

Case Reports

Menkes' Kinky Hair Disease: New Considerations

Madhulika Kabra
Arun K. Gangakhedkar
Gauri Rao Pasi
Rohit Manoj
I.C. Verma

Kinky hair disease (KHD) was first described by Menkes *et al.*(1). Ten years later Danks *et al.* suggested that the primary defect is in copper transport leading to copper deficiency(2). It is a X-linked recessive disorder. The gene for KHD is about 200 kb in size and is located on the long arm of X chromosome (Xq13.3). The cDNA has been recently sequenced and is known to code for a protein of 1500 amino acids(3).

The incidence of KHD has been estimated to be around 1-2 per 100,000 live male births(4). There is only one published report from India(5); We describe two cases of KHD, emphasizing clinical diagnosis and report exciting recent developments in the diagnosis and treatment of the disorder.

From the Genetics Unit, Department of Pediatrics, W.H.O. Collaborating Center in Genetics, All India Institute of Medical Sciences, New Delhi 110 029.

Reprint requests: Professor I.C. Verma, Genetics Unit, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029.

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Case Reports

Case 1: A 9-month-old boy was evaluated for developmental delay and seizures. He was born to a second gravida mother married non-consanguineously. There was no history of birth asphyxia. Seizures commenced at four months of age, which were initially focal and then became myoclonic. The boy had not achieved head holding or social smile.

On examination the child was fair colored with chubby cheeks, sparse and brittle hair and eyebrows (*Fig. 1a*). His weight was 7 Kg (<5th centile NCHS), length 72 cm (50th.centile NCHS) and head circumference 46.8 cm (75th-90th centile NCHS). Anterior fontanel was wide but bot bulging. There was generalized hypotonia, although the deep tendon reflexes were brisk. Funus showed early papilledema. There was no organomegaly. CSF examination was normal.

Investigations revealed a normal hemogram, liver and renal functions, serum calcium, serum ammonia, arterial blood gas analysis, urine and plasma amino acids and absence of reducing substances in the urine. Serum copper was 3.6 µg/ dl (normal 70-140 µg/dl) and serum ceruloplasmin was 152.8 mg/dl (normal 197-257 mg/dl). Skeletal survey was normal. EEG was abnormal showing right sided spike and wave discharges. CT scan showed bilateral subdural collections suggestive of hematomas with cerebral atrophy. Hair microscopy showed *pili torti* and monilithrix (*Fig. 2*).

The characteristic facies and hair changes suggested a diagnosis of Menkes KHD, which was confirmed on the laboratory

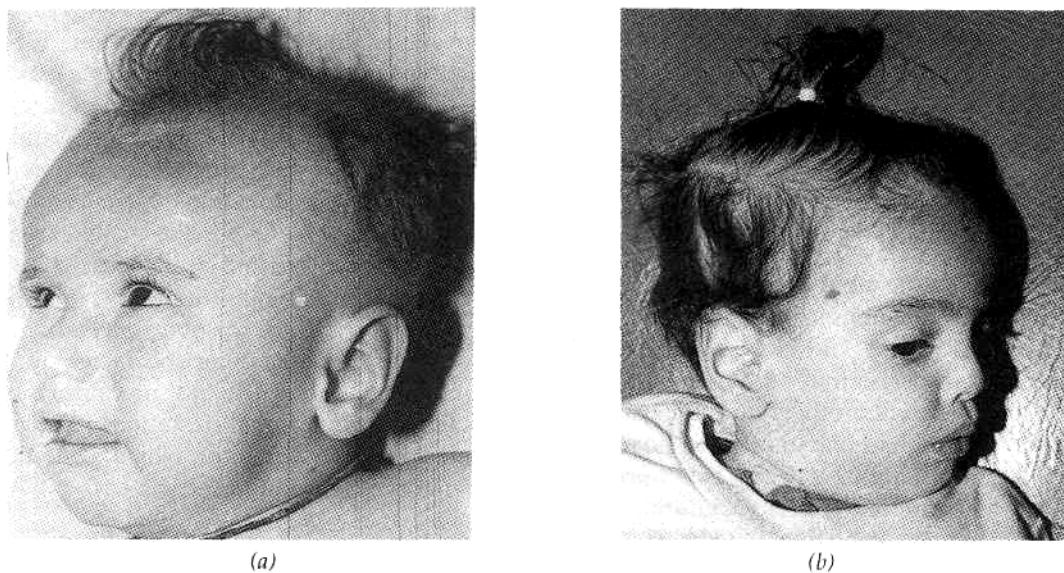


Fig. 1. Clinical photographs of Case 1 (Fig. 1a) and Case 2 (Fig. 1b) hair and eyebrows, chubby appearance of cheeks and fair color.

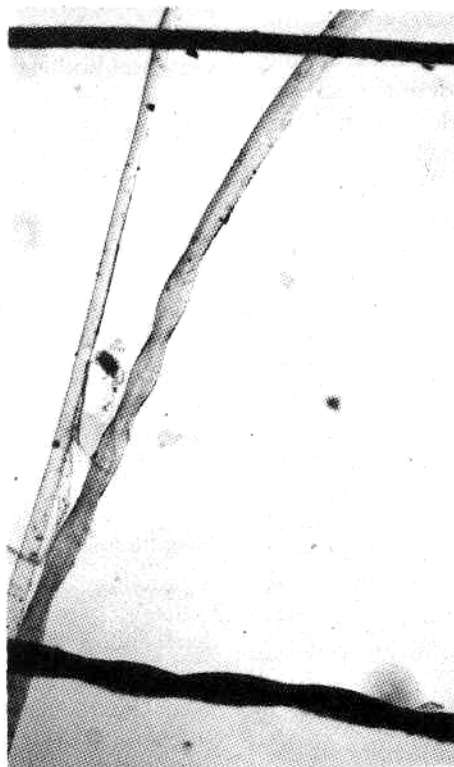


Fig. 2. Microscopic appearance of the hair showing monilithrix and pili torti.

tests. He was given symptomatic treatment. On follow up the condition of the baby deteriorated and he expired at one and half year of age.

Case 2: A six-month-old boy born to non-consanguineous parents presented with developmental delay. There was a family history of one male sib dying at the age of 1.5 years with developmental delay and seizures, most likely due to Menkes disease. There was one normal sister. The mother had one normal brother, and two sisters each of whom had one unaffected boy, and two normal daughters. Baby was born by lower segment cesarean section and there was no history of birth asphyxia. The boy had achieved social smile at four months and had partial neck holding at age 6 months.

His weight was 6 Kg (<5th centile NCHS), length 65 cm (10th-25th centile NCHS) and head circumference 43 cm (25th-50th centile NCHS). He had fair skin, light colored irides, pudgy cheeks, coarse depigmented hair (*Fig. 1b*). There was no organomegaly. He was hypotonic. Photograph of the previous male sib showed a similar face and hair.

A neuro-metabolic work-up was normal. Serum ceruloplasmin level was 89 mg/dl (normal range 230-330 mg/dl) and serum copper was 48 (µg/dl (normal 70-140 µg/dl)). Hair microscopy showed pili torti. EEG and skeletal survey were normal. A non-contrast CT scan of brain showed prominent sulci and foliae of cerebral and cerebellar hemispheres, respectively; mega cisterna magna and prominent basal cisterns, suggestive of global brain atrophy.

Discussion

There is considerable variability in the severity of the clinical features(6). In the classic form hypothermia and poor feeding are observed in the neonatal period,

followed by seizures. Fades are characteristic with cherubic appearance and reduced facial movements(7). There is hypotonia and poor head control with progressive deterioration of neurologic functions. Hairs are discolored and friable. Under the microscope the hair appear twisted (pili torti), hair shafts vary in diameter (monilithrix) and are fractured (trichorhexis nodosa)(1). Both of our cases had characteristic facies and hair changes (pili torti and monilithrix). *Table I* shows clinical manifestations related to defects in the enzymes which contain copper and other manifestations of the disease.

In our cases radiographs of long bones and skull were normal. Radiologically long bones may show osteoporosis, metaphyseal spurring, periosteal reaction and scalloping of the posterior aspects of the vertebral bodies(8,9). Cerebral and systemic arteries are elongated and tortuous on arteriography although these are best visualized by magnetic imaging

TABLE I-Clinical Manifestations of Menkes Disease Related to Defective Copper Containing Enzymes.

Manifestations	Affected-enzyme
Depigmented hair, skin pallor	Tyrosinase
Frayed and split arterial intima, (defect in elastin and collagen cross linking)	Lysyl-oxidase
Kinky hair	Monoamine oxidase
Hypothermia	Cytochrome oxidase
Skeletal demineralization	Ascorbate oxidase
Expressionless face, full cheeks, mental retardation, feeding problems, dry skin, seizures, short stature, sparse hair/ alopecia	Multiple enzymes

(9). Neuro-imaging frequently shows cerebral atrophy, subdural effusions, as was seen in one of our case. EEG generally shows abnormalities.

Mean age at death is about 19 months. Milder forms of the disorder exist, in which child may be normal till first or second year of life. Common symptoms include ataxia, mild mental retardation or extrapyramidal movement disorders. Occipital horn syndrome is also considered to be a milder variety, and is probably allelic with KHD(IO).

Normally serum ceruloplasmin and copper are low in the neonatal period and do not reach the adult levels until one or two months of age. For diagnosis, these tests may be done serially to show the failure of the expected rise(4). The diagnosis is best confirmed by copper measurements in the tissues and 64 Cu uptake studies in the cultured fibroblasts(4,6).

Treatment of KHD remains unsatisfactory. Oral or parenteral therapy with copper salts has not been convincingly effective. Copper histidinate has been used for parenteral therapy because it crosses the blood brain barrier. Histidine has been shown to enhance the uptake of copper in human trophoblast cells in the presence of serum, a phenomenon considered to be due to release of copper that is bound to albumin(1). Recently an affected boy treated with copper histidine from infancy has been reported to have developed normally upto age 14 years(12). Copper histidine therapy should be given in all cases diagnosed early. Ethambutol, an antitubercular drug has also been tried with oral copper. Metabolites of ethambutol chelate zinc which reduces cellular metalothionine and makes more copper available for copper dependent enzymes(6). Prenatal diagnosis is possible by doing copper binding studies on amniotic fluid cells (4,13) by demonstrating increased copper content of chori-onic villi in the first trimester or by DNA studies(13). This option should be provided to all couples.

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