Menkes Disease

Disorders of elastic tissue

James W. Patterson MD, FACP, FAAD, in Weedon's Skin Pathology, 2021

Menkes' Syndrome

Menkes' kinky hair syndrome (OMIM309400) is a rare multisystem disorder of elastic tissue transmitted as an X-linked recessive trait.[638–640] The defective gene*(ATP7A)* has been localized to chromosome Xq12–q13.[641,642] Characteristically, the hair is white, sparse, brittle, and kinky. It looks and feels like steel wool. Pili torti and, occasionally, monilethrix are present. Neurodegenerative changes, vascular insufficiency, hypothermia, and susceptibility to infections are other manifestations of this syndrome.[39,640] Mild forms occur.[643]

The finding of reduced serum copper levels led to the view that Menkes' syndrome was a simple copper deficiency state akin to that seen in copper-deficient sheep.[644,645] It is now thought to be due to a spectrum of mutations in the copper-transporting ATPase gene,*ATP7A*.[7] There is reduced activity of the copper-dependent enzyme lysyl oxidase in fibroblasts derived from the skin of patients with this syndrome.[646] This enzyme is necessary for the cross-linking of elastin.[4] In the past, it had been suggested that this syndrome should be reclassified with Ehlers–Danlos syndrome type IX. However, type IX is no longer included within the EDS spectrum, and cases in this category are now regarded as mild variants of Menkes syndrome or as X-linked cutis laxa (seep. 430).

Histopathology

There are various hair shaft abnormalities, including pili torti, monilethrix, and trichorrhexis nodosa.[640] The internal elastic lamina of vessels is fragmented, and there is intimal proliferation. Dermal elastic tissue appears to be unaffected.

Electron microscopy

The elastic fibers in the reticular dermis show a paucity of the central amorphous component while retaining normal microfibrillary material.[641]

S.G. Kaler, in Encyclopedia of the Neurological Sciences (Second Edition), 2014

Abstract

Menkes' disease was first described by John Menkes (as a child neurology trainee) in 1962 as an often lethal X-linked recessive condition featuring infantile neurodegeneration, seizures, failure to thrive, and connective tissue abnormalities. Early diagnosis and treatment, including gene therapy, hold promise for improved outcomes. Occipital horn syndrome is a milder allelic variant of Menkes' disease caused by leaky splice junction or hypomorphic missense mutations, which do not completely abrogate ATP7A-mediated copper transport and that largely spare the central nervous system. ATP7A-related distal motor neuropathy is a recently identified allelic variant that involves a gradual, adult-onset distal motor neuropathy resembling Charcot–Marie–Tooth disease type 2.

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Diseases of the Skin Appendages

William D. James MD, in Andrews' Diseases of the Skin, 2020

Menkes Steely (Kinky) Hair Syndrome

Pili torti and often monilethrix and trichorrhexis nodosa are all common in the hairs in this sex-linked recessively inherited disorder. It has also been called steely hair disease because the hair resembles steel wool. The characteristic ivory color of the hair appears between 1 and 5 months of age. Drowsiness, lethargy, convulsive seizures, severe neurologic deterioration, and periodic hypothermia ensue, with death at an early age. Hairs become wiry, sparse, fragile, and twisted about their long axis. Osteoporosis and dental and ocular abnormalities are common. The skin is pale and the face pudgy, and the upper lip has an exaggerated “Cupid's bow” configuration. The occipital horn syndrome, primarily a connective tissue disorder, is a milder variant of Menkes syndrome. Patients have a deficiency of serum copper and copper-dependent enzymes, resulting from mutations in the*ATP7A* gene. The gene encodes a trans–Golgi membrane–bound copper transporting P-type ATPase. Loss of this protein activity blocks the export of dietary copper from the GI tract and causes the copper deficiency. Low serum copper and ceruloplasmin levels are characteristic, but are not seen in all patients; levels are particularly variable in the first weeks of life. Other tests helpful for screening include the ratio of catechols, such as dihydroxyphenylalanine, to dihydroxyphenylglycol. High levels of the catechols dopa, dihydrophenylacetic acid, and dopamine and low levels of dihydroxyphenylglycol are characteristic. Studies of copper egress in cultured fibroblasts have also been used.

Early detection allows for genetic counseling and institution of copper histidine treatment, which has shown promising results in some infants. Pamidronate treatment is associated with an increase in bone mineral density in children with Menkes disease. In zebra fish, antisense morpholino oligonucleotides directed against the splice-site junctions of two

mutant calamity alleles were able to correct the molecular defect. Also,l-threo-dihydroxyphenylserine can correct neurochemical abnormalities in a mouse model. This is a promising area for research.

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Conditions Confused with Head Trauma

Christopher S. Greeley MD, in Child Abuse and Neglect, 2011

Menkes disease (MD) has also been reported as a potential mimic of AHT.[142,143] Menkes disease, often called Menkes kinky hair syndrome, is an X-linked recessive disease resulting from a mutation that codes a copper transport enzyme.[144] The defect results in a systemic deficit of copper and subsequent global dysfunction of copper-dependent enzymes. This most notably results in poor collagen and elastin formation. Clinical hallmarks of MD are rapid and early neurological degeneration (within months of birth), poor growth, skeletal findings, and characteristic hair (pili torti). The hair in MD is short, friable, and twisted and has poor pigment, although fetal hair is unaffected. Blood vessels are tortuous and friable and are susceptible to rupture and bleeding with routine activities. This can result in intraabdominal or intracranial hemorrhage.[142,144] The skeletal manifestations include Wormian bones and metaphyseal defects (similar to the classic metaphyseal lesions associated with child physical abuse).[145] Long bone metaphyseal findings can also resemble those found in scurvy. The combination of ICH and metaphyseal fractures can pose as findings very similar to those of AHT.

The most common ophthalmologic findings described in MD include poor visual acuity and decreased retinal and iris pigmentation. RHs have not been a described feature of "classic" MD and thus may be crucial in distinguishing this condition from AHT.[146] Testing for MD can be done by simply microscopically examining scalp hairs for the characteristic pili torti. In addition, serum copper ceruloplasmin levels will be profoundly depressed. Infants with MD also have characteristic facies, including a high-arched palate, flat central face, and hypoplastic mandibles.

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Disorders of Hair

Robert M. Kliegman MD, in Nelson Textbook of Pediatrics, 2020

Menkes Kinky Hair Syndrome (Trichopoliodystrophy)

Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal to sparse at birth but

is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Mutations in the*ATP7A* gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the 1st 2 mo of life.

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Menkes Disease and Other ATP7A Disorders

Juan M. Pascual, John H. Menkes, in Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Fifth Edition), 2015

Introduction

Menkes disease (MD), also known as kinky hair disease, is a multifocal, degenerative disease of gray matter first described in 1962 by Menkes et al.[1] Some 10 years later, Danks et al.[2,3] found that serum copper and ceruloplasmin levels were reduced and suggested that the primary defect in MD involved copper metabolism. In 1993, three groups of workers isolated the gene (*ATP7A*) whose defect is responsible for the disease and found that it encoded a transmembrane copper-transporting P-type ATPase (MNK, or *ATP7A*) and that the disease results from a widespread defect in intracellular copper transport and consequent copper maldistribution. Today, three distinct phenotypes resulting from *ATP7A* defects are recognized: MD, occipital horn syndrome (OHS), and *ATP7A*-related distal motor neuropathy.[4,5] *ATP7A* is located in the trans-Golgi network and encoded by the X chromosome, causing the progressive copper deficiency disorders—Menkes disease and occipital horn syndrome—in addition to a late-adolescence distal motor neuropathy that resembles Charcot–Marie–Tooth disease type 2 and which is not associated with copper deficiency.

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Menkes Disease and Other ATP7A-Related Phenotypes

Stephen G. Kaler, in Primer on the Autonomic Nervous System (Third Edition), 2012

Publisher Summary

Menkes disease (MD) is an inborn disorder of copper metabolism with multisystem ramifications. It is caused by defects in an X-chromosomal gene that encodes an intracellular copper-transporting ATPase, ATP7A. The newly described ATP7A-related DMN phenotype features progressive distal motor neuropathy with mild sensory loss and no central nervous system effects. The biochemical phenotype in MD involves low levels of copper in plasma, liver, and brain due to impaired intestinal absorption, reduced activities of numerous copper-dependent enzymes, and paradoxical accumulation of copper in certain tissues. Clinical features of MD conceivably attributable to DBH deficiency include temperature instability, hypoglycemia and eyelid ptosis, and autonomic abnormalities that may result from selective loss of sympathetic adrenergic function. Partial deficiency of DBH is responsible for a distinctively abnormal plasma and CSF neurochemical pattern in Menkes patients. Early diagnosis and institution of subcutaneous copper injections has been successful in about 20% of MD infants treated within the first several weeks after birth.

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Biological Aspects of Copper

Mauricio Latorre, ... Ricardo Uauy, in Clinical and Translational Perspectives on WILSON DISEASE, 2019

Menkes Disease is an X-linked recessive disorder of copper absorption due to a mutation in the *ATP7A* gene; this gene encodes a copper membrane-transporter expressed in all tissues except liver (see Chapter 43: Menkes Disease and Other Disorders Related to *ATP7A*). Mutation in *ATP7A* leads to generalized copper deficiency by a failure of copper efflux from intestine, which results in a low absorption into the blood [18]. The symptoms appear by 2 months of age and include hypothermia, neuronal degeneration, mental retardation, abnormalities in hair, bone fragility, and aortic aneurysms [19]. These clinical manifestations are attributable to a malfunction of copper-requiring enzymes such as lysyl oxidase, cytochrome *c* oxidase, and superoxide dismutase [20].

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Menkes Disease and Other Disorders Related to ATP7A

Cynthia Abou Zeid, ... Stephen G. Kaler, in Clinical and Translational Perspectives on WILSON DISEASE, 2019

Laboratory and Imaging Studies

Menkes disease is suspected in infants with a family history of male relatives showing similar symptoms or in boys with the typical neurological and skin changes. Diagnosis can be confirmed by a combination of imaging, molecular, and biochemical studies.

Imaging studies such as brain magnetic resonance imaging (MRI) show diffuse cerebral atrophy with ventricular dilation, tortuous brain vessels, and subdural hematomas. The electroencephalogram (EEG) is abnormal in a high proportion of Menkes disease patients [9–12]. Light microscopy is another helpful tool to support the diagnosis, by looking for pathognomonic pili torti changes in hair [8]. The diagnosis of Menkes disease is ultimately confirmed by the molecular analysis and sequencing of the *ATP7A* gene. This allows for identification of mutations. The response to copper treatment may depend on the *ATP7A* defect detected [19,20]. Serum copper and ceruloplasmin levels are typically low in patients with Menkes disease. However, before 2 months of age, serum copper levels in affected males overlap with those of normal infants, since serum copper levels are physiologically low at that age. Therefore, screening of at-risk newborns is based on plasma (and/or cerebrospinal fluid) levels of neurochemicals influenced by dopamine-β-hydroxylase function [18,19]. When the activity of this enzyme is diminished due to ATP7A dysfunction, accumulation of proximal metabolites [that is, dihydroxyphenylacetic (DOPAC) acid and dopamine] along with decreases in the distal reaction products [dihydroxyphenylglycol (DHPG) and norepinephrine] is distinctive. Therefore, in newborns with Menkes disease, the ratios of DOPAC to DHPG and dopamine to norepinephrine are greatly elevated in comparison to healthy infants [19]. Measuring blood catecholamines and calculating these ratios are the current practice used for newborn screening of at-risk newborns in the presymptomatic stage [19]. Eventually, population-based newborn screening may be feasible based on molecular or biochemical analysis of newborn dried blood spots.

The Cerebellum: Disorders and Treatment

Ginevra Zanni, Enrico Bertini, in Handbook of Clinical Neurology, 2018

Menkes syndrome (MIM#309400)

Menkes disease is an X-linked recessive neurodegenerative disorder caused by mutations in *ATP7A*, a copper-transport ATPase (Chelly et al., 1993; Mercer et al., 1993; Vulpe et al., 1993). In the classic form of Menkes disease, patients have severe neurodegeneration, leading to death by 3 years of age. They develop little or no motor skills, do not acquire language skills, and many experience seizures. Affected individuals also manifest kinky, steel-colored hair, and tortuous blood vessels. Biochemical markers of the disease include low serum levels of copper and ceruloplasmin, and altered cerebrospinal fluid catechol levels.

Complete loss-of-function mutations in *ATP7A* result in Menkes disease, whereas less severe defects produce the allelic disorder, occipital horn syndrome. The latter phenotype involves mainly complications associated with connective tissue, including skin and joint laxity, tortuous blood vessels, and hernias. These individuals may also have dysautonomia, related

to reduced activity of dopamine-β hydroxylase, a copper-dependent enzyme. However, they show normal or only mildly delayed cognitive abilities, rather than the hallmark neurodegeneration associated with Menkes disease.

In a family of Hispanic descent with three affected brothers showing cerebellar hypoplasia, delayed motor milestones, and mild intellectual disability, a splice site mutation of *ATP7A* resulting in reduced gene and protein expression was identified (Donsante et al., 2007).

In a family with isolated X-linked ataxia and cerebellar atrophy, Protasova et al. (2016) detected a deletion of *ATP7A* in addition to a missense mutation in *ABCB7* (see Chapter 10).

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