Neonatal Erythroderma as a First Manifestation of Menkes Disease

abstract

Menkes disease is an X-linked recessive lethal multisystemic disorder of copper metabolism. Progressive neurodegeneration, connective tissue disturbances, and peculiar kinky hair are the main manifestations. The low serum copper and ceruloplasmin suggests the diagnosis, which is confirmed by mutation analysis of the ATP7A gene. We report an exceptional presentation of classic Menkes disease with neonatal erythroderma. Genetic study revealed a deletion in exons 8 to 12 in the ATP7A gene. This study could allow pediatricians and pediatric dermatologists to diagnose the disorder as early as possible to establish prompt treatment with parenteral copper-histidine supplementation to improve prognosis. Pediatrics 2012;130:e239–e242
Menkes disease (MD; Online Mendelian Inheritance in Man number 309400), also known as kinky hair disease, is a lethal multisystemic disorder of copper metabolism. MD is inherited as an X-linked recessive trait, and as expected the majority of patients are males. MD is characterized by abnormal facies, progressive cerebral degeneration, and hair abnormalities. This syndrome results from mutations in the \textit{ATP7A} gene (Online Mendelian Inheritance in Man number 300011), which encodes a copper transporting adenosine triphosphatase that regulates intracellular copper homeostasis.

A 2-month-old boy with an atypical presentation of MD with neonatal erythroderma is reported. To our knowledge, this is the first case of neonatal erythroderma associated with MD.

**PATIENT PRESENTATION**

An 11-day-old white boy was admitted to the neonatal unit for evaluation of congenital erythroderma, sparse and brittle hair, and decreased muscle tone. The patient was born at 38 weeks of pregnancy by caesarean delivery. The parents of the patient were healthy and nonconsanguineous. Family history was remarkable because of the death of 2 maternal uncles, 1 dying during the neonatal period and the other at the age of 4 months without definitive diagnosis, the latter suffering from seizures and failure to thrive.

Physical examination revealed a generalized erythema of the skin associated with exfoliation (Fig 1A). The face was characterized by epicanthus, flattened nose, sagging ears, horizontal eyebrows, pudgy cheeks, and sparse, thin, and brittle hair. The patient was discharged from the hospital without diagnosis and pending studies.

Erythroderma improved spontaneously without treatment in 2 months (Fig 1B), but the hair abnormalities with sparse, thin, and brittle hair persisted (Fig 1C). The patient was admitted to our hospital for evaluation of truncal hypotonia, lethargy, and focal clonic seizures when he was 2 months old. Examination revealed a severe hypotonia with normal tendon reflexes, lethargy, cutis laxa, and kinky hair. EEG revealed focal status epilepticus with seizures originating in both hemispheres. MRI revealed cortical and subcortical hemorrhages at the occipital lobes. Skeletal radiograph revealed spurs of the long bones, metaphyseal widening, and wormian bones. Optical and electron microscopic study of the hair shaft was performed revealing atypical pili torti with irregular twisting (kinky hair) (Fig 2). Radiograph microanalysis of the hair did not reveal specific changes in the sulfur or copper contents.

These clinical features were suggestive of classic MD. Blood test investigations revealed decreased serum ceruloplasmin (66 mg/L; reference range: 150–450) and copper concentrations (7 μg/dL; reference range: 60–140).

Genetic study revealed a deletion in exons 8 to 12 (c.1870-?_2629+?del) in the \textit{ATP7A} gene. The MLPA analysis (SALSA MLPA kit P104-B, MRC Holland, Amsterdam, Netherlands) indicated that exons 8 to 12 were deleted. This was confirmed by multiplex polymerase chain reaction, using primer sets flanking selected exons in the same polymerase chain reaction as described previously. The same mutation was present in his mother. The resulting transcript is expected to be out of reading frame.

With the diagnosis of MD, subcutaneous copper-histidine supplementation was prescribed, but no improvement was observed. Unfortunately, the patient died at the age of 2 years due to respiratory failure in the context of bronchospasm and respiratory infection.

**DISCUSSION**

The clinical spectrum of MD encompasses several distinct variants, the classic MD being the most severe form. This disease is characterized by developmental delay, progressive neurologic degeneration, epilepsy, and hair abnormalities. MD is due to mutations in the \textit{ATP7A} gene. The abnormal gene causes a failure of copper absorption...
and its intracellular transport with subsequent accumulation of copper in the cytosol of many cells and a relative deficiency in some organs and tissues (mainly brain, liver, bones, elastin, hair, and skin). Reduced concentrations of serum copper and ceruloplasmin are the biochemical hallmark for the diagnosis. The patients are typically diagnosed at 3 to 6 months of age, often due to the association of seizures with abnormal hair, which is the striking feature of the disease. The hair is light, very fine, sparse, and fragile. Several hair shaft abnormalities have been documented, with pili torti being the most common. These abnormalities are observed by routine light microscopic examination with polarized light. Trichorrhexis nodosa, moniliform aspects of hair shaft, trichoclasis, and trichoptilosis have also been reported. The face is characterized by its hypotonia, giving a chubby-cheeked appearance (partdridge profile). Micrognathia and an ogival palate can occur. Radiologically, osteoporosis of the long bones, metaphyseal spurs, and numerous wormian bones near the lambdoid sutures are typical findings. Aneurysms can occur, leading to subdural, cerebral, or intestinal hemorrhages.

Epilepsy is a frequent and early feature in MD. Focal status epilepticus is characteristic in the early stage of the disease, followed by infantile spasms and multifocal seizures. Some authors suggest a careful hair examination in patients with delayed developmental delay and early epilepsy without clear etiology. Severely affected patients with MD usually die before the third year after birth due to central nervous system dysfunction. Copper-histidine supplementation is an effective treatment when administered soon after birth, and neurologic development can be maintained. By contrast, there is a reduced neurologic benefits when copper-histidine treatment is initiated after 2 months of age.

Our case report was typical for many clinical features of the classic MD but also presented transient neonatal erythroderma. Neonatal erythroderma is rare, and its frequency is unknown. Pruszkowski et al studied 51 infants with erythroderma in a specialized pediatric department and identified that the most frequent diagnoses (in descending order) were immunodeficiency, ichthyosis, Netherton syndrome (NS), atopic dermatitis, and psoriasis. NS has been recently classified as a type of ichthyosis. To our knowledge, MD is not considered among the possible etiologies of neonatal erythroderma in medical literature nor in textbooks of dermatology.

The etiological diagnosis of neonatal erythroderma is difficult to establish owing to the poor specificity of clinical signs. Leclerc-Mercier et al demonstrate that skin biopsy is helpful for the diagnosis of early erythroderma of infancy, especially in cases of immunodeficiency and NS. Immunostaining with LEKTI (Lymphoepithelial Kazal type related inhibitor) antibody allows the diagnosis with a sensitivity and specificity of 100% in NS.

The study of the hair shaft is helpful for diagnosis of NS, although the typical trichorrhexis invaginata often emerges after the age of 10 months. However, examination of the hair shaft is indeed necessary and helpful for early diagnosis of MD.

Definite diagnosis of MD requires the detection of mutations in the ATP7A gene. Gross ATP7A deletion is the disease-causing mutation in 14.9% of the patients with MD, resulting in the classic phenotype with death in early childhood. The deletion extended from exon 8 to exon 12 detected in our patient is in line with these results, but to our knowledge, the deletion extended from exon 8 to exon 12 is not previously described.

In our patient, the erythroderma was attributed to MD. The clinical course and laboratory findings allow us to rule out immunodeficiency, NS, and other metabolic disorders, although other causes of neonatal erythroderma were not excluded completely.

We report the association between MD and neonatal erythroderma. To our knowledge, this interesting presentation has not been previously described. Only future reports and observations will confirm if this association really exists. We propose that study of neonatal erythroderma should include serum copper and ceruloplasmin levels and light microscopy study of the hair to establish early diagnosis of MD and an early treatment with copper-histidine to maintain neurologic development. Genetic diagnosis allows us to proceed with genetic counseling for parents.
REFERENCES


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