Menkes kinky hair disease (Menkes syndrome). A case report

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SUMMARY

Menkes disease (MD) is a rare genetic neurodegenerative disorder. It is caused by a mutation in the ATP7A gene, which codes for the copper-transporting ATPase in the cell organelles. Dysfunction of many copper-dependent enzymes results in low concentrations of copper in some tissues and accumulation of copper in others. We report on a boy that at the age of 2 months presented with encephalopathy with epileptic seizures and later had a progressive developmental disorder. Despite treatment with various antiepileptic drugs, some seizures still persisted. Our diagnosis was made on the basis of clinical and laboratory findings. We also plan to confirm the diagnosis genetically. To the best of our knowledge, this is the first reported case of MD in Slovenia. Treatment of MD is usually not successful, especially in sporadic cases, because it usually begins too late. Early neonatal treatment may be successful in half of the cases.

Introduction

Neurodegenerative disorders encompass a number of heterogeneous diseases that develop as a consequence of specific genetic and biochemical defects or chronic viral infections, as well as a group of disorders of yet unknown etiology. Progressive deterioration of neurological functions is a characteristic of neurodegenerative disorders. We distinguish between diseases that primarily affect the white or gray matter of the brain according to the age at onset of the disease, the rate of progression, and principal neurological deficiencies (1, 2).

Menkes disease (MD) belongs to a group of diseases that mainly affect the gray matter of the brain. The predominant clinical findings are twisted, kinky, short, sparse, coarse, whitish, silver, or gray hair, eyebrows, and eyelashes. Children with MD have sagging cheeks and ears, a depressed nasal bridge, a high arched palate, and delayed dentition (3). Progressive cerebral degeneration is manifested in loss of developmental stages, seizures, truncal hypotonia with limb hypertonia and temperature instability (4–6). Ocular manifestations include ptosis, visual inattention, optic disc pallor, decreased papillary responses to light, hypoplasia, and hypopigmentation of the iris (7). Because of the

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connective tissue fragility, hernias, bladder diverticuli, loose skin, and hypermobile joints occur (8, 9). Vascular fragility can result in arterial ruptures, thromboses, and infarcts (10). Children can be born with congenital fractures, and later in life the bones are deformed and osteoporotic, with metaphyseal spurs and widening of the posterior portion of vertebral bodies (11). Patients may have bleeding diathesis, including urinary bladder, abdominal, and intracranial hemorrhages (12, 13).

MD is one of the four known disorders of copper metabolism. Together with *occipital horn syndrome*, it results from copper deficiency secondary to disturbances in copper transport. *Wilson's disease* and *Indian childhood cirrhosis*, on the other hand, result from the toxic effects of copper accumulation in the liver (14). In healthy children, concentrations of plasma copper and ceruloplasmin tend to be low during the first 3 weeks of life, may decrease even after the 6th week of life, and can sometimes be low even up to 6 months of age. In any case, plasma copper below 25% of normal range and low plasma ceruloplasmin concentrations can be diagnostic of MD after the 3rd week of life (15).

Case report

L. M. was born in March 2005 to healthy unrelated parents at 35 weeks gestational age; birth weight 2,100 g (10th–50th percentile), birth length 43 cm (5th percentile), head circumference 37.5 cm (1.5 cm > 95th percentile), and Apgar score 8/9. Due to respiratory distress, he needed an increased percentage of oxygen in inhaled air for 5 days and was treated with antibiotics because of suspected infection. He was discharged from the hospital on his 13th day of life.

The infant was well until the age of 2.5 months, when the parents noticed eyelid twitching, gazing directly upwards, transitory arm stiffness, and body atony. He was admitted to the hospital, where the convulsions discontinued after diazepam. He was afebrile with no signs of infection, and the results of laboratory tests (blood, urine, cerebrospinal fluid (CSF)), microbiological cultures (blood, CSF, stool), and imaging studies (chest X-ray, head and abdomen ultrasound) were unremarkable. The ophthalmologist noticed poor fixation. The first electroencephalogram (EEG) was abnormal, but the second EEG was appropriate for his age. The infant was discharged from the hospital without treatment.

At the age of 3 months, similar seizures recurred while the infant was afebrile. Further tests (urine organic acids, serum amino acids, blood lactate and pyruvate levels, blood gas analysis) were carried out to screen for possible metabolic disorders, but all results were within normal limits. The EEG was abnormal with pseudoperiodic complexes of biphasic sharp waves and slow waves over the left hemisphere, with spikes over the left temporo-occipital lobe. Magnetic resonance imaging (MRI) showed cortical atrophy, and there was also an intensified signal in the basal ganglia, cerebellum, and brainstem (Figure 1). After the emergency, treatment with diazepam phenobarbital was introduced. Neurologically, axial hypotonia and loss of head control were noticed.

Two weeks later he had an episode of tonic-clonic convulsions. Neurological assessment disclosed hypotonia, poor spontaneous movements, and only occasional eye-to-eye contact. The EEG was abnormal with intermittent dysrhythmic activity over both hemispheres. Magnetic resonance angiography (MRA) showed extreme tortuosity of the intracranial vessels (Figure 2). Due to repeated convulsions while on phenobarbital treatment, carbamazepine was added.

At the age of 4.5 months he had frequent convulsions despite the introduction of a third antiepileptic drug (vigabatrin, in addition to phenobarbital and carbamazepine); his distress continued and he was re-admitted to our department.

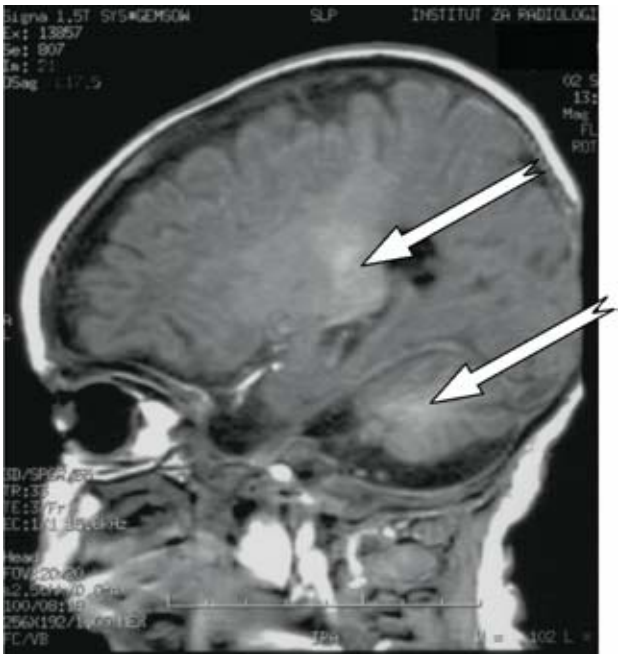
In addition to the above signs we noticed a high arched palate and a right-sided inguinal hernia. His hair was sparse, and the typical clinical appearance was not pronounced, especially not in the very early course of the disease (Figure 3). Developmental delay was prominent with truncal hypotonia and limb hypertonia. Specific MRI and MRA changes, together with distinct clinical signs, caused us to suspect a neurodegenerative disorder, and MD was then confirmed by low levels of plasma copper and ceruloplasmin. We are attempting to confirm the diagnosis by molecular genetic testing. Modification of antiepileptic therapy reduced seizures by about 50%, but erratic myoclonus and some clonic seizures persisted.

Discussion

MD is a degenerative, X-linked, recessive, multisystem disorder. So far more than 160 different mutations of the ATP7A gene on the long arm of the X chromosome close to the centromere have been described (15–17). ATP7A gene codes for a copper-binding enzyme P-type ATPase that is essential for intracellular copper transport and metabolism. The disease is also called a disorder of copper maldistribution. The reduction, complete absence, or functional impairment of this enzyme results in the accumulation of copper in the cytosol of many cells. The copper concentration is high in the gut, kidney, spleen, pancreas, muscles, and placenta, with the exception of the liver and brain, where the concentration of copper is reduced. The plasma concentration of copper is also low (15, 18).

The low concentrations (2–5%) of normal ATP-ase in blood are sufficient to permit the development of

Figure 1. Magnetic resonance imaging of the brain of a patient with Menkes disease. There is high signal intensity in the basal ganglia and cerebellum (white arrows). Wide subarachnoid space frontally and around the cerebellum with ventriculomegaly represent diffuse atrophy of the brain and cerebellum.



the milder phenotype, also called *occipital horn syndrome*, *Ehlers-Danlos type IX*, or *X-linked cutis laxa* (16, 18–20). Patients with the mild phenotype predominantly have connective tissue and bone signs. They have hyperelastic skin, hyperextensible joints, hernias, and urinary bladder diverticuli. The disease is named after skeletal abnormalities: the occipital exostoses ("horns"), which are wedge-shaped calcifications at the occipital insertion of the trapezius and sternocleidomastoid muscles.

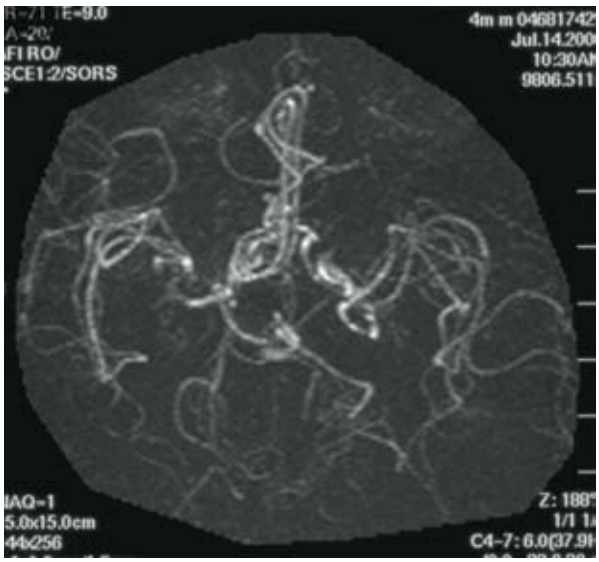


Figure 2. Magnetic resonance angiography of intracranial vessels shows the "corkscrew" appearance of elongated and tortuous cerebral vessels.

Copper is an essential trace element needed for the activity of many enzymes. The lack of copper leads to decreased activity of cytochrome C oxidase in the respiratory chain, which accounts for many neurological symptoms. The enzyme lysyl oxidase connects the collagen and elastin fibers, and reduced activity leads to fragility of connective tissue and blood vessels. The superoxide dismutase is an antioxidant enzyme in Purkinje cells. Its inactivity in MD results in profound loss of Purkinje cells. Tyrosinase is essential for melanin synthesis and its deficiency causes hair and skin hypopigmentation. The structural hair changes result from a defect in a copper-enzyme dependent cross-linkage of disulfide bonds in keratin. Ceruloplasmin is a plasma copper-transporting protein that is low in patients with MD. The reduced activity of ascorbate oxidase induces skeletal changes, as seen in scurvy. Deficiency of dopamine β-hydroxyilase is evident in abnormal plasma and CSF concentrations of catecholamines. Peptidyl-glycine α-amidating monooxygenase is required for the synthesis of neuroendocrine hormones (corticotropin-releasing hormone, thyrotropin-releasing hormone, calcitonin and vasopressin) (4–6, 15).

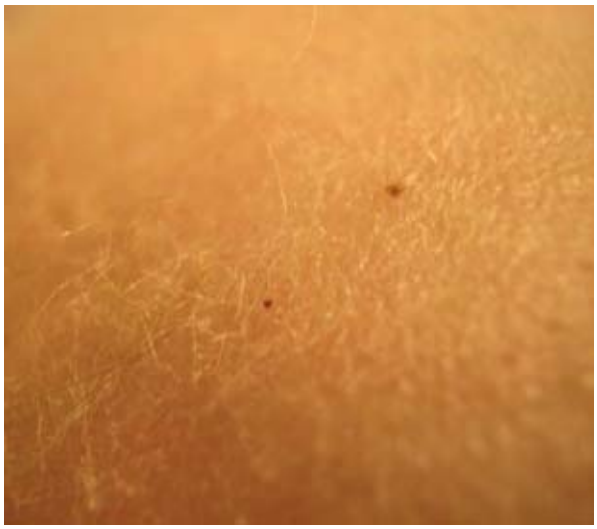


Figure 3. Abnormal, depigmented, short, sparse, and twisted hair in a patient with Menkes disease.

MD almost exclusively affects males, but there are some reports of affected females with a genetic disorder of the X chromosome (translocations among autosomes and the X chromosome, sex chromosome aneu-

ploidy, or unfavorable lyonization) (4, 21, 22). Incidence is estimated at a range of 1 per 35,000–300,000 live births; in one third of patients the disease is a consequence of *de novo* mutation (6, 15). There is no race predilection. The disease becomes evident at the age of 2 to 3 months; patients die by the time they are 3 to 4 years old usually because of pneumonia, although some patients with MD may die suddenly (4, 6, 23).

Diagnosis is suspected on the basis of the typical facial expression, characteristic appearance of the hair, and seizures. Some authors suggest a careful hair and eyebrow clinical exam in patients with delayed developmental milestones and early epilepsy without clear etiology (24). Low plasma copper and ceruloplasmin concentrations confirm the diagnosis. Because low plasma concentrations of copper and ceruloplasmin can be found in healthy children within the first weeks or even months of life, low concentrations are more meaningful after this time (15, 25). The concentrations of plasma and CSF catecholamines tend to be abnormal at all ages (4–6, 25). In the past, the final diagnosis was made by cultured skin fibroblasts and lymphoblasts, which showed impaired metabolism of copper. Today this method is being replaced by molecular genetic testing, available in certain laboratories, to confirm the diagnosis for carrier testing or for prenatal diagnosis (25). After birth we can detect increased placental copper levels (4–6).

Abnormalities can be detected by some non-specific tests such as EEG, visual-evoked potentials, electroretinogram, and brainstem evoked acoustic potentials (4–6). Imaging studies (CT in MRI) reveal white matter demyelinization, tortuous blood vessels, atrophy, and subdural hematomas. Angiography and MRA display elongated and tortuous vessels (26, 27).

Differential diagnosis includes Leigh disease (subacute necrotizing encephalomyelopathy), phenylketonuria, and certain diseases with specific hair findings (4–6). The low concentrations of copper and ceruloplasmin are, however, typical only of MD.

Oral treatment with copper salts does not change the serum copper and ceruloplasmin concentrations and there is no clinical improvement (4–6, 15). Parenteral copper chloride and copper L-histidine are currently under investigation. Some reports suggest that if parenteral treatment starts early in neonatal life, up to the 2nd month of life, it may be successful in up to 50% of cases. The clinical response to parenteral treatment is more evidently detected in neurological improvement than in connective tissue defects (28). Metaphyseal widening and spurring and periosteal thickening regress. Concentrations of serum catecholamines normalize (4–6, 28, 29). If treatment is started after the critical time of 2 months, it is not of much help to the patient (28, 29). There is a case report (4) of a boy with classic MD that was diagnosed at birth and was treated with parenteral copper from the 8th day of life up to the 4th year. He began walking at 14 months and normal neurological development followed. In 2002 he was 8 years old and was attending elementary school.

Conclusion

MD can be diagnosed on the basis of clinical signs and laboratory findings, and genetically confirmed in certain laboratories. Treatment is usually not successful, especially in sporadic cases, because it usually starts too late. Only early treatment in the neonatal age is helpful in half of the cases.

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