PREGLED LITERATURE – REVIEW ARTICLE

New insights into rare metabolic diseases in paediatric practice

Savremeni stavovi o retkim metaboličkim bolestima kod dece

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Summary Rare diseases are those that affect at most one in 2000 persons worldwide. According to the date around 6000-7000 rare diseases have been described until now. Although there are so many differences between rare diseases patents that are affected are facing with the more or less same difficulties. Before a final diagnose they usually spend a few years losing a precious time for the treatment. The aim of this review article is to give insight into a several rare diseases that are successfully treated by enzyme replacement therapy (ERT). A complete search of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE and Pub Med up to January 2018 was carried out. Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal a-galactosidase A activity. Gaucher disease is characterized by a deficiency of acid β-glucosidase and accumulation of glucosylceramide within lysosomes of tissue macrophages. The accumulation of glucosylceramide is responsible for the manifestations of Gaucher disease, including hepatomegaly, splenomegaly, thrombocytopenia, and anemia. MPS I characterized the defect in the gene for α-L-iduronidase (IUDA), an enzyme that degrades glycosaminoglycans (GAGs) in lysosomes. Pompe disease is a rare, progressive, debilitating and often fatal neuromuscular disorder resulting from the deficiency of a lysosomal enzyme, acid alpha-glucosidase (GAA). Enzyme testing on Dried Blood Spots (DBS) is a 1st tier/screening test for all four above mentioned metabolic rare diseases. An enzyme replacement therapy is the only effective treatment patients with Fabry disease, Pompe disease, Gausher disease and MPS I.

Key words: lysosomal enzyme, replacement therapy, rare disease

Sadržaj Retke bolesti su one bolesti koje pogađaju jednu od 2000 osoba širom sveta. Prema podacima oko 6000-7000 retkih bolesti je opisano do sada. Iako su one veoma različite oboleli se susreću sa slićnim problemima. Pre posatvljanja dijagnoze ponekad prođe i nekoliko godina, tokom kojih oni izgube dragocene vreme da započnu sa terapijom. Cilj ovog revijalnog rada je da da uvid u nekoliko retkih bolesti koje se uspešno tretiraju enzimskom supstitucionom terapijom. Istraživanje je sprovedeno pretragom the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane bibliotike, MEDLINE i Pub Me do januara 2018. Fabrijeva bolest je progresivno X vezano nasledno oboljenje poremećaja metabolizma glikosfingolipida usled odsustva ilii smanjne aktivnosti lizozomskog enzima a-galaktozidaze. Gošeova bolest se karaktriše nedostatkom ili kisele β-glucozidaze u akumulacijom glukozilceramida u lizozomima tkivnoh makrofaga. Akumulacija glukozilceramida je odgovoorna za kliničku sliku Gošeove boelsti koju karakteriše hepato, splenomegalija, trombocitopneija i anaemija. MPS I progresivne, nasledne bolesti koje nastaju kako posledica genske mutacije gena za α-L-iduronidazu (IUDA), enzim kojji razlaže glicozaminoglikane (GAGs). Pompeova bolest je retko progresivno oboljenje koje dovodi do nesposobnosti i fatalnog neuromišićnog poremećaja koja nastaje kao posledica nedostataka lizozomalnog enzima alfa glukozidaze. Enzimsko testiranje iz suve kapi krvi je ključno za dijagnozu sve prethodno četiri pomenute retke bolesti. Enzimska supstituciona terapija je jedini efikasna tretman pacijenata sa Fabrijevom bolešću, Gošeovom bolešću, Pompeovom bolešću i MPS I.

Ključne reči: lizozomski enzim, supstituciona terapija, retke bolesti

Introduction

Rare diseases are those that affect at most one in 2000 persons worldwide. According to the date around 6000-7000 rare diseases have been described until now. (1) 6%-7% (around half of million) of Serbian population suffer from some kind of rare diseases although many of the patients remain undiagnosed.

The main characteristics of rare disease are: 80% of them are genetic, while the rest are caused by viral infections, allergies, or under the influence of environmental factors such as pollutants. They can be also degenerative or proliferative. In 50% of the cases the first symptoms are present at birth or developed in the first years of life. Unfortunately 30% of children with diagnosed rare disease live less than 5 years. (2) For more than 95% of rare

disease there is no treatment. Most commonly rare disease leads to permanent invalidity. Although there are so many differences between rare diseases patents that are affected are facing with the more or less same difficulties. Before a final diagnose they usually spend a few years losing a precious time for the treatment. As they are very uncommon there is both a lack of information on them, as well as physicians who are familiar with the clinical symptoms, diagnosis and treatment. The costs of treatment are very high including very expensive drugs and overall care. The quality of life is usually very impaired with a huge impact on social life. (3) Registries for rare disease are of extremely importance for better understanding of all cases in one population. Registration is a process of collecting and analysing all data of the patients that are affected with the aim to put insight in an exact number of the persons with rare diseases as well as to help experts to calculate incidence of the certain rare disease and distribution according to the age, gender ect. Geographical distribution, environment, age are all factors that can influence rare disease. 350 million of patients suffered from some kind of a rare disease worldwide. (3)
The aim of this review article is to give insight into a several rare diseases that are successfully treated by enzyme replacement therapy (ERT).

Materials and methods

A complete search of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE and Pub Med up to January 2018 was carried out.

Discussion

Fabry Disease – Progressive, debilitating, life-threatening but under-recognized

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal a-galactosidase A activity. FD is pan-ethnic and the reported annual incidence of 1 in 100,000 may underestimate the true prevalence of the disease. Both males and females can be affected. FD is X linked dominant disease. That means that children of affected mothers have 50% chance of inheriting a mutation regardless of gender. All daughters of affected fathers will inherit a mutation. No sons of affected fathers will inherit the mutation. Males usually present with typical clinical signs and symptoms whereas females are usually suffered from less severe disease, but they can be also symptomatic (unusual for X linked disease). Due to the deficit in the gene encoding α-galactosidase A (α-Gal A)1, 2 males have deficient or undetectable α-Gal A activity (often <1% residual enzyme activity). This deficient leads to a progressive, multisystem lysosomal accumulation of GL-3.Vascular endothelial and smooth muscle cells, multiple renal cell types, including podocytes, cardiomyocytes, conduction system cells, neural cells, multiple other cell types such as vascular endothelial and smooth muscle cells, multiple renal cell types can be places for GL-3 accumulation.
GL-3 accumulation triggering a cascade towards tissue and organ damages. Two stages of the disease can be distinguished subclinical phase and clinical phase. (4)

Table 1. Early signs and symptoms of Fabry disease

Organ system Sign/Symptom
Nervous system
Acroparesthesias Nerve deafness Heat intolerance Hearing loss, tinnitus
Gastrointestinal tract
Postprandial bloating pain early satiety Difficulty gaining weight
Skin
Hypohidrosis Angiokeratomas
Eyes
Corneal and lenticular opacities Vasculopathy (retina, conjunctiva
Kidneys
Microalbuminuria Proteinuria Impaired concentration ability Hyperfiltration Increased urinary Gb3 excretion
Heart
Impaired heart rate variability Arrhythmias ECG abnormalities (shortened PR interval) Mild valvular insufficiency

Fabry disease at the pediatric age

Due to no specificity of signs and symptoms it is an extremely difficult to diagnose a disease at paediatric age. Young boys rather than girls can present with early neural damage primarily involves small nerve fibers of the peripheral somatic (5) and autonomic nerve systems (6) with onset of related symptoms generally. (7-10) Two types of pain have been described: episodic crises ("Fabry crises") characterized by agonizing burning pain originating in the extremities and radiating inwards to the limbs and other parts of the body, and chronic pain characterized by burning and tingling paraesthesia. (11) Rheumatoid arthritis, rheumatic fever, Raynaud's disease, systemic lupus erythematosus (SLE) should be consider as differential diagnosis.
Due to deposition of Gb3 in autonomic ganglia of bowel and mesenteric vessels FB patients can suffer from gastrointestinal problems such as postprandial pain,

diarrhoea, nausea, and vomiting, that are common , but under-estimated, manifestation of FD. (12,13) Fabry patients can be presented with anorexia and problems with weight gain. Diarrhoea-predominant irritable bowel syndrome (IBS) is a differential diagnosis. (14) Gb3 accumulation in sweat gland leads to the absence (anhidrosis) or a decreased ability of sweating (15) to sweat (hypohidrosis) (16) with decreased skin impedance (17) is a significant problem for patients and can cause heat (18) and exercise intolerance. (19)
The most common skin presentation is angiokeratoma red-purple, non-blanching skin lesion usually in area from umbilicus to thigh, also often on mucosa membranes.
In a cohort of 35 paediatric patients (15 boys and 20 girls, median age 12,6 years), cornea verticulata was detected in 73% of boys and 70% of girls. Tinnitus may be an early symptom and hearing loss has been reported in children. (20) Chronic fatigue and difficulty gaining weight may also frequently occur, particularly during adolescence. High flow priapism can also be observed in young boys affected with FD. Despite the absence of major organ dysfunction, these symptoms, individually or in combination, may cause significant morbidity limiting the child's physical, school and social performances. (21) Early signs of cardiac and cerebrovascular abnormalities may be present during adolescence in both genders. Signs of involvement of the sinus node and conduction system (e.g. shortened PR interval, arrhythmias,impaired heart rate variability, and mild valvular insufficiency) have been demonstrated. (22) Although rare, evidence of microvascular ischemic brain involvement on magnetic resonance imaging (MRI) may be detectable at young ages. (23) Males are diagnosed at median age of 24 years, and females at medina age of 31 years. Diagnosis delay approximately 15 years has been reported. Early recognition of signs and symptoms of FD and identification of patients in an early stage of the disease through family screening are of extremely importance. (24-36)

Kidney involvement

When we are talking about classic type of FD we usually consider kidney type.
While the pathogenesis of kidney failure is almost clearly understood in adults the natural course of Fabry nephropathy in children or adolescent patients is still not explained. It is an extremely rarely that children or adolescents develop clinical signs kidney failure although potentially irreversible changes to glomeruli, interstitial tubules and vascular structures appear before the first appearance of microalbuminuria can be observed in renal biopsy specimens from children. Podocyte foot process effacement has been reported and indicates focal segmental glomerulosclerosis.

A decline in glomerular filtration rate (GFR) is uncommon at paediatric ages but may be seen as early as adolescence (37,38) Studies on renal function in children with FD have mainly been done using estimated creatinine-based GFR. The widely used original Schwartz formula (39) substantially overestimates GFR with a low accuracy, whereas the new abbreviated Schwartz formula (40) shows relatively good performances with a mean GFR overestimation of 5.3 ml/min/1.73 m2, being only slightly superior to the Counahan-Barratt formula. (41) The new abbreviated Schwartz formula should replace the original Schwartz formula in the routine follow-up. of children with FD. (42) The current creatinine-based GFR formulas are all hampered by low accuracy in the "creatinine-blind" GFR range. Supplemental measured GFR is, therefore, recommended in patients where hanges in GFR have potential impact on important treatment regimens. (42)

Gaucher disease

Gaucher disease is characterized by a deficiency of acid β-glucosidase and accumulation of glucosylceramide within lysosomes of tissue macrophages. The accumulation of glucosylceramide is responsible for the manifestations of Gaucher disease, including hepatomegaly, splenomegaly, thrombocytopenia, and anemia.

Glucosylceramide accumulates in the lysosomes of certain cells, primarily tissue macrophages. (43) Gaucher cells are macrophages—monocytic cells engorged by the presence of the incompletely degraded lipid glucocerebroside in the lysosome. At high magnification, these cells present with a fibrillary type of cytoplasm ("wrinkled tissue paper appearance") and an eccentrically displaced nucleus. Disease associated with a high cellular membrane turnover can sometimes be associated with "pseudo-Gaucher cells." Pseudo-Gaucher cells have been reported in chronic granulomatous leukemia, thalassemia, multiple myeloma, Hodgkin's disease, plasmacytoid lymphomas, and in AIDS in a patient with Mycobacterium avium infections. (44,45) Gaucher disease, previously described as having discrete phenotypes, is now recognized to encompass a continuum of clinical findings from a perinatal-lethal form to an asymptomatic form or one that is diagnosed initially in the elderly. Nonetheless, this wide spectrum of clinical findings and broad variability in patient presentation is still described by clinical subtypes, which are useful in determining prognosis and management.

Three clinical types are delineated by the absence (type 1) or presence (types 2 and 3) of primary CNS involvement. Gaucher disease type 1 has been described in various ethnic groups, although it is prevalent among individuals of Ashkenazi Jewish heritage (carrier frequency 1 in 12-15)4. Gaucher disease types 2 and 3 are found primarily in non-Jewish individuals; perhaps because the major disease mutation among the Ashkenazi Jewish patients, the N370S gene defect, precludes CNS involvement.The glucocerebrosidase gene has been mapped to chromosome 1q21. It comprises 11 exons (coding portion of the gene). There are over 300 identified glucocerebrosidase gene defects (mutations).4 The majority of identified mutations

represent single-base substitutions, primarily exonic missense mutations. These mutations result in mRNA instability, and/or a severely truncated protein, or an enzyme with altered activity and/or conformation. Certain mutations, such as N370S and L444P, account for a significant proportion of gene defects among patients. (46,47)

In Europe, the US & Canada, Israel and other European-derived Caucasian populations the most prevalent form is type 1 (non-neuronpathic) disease . Although characterized by the absence of primary neurologic involvement, type 1 disease patients may demonstrate marked hepatosplenomegaly, severe anemia, and thrombocytopenia due to marrow infiltration and splenic sequestration, and may also have disabling bone disease. An early age of onset appears to correlate with more severe presentation of disease. In addition to the typical findings of hepatosplenomegaly, anemia, thrombocytopenia, and bone disease, children with severe involvement may often also show signs of growth and pubertal delay. Fatigue, abdominal distention, and bleeding tendencies are also common complaints. Type 2 Gaucher disease is associated with rapid progression, limited development, and neurodegeneration leading to death usually in the second year of life. In contrast to types 1 and 3, patients do not usually live long enough to develop skeletal manifestations. Gaucher disease type 3 is characterized by wide heterogeneity in presentation. Patients may have onset before 2 years of age. In contrast to type 2 patients, they often have a more slowly progressive course with a life span that can extend into adulthood. Oculomotor apraxia, saccadic initiation failure, and opticokinetic nystagmus are frequently noted. Generalized tonic-clonic seizures and progressive myoclonic epilepsy have been observed in some patients. Dementia and ataxia have been observed in the later stages of chronic neurologic disease. It should be noted that the neurologic complications observed in patients with Gaucher disease type 3 develop along with the extra-neurologic problems found in the typical patient with Gaucher disease type 1 (eg, anemia, thrombocytopenia, hepatosplenomegaly). Also similar to the findings in Gaucher disease type 1, Gaucher disease type 3 patients with progressive disease may manifest severe bone and lung involvement. In fact, some patients have been initially diagnosed as having Gaucher disease type 1 before onset of the neurologic problems. (48-50) Gaucher disease is an autosomal recessive disorder. “Autosomal recessive” means that a person must inherit 2 defective copies of the gene, one from each parent, to develop the disease. Carriers of a mutation in the GBA gene are asymptomatic for Gaucher disease (due to the fact that they have a working copy of the GBA gene as well). When both parents are carriers of a mutation in GBA, there is a 25% chance with each pregnancy of conceiving a child with Gaucher disease. There is a 50% chance of having a child who is a carrier (like parents), and a 25% chance that the child will be neither a carrier nor affected with the disease. (51)

Mucopolysaccharidosis I

Mucopolysaccharidosis I is an inherited, multi-systemic, life-threatening disease. According to the epidemiological and registry data estimated world-wide incidence: 1:100,000 births. The disease is pan-ethnic but prevalence varies in different populations. The majority of recognized patients have the severe form of the disease called “Hurler „phenotype, but also attenuated “Hurler-Scheie” or “Scheie” phenotypes have been described in some patients with mild to moderate form. MPS is autosomal recessive disease which means that both parents must be carriers of MPS I. If both parents are affected their offspring have 25% chance to have a disease. MPS I characterized the defect in the gene for α-L-iduronidase (IUDA), an enzyme that degrades glycosaminoglycans (GAGs) in lysosomes. The affected patients have less than 1% of normal IUDA activity that leads to progressive, multisystemic accumulation of GAGs (dermatan and heparan sulfates). Clinical presentation and organ involvement varies with phenotype and extent of disease progression. Phenotype specificity: macrocephaly, progressively coarse facial features, macroglossia, corneal clouding, hepatosplenomegaly, inguinal, umbilical hernias, toe walking, abnormal gait, cardiac involvement: cardiomyopathy, valvular disease, Ear, Nose and Throat (ENT): chronic rhinorrhoea, recurrent otitis media, enlarged tonsils and adenoids, obstructive sleep apnoea, hearing loss, respiratory: recurrent lower respiratory tract infections, reactive airways disease, neurodevelopmental: developmental delay, cognitive impairment, hydrocephalus, carpal tunnel syndrome; orthopaedic / musculoskeletal: dysostosis multiplex, lumbar kyphosis, joint contractures. Changes in appearance (facial coarsening) are progressive, and in severe MPS I are often what initially prompts parents to seek medical help. Not all patients have all these characteristics and patients with attenuated MPS I often have normal or only subtly altered appearance. (52)

Pompe disease

Pompe disease is a rare, progressive, debilitating and often fatal neuromuscular disorder resulting from the deficiency of a lysosomal enzyme, acid alpha-glucosidase (GAA). Pompe disease results from mutations leading to deficiency of GAA enzyme activity and progressive lysosomal glycogen accumulation. Glycogen accumulation leads to progressive muscle weakness, loss of respiratory function, and often premature death. Pompe disease is characterized by progressive degeneration of skeletal, respiratory and, in infants, cardiac muscle. Signs and symptoms of the disease may begin anywhere from early infancy through adulthood. Encompasses a single-disease continuum with variable rates of disease progression. Pompe disease is also known as acid maltase deficiency (AMD), glycogen storage disease type II (GSD-II), and glycogenosis type II. (53) Infants with Pompe disease usually present with symptoms within the first months of life, and have a rapidly progressive disease course that is usually fatal by one year of age. They have

little to no detectable enzyme activity (<1%). On the other side children and adults with Pompe disease have a less rapid and more variable disease course, where symptoms may begin anywhere from infancy to adulthood and low to moderate GAA activity (1-30%). (54) The deficiency of GAA results in glycogen accumulation within the lysosomes in virtually all tissues, with profound effects in cardiac, skeletal, and respiratory muscle. (55)

While the exact process by which muscle function is inevitably lost is still unknown, the depiction below illustrates conceptually the progression of disease at the cellular level. Progressive glycogen accumulation causes inflammation, fibrosis, and disruption of contractile elements of muscle. (56) The disease is autosomal recessive inheritance that means both parents must be carriers of GAA gene mutations. Children of affected parents have25% chance to have Pompe disease. Males and females are equally likely to be affected. (55)

Diagnosis of rare diseases

Enzyme testing on Dried Blood Spots (DBS) is a 1st tier/screening test for all four above mentioned metabolic rare diseases. The test is easily performed and inexpensive. A positive DBS enzyme test requires confirmatory test for definitive diagnosis by evidence of enzyme level in blood (lymphocytes, mixed leukocytes), skin fibroblasts or muscle. The other possibility is genetic testing to identify of specific gene mutation by sequence analysis (usually blood, and can also be performed from the same DBS sample used for first-tier enzyme activity testing). (57,58)

Enzyme replacement therapy

An enzyme replacement therapy is the only effective treatment patients with Fabry disease, Pompe disease, Gausher disease and MPS I. ERT is usually given intravenous every other week. For some of those diseases like Fabry and Gausher oral treatment is also available. The treatment usually effective if it stars on time, that is often not a case due late diagnosis. Concerning the safety a majority of concerns are related to infusion associated reaction (IAR) that can be prevented by adequate pre medication.

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