

Menkes' disease

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Abstract

Menkes disease is linked to mutations of a gene localized on chromosome Xq13.3, ATP-7 A, coding for an intracellular copper-transporting protein. Menkes and "occipital horn syndrom are allelic. The resulting free-copper deficiency alters the functioning of copper-dependent enzymes, thereby causing the symptoms of the disorder. These include intrauterine growth retardation and progressive neurological deterioration, with appearance of axial hypotonia, spasticity, convulsions, and hypothermia within the first months of life. Gliosis leads to the development of microcephaly. Hair has a remarkable phenotype : sparse, hypopigmented, dull, twisted and brittle. Microscope examination reveals pili torti. Osteoporosis is also present. Aneurysms develop in long, tortuous vessels with irregular lumens, giving rise to subdural, cerebral and intestinal hemorrhages. The diagnosis is made based on serum (low) and fibroblasts (elevated) copper concentrations. Death usually occurs early in childhood. Various gene mutations have been detected. The disease is X-linked. Familial molecular biology studies can identify female carriers (who may have areas with affected with hair abnormalities) and affected fetuses (prenatal diagnosis may also be made by measuring copper concentrations in chorionic villi or cultured amniocytes). Treatment consists of parenteral injections of copper. When started early, treatment prevents neurological signs and survival is prolonged. The incidence of the disease is 1/300,000 births.

Keywords

Copper transport / Menkes' disease / kinky hair / pili torti / ATP 7 A gene / chromosome Xq

Name of the disease and synonyms

Menkes' disease, kinky hair syndrome or copper-transport disorder

Diagnostic criteria/definition

This disease is caused by the defective intracellular transport of copper, which results in

a deficit of free copper and gives rise to diffuse lesions (arteries, skeleton, hair, brain, etc.).

Incidence

It is around 1/300,000 live births.

Clinical description

Menkes' disease is manifested by retarded intrauterine growth that persists after birth.

The neurological deterioration is progressive: in the classical form, neurological disorders appear during the first 2 months of life: axial hypotonia and spasticity, hypothermia, partial and generalized convulsions, and feeding difficulties. Microcephaly progressively develops. The neurological disorders are attributable to the cerebral and cerebellar degeneration with gliosis.

The phenotype is remarkable by the striking characteristics of the hair: sparse, hypopigmented, dull, straight, and brittle with a tendency to break.

Under the microscope, the characteristic twisted hair (pili torti) and monilethrix can be seen.

The face is characterized by its hypotonus, giving a chubby-cheeked appearance; micrognathia; and an ogival palate.

The skin is dry, irregularly pigmented and thick.

Radiologically, one notes osteoporosis of the long bones, the presence of metaphyseal spurs and numerous wormian bones near the lambdoid sutures.

The blood vessels are tortuous and elongated, with an irregular lumen due to the abnormal development of the elastic lamina and thickening of the intima. Aneurysms can occur, leading to subdural, cerebral or intestinal hemorrhages.

The neurological deterioration is progressive and death usually occurs early during childhood.

Management and treatment

Parenterally administered copper-histidine is prescribed to correct the serum copper concentration. If this therapy is initiated before the appearance of convulsions and neurological deterioration, it may prevent them and prolong survival. However, it is unable to avoid the development of other manifestations (orthostatic hypotension, aneurysms, chronic diarrhea). The success of copper replacement therapy is variable, probably depending on mutation type.

Etiology

Menkes' disease is linked to a mutation of a gene localized on chromosome Xq13.3 and coding for a copper-transport protein, MNK, which has 6 sites for copper transport and 6-8 transmembrane domains, called Cu²⁺-transporting ATPase-alpha polypeptide (ATP 7 A). This protein travels between the Golgi apparatus and the cytoplasmic membrane,

transporting copper towards the exterior of the cell.

Mutations in the gene lead to the defective synthesis of this protein and thus the defective intestinal absorption of copper, as well as defect in supplying copper to the central nervous system.

The resulting perturbed functioning of copper-dependent enzymes - cytochrome oxidase, tyrosinase, lysyl oxidase, monoamine oxidase, ascorbate oxidase - explains the symptoms of the disease, respectively, hypothermia, depigmentation of the hair and skin, lesions in the intima of vessels, the twisted hair, the demineralization of the skeleton. The deficiency of dopamine beta-hydroxylase, also a copper-dependent enzyme, might also play a role in the symptoms of this disease.

Methods for the biological diagnosis

The diagnosis relies on the dosage of serum copper and ceruloplasmin whose concentrations are low. The copper concentration is elevated in fibroblasts and the placenta.

Diverse mutations of the gene have been found: partial deletions, splicing mutations, point mutations; 90% of the mutations culminate in the synthesis of a truncated protein.

Genetic counseling

Menkes' disease is a recessive X-linked affection. Heterozygous females are neurologically normal. They can have areas of abnormal, twisted and depigmented hair.

Biologically, in the women at risk, multiple skin biopsies are needed to demonstrate the accumulation of copper in certain zones of fibroblasts.

A molecular biological study of the family is possible and genetic counseling is usually based on polymorphism(s) identified.

Prenatal diagnosis

Prenatal diagnosis can be obtained in two ways:

- after determination of the foetal sex by sampling of maternal blood or the chorionic villi, when a male, evaluation of the accumulation of copper in the chorionic villi or cultured amniocytes; or better :
- by molecular biology if a familial study is undertaken, and/or if the mutation is found in the mother .

Non-resolved questions and comments

The occipital horn syndrome is also caused by mutations in the same *ATP 7 A* gene; the lesser severity of its clinical picture is linked to the partial conservation of the protein's activity.

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