Prikaz primera dveh sorojencev s pozno infantilno obliko metakromatske levkodistrofije

Two siblings with late infantile form of Metachromatic leukodystrophy – a case report

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Izvleček

Metakromatska levkodistrofija je avtosomno recesivna nevrodegenerativna bolezen. V osnovi gre za pomanjkanje encima arylsulfatase A oz. njegove aktivnosti, zaradi česar pride do kopičenja sulfiranih glikosfingolipidov v beli možganovini. Glede na pojav kliničnih znakov ločimo pozno infantilno, juvenilno in odraslo obliko bolezni. Bolezen je bila do nedavnega neozdravljiva. V prispevku prikazujemo primer sestre in brata, ki imata pozno infantilno obliko bolezni. Pri deklici je bila diagnoza postavljena, ko je bila bolezen že v napredovali fazi, zato je bila usmerjena v program paliativne oskrbe. Pri mlajšem bratu je bila bolezen ugotovljena v predsimptomatski fazi. Uvedeno je bilo eksperimentalno genetsko zdravljenje, ki je znatno spremenilo potek bolezni.

Abstract

Metachromatic leukodystrophy is an autosomal recessive neurodegenerative disease. The underlying mechanism of disease is the lack of arylsulphatase A, which leads to the accumulation of sulphated glycosphingolipids. Three forms of disease are recognized based on clinical onset, including infantile, juvenile, and adult forms. Until recently, metachromatic leukodystrophy was untreatable. In this article, we present the cases of a sister and brother with the late infantile form. The female was diagnosed when the disease was at an advanced stage, and thus, was treated palliatively. Her younger brother was diagnosed at the presymptomatic stage and experimental genetic treatment was conducted, which markedly Improved the course of disease.

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INTRODUCTION

Metachromatic leukodystrophy (MLD) is an autosomal recessive neurodegenerative disease of the white matter. The main cause of MLD is a deficiency of arylsulfatase A (ARSA), which is essential for the hydrolysis of sulphated glycosphingolipids. The deficiency of ARSA activity results in the storage of the sulphated glycosphingolipids inside the neuronal white matter. Over the clinical course of the disease, signs of upper and lower motor neuron pathology are observed. The clinical manifestation begins with irritability, inability to walk, and hyperextension of the knees. Following the progression of the disease, cognitive decline, psychiatric signs, and myoclonic seizures appear. Progressive muscle wasting leads to evident hypotonia and deep tendon reflexes become diminished or absent. Ocular signs progress from nystagmus to optic atrophy. In the late infantile form of MLD, clinical manifestations appear between the 12th and 18th months (M) with swift progression to tetraparesis and death during the first decade of life. The clinical signs of the juvenile form of MLD appear before 20 years of age (Y), while in the adult form, clinical manifestations become evident after 20 Y (1). Until a few years ago, there was no effective treatment for MLD (2,3). A genetic treatment was introduced in the last decade, and appears promising, but must be initiated at the pre-symptomatic or early symptomatic stages (4-6). Thus, efforts toward early diagnostic measures including the improvement of neonatal screenings are essential (7,8).

CASE PRESENTATION

The case concerns a family of healthy, non-consanguineous parents and three children. The first-born child (June 2014) was a healthy female. The second-born child was also a female (February 2017) and the third-born child was a male (February 2019) who were both affected by the late infantile form of MLD.

The second-born female had normal motor and cognitive development during the first year of life; however, she suffered several respiratory infections with an obstructive pulmonary component. During the infections, her motor milestones halted or regressed. The parents reported that the child would refuse to stand on her feet or walk for approximately 2 weeks. The child began walking without support at 15 M. At 20 M she was examined by a developmental neurologist, who described normal motor and cognitive development, except axial hypotonia. One month later, she was hospitalised due to a simultaneous parainfluenza and Chlamydophila pneumoniae infection. At 22 M, she was hospitalized again due to influenza. After hospitalisation, she began to complain of leg pain and at 24 M she stopped walking, but was able to sit without support. At 25 M she was hospitalized at the University Paediatric Clinic of Ljubljana due to evident motor regression, generalised muscular weakness (including facial muscles), muscular pain, inability to be seated without support, and lacking deep tendon reflexes. A lumbal puncture revealed elevated protein. Electromyography (EMG) was consistent with a demyelinating process. A diagnosis of Guillaine-Barre syndrome was suggested and after the first therapy with intravenous immunoglobulins, the clinical signs improved, except for the muscular weakness in the legs. Despite intensive physiotherapy and repeated immunoglobulin treatment, progressive motor deterioration was noted. Further diagnostics were performed for neuro-degenerative diseases.

Magnetic resonance imaging (MRI) of the brain at 28 M revealed bilateral symmetrical alterations of the deep periventricular white matter and corpus callosum, as well as changes to the thickness of the cervical nerve roots. Low ARSA activity was found in the peripheral blood. Genetic testing at 30 M confirmed the diagnosis of MLD and due to the advanced clinical signs, the patient was referred to a palliative care program.

The disease progressed as expected. At 3 Y, the patient was unable to sit independently, but she could lift her head. Despite progressive motor decline, her cognitive development was good. At 3 Y and 2 M, oral feeding became impossible, and a nasogastric tube was inserted. At 3 Y and 6 M, her cognitive

and motor performance declined rapidly and she was able to communicate only with her eyes. Permanent salivation, painful muscle spasms, rigidity and grand mal epileptic episodes developed. Therapy with morphine, gabapentin, levetiracetam, clonidine, and glycopyrrolate was introduced to reduce the pain, seizures, salivation, and other symptoms. By 4 Y, the patient was completely bedridden, with almost no communication. A percutaneous gastrostomy was used to facilitate nutrition.

The patient required frequent upper respiratory tract aspirations, urinary bladder catheterisations, and regular therapy with lactulose or macrogol to maintain regular defecation. Regular physiotherapy once per week and an annual 2-week rehabilitation at a seaside children's rehabilitation centre are included in the palliative care to reduce the spasticity, pain, and respiratory difficulties. She suffers frequent respiratory and urinary infections, which are treated with oral antibiotics.

The male child was born at 40 weeks of gestational age after an uneventful, normal pregnancy. His early developmental milestones were normal. The boy was 8 M of age when his older sister was diagnosed with MLD and he underwent immediate biochemical and genetic testing. Low ARSA activity was detected in the peripheral blood (< 1 nmol/hr/mg). The same mutations as his older sister were found, confirming the MLD diagnosis. As the patient was in the pre-symptomatic stage of the disease, he was enrolled in a clinical study for the treatment of MLD with gene therapy. After the parents' written consent was obtained, his inclusion into the study began at the San Raffaele Hospital in Milano, Italy (4-6).

The patient's brain MRI was normal and electroencephalography (EEG) showed no pathological significance. Electromyography (EMG) registered normal sensory and motor conduction. The brainstem evoked auditory potentials with mild left side peripheral hearing loss (increased latency at high frequences 90-95 dB).

At 10 M the patient underwent transplantation of autologous cryopreserved bone marrow CD34+ cells transduced ex vivo with lentiviral vector encoding human ARSA cDNA after a conditioning regimen with intravenous Busulfan. After therapy, normal ARSA activity was noted in the peripheral blood and has remained within the normal range 4 years later. The patient has regular check-ups twice per year at the San Raffaele Hospital in Milano. His cognitive development is assessed regularly by a development neurologist and a psychologist. He pronounced his first words at 11 M, two-word sentences at 19 M, three-word sentences at 21 M, and sentences of six words or more at 26-27 M. He began crawling at 9 M, and began walking independently at 16 M. His motor development is impaired, with gait instability, hyperextensions of the knees, lower limb weakness, and mild spasticity, but he can walk, jump, run, and ride a bicycle. He attends regular physiotherapy two times per week and once per year he attends 2-week rehabilitation sessions with his sister in a children's rehabilitation centre near the seaside. At 5 Y, the patient attended a 4-week rehabilitation session in the national rehabilitation centre, which included physiotherapy, occupational therapy, and speech therapy. He is supported with ankle foot orthosis and is very communicative and curious, and his motor functions are improving.

The patient attends kindergarten with the support of a personal assistant due to his motor instability. In September 2025, he will begin attending school.

Discussion from the view of a primary care paediatrician

This study detailed two siblings with the same type of a rare neurodegenerative disease. The female's diagnosis was discovered based on progressive clinical manifestations of leukodystrophy. Due to the clinical signs of motor impairment, with brain, spine and peripheral nerve white matter degeneration, no adequate therapy could be provided.As the first rule of paediatric palliative care is to never stop treating the patient, we tried everything to help the family, and make the patient's life easier. Despite losing her ability to see, hear, and speak, the patient remains highly perceptive to touch and responds differently, depending on the person touching her. It is very important that the patient has access to medical care professionals who understand her needs, and have the confidence of the family (9-12).

The male patient was a healthy baby when the parents were informed of the female's diagnosis. A few weeks later, the boy received the same diagnosis. A new gene therapy for MLD was being conducted in the San Raffaele paediatric hospital in Milano, Italy. As the boy lacked clinical signs of MLD, the therapy was proposed to his parents with descriptions of its potential risks and benefits. They went through a process of doubt and fear of whether the therapy would provide a better life to their child or simply prolong the suffering. The fears and uncertainty regarding whether the therapy would be successful or not persisted through the boy's first years of life, and will probably last for his life. But his mental development appears excellent. Although he suffered motor impairment, he is a positive, healthy, and happy child.

The eldest child was approximately 4 Y when her younger sister became ill. Later, the brother travelled for treatment, and their mother needed to remain with him. The grandparents supported the family by taking care of the second child. During that time, psychological support was offered to the eldest child and she is currently attending primary school, receiving excellent grades, and is doing well in sports. The family is well organised regarding the treatment of the younger children, while attempting to live their family life as normal as possible. The support of the extended family (e.g., the children's grandparents) is precious.

CONCLUSIONS

The late infantile form of MLD is a neurodegenerative disease with a swift progression. When left untreated, it leads to death within the first decade of life. There have been no efficient therapies for MLD until recently (2,3). Gene therapy with transduced autologous haematopoietic stem cells appears effective, but must be initiated during the pre-symptomatic phase (4-6); and therefore, an early diagnosis is crucial. The implementation of newborn screening along with available gene therapy will provide improved lives for affected children and their families (7, 8). Paediatric palliative care should be a standard practice in paediatric primary care for all children with untreatable and terminal diseases (9-12).

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