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PREGLED
REVIEW

METACHROMATIC LEUKODYSTROPHY – WHAT IS NEW?

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Lysosomal storage disorders have long been considered as not specifically treatable. This is changing now for a number of these diseases and is the case also for metachromatic leukodystrophy. Metachromatic leukodystrophy is a rare inborn error of metabolism caused by arylsulfatase A deficiency and if left untreated it leads to severe neurological symptoms and early death in pediatric patients. This paper gives an update on the genetics, pathophysiology and clinical course of metachromatic leukodystrophy and discusses the treatment protocols which are currently developed for metachromatic leukodystrophy, such as stem cell transplantation and enzyme replacement as well as gene therapy approaches.

Descriptors: LEUKODYSTROPHY, METACHROMATIC – diagnosis, genetics, physiopathology, therapy

INTRODUCTION

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by a mutation in the arylsulfatase A (ASA) gene and deficiency of this enzyme. The defect results in the accumulation of galactosylceramide-3-0-sulfate (sulfatide) predominantly in the central (CNS) and peripheral nervous system (PNS) causing demyelination. MLD occurs with an estimated incidence of 0.6 to 1 per 100 000 live births (1, 2) in the European population. In general, the disease occurs in all ethnicities.

As therapeutic options are currently developing, this disease has gained more interest in the last years, and knowledge has increased also on the natural course of the disease. Therefore this paper gives an update on MLD with respect to the genetics, pathophysiology and clinical course of MLD and the treatment protocols that are currently developed.

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CLINICAL PRESENTATION

The clinical phenotype of MLD is due to the global and progressive loss of myelin and clinically relevant pathology is limited to both CNS and PNS. Demyelination causes various neurologic symptoms which are finally lethal.

Three major forms of MLD are usually distinguished based on the age at onset: late infantile form with the onset of clinical symptoms before 30 months of age as the most frequent form; juvenile form with the onset between 2 1/2 and 16 years; and adult form with the onset after 16 years of age (3-5).

In the late infantile form, children develop symptoms usually in the second year of life after an initially normal development. Symptoms involve gait problems due to neuropathy and spasticity, ataxia and mental regression. The course of disease is highly invariable and stereotypic and leads to a complete loss of motor function usually before the age of 3 ½ years. Deterioration of gross motor function in juvenile MLD is more variable concerning age range and dynamics. There may be impaired fine motor skills, concentration and behavioral problems as first symptoms. However, once the loss of independent walking occurs in juvenile patients, their gross motor function declines as rapidly as in the late infantile form (5). In the adult forms, psychotic symptoms and behavioral abnormalities often precede or accompany a decline of intellectual capacities and motor function (6), which may delay the diagnosis considerably (7).

The disease usually affects both the PNS and CNS. Whereas early involvement of the PNS has been noted in a number of patients, there are patients with marked demyelination in the CNS while the PNS system is preserved.

Two typical case histories illustrate late infantile and juvenile MLD. Gross motor decline is measured with a score that has been specifically developed for MLD, the gross motor function classification of MLD (GMFC-MLD) (8). The gross motor function course of these two cases is shown in Figure 1.

Late infantile MLD. This little boy had an unrevealing family history, pregnancy and birth; his early development was also normal – he learned to sit at seven months, crawled at eight months and walked at 14 months. At 18 months, however, walking became unstable and broad based with recurvated knees due to polyneuropathy. Six months later, he developed spasticity

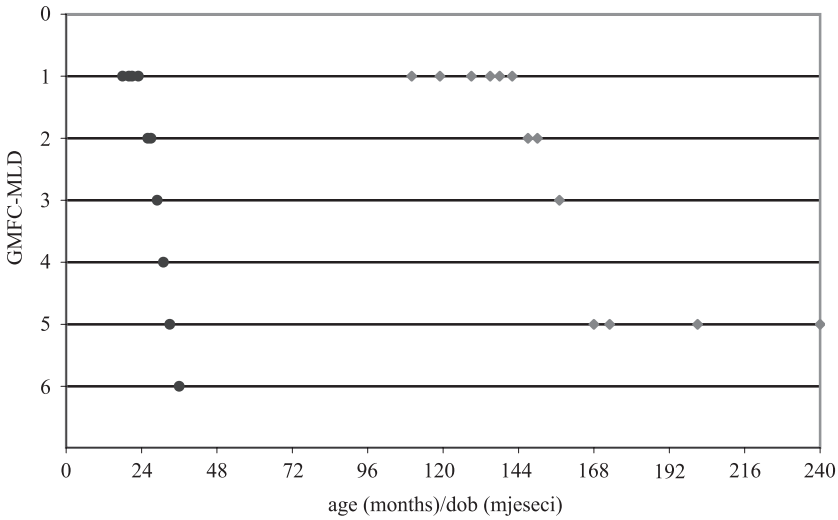

Figure 1. *Gross motor course of the two children with late infantile (left) and juvenile MLD (right), discussed in the text. GMFC-MLD: level 0 – walking without support with quality of performance normal for age. Level 1 – walking without support, but with reduced quality of performance, i.e. instability when standing or walking. Level 2 – walking with support. Walking without support not possible (less than five steps). Level 3 – sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible. Level 4 (a) sitting without support, but no locomotion; or (b) sitting without support not possible, but locomotion such as crawling or rolling. Level 5 – no locomotion or sitting without support, but head control is possible. Level 6 – loss of any locomotion as well as loss of any head and trunk control.*
Slika 1. *Slijed propadanja motoričkih funkcija kod dvoje djece s kasnom infantilnom (lijevo) i juvenilnom MLD (desno), opisane u tekstu. GMFC-MLD: razina 0 – hoda bez pomoći i kvaliteta hoda normalna za dob. Razina 1 – hoda bez pomoći, ali kvaliteta hoda smanjena, tj. nestabilnost kad stoji ili hoda. Razina 2 – hoda uz pomoć. Hodanje bez pomoći nije moguće (manje od pet koraka). Razina 3 – sjedi bez potpore, pomiče se puzanjem ili prevrtanjem. Hodanje uz pomoć ili bez nje nije moguće. Razina 4 (a) sjedi bez potpore, ali se ne pomiče; ili (b) sjedenje bez potpore nije moguće, ali se pomiče puzanjem ili prevrtanjem. Razina 5 – ne pomiče se niti sjedi bez potpore, ali kontrolira glavu. Razina 6 – gubitak svake kretnje, kao i gubitak kontrole glave i trupa.*

with equinus foot position, and independent walking was lost. Language development was normal up to then (first words at 14 months, two word combinations at 20 months). After the loss of walking, a rapid decline set in: at 28 months he could no longer walk with aid, but sit and roll over, the latter was lost 2 months later, trunk control at 30 months and at 36 months all gross motor functions were lost. Swallowing problems developed around 30 months. Cognitive decline paralleled motor decline and at 30 months he did not talk any more, at 3 ½ years understanding of speech also disappeared. He survived several years in this severely impaired condition.

Juvenile MLD. This girl developed completely normal until the age of 6 years, when behavioral problems were observed (impulsivity and concentration problems); two years later walking became clumsy. This situation was rather stable with the exception of somewhat deteriorating school results necessitating moving to a special school. Four years later, at the age of 12 years, gross motor dysfunction progressed and she lost the ability to walk without aid. A rapid decline of motor function followed thereafter and she could no longer walk with aids at 13 years, lost trunk control at 14 years and showed severe spasticity. Mental decline was observed during the same period and at around 12 ½ years, active speech was lost. Thereafter, she was relatively stable and showed still some head control at the age of 20 years; she was blind, but still had some basic communication skills (laughed when talked to).

LABORATORY DIAGNOSIS

Diagnosis of MLD is based on two biochemical parameters: deficiency of ASA activity in leukocytes and sulfatide excretion in urine. The latter is important

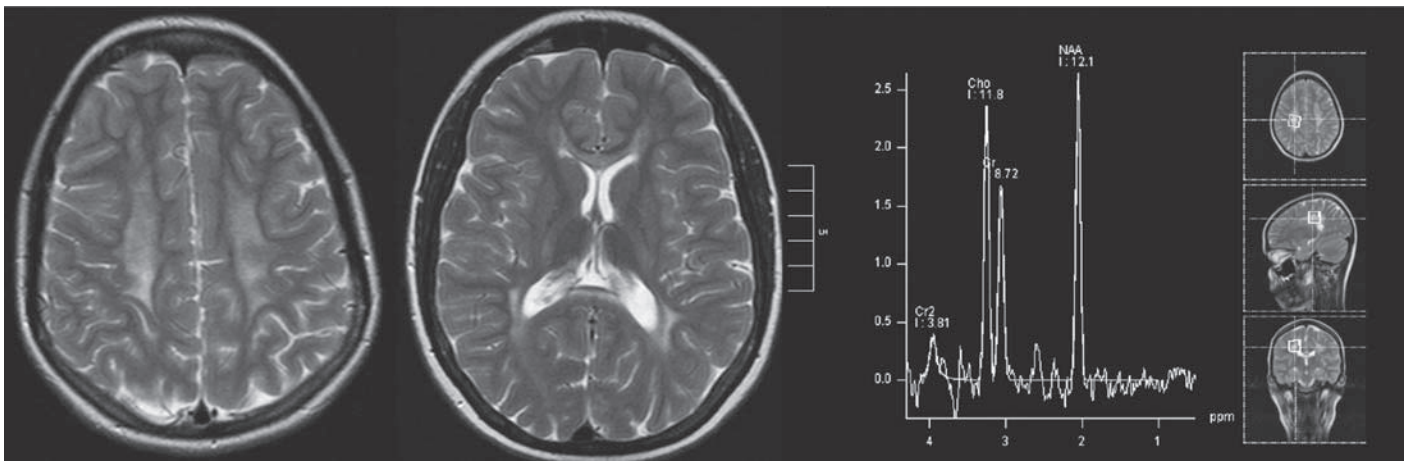

Figure 2. *Typical early MRI signs in a juvenile MLD patient at onset of the disease (14-year-old, mild polyneuropathy, diagnosis because of affected sibling); T2w images. The central white matter is hyperintense, U-fibers are still myelinated (left). The projection fibers are not yet affected (capsula interna still hypointense), but the corpus callosum is already hyperintense (middle). MR spectroscopy shows clear abnormalities in the central white matter: high choline and low NAA (right). By the courtesy of Prof. Th. Nägele, Department of Neuroradiology, Tübingen University Hospital.*
Slika 2. *Tipični rani znaci na MRI u bolesnika s juvenilnom MLD kod nastupa bolesti (14-godišnje dijete, blaga polineuropatija, dijagnoza provedena zbog oboljelog brata/sestre); T2w prikazi. Centralna bijela tvar je hiperintenzivna, U-vlakna još su mijelinizirana (lijevo). Projekcijska vlakna još nisu zahvaćena (capsula interna je još hipointenzivna), ali je corpus callosum već hiperintenzivan (u sredini). MR spektroskopija pokazuje jasne nenormalnosti u centralnoj bijeloj tvari: visok kolin i nizak NAA (desno). Preuzeto ljubaznošću prof. dr. Th. Nägele, Department of Neuroradiology, Tübingen University Hospital.*

to confirm the diagnosis, firstly because enzyme deficiency may result from pseudodeficiency, which does not lead to a disease, and secondly because normal ASA activity does not exclude the diagnosis of MLD since MLD may be due to saposin B deficiency. Thus, pseudodeficient individuals who are healthy have low ASA activity, but do not excrete sulfatide, whereas saposin B deficient patients who develop MLD have normal ASA activity, but excrete sulfatide. The definitive diagnosis of saposin B deficiency depends on gene sequencing or direct demonstration of saposin deficiency via Western Blots. This activator deficiency causing MLD is very rare, however. Given the difficulties of laboratory diagnosis due to pseudodeficiencies and saposin deficiencies, a specialized laboratory should be consulted to ensure proper diagnostic procedures. Prenatal diagnosis through enzyme measurement is possible.

Diagnosis may also be done by molecular genetics. Because of the higher costs and the fact that enzyme measurement may be more reliable, we believe this should be done to supplement the biochemical diagnosis when, for example, an unknown mutation is found, but not as a screening.

GENETICS

The gene for ASA is located on 22q 13.31-qter. The *ASA* gene is a small gene in which the eight exons encompass only about 3 kb of the genomic sequence. More than 150 mutations are known (9). Among Caucasians, only a few of them are frequent (c.459+1G>A, p.426P>L, p.179I>S) accounting for ~ 60% of all alleles, whereas many of other mutations are only found in few, mostly single families.

There is a certain genotype/phenotype correlation in MLD. Homozygosity for mutations which do not allow the synthesis of any functional enzyme always causes the severe late infantile form of disease, one allele associated with residual enzyme activity mitigates the disease and causes a juvenile form, whereas homozygosity for two alleles with residual ASA activity in most cases causes a late juvenile or even adult form of MLD (10). Residual enzyme activity, thus, is one determinant of clinical severity. However, clinical variability in late onset patients may be considerable and is reported even in siblings with identical ASA genotype (11, 12). This indicates that other genetic or epigenetic factors influence the phenotype substantially. Therefore, prediction of the individual disease course based on genotype analysis must be done with great caution.

PATHOPHYSIOLOGY

ASA is involved in degradation of the myelin sphingolipid, 3-O sulfogalactosylceramide (sulfatide) (9). Its deficiency results in accumulation of sulfatide and the lysolipid of sulfatide, lysosulfatide. They have potent biological activities such as inhibition of proteinkinase C, interference with IGF-1 signaling and phospholipase A2 activation (13, 14). For these reasons, they are considered to play an essential role in the pathogenesis, although their exact mode of action in the in vivo situation is not entirely clear. In a mouse model of MLD, early symptoms correlated with the increase of sulfatide in neurons in the absence of demyelination (4). Therefore, this disease should not be considered as affecting oligodendrocytes only. In human, symptoms may also be caused by neuronal storage before the symptoms due to demyelination predominate the clinical picture.

In addition, sulfatide accumulation has been reported to stimulate inflammatory processes and apoptosis by increased secretion of inflammatory cytokines. Sulfatides also play a role in intracytoplasmic calcium homeostasis, which may lead to cellular apoptosis (15).

DIAGNOSIS BY MRI

Central white matter is early affected. T_2 weighted (T2w) imaging typically shows butterfly-shaped confluent white matter hyperintensities with a characteristic tigroid pattern. Regardless of the type of disease, corpus callosum is involved early. As the disease progresses, there is increasing white matter involvement including U-fibers and later cerebellar white matter as well as cerebral atrophy (16). MR spectroscopy (MRS) is abnormal early and shows an increase of choline containing compounds and a NAA decrease, indicating demyelination; lactate is often elevated (17).

Standardized tools have recently been developed to evaluate MRI in MLD. A scoring system similar to that used in ALD has been introduced (18) and was used to describe MRI changes in a nation wide patient cohort (16). In late infantile MLD, the score increased rapidly with disease progression, whereas in the juvenile form patients already showed clear white matter changes at disease onset (Figure 2). As demyelination is a hallmark of MLD and its evaluation is especially important not only to describe disease progression but also changes under therapy, a semi-automatic morphometric method has been introduced which allows to quantify white matter changes (demyelination load) (19).

TREATMENT

Currently, there is no standardized treatment protocol available for patients with MLD. But several approaches are already studied in the human situation, all having in common the aim to substitute the deficient enzyme activity either by exogenous or endogenous enzyme replacement.

Exogenous enzyme replacement

A phase I/II study with intravenous replacement of ASA has not resulted in any benefit in late infantile MLD patients (20), therefore an intrathecal replacement study of recombinant ASA is now started. The basis for this is the observation that in the mouse model, much lower enzyme doses are needed in the intrathecal as compared to *i.v.* approach to decrease sulfatide storage in macrophages, oligodendrocytes and also neurons, and to achieve better motor function (21, 22).

Endogenous enzyme replacement

Hematopoietic stem cell transplantation (HSCT) is thought to result in at least partial endogenous and continuous enzyme replacement. It is assumed that donor monocytes secreting arylsulfatase invade the brain after HSCT, differentiate into microglia and supply enzyme to deficient resident glia and possibly neurons (23, 24), which takes probably more than 18-24 months. Single case reports indicate a delay or stop of disease progression in patients with juvenile MLD, when done early during the disease or in presymptomatic patients (25-27). Critical discussion of the results is hampered, however, by the fact that comparison to the natural course of the disease in a larger patient group was not possible. In view of the rapid decline of motor and also cognitive function so typically observed in late infantile and juvenile MLD once independent walking is lost, it seems essential that

HSCT is done early enough before this decline sets in.

Endogenous enzyme replacement could also be achieved by a genetic approach and two studies are currently under way, both phase I/II studies (24, 28): HSCT based gene therapy in preclinical late infantile patients and preclinical or early clinical juvenile patients and adenoassociated virus (AAV) mediated gene therapy based on direct multiple injection of ASA expressing viral vectors into the brain of patients; here early symptomatic late infantile and early juvenile patients are included (28).

Thus, taken together, the effect of these treatments cannot yet be judged on, and although HSCT has the longest follow-ups of patients, even there it is not entirely clear which patients should be treated and when. The future may show that a combination of therapies will be needed to arrive at a satisfactory outcome in newly diagnosed individuals.

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Authors declare no confilct of interest.

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S a ž e t a k

METAKROMATSKA LEUKODISTROFIJA – ŠTO JE NOVO?

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Dugo se vjerovalo kako ne postoji specifičan oblik liječenja lizosomskih bolesti nakupljanja. Taj stav se danas mijenja za neke od ovih bolesti, pa tako i za metakromatsku leukodistrofiju. Metakromatska leukodistrofija je rijetka greška metabolizma uzrokovana deficijencijom arilsulfataze A koja, ako se ne liječi, dovodi do teških neuroloških simptoma i rane smrti kod djece. Ovdje se prikazuju najnovija saznanja o genetici, patofiziologiji i kliničkom tijeku metakromatske leukodistrofije te se raspravlja o protokolima liječenja metakromatske leukodistrofije koji su u razvoju, kao što je presađivanje matičnih stanica i nadomještanje enzima, te genska terapija.

Deskriptori: LEUKODISTROFIJA, METAKROMATSKA – dijagnoza, genetika, patofiziologija, terapija

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