



## THE REALITY OF THE MANAGEMENT IN PATIENTS WITH RARE INBORN METABOLIC DISEASES IN SLOVAKIA

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Recently, from 6,000 to 8,000 rare diseases have been registered, of which over 1,000 are inherited metabolic diseases.

In Slovakia, a nationwide newborn screening for phenylketonuria – an inherited metabolic disease that occurred frequently in our country – has been performed over the last 40 years. Special workplaces in Bratislava, Banská Bystrica and Košice were set up to provide optimal availability of treatment for patients with phenylketonuria.

Today, Inherited Metabolic Diseases Centre in Children's Faculty Hospital in Bratislava uses the laboratories at the Department of Laboratory Medicine and Molecular Genetics at the 2<sup>nd</sup> Paediatrics Department. When finalizing the diagnosis, we cooperate with the Institute of Medical Biology, Genetics and Clinical Genetics, Faculty of Medicine and University Hospital in Bratislava. However, international cooperation is needed. Clinical and ambulatory care of patients with inherited metabolic diseases is in the centre distributed to the paediatric and neurological departments.

In recent years, the problem of inherited metabolic diseases has no longer been just a paediatric problem. While in past the majority of patients did not live to adulthood, today, thanks to new drugs and therapeutic procedures, it has been changed. Improving the knowledge of the pathogenesis, diagnosis and especially substitution therapy, patients can reach the age of adulthood and they can even be diagnosed in adulthood. The paper provides personal experience with the treatment of inherited metabolic diseases in Slovakia, mainly the substitution therapy.

**Keywords:** *inherited metabolic disease in Slovakia – substitution therapy – paediatrics*

The whole society has become more used to dealing with initiatives to prevent the increasing number of patients with “civilization diseases” or epidemics. Rare diseases are life-threatening or chronically debilitating diseases affecting, according to statistics, from 27 to 36 million of the European population. Support for diagnosis and treatment of rare diseases is mainly a question of solidarity with the weaker, disabled and severely ill patients. Recently, from 6,000 to 8,000 rare diseases have been registered, of which over 1,000 are inherited metabolic diseases. In Slovakia, a nationwide newborn screening for phenylketonuria – an inherited metabolic disease that occurred frequently in our country – has been performed over the last 40 years. Special workplaces in Bratislava, Banská Bystrica and Košice were set up to provide optimal availability of treatment for patients with phenylketonuria.

After the split of Czechoslovakia in 1993, it was necessary to provide diagnosis and treatment also for patients with other inherited metabolic diseases (IMD), which were previously performed by the Institute of Inherited Metabolic Disorders in Prague. In addition, Slovakia has had patients with diagnosed IMD, for whom it was necessary to ensure monitoring of treatment using special, previously unused techniques. Progressively, it has been managed to build quite a solid laboratory base. Diagnosis is only the beginning of lifelong care for IMD patients. To be beneficial to patients, a special clinical and ambulatory care must be established. Since the most serious manifestations of an IMD are usually manifested in the early childhood and directly threaten patient's health and life, it is only natural that such workplace started to be formed in a paediatric department. Today, IMD Centre in Children's Faculty Hospital in Bratislava uses laboratories in the Department of Laboratory Medicine and Laboratory of Molecular Genetics at the 2nd Paediatric Department. When finalizing the diagnosis, we cooperate with the Institute of Medical Biology, Genetics and Clinical Genetics, Faculty of Medicine and University hospital in Bratislava. However, in case of such rare diseases as IMDs, it would be nothing without international cooperation. Clinical and ambulatory care of IMD patients is distributed to the paediatric and neurology departments within the centre. In recent years, IMDs have no longer been just paediatric problems. While in the past the majority of patients did not live to adulthood, today, thanks to new drugs and therapeutic procedures, it has been changed. Due to improving of the knowledge of IMD pathogenesis, diagnosis, and especially therapy; patients can reach the age of adulthood and they can even be diagnosed in adulthood.

Some IMDs are acute and often life-threatening, particularly in childhood. It is necessary for a department to be prepared to deal with the treatment of this condition. These patients were often treated with drugs which are not common in daily practice. These must be always available for the patients with their lives at stake. Otherwise it may cause irreparable damage to patients' health condition or patients' death. For these reasons, creating centres where these drugs and trained medical team are always available is essential for IMD patients.

As far as the group of chronic inherited metabolic diseases is concerned, it is necessary to monitor efficiency of the treatment and to predict its complications correctly. Often, it is possible only on the basis of clinical experience. When one considers the number of patients with various diseases, it is clear that quality of care cannot be ensured in every department in Slovakia.

So what does it actually look like today in the management of Slovak patients with inherited metabolic diseases in CIMD in Children's Hospital in Bratislava?

Although the centre formed in 1993 and has had a lot of support from the hospital, it is still struggling with the lack of material and staff, which has been highlighted especially since the extension of nationwide neonatal screening.

So far, the centre has diagnosed 405 patients, 10% of which are adults. Most of them needed to be put on a special pharmacological or dietary therapy, the effect of which should be monitored.

A third of IMDs is now treatable or therapeutically influenceable. Their diagnostics is increasingly getting to the forefront. It is a fact that only diseases that are probable during patient's examination are involved in process. The centre has been actively participating in both undergraduate and postgraduate training of doctors, and it has also been organizing professional events, where they have presented their practical experience, new diagnostic and therapeutic procedures. In recent years, causal therapies for some diseases, e.g. enzyme replacement therapy, have been discovered and registered, and a wider target search started.

If a doctor suspects an IMD to occur in a patient while, he/she has to consult CIMD. In case of a paediatric patient in an acute state, upon the consultation, the doctor completes evaluations, adjusts therapy, and after stabilization of the clinical condition he/she can send the patient to a care centre. In case of ambulatory patients, we prefer such consultation to be performed and an ambulatory examination to be arranged by the doctor, not by a family member or even by the patient himself, because the lack of objectiveness when consulting health problems and interpreting the results of tests can cause difficulties in differential diagnostic process. In case of an adult patient's examination at CIMD, it may be performed only after the approval of exceptions to the age by health insurance company, which obviously delays testing itself and increases administration.

In case of confirmed IMD, treatment of the disease is indicated and monitored by doctors at CIMD. Cooperation between CIMD and general practitioners remains. After having diagnosed a patient with IMD, an extensive administrative process starts alongside the therapeutical and preventive care, in order to provide the therapy itself. Its range depends on the concrete drugs required for the disease. Many drugs are under special supervision.

Although the EU has ensured authorisation of majority of drugs used for IMD in EMA, there are still some long-term-used drugs (e.g. biotin) requiring exceptions for individual import by Ministry of Health of the Slovak Republic (MH SR). There are also drugs used for treatment of metabolic patients, which are already registered in the Slovak republic but not in the indication of the metabolic disease, or no form for long-term, chronic usage is registered (e.g. calcium folinate p.o. for treatment of cerebral folate deficiency). Also in this case, we start with a request for transport confirmation by MH SR; in the case of acceptance, we submit an application to the health insurance company to secure the payment for their client's therapy.

Upon obtaining all the approvals (there is always a one month period from the appeal to the decision), the drug can be ordered in a pharmacy.

There are several registered but not categorised drugs for treatment of IMDs. In such case the therapy follows the approval of the revising doctor in patient's health insurance

company. According to internal decision of particular health insurance companies, this approval is valid for 3 - 6 months. But considering the character of a metabolic disease, the therapy is long-term to life-long. A special situation comes with a patient that requires intravenous enzyme replacement therapy. An effective therapy requires the application of an enzyme once in seven or fourteen days, depending on the particular disease. There are patients from all over the republic diagnosed, so after the initial applications of the enzyme and ascertainment of patient's tolerance to the drug, application of the therapy in his region is required. The approval by health insurance company to ambulatory application of the infusion therapy, the required device and an institutional pharmacy providing the drug are needed for application of the therapy by the providing health care unit. It is not easy to find such a health care provider in the region of patient's abode. If it is found, CIMD asks the patient's health insurance company to enter necessary information about the health care provider to the database to enable the supply of the required drug and realization of the therapy. The doctor from CIMP also instructs the medical staff on application and itemization of the therapy. Sometimes, this process, start of which was very difficult, can be complicated. We have experienced a situation when the amount of enzymes needed was not available for already treated patients because of a technical problem of the producer. Application of the drug in the providing medical unit can be also complicated by a change in the information system of a health insurance company.

The described administrative process is hard not only to be read but also to be realized by a doctor whose first aim is to diagnose the disease and to indicate a therapy. In our centre we are providing the therapy by 12 preparations for 33 patients in the described way of application for the therapy. Decrease in frequency of administering such requests would be a great relief for us.

It is not the only paperwork necessarily provided by a doctor from the centre.

The doctor is supposed to manage the calculation of financial costs of investigation and an approval at health insurance company to cover the costs for the diagnostic process provided by foreign company, must be administered.

A special, exactly defined diet is an essential therapeutic intervention for several metabolic diseases. The diet needs to be regularly modified according to current metabolic needs of the patient considering his/her age and current weight. Such an ambulant process is not accepted by health insurance companies and the actual catalogue of laboratory tests does not count with the covering of the real costs of highly specified laboratory examinations and their frequency.

There is the same problem with accepting repeated hospitalizations of IMD patients in case of an acute decompensation of the IMD during one month. Then, the costs for health care are completely covered by the hospital. If we worked according to the mentioned rules of health insurance companies, patients would not be treated *lege artis*, and in acute decompensation their lives would be directly threatened.

In case of making the diagnosis of a currently untreatable IMD, the patient is provided with symptomatic and social therapy. In such cases there are more problems with the social system than in case of treatable IMDs - the social system does not recognize the diagnose „inherited metabolic disease“ in its compensation system. The patients' association for rare genetic disorders provides help for such patients, so that they are not left alone in dealing with their problems. The association was

founded by patients and their families who had already experienced and were experiencing all the troubles. They can advise each other how to deal with the hard destiny.

As the diseases are genetic, it is necessary to provide genetic advice and prenatal diagnosis, independently of whether the disease is treatable or not. For this purpose, to manage a complex health care, the Genetic outpatient department was founded in CIMD in the 2nd Department of Paediatrics.

Thanks to a great personal input of all the employees of CIMD, the centre has succeeded. Improvement of IMD diagnosis and treatment, and the start of the screening programmes have lead to an increase in the number of patients. Therefore, an increase in the number of doctors - specialists and trained medical staff will be required to take care of the patients. But the postgraduate training in the field of inherited metabolic diseases has not been founded in the system of postgraduate training. This specialization is necessary to be provided for Slovak patients with metabolic diseases with medical care comparable to that in other countries of the EU.

This is the aim of the CIMD in Children's Hospital in Bratislava. By now, the positive results of all the effort in the complicated process of providing the diagnosis or the special therapy have been noticeable. Many patients, formerly suffering from a body destroying disease, are now able to participate in everyday life and live valuable life.

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## **REALITA STAROSTLIVOSTI O PACIENTOV SO ZRIEDKAVÝMI VRODENÝMI METABOLICKÝMI CHOROBAMI V SR**

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### **2. DK LF UK a Centrum dedičných metabolických porúch Detská fakultná nemocnica s poliklinikou Bratislava**

V súčasnosti poznáme 6000 – 8000 zriedkavých chorôb, približne 1000 z nich tvoria vrodené metabolické choroby.

Na Slovensku prebieha národný skríningový program, v rámci neho sa už 40 rokov skrínuje fenylketonúria – vrodená metabolická choroba.

Liečba prebieha v špeciálne určených centrách v Bratislave, Banskej Bystrici a Košiciach. Centrum vrodených metabolických chorôb pri Detskej fakultnej nemocnici v Bratislave spolupracuje s genetickými laboratóriami druhej detskej kliniky. Pri finálnom určení diagnózy spolupracujeme tiež s Oddelením lekárskej biológie genetiky a klinickej genetiky lekárskej fakulty a Univerzitnej nemocnice v Bratislave. Potrebná je tiež medzinárodná spolupráca. Klinická a ambulantná starostlivosť pacientov s vrodenými metabolickými chorobami prebieha v spolupráci s detskými a neurologickými oddeleniami.

V ostatných rokoch problematiky liečby vrodených metabolických chorôb nie je len otázkou pediatrov. Kým v minulosti sa pacienti nedoživali dospelosti, dnes vďaka substitučnej liečbe pacienti sa dožívajú dospelosti, dokonca môžu byť diagnostikovaní až v dospelosti. V práci prezentujem vlastné skúsenosti s liečbou vrodených metabolických chorôb na Slovensku.

***Acta Fac. Pharm. Univ. Comen. 2013, Suppl VIII:16-21.***