Mystery Case: Tortuous hairs and tortuous blood vessels

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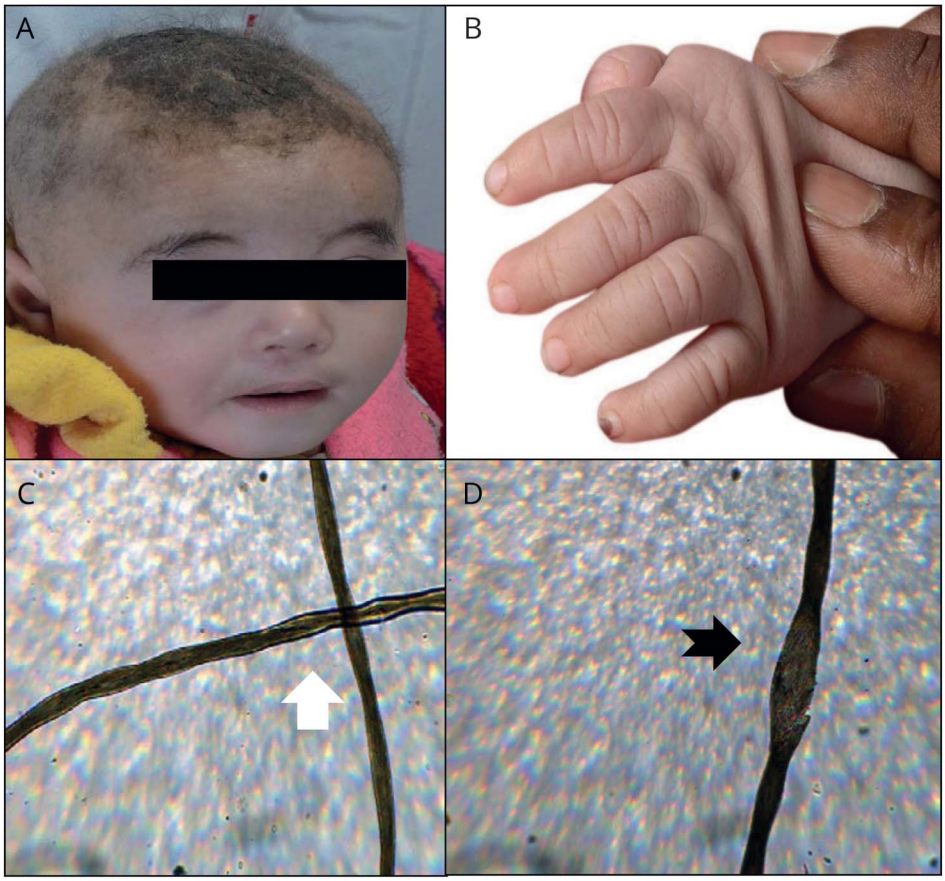
Figure 1 Clinical features and hair microscopy



(A) Facial appearance: thin, sparse, short, silvery, wiry hairs and epicanthus. (B) Loose skin folds over dorsum of hand. Hair microscopy: (C) pili torti (180-degree twisting of hair shaft) and (D) trichorrhexis nodosa (formation of nodes along the hair shaft with breakage).

A 5-month-old boy, born to a third-degree consanguineous couple, presented with drug-refractory seizures. On examination, he had microcephaly, abnormal scalp hairs (figure 1A), loose skin folds (figure 1B), and generalized hypotonia. Based on hair microscopy (figure 1, C and D), radiologic findings (figure 2, A–D), and a pathogenic mutation in the *ATP7A* gene (c.4006-1G>C, intron 20), a diagnosis of Menkes disease was confirmed.

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Discussion

Dysfunction of multiple copper-dependent enzymes in Menkes disease, like lysyl oxidase (crosslinks elastin) and sulfhydryl oxidase (crosslinks keratin), results in abnormal vessels, skin, and hair.[1] Mechanical instability of vessel collagen and remodeling could be mechanisms for the

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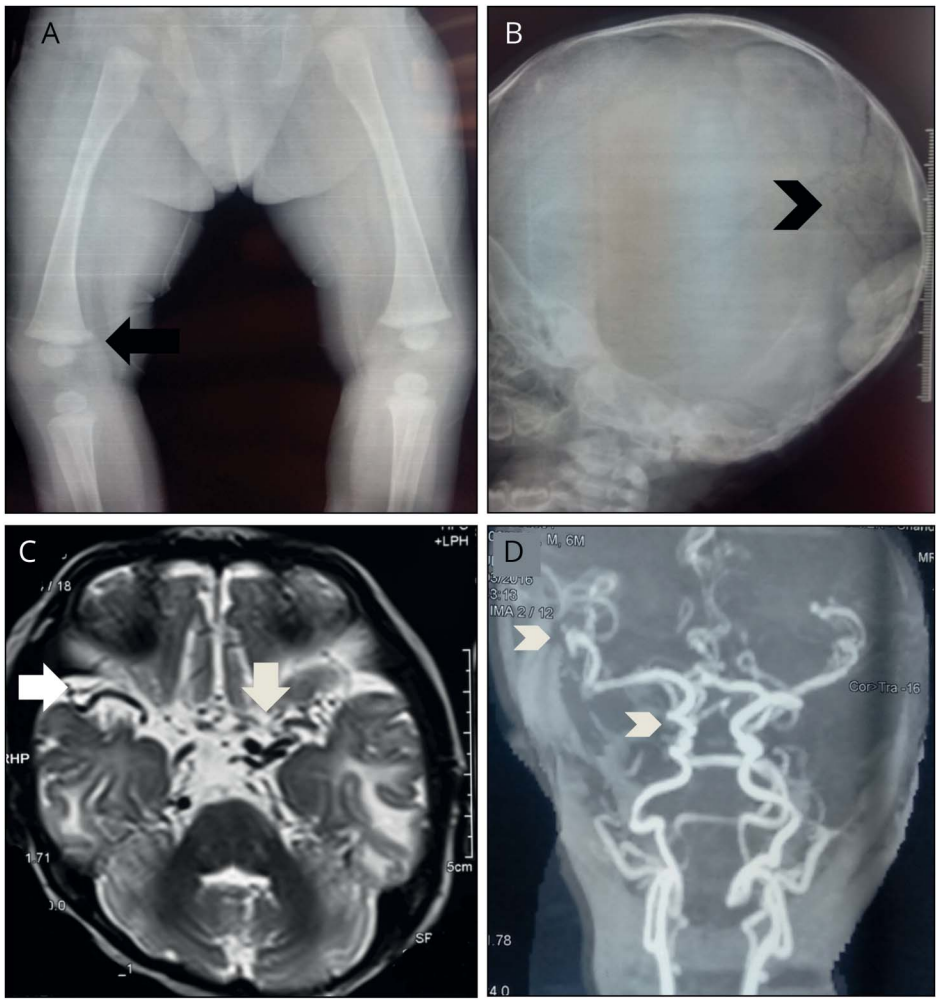
Figure 2 Skeletal X-rays and MRI of the brain



Skeletal X-rays: (A) metaphyseal spurs and (B) wormian bone (intrasutural bones) in the skull. (C) T2-weighted axial MRI section at the level of basal cisterns shows multiple dilated tortuous vessels. (D) Time-of-flight magnetic resonance angiography shows tortuous extracranial and intracranial arteries.

initiation and development of tortuous blood vessels.[2] Early initiation of copper-histidine therapy may modify disease progression, but prognosis remains poor.

Author contributions

I.K.S.: patient management, literature review, and initial draft manuscript preparation. R.S.: patient management, critical review of manuscript for important intellectual content, and final approval of the version to be published. S.V.: analysis of the radiologic data and critical review of manuscript. A.R.: analysis of hair microscopy and critical review of the manuscript. N.S.: clinician in charge, concept and design of the report, critical review of manuscript for important intellectual content, and final approval of the version to be published.

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Disclosure

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Mystery Case responses

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. We received 148 responses. The majority of respondents (80%) had been in practice for 1–4 years; 68% were residents or fellows, while 20% were faculty/board-certified physicians. A total of 51% resided outside the United States. A wide range of practice settings was represented.

First, respondents were presented with a brief summary of the patient's presentation (5-month-old boy born to

a consanguineous couple, presenting with drug-refractory seizures and hypotonia on examination) and asked to identify the key findings in figure 1, A and B. Microcephaly was correctly identified by 23% of the respondents, kinky hairs by 60%, loose skin folds by 39%, pili torti (twisted hairs) by 22%, and trichorrhexis nodosa (weak points or nodes causing hair to break off easily) by 9%. The hair abnormality was incorrectly identified as alopecia areata by 29% of the respondents; this term refers to an autoimmune baldness that may sometimes be associated with neuroimmunologic conditions like myasthenia gravis.[1]

Second, respondents were shown the child's skeletal X-rays and MRI/magnetic resonance angiography brain (figure 2, A–D), and asked to identify the key findings. Tortuous intracranial arteries were correctly identified by 55% of the respondents, and tortuous extracranial arteries by 28%. The more subtle finding of metaphyseal spurs was correctly identified by 21%, and wormian bone (extra bone within cranial sutures) by 17%. A total of 22% incorrectly identified the patient's bone abnormality as fibrous dysplasia; this involves replacement of normal bone with large fibrous stroma and islands of immature woven bone and can be seen in disorders like McCune-Albright syndrome (with precocious puberty and café-au-lait spots).[2]

Finally, when asked to identify the most likely diagnosis (and associated gene) for the patient on the basis of these findings, 72% of the respondents correctly identified this as a case of Menkes disease with *ATP7A* mutation. The most frequent alternative choice was mucopolysaccharidosis IIIA (5%), a severe early childhood neurologic condition caused by autosomal recessive *SGSH* mutations. In addition to developmental delay and behavioral problems, these patients can also have seizures as well as hair and skeletal abnormalities, with coarse hair texture, stiff joints, and dense calvaria. Tortuous vessels are not usually described in mucopolysaccharidosis IIIA.[3]

This Mystery Case provides a succinct overview of key clinical and radiologic findings in Menkes disease.

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