Short Communication

Menkes disease and response to copper histidine: An Indian case series

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Abstract

Background: Menkes disease (MD) is an X-linked recessive neurodegenerative disorder caused by mutations in *ATP7A* gene. Depending on the residual *ATP7A* activity, manifestation may be classical MD, occipital horn syndrome, or distal motor neuropathy. Neurological sparing is expected in female carriers. However, on rare occasions, females may manifest with classical clinical phenotype due to skewed X-chromosome inactivation, X-autosome translocation, and XO genotype. Here, we describe a small series of probands with MD and their response to copper histidine therapy. This series also includes a female with X-13 translocation manifesting neurological symptoms. **Methods:** The clinical profile, laboratory and radiological data, and follow-up of four children with MD were collected from the hospital database and are being presented. **Results:** All the four children in our series had developmental delay, recurrent respiratory tract infections, hair and skeletal changes, axial hypotonia, tortuous vessels on imaging, low serum copper, ceruloplasmin, and elevated lactate. Fetal hypokinesia and fetal growth retardation were present in two cases. Failure to thrive was present in three children and only one child had epilepsy. Subcutaneous copper histidine was administered to all children. The average time lapse in the initiation of treatment was 20.3 months, and average duration of follow-up was 14.3 months. **Conclusion:** We conclude that copper histidine therapy is beneficial in reversing the skin and hair changes, improving appendicular tone, socio-cognitive milestones, and improving weight gain, and immunity. Early diagnosis and management of MD are essential to have a better clinical outcome. More research is needed to explore and devise new strategies in the management of patients with MD.

Key Words

ATP7A, copper histidine, Menkes disease, X-linked recessive

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Ann Indian Acad Neurol 2017;20:62-68

Introduction

Menkes disease (MD), described by John Menkes in 1962, is an X-linked recessive neurodegenerative disorder with copper transport defect.[1] MD is caused by pathogenic variants in *ATP7A* gene coding for a copper transporting ATPase, located at Xq21.1. Mutations can result in classical MD, occipital horn syndrome, and distal motor neuropathy depending on the residual *ATP7A* activity. In this report, we describe the clinical profile, laboratory and radiological findings of a series of patients with MD and their response to copper histidine therapy.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.199907

Methods

The clinical profile, laboratory and radiological data of four children with MD were collected from the hospital database. Informed consent for the clinical photograph was obtained from the parent. Case history, diagnosis, management, and follow-up of four children with MD are briefly discussed below.

How to cite this article: Yoganathan S, Sudhakar SV, Arunachal G, Thomas M, Subramanian A, George R, *et al.* Menkes disease and response to copper histidine: An Indian case series. Ann Indian Acad Neurol 2017;20:62-8.

Received: 21-06-16, **Revised:** 08-08-16, **Accepted:** 04-09-16

Patient 1

A 22-month-old girl was brought with concerns of delay in attaining milestones. Mother's antenatal period was complicated by hyperemesis gravidarum and urosepsis. The baby was delivered full term by caesarean section due to breech presentation. Birth weight was 1800 g and baby had feeding difficulty from early neonatal period. Later, she had developed abdominal distension and multiple episodes of vomiting and was managed as presumptive sepsis. Sparse hypopigmented scalp hair and hypotonia were observed. She had recurrent respiratory tract infections requiring frequent antibiotic therapy. She had only a partial head control at 1 year of age, but she could reach for toys, wave bye-bye, and speak single word with meaning. She was brought to our center at 22 months of age for detailed evaluation of developmental delay and recurrent vomiting.

Anthropometric assessment revealed weight of 6.2 kg and length of 73 cm. Both weight and length were less than third centile, and her head circumference was 49.5 cm (97th centile). Frontal bossing and biparietal prominence were also observed. She had sparse, wooly, hypopigmented scalp hair [Figure 1a] and hyperlaxity of joints. She was alert and active and was interacting with the parents. Hypotonia with diminished deep tendon reflexes was observed.

Possibilities of copper transport defect, biotinidase deficiency, and trichothiodystrophy were considered. Laboratory investigations of this child are listed in Table 1. Hair microscopy had shown pili torti and trichorrhexis invaginata. Magnetic resonance imaging (MRI) of the brain had shown tortuous vessels with mild cerebellar and cortical atrophy [Figure 2a-d]. Barium swallow had shown gastroesophageal reflux up to the carina. Chromosomal analysis by G-banding revealed an abnormal karyotype 46,X,t(X;13)(q21;p11)[20] in all the 20 metaphases analyzed. Parental chromosomal analysis by G-banding did not identify any abnormalities.

Based on the clinical phenotype, karyotype abnormality, and laboratory parameters, female manifesting MD was diagnosed. She was treated with oral domperidone and lansoprazole for gastroesophageal reflux disease. MD was managed with subcutaneous copper histidine therapy at a dose of 125 mcg once daily for 1 week, 125 mcg twice daily for next week, and then 250 mcg once daily.

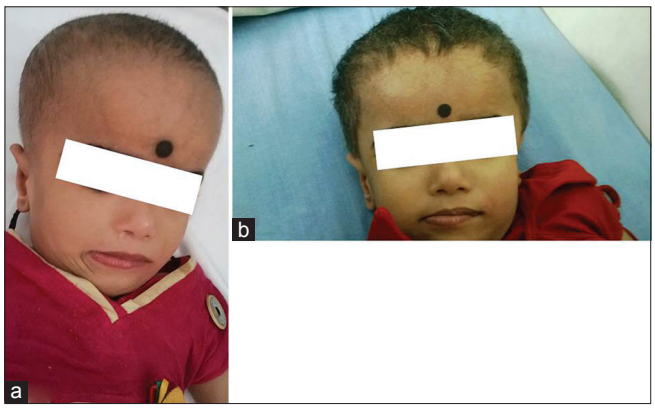

Figure 1: Clinical photograph of a female manifesting Menkes disease before (a) and after treatment (b) with copper histidine therapy. (a) Show frontal bossing, sparse wooly hypopigmented scalp hair. (b) Show increased hair growth and pigmentation of scalp hair

Follow-up assessment at 6 months and 1 year had revealed a significant improvement in growth and pigmentation of scalp hair [Figure 1b], appendicular muscle tone, gain in socio-adaptive milestones, feed tolerance, weight gain, reduction in recurrent respiratory tract infections, and rise in serum copper and ceruloplasmin [Table 2].

Patient 2

A 2-month-old boy, younger of the twins, born to a non-consanguineously married couple was referred to our institution for the evaluation and management of refractory seizures. Mother had conceived after an intrauterine insemination. She had conceived triplets, and fetal reduction was done by the treating obstetrician at the 12th week of gestation. Fetal hypokinesia was reported from 35 weeks of gestation. Baby was delivered full term by elective caesarean section with a birth weight of 2050 g. His skin and hair were light colored. He had lethargy and refusal of feeds from the 2nd day of life. Hypoglycemia and hyperbilirubinemia were managed appropriately in a neonatal intensive care unit. Floppiness and poor sucking were noticed from the early neonatal period. At 2 months of age, there were no developmental gains except for startle response to loud sounds. There were multiple brief episodes of eye blinking with vacant stare and also multifocal clonic seizures from the 15th day of life.

His length was 61 cm (50–97th centile) while head circumference (36.2 cm) and weight (3540 g) were <3rd centile. He had sparse, hypopigmented scalp hair, prominent ridging of sutures, pudgy cheeks, hyperlaxity of joints, and fair complexion. There was no visual fixation or following to light. Profound axial and appendicular hypotonia were observed. Muscle stretch reflexes were brisk.

Diagnosis of MD was established based on the findings summarized in Table 1. MRI of the brain and skeletal findings are shown in Figures 2a-d and 3a, b. He was initiated on copper histidine treatment from the 2nd month of age and dosage was gradually stepped up to 250 mcg twice daily. Major motor seizures were controlled after 2 months. However, he had developed multiple myoclonic jerks per day which were partially controlled after optimizing the doses of antiepileptic medications. He had poor oropharyngeal coordination resulting in recurrent aspiration and respiratory tract infections. Nasogastric feeds were initiated to minimize the risk of aspiration. Follow-up assessment after 12 months is summarized in Table 2. He had minimal neck control, social smile, visual fixation to toys, and he could make cooing sounds during this neurodevelopmental assessment.

Patient 3

A 13-month-old boy born second in birth order was brought for the evaluation of developmental delay. Mother had perceived quickening from 7th month of gestation. Baby was delivered full term by vaginal delivery with a birth weight of 3000 g. Baby had respiratory distress and feeding difficulty in the form of suck-pause-suck cycle from the 1st day of life. He had partial neck control, midline hand regard, babbling, and

Table 1: Baseline clinical, laboratory and imaging findings of children with Menkes disease

Features	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Male	Male	Male
Age at onset of symptoms	Birth	Birth	Birth	Birth
Age at presentation to our center	22 months	2 months	13 months	Neonatal period
Hair changes	+++	+++	+++	+
Fair skin complexion	+	+++	+++	-
Fetal hypokinesia	+	+	-	-
Prenatal growth retardation	+	+	-	-
Failure to thrive	+	+	-	+
Axial hypotonia	+++	+++	+++	+++
Appendicular hypotonia	+++	+++	-	-
Microcephaly	+	+	+	+
Recurrent respiratory tract infections	+	+	+	+
Autonomic symptoms	-	-	-	-
Copper (μg%)	16	8	24	14
Ceruloplasmin (U/L)	133	<45	85	90
Hb (gm/dL)	12.7	12.1	12	12.3
Lactate (mmol/L)	2.3	3.7	5.6	4.7
Liver enzymes	Normal	Normal	Normal	Normal
Skeletal changes	Mild diffuse osteopenia	Metaphyseal widening of the radius and ulna Mildly prominent anterior ends of ribs	Atlantoaxial dislocation with anterior atlantodental interval of 5.7 mm	Osteopenia
MRI of the brain findings	Tortuosity of anterior and posterior vasculature Diffuse cerebellar and cerebral volume loss Periventricular and deep white matter hyperintensity	Mildly tortuous vessels Cerebellar volume loss Delay in myelination	Marked tortuosity of the anterior and posterior vessels Significant hypomyelination	Markedly tortuous vessels Mild cerebellar volume loss Callosal thinning Hypomyelination
Time of initiation of definitive therapy (months)	28	2	13	38
Ultrasound abdomen and pelvis	Normal	Normal	Normal	Normal
Copper histidine therapy	Yes	Yes	Yes	Yes
Compliance with therapy	Yes	Yes	Yes	No

Normal laboratory range for serum copper (μg%) = 70-170, serum ceruloplasmin (U/L) = 200-1110, and blood lactate (mmol/L) = 0.3-1.3. + = Present, - = Absent, +++ = Profound/severe, MRI = Magnetic resonance imaging

Table 2: Post-treatment clinical, laboratory and imaging findings of children with Menkes disease

Post-treatment	Patient 1	Patient 2	Patient 3
Follow-up duration (months)	17	15	11
Pigmentation of hair	Yes	Yes	Yes
Change in skin complexion	Yes	Yes	Yes
Motor development	Minimal gain	Minimal gain	Minimal gain
Socio-cognitive skills gain	Yes	Yes	Yes
Tone changes	Appendicular tone improved	Appendicular tone improved	No change
Seizure control	NA	90% reduction in the frequency of myoclonus	NA
Feeding difficulty	-	+++	-
Weight gain	+	+	+
Recurrent respiratory infection	-	+++	-
Copper (μg %)	72	62	60
Ceruloplasmin (U/L)	497	415	-
Recruitment of symptoms while on copper histidine therapy	Mild generalized dystonia	None	None

Normal laboratory range for serum copper (μg%) = 70-170 and serum ceruloplasmin (U/L) = 200-1110. + = Present, - = Absent, +++ = Profound/severe, NA = Not applicable

social smile by 12 months of age. Visual tracking to light and auditory localization were present. Floppiness of limbs, fair skin complexion, and sparse hypopigmented scalp hair were noticed since birth. He was placed on liquid feeds as he had

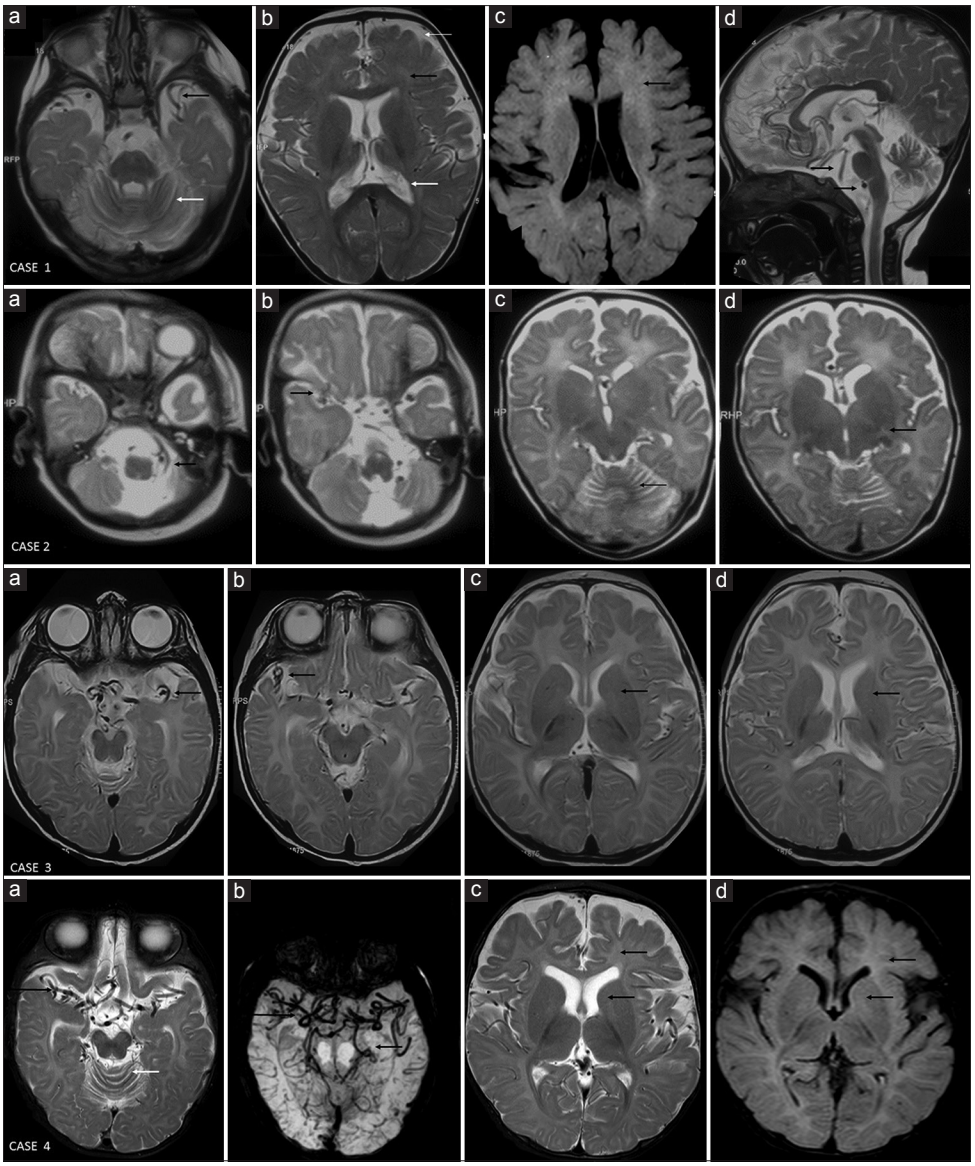

Figure 2: (a-d) Magnetic resonance imaging of the brain findings in our series of patients with Menkes disease. Case 1 (a-d): Magnetic resonance imaging of the brain at 14 months - T2 axial image (a) shows cerebellar volume loss (white arrow) and tortuous middle cerebral arteries (black arrow). Posterior vasculature also appears tortuous (black arrows in d). T2 axial and T2 FLAIR images (b and c) shows abnormal myelination (black arrows) and cerebral volume loss as evidenced by ventricular and anterior subarachnoid space prominence (white arrows in b). Case 2 (a-d): Magnetic resonance imaging of the brain at 2 months - T2 axial images show tortuosity of posterior (black arrow in a) and anterior vasculature (black arrow in b), cerebellar volume loss (black arrow in c), and delayed myelination of posterior limb of internal capsule (black arrow in d) corresponding to appearance at birth. Case 3 (a-d): Magnetic resonance imaging of the brain at 8 months - T2 axial images showing marked tortuosity of the anterior vessels (black arrows in a and b). Delayed myelination corresponding to <6 months was observed (black arrow in c and d) in view of absent myelination of anterior limb of internal capsule. Case 4 (a-d): Magnetic resonance imaging of the brain at 9 months - T2 axial images (a) and susceptibility weighted imaging (b) show markedly tortuous anterior and posterior vessels (black arrows). Mild superior cerebellar volume loss is also seen (white arrow in a). T2 axial (c) and T2 FLAIR (d) images show features of hypomyelination with absent myelination of anterior limb of internal capsule and increased signal of deep white matter (black arrows)

difficulty in swallowing solid feeds. He had recurrent upper respiratory tract infections.

His weight was 9 kg (3rd–50th centile), length was 80 cm (50–97th centile), and head circumference was 41.5 cm (<3rd centile). He had sparse hypopigmented wiry hair, fair skin complexion, pudgy cheeks, perianal eczematous dermatitis, and loss of subcutaneous fat. There was no eruption of primary dentition. The child had good eye contact, but there was no interaction with the parents. Visual fixation and following to light were present. Spasticity involving all four limbs was observed. Bilateral cortical thumbs, tendo achilles contractures, asymmetric tonic neck reflex and brisk deep tendon reflexes with bilateral ankle clonus were observed.

MRI of the brain and skeletal findings are shown in Figures 2a-d and 3c. Diagnosis of MD was established based

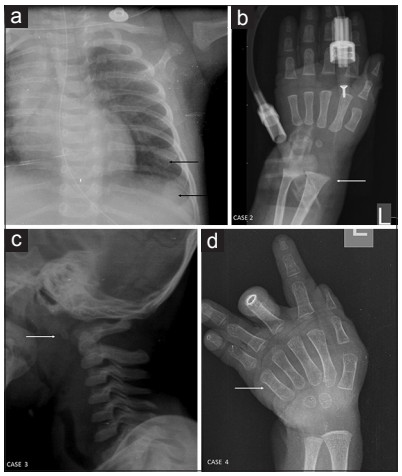

Figure 3: (a-d) Skeletal findings in our series of patients with Menkes disease. Chest radiograph (a) of Case 2 shows prominence of anterior ends of ribs (black arrows). Hand radiograph (b) of Case 2 shows mild metaphyseal flaring of both radius and ulna (white arrow). Lateral cervical spine radiograph of Case 3 (c) shows atlantoaxial dislocation (white arrow) with anterior atlantodental interval measuring 5.8 mm. Hand radiograph of Case 4 (d) shows diffuse osteopenia (white arrow)

on the findings summarized in Table 1. He was initiated on copper histidine therapy, and follow-up assessment is summarized in Table 2. He had shown a significant improvement in socio-adaptive skills with only minimal improvement in motor skills.

Patient 4

A 38-month-old child was born second in birth order to a non-consanguineously married couple was brought with a history of delay in attaining milestones. Mother had antepartum hemorrhage, and the baby was delivered by an emergency caesarean section at 36 weeks of gestation with a birth weight of 2330 g. He had neonatal jaundice and was treated with phototherapy. He had recurrent lower respiratory tract infections and stiffness of all four limbs. There was no head control, midline hand regard, or social smile at 3 years of age but he could make cooing sounds.

His head circumference was 43 cm, height was 72 cm, and weight was 6360 g (all below 3rd centiles). He had sparse hair with coarse texture, pili torti, perianal dermatitis, high arched palate, open mouth, gingival prominence, cutis laxa, profound axial hypotonia, and appendicular hypertonia with brisk muscle stretch reflexes. This child had no eye contact and he was not interacting with the parents.

Diagnosis was based on the findings summarized in Table 1. MRI of the brain findings and skeletal changes are shown in Figure 2a-d and 3d. Mutation analysis by Sanger sequencing of *ATP7A* gene revealed hemizygous substitution of single nucleotide in exon 13 at position c.2686C>T [genomic coordinate-X:78020303, hg38 build; Transcript ID ENST00000341514] leading to the substitution of amino acid glutamine by a stop codon, p.Q896Ter. This substitution of glutamine by premature stop codon has been previously reported and is a recognized cause of the disorder with HGMD ID-CM970131. Child was initiated on treatment with copper histidine but the parents had discontinued the copper histidine injections after 6 weeks.

Discussion

The pathophysiology of MD was reported by David Danks in 1970.[2] *ATP7B* is expressed in liver whereas *ATP7A* is expressed in all organs except liver. Up to 170 different mutations have been identified in *ATP7A* gene. Incidence of MD has been reported to vary from 1:50,000 to 1:360,000.[3,4] There is a defect in the functioning of cuproenzymes such as cytochrome oxidase, tyrosinase, superoxide dismutase, dopamine beta hydroxylase, lysyl oxidase, and sulfhydryl oxidase in children with MD. As a result, cellular metabolism, free radical scavenging, pigment formation, catecholamine production, and cross-linking of collagen, elastin, and keratin are impaired.[5]

Neurological sparing is expected in female carriers. Females may manifest the disease in cases of Turner syndrome, X-Autosome translocation, and unfavorably skewed X inactivation.[6-9] First case of our series had balanced X-autosome translocation 46,X,t(X;13)(q21;p11)[20] manifesting with classical MD. As expected by usual patterns of X inactivation observed in the majority of X-autosome balanced translocations, the X homolog involved in the X-autosome translocation which has an intact XIC at Xq13 (X-inactivation center) remains active, and the normal X chromosome gets inactivated. Although the karyotype appears balanced, we presume that the breakpoint region at Xq21 has disrupted *ATP7A* gene. It is likely that the normal X is inactivated, and the translocated X with the disrupted *ATP7A* gene is active, resulting in deficient ATP7A protein to explain the manifesting carrier status.

All the four children had developmental delay, recurrent respiratory tract infection, hair changes, axial hypotonia, osteopenia, tortuous vessels on imaging, low serum copper, ceruloplasmin, and elevated lactate levels. Fetal hypokinesia and fetal growth retardation were reported in Cases 1 and 2. Failure to thrive was present in Cases 1, 2, and 4 and epilepsy was present in only Case 2. Grade II spasticity was observed in Cases 3 and 4.

Defect in the functioning of various cuproenzymes could possibly explain the various clinical manifestations observed in our cases. High arched palate, tortuous vessels, loose skin, hyperlaxity of joints, and skeletal changes might result from the defective functioning of lysyl oxidase. Hypotonia and elevated lactate may be related to defective functioning of cytochrome oxidase. Hypopigmented hair and skin result from the defect in functioning of tyrosinase while abnormal hair and dry skin result from impaired functioning of sulfhydryl oxidase. Extrapyramidal symptom in Case 1 and seizures in Case 2 may be due to lack of functioning dopamine β-hydroxylase and peptidylglycine α-amidating monooxygenase, respectively. Susceptibility to infection results from impaired activity of superoxide dismutase. Anemia was not observed in any of our patients although expected to occur as a result of decreased ceruloplasmin and hephaestin.

Excessive tortuosity of the cerebral and extracranial systemic arteries, poor myelination, cerebral atrophy with subdural hygromas, and hematomas has been reported in patients with

MD. Transient bilateral temporal lobe white matter signal changes and infarct-like lesions may be seen early in the course. MD shows distinct but nonpathognomonic skeletal changes resembling scurvy, rickets, and nonaccidental trauma. Multiple Wormian bones, metaphyseal flaring, flaring of anterior ends of ribs, epiphyseal fragmentation, expansion of lateral clavicles, small mandible, posterior vertebral scalloping, and posterior vertebral defects result from bone dysplasia.[10] Osteopenia with increased fracture incidence, metaphyseal cupping, and corner fractures can be attributed to weakening of bone. Atlantoaxial dislocation seen in our case is an uncommon finding and could be related to ligamentous laxity.

Subcutaneous administration of copper histidine is the recommended treatment despite the lack of definitive cure in all patients. Oral copper therapy is ineffective as it gets trapped in the intestine and unavailable for utilization. Favorable results from copper histidine therapy have been reported in the literature.[11-13] Dosage of copper histidine used in the treatment of MD varies from 200 to 1000 μg/day.[14] Life expectancy in untreated children with MD is <3 years. Progression of disease and fatal outcome have been reported even after the initiation of treatment.[15] Although gains of myelination and neurodevelopment have been reported with copper histidine therapy, it was not beneficial for skeletal changes. Copper histidine therapy in our patients was beneficial in improving appendicular tone, socio-cognitive milestones, and hair pigmentation and reducing the susceptibility to infection with appropriate weight gain. There was no convincing improvement in axial tone or motor milestones in our patients and feed intolerance persisted in Case 2. This could possibly because of delay in the initiation of treatment due to the initial lack of availability of copper histidine, vulnerability of the developing brain during the critical period of myelination, and failure to revert the function of lysyl oxidase. Probable lack of residual activity of *ATP7A* in Case 2 can explain the severe phenotype with persistent seizures and feed intolerance. A recent clinical trial had concluded that the success of treatment outcome in MD depends on the time of initiation of treatment and severity of *ATP7A* mutation that determines the capacity of copper transport in the affected children.[16]

To the best of our knowledge, this is the first report of a female with MD treated with copper histidine from India, and we have observed only a partial response with no major gain in motor milestones. None of our children had any adverse effects related to copper histidine therapy. As the brain myelination completes by 24 months and with expected risk of nephrotoxicity due to prolonged copper histidine therapy, the desired duration of treatment should not be more than 3 years.[11] Disulfiram has also been tried in patients with MD without much benefit.[17]

Conclusion

Early diagnosis and management of MD are essential to have a better clinical outcome. We conclude that copper histidine therapy is beneficial in reversing the skin and hair changes, improving appendicular tone, socio-cognitive milestones, improved weight gain, and immunity. More research is needed to explore and devise new strategies in the management of patients with MD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment

We acknowledge Vivi Srivastava, Professor of Cytogenetics who helped in performing karyotyping in one of our patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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