are required to establish the full efficacy of ERT and its impact on health-related quality of life and survival [49, 55, 56].

Substrate reduction therapy (SRT) is available for certain glycosphingolipidoses, wherein the use of a small molecular agent (miglustat in Gaucher disease) has been shown to inhibit precursor synthesis, reduce tissue substrate burden and alter the rate of disease progression [57]. Eliglustat given orally to patients with GD type 1 appears to result in favorable responses, comparable to that seen with enzyme therapy [58]. Use of pharmacologic chaperones, molecules which restore enzymes and increase their residual activity (migalastat in Fabry disease) consider further examinations [59]. Gene therapy or agents that influence proteostasis regulation are still under investigation and present experimental form.

Therapeutic options under investigation involve HSCT with autologous cells that have been genetically modified to constitutively express supra-physiological enzyme levels[60]. Additionally, trials with recombinant enzyme administered intravenously and intrathecally, to bypass the BBB, have been undertaken or are on-going [61].

Another very important fact that should be highlighted is that many of the medications used for the treatment of IEMs are, in general, of high cost. For example, a patient simulation model was used to analysis costs and effects of ERT (cost per injection of alglucosidaseα is 356 pounds) compared to costs of effects of supportive therapy (ST) in patients with Pompe disase, ST receiving patients were modelled not to survive the first half year of life; whereas the life expectancy in the ERT patients was modelled to be almost 14 years. But, incremental costs were estimated to be 7.0 million euros, which primarily consisted of treatment costs (95%) [62]. Another example is carglumic acid, licensed drug for the treatment of hyperammonaemia due to N-acetylglutamate syntase deficiency and organic acidemia. Initially dose for child is 100-250 mg/kg dailly in 2-4 divided doses, and one pack (60-tablets) costs 3499.00 pounds [63].

In the Republic of Serbia, according to 2015-drug list of the Health Insurance Fund (Republicki fond za zdravstveno osiguranje – RFZO) 7 INN drugs for metabolic diseases were listed. There are medications for LSDs, such as Fabry disease (agalsidaseβ), Gaucher disease (imiglucerase), Hunter disease (idursulfase), Pompe (alglucosidaseα) and Hurler disease (laronidase) [64]. For example, 19 drugs used in metabolic disorders were included in the latest edition of the British national formulary. [63]

5. NEWBORN (NEONATAL) SCREENING (NBS)

In many European countries newborn screening has been introduced over half of century, as an important public health programme. Policy making concerning which conditions to screen for differs per country. It may depend on national health care politics, financial possibilities, local medical professional interests and habits, input from parent advocacy groups, etc. Consequently, countries with a lower socio-economic status have a smaller screening panel [65]. The survey for the evaluation of regulations and practices of population newborn (neonatal) screening (NBS) for rare disorders in Member States of the European Union, as well as candidate, potential candidate and EFTA countries, comes from the initiatives directed by the European Commission within the EU Programme of Community Action in Public Health. The EU Council Recommendation for an Action in the Field of Rare Diseases (European Commission 2009) , predicts the adoption of national plans and strategies for rare diseases within 2013, and sets up the lines for the cooperation and coordination between Member States in order to better utilise national resources and expertise as well as reducing inequalities in the access to high quality care [66]. According to this survey, Serbia as potential EU member, screened just one condition which belongs to inborn errors of metabolism. It is PKU, the second most screened rare disease in EU.

The number of diseases screened for in the newborn period has dramatically increased with introduction of MS/MS multiplex analyses. The complexity of the interpretation of MS/MS newborn screening results has prompted the development of algorithms for proper confirmatory testing and differential diagnosis of all detectable IEMs

(http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm). The majority of metabolic disorders

can be recognised by MS/MS, but some IEMs and endocrine and hematologic disorders are identifiable through more traditional screening methods (e.g., enzyme assays, immunoassays, electrophoresis). Advances in therapeutic interventions for IEMs are constantly increasing the importance of NBS. But, early diagnosis of the disease on its own, doesn't have to ensure patient survival. However, all metabolic disorders can not be identified by NBS, and therefore some patients can be missed. Hence, a symptomatic patient, at any age, should be investigated despite normal NBS results. The combination of effective therapies and prompt diagnosis could completely change the prospect for IEMs patients[36, 67, 68].

6. CONCLUSION

Rare diseases represent public health priority and universal challenge. Rare pediatric diseases are genetically determined and reflected in severe biochemical disorders and short life expectancy. In most countries in the world, including our own, the disease is detected late, due to costly therapy, which is in some diseases very effective, but rarely used. There is a strong need for improving health care systems and making appropriate professional care. Main gold is reaching a uniform screening panel in Europe and avoiding diagnostic odyssey. It goes beyond the capabilities of most countries in the world, so international coordination and cooperation is indispensable. By recent ratification of the Zoja's law, Serbia made first steps towards adoption of series of legislative acts, construction of newborn (neonatal) screening program and cooperation with developed countries related to faster diagnosis and the medical treatment of children with rare diseases.

Sažetak

Već se realizuju napori međunarodnih organizacija kao što su Svetska zdravstvena organizacija (SZO), međunarodni fond za decu Ujedinjenih nacija (UNICEF), kao i mnogih drugih nacionalnih državnih i nevladinih organizacija da se u praksi poboljšaju zdravstveni standardi i opšta briga za zdravlje ljudi. U preporukama Saveta evropske Unije retke bolesti se definišu kao hronično onesposobljavajuće i po život opasne kada se pojave u ne više od pet na 10000 osoba jedne zajednice. U Srbiji, ima više od 500 000 osoba sa retkim bolestima. Stoga su biohemijska genetska ispitivanja i skrining testovi kod novorođenčadi neophodni za rano prepoznavanje i adekvatno zbrinjavanje kod tih poremećaja, jer se samo na taj način mogu smanjiti morbiditet i mortalitet i poboljšati zdravstveno stanje obolelih. U urođene greške spadaju poremećaji metabolizma (IEMs-Inborn Errors of Metabolism) aminokiselina, masti i ugljenih hidrata, a njihov najveći deo spada u grupu autozomno recesivne naslednosti. Pored navedenih IEMs, praćenih efektima intoksikacije, energetskog deficita, postoji još jedna grupa oboljenja koja dovodi do poremećaja u sintezi ili katabolizmu kompleksnih molekula (lizozomni i peroksizomalni poremećaji, poremećaj intracelularnog prometa i metabolizma). Terapija IEMs se zasniva na kombinaciji dijetetskih mera i primene lekova. Vrlo je važno pri tome napomenuti da su mnogi lekovi koji se primenjuju u terapiji retkih bolesti, uopšte uzev, veoma skupi. Napredak u terapiji obolelih od IEMs sve više ukazuje na značaj tandemske masene spektrometrije i tradicionalnih skrining metoda (enzimski i imunotestovi, elektroforeza) u okviru skrininga novorođenčadi. I konačno, nedavnim usvajanjem Zojinog zakona, Srbija je učinila prvi korak ka usvajanju niza pratećih propisa kojima bi bio regulisan program neonatalnog skrininga i saradnji sa razvijenim zemljama u svetu radi ubrzanja dijagnostike i lečenja dece sa retkim bolestima.

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