

Menkes Disease in Affected Females: The Clinical Disease Spectrum

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Menkes disease (MD; OMIM 309400) is an X-linked, neurodegenerative disorder resulting from deficient activity of copper-dependent enzymes and caused by alterations in the *ATP7A* gene. In its classic form, it manifests in boys with hypotonia, seizures, skin and joint laxity, hair twisting (*pili torti*), cerebrovascular tortuosity, and bladder diverticulae. Menkes disease phenotypes have been reported in females with X; autosome translocations-disrupting *ATP7A* gene function- or *ATP7A* gene alterations. Those females manifest variable clinical findings, some of which, such as *pili torti*, seizure presence and/or age of onset, cerebrovascular tortuosity, degree of intellectual disability, and bladder diverticulae are largely under-reported and under-studied. Here, we report on three females with Menkes disease and variant phenotypes, sharing characteristic features, one with classic Menkes disease and two with Menkes disease variants. We conclude that Menkes disease in females manifests with a variable spectrum of clinical findings but a few are uniformly present such as neurodevelopmental disability, hypotonia, and connective tissue findings. Others, such as seizures, cerebral atrophy, and cerebrovascular tortuosity may be present but are under-reported and under-studied. We propose that the diagnosis of Menkes disease or variants in females with suspicious clinical findings is an important one to consider as early treatment with parenteral copper may be considered. The effect of this treatment on the disease course in females with MD is unknown and remains to be seen. © 2014 Wiley Periodicals, Inc.

Key words: Menkes disease; Menkes syndrome; *ATP7A*; kinky hair syndrome; *pili torti*; copper deficiency

INTRODUCTION

Menkes disease (MD; OMIM 309400) is an X-linked neurodegenerative disorder resulting from subnormal Copper (Cu) transport

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and resultant deficient activity of Cu- dependent enzymes. This transport is facilitated via an ATPase encoded by the *ATP7A* gene on chromosome Xq21.1. This is a rare disorder with an estimated incidence of 1 in 100,000 births [Kaler et al., 2010].

Classic features include hypotonia, developmental delay, seizures, skin and joint laxity, “twisted” hair (*pili torti*) with or without hypopigmentation, and connective tissue findings, such as cerebrovascular tortuosity and bladder diverticulae. A milder form is occasionally seen in males with mild intellectual disability, muscle weakness, tremor, ataxia, connective tissue signs, *pili torti*, and later-onset seizures [Kaler et al., 2010].

MD variant phenotypes have been reported in some females [Barton et al., 1983; Favier et al., 1983; Gerdes et al., 1990; Moller et al., 2012], mostly associated with X- autosome translocations disrupting the *ATP7A* locus [Abusaad et al., 1999; Beck et al, 1994;

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Kapur et al., 1987; Sirleto et al., 2009; Sugio et al., 1998]. Heterozygous females were previously thought to be asymptomatic; however, half of obligate carrier females show regions of *pili torti* [Moore and Howell, 1985]. No females with classic MD have been reported to our knowledge.

Early treatment with parenteral copper (Cu) has been tried in some boys with classic MD and improved the neurodevelopmental outcome in a subset of them [Kaler et al., 2008; Kaler et al., 2010]. Cu treatment has never been studied in females with MD or variants.

Here, we describe the clinical manifestations and laboratory findings in a female with classic MD and two others with MD variants; we also summarize the published reports of females with MD.

CLINICAL REPORT

Patient 1 is a 22-month-old girl who presented at 7 months old with hypotonia. Physical exam showed myopathic face with sagging cheeks, “kinky” hair with silvery streaks, skin and joint laxity, and truncal hypotonia. On microscopic hair examination, 20% of sampled hair shafts showed *pili torti*. She had low serum Cu at 19 mcg/dL (normal 24–152) and low serum ceruloplasmin at 9 mg/dL (normal 15–43) at 7 months of age. Radiographs showed “wormian” skull bones and general osteopenia. She had marked cerebrovascular tortuosity (Fig. 1) and delayed brain myelination. She had no bladder diverticulae by ultrasound. *ATP7A* gene analysis showed a heterozygous, frameshift mutation in exon 17 (c.3445delC), predicted to be pathogenic. SNP-array CGH analysis showed a maternally-inherited, heterozygous 500 Kb deletion at Xq28 (not including the *ATP7A* gene), associated with X-linked intellectual disability. Parenteral Cu therapy was initiated at

8 months old and, at 22 months old, she has severe global developmental delay and hypotonia but no seizures. She is gastrostomy tube dependent for feeding due to failure to thrive.

Patient 2 is a 4-year-old girl, first evaluated at 2 weeks old for “silvery hair tips.” Initial exam showed excess nuchal skin, normal neurologic exam, and normal head circumference. Family history was notable for epilepsy in her mother who also had “coarse” hair with silvery tips in infancy. Patient 2 developed seizures at 5 weeks of age and gastrostomy tube feedings were initiated at 5 months of age due to feeding problems. She had low normal serum Cu at 70 mcg/dL and low normal serum ceruloplasmin at 21 mg/dL. SNP-array CGH analysis was normal. *ATP7A* gene analysis showed a heterozygous deletion of exons 8–12, predicted to be pathogenic as well as 2 polymorphisms (c.2299G>C, IVS13–29C>A). She had marked cerebrovascular tortuosity, and brain atrophy. At 4 years old, she has severe hypotonia, marked intellectual impairment, epilepsy managed with two anticonvulsants, dystonia, and microcephaly. She is exclusively gastrostomy tube fed.

Patient 3 is a 7-year-old girl, initially evaluated at 15 months of age, for poor growth and developmental delay. Initial Examination showed myopathic facies, coarse hair, skin and joint laxity, hypotonia, truncal ataxia, and dystonia. Radiographs showed “wormian” skull bones and general osteopenia. Cerebellar atrophy and marked cerebrovascular tortuosity were present. At 7 years old, mitral valve prolapse with mild mitral regurgitation and severe aortic root dilation were noted. She has two large, widely-communicating diverticulae. Serum Cu was low at 11 mg% (normal: 85–150) and ceruloplasmin was low at 13 mg% (normal: 20–43) at initial presentation. *ATP7A* gene analysis showed the same two heterozygous polymorphisms (c.2299G>C, IVS13–29C>A) as in Patient 2 but no pathogenic mutations or deletions. Parenteral Cu was initiated at 2.5 years of age. At 7 years old, she has severe global developmental delay, hypotonia, epilepsy, a movement disorder, and progressive aortic root dilation.

DISCUSSION

This is the first report of classic Menkes disease in a female. We additionally report two females with MD variants and summarize all published reports of affected females with MD and variants in Tables I and II. A total of 18 females with MD phenotypes have been reported to date including the present report.

Ten of 18 reported affected females exhibit low serum Cu and ceruloplasmin levels. As evidenced by the severe manifestations in females with normal serum Cu and ceruloplasmin but a pathogenic change in the *ATP7A* gene (see Patient 2), these biochemical parameters are of limited diagnostic utility although they constitute a useful biomarker for laboratory monitoring while on Cu therapy (if initiated) provided that they were low at diagnosis. It is, thus, recommended that females with suspected MD or variant phenotypes undergo molecular genetic testing even if biochemical parameters are normal, if a high degree of clinical suspicion remains.

Hair abnormalities such as “kinky hair” (*pili torti*) or scattered hypopigmentation are characteristic findings in females and were reported in 46% of heterozygous females with MD [Moore and Howell, 1985]; these hair findings are uniformly found in males with classic MD. Patient 1 exhibited characteristic *pili torti* and

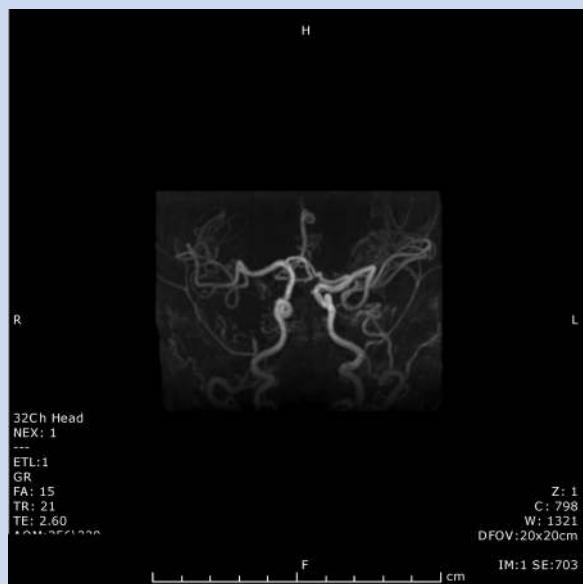


FIG. 1. MR Angiogram showing extensive cerebrovascular tortuosity in patient 1 with classic Menkes disease.

TABLE I. Clinical Findings in All Reported Affected Females With MD and Variant Phenotypes

Report	Hypotonia	ID	Epilepsy	Brain atrophy	CV tortuosity	"Kinky" hair	Cu therapy	Last report
Barton et al., 1983	x		x	x		x		2.5 Y/ death
Favier et al., 1983	x	x	x			x		34 Y
Kapur et al., 1987	x		x	x		x		unknown
Gerdes et al., 1990	x	x	x			x		5 Y
Beck et al., 1994	x			x		x		unknown
Sugio et al., 1998	x		x	x			x	unknown
Abusaad et al., 1999	x		x	x		x		18 M/ death
Sirleto et al., 2009	x		x		x			26 M
Moller et al., 2012	x	x		x		x		9 Y
		x					x	22 Y
	x	x				x		10 Y
	x	x						2 Y
	x	x	x					41 Y
		x			x			14 Y
	x	x	x					29 Y
Present report	x	Unknown		x	x	x	x	22 M
	x	Unknown	x	x	x			4 Y
	x	x	x	x	x		x	7 Y

ID, intellectual disability; CV, cerebrovascular; Cu, Copper; Y, years; M, months.

scattered hair hypopigmentation while Patient 2's first presenting sign was scattered hair hypopigmentation. This clinical finding is characteristic of the disease and hair microscopy can be an important part of the clinical evaluation for MD.

Seizures and abnormal neuroimaging findings (cerebrovascular tortuosity, cerebral atrophy) are noted in 11 of 18 of all reported

females. In a study by Kaler et al. [2010] only 12.5% of 24 male patients with classic MD, diagnosed and treated prior to 6 weeks of age, manifested clinical seizures, whereas 46% of them had at least one abnormal EEG tracing. The authors proposed that early identification and treatment of classic MD "improves brain electrical activity and decreases seizure occurrence in classic MD",

TABLE II. Biochemical and Genetic Findings in all Reported Affected, 2012 Females With MD and Variant Phenotypes

Report	Low serum Cu, ceruloplasmin	Cytogenetic abnormality	ATP7A alteration
Barton et al., 1983	unknown	Mosaic TS	Unknown
Favier et al., 1983			Unknown
Kapur et al., 1987	x	46,X, t(X;2) [q13;q32.2]	Unknown
Gerdes et al., 1990	x		Unknown
Beck et al., 1994	x	46,X, t(X;1) [q13;q12]	Unknown
Sugio et al., 1998	x	46,X, t(X;21) [q13.3;p11.1]	Unknown
Abusaad et al., 1999	x	46,X, t(X;13) [q13.3;q14.3]	Unknown
Sirleto et al., 2009	x	46,X, t(X;16) [q13.3;p11.2]	Unknown
Moller et al., 1998	x		exon 6 deletion
	Unknown		exon 6–9 deletion
	Unknown		intronic missense
	x		c.2179G>A
			c.2383C>A
			exon 1 deletion
Present report	x	Xq28 deletion	c.532G>T
	x		c.3445delC
			exon 8–12 deletion
			negative

TS, Turner syndrome.

although “it could not prevent severe intellectual disability.” In fact, parenteral Cu was initiated in Patient 1 in early infancy and she has not developed seizures to date, which may in part be due to early diagnosis and treatment. In Patient 2, however, the severe degree of developmental delay and seizures at diagnosis together with the normal serum Cu and ceruloplasmin levels were judged as making it unlikely that Cu therapy would be of clinical benefit, and, thus, it was not initiated.

Current management of MD in females focuses on symptomatic management and targeted interventions in areas of physical and cognitive disabilities. Treatment with parenteral Cu is not standard of care in either males or females with classic or variant MD but it may be offered on a case-by-case basis recognizing the variable clinical benefit shown in studies of males with classic MD [Kaler, 1998]. Some males, when treated prior to neurologic symptom onset, showed improved clinical outcomes whereas others showed only symptomatic relief from irritability or sleep disturbance with no effect on overall neurocognitive outcome [Kaler, 1998]. Targeted pharmacologic therapies, including parenteral Cu, have not been systematically studied in females with classic or variant MD, likely due to many factors, such as the overall rarity of the disease, great variability in clinical manifestations in females making the diagnosis difficult, and potentially low index of suspicion and/or unfamiliarity with MD in general pediatric practice.

In summary, this report illustrates the variability in both the presence and/or severity of clinical manifestations in females with MD and variant phenotypes requiring a high index of clinical suspicion during evaluations. Serum Cu and ceruloplasmin levels in those females can be variable with some showing low levels and others showing normal levels even in the presence of pathogenic *ATP7A* gene alterations. Molecular genetic testing in these cases is fundamental. Importantly, females with MD and variants, if diagnosed and treated early, may benefit from Cu therapy, but the effect of this therapy on the overall disease course remains to be seen.

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