

Seizures of unknown etiology associated with brittle hair: A diagnostic challenge



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INTRODUCTION

Menkes disease (MD) is a rare X-linked recessive disorder caused by defective copper metabolism, which is associated with inactivating mutations in the ATP7A gene. It has an estimated incidence of 1 in 35,000 live births.¹⁻³ Clinical manifestations usually begin during early infancy and include progressive neurodegeneration, connective tissue disturbances, failure to thrive, intractable seizures, and kinky, brittle hair. Children who develop MD tend to suffer from progressive neurologic deterioration and are likely to die before they reach 3 years of age. We report a case of MD in a previously healthy 3-week-old infant who presented to the emergency department with recurrent seizures of unknown etiology and with associated brittle hair. A multidisciplinary evaluation (which should include the early recognition of the distinctive hair) is vital, highlighting the crucial role dermatologists can play in formulating a prompt diagnosis, followed by the timely initiation of treatment in what is, most often, a fatal disease.⁴

CASE REPORT

A 6-week-old Hispanic infant who had been admitted to the pediatric intensive care unit due to a 3-week history of seizures (the etiology of which had not been identified) was referred to our service for evaluation of his sparse, brittle hair. The patient was the first-born child of nonconsanguineous parents; he had been delivered at term, weighing 6 pounds, with a head circumference of 13.2 inches; there had been no prenatal or neonatal complications (including bony abnormalities) before his visit to the emergency department. The patient's mother

Abbreviations used:

LM: light microscopy
 MD: Menkes disease
 PT: pili torti
 TN: trichorrhexis nodosa

had brought the 3-week-old newborn to the ED when she noticed that he was making repetitive, involuntary movements; additionally, it was ascertained that the newborn had also been suffering from poor oral intake and failure to thrive. His involuntary movements were myoclonic and focal in nature, initially affecting his extremities but eventually progressing to generalized involvement. The mother mentioned that the texture of his hair had changed since his birth. The family history was unremarkable except for the mother (and a first-degree maternal cousin) having adult-onset epilepsy. The mother had no history of pili torti (PT) or hypopigmentation.

A physical examination revealed an infant of fair complexion, with chubby cheeks, micrognathia, and a depressed nasal bridge. His scalp hair was short, sparse, dull, brittle, and light-colored; it had a kinky appearance and an irregular texture (Fig 1). His eyebrows and eyelashes were similarly affected. Broken hair shafts were noted in both the occipital and temporal areas, along with yellowish scaly patches solely in the occipital region. In addition, the infant had shiny, lax, doughy skin on the backs of both hands (Fig 1). No other associated mucocutaneous findings were identified. A neurologic examination was remarkable for generalized hypotonia, head lag, and brisk reflexes.

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Fig 1. **A**, Scalp hairs were short, sparse, dull, brittle, and light-colored, with kinky appearance and irregular texture. **B**, Shiny, lax doughy skin was appreciated on bilateral dorsal hands.

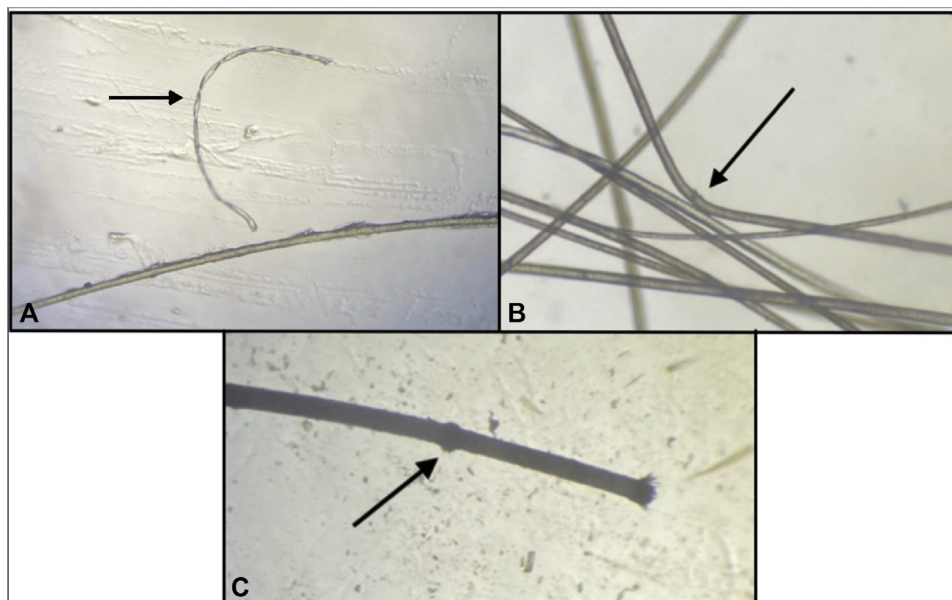


Fig 2. Photomicrographs of hair on routine light microscopy. **A**, Pili torti; the hair shaft revealed abnormal flattening and twisting along its long axis in comparison to a normal hair shaft in parallel (*black arrow*.) **B**, Trichorrhexis nodosa; there is a fracture and abnormal bending in the midportion of the identified hair shaft (*black arrow*.) **C**, Close-up image of the hair shaft shows a node and a distal break resembling the end of a paintbrush or broom, classic of trichorrhexis nodosa (*black arrow*.)

The infant's baseline laboratory tests and imaging (magnetic resonance imaging, computed tomography, and electroencephalogram) studies were unremarkable, except for the finding of normocytic anemia. Light microscopy (LM) of the hair shafts

was performed, resulting in the findings of pili torti and trichorrhexis nodosa (TN) (Fig 2). Dermoscopy revealed light-colored, flattened hair with sharp kinks at irregular intervals and white nodules along the hair shafts (Fig 3). Given the clinical findings of

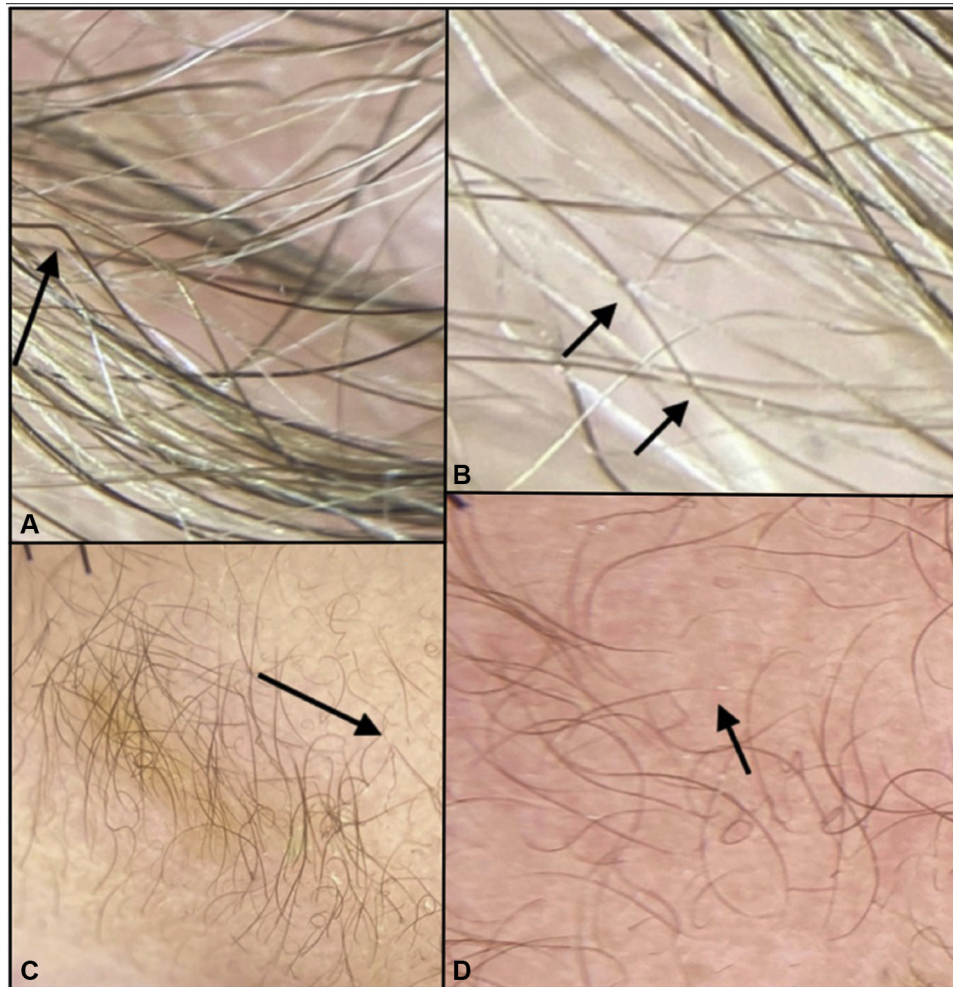


Fig 3. Dermoscopy of hair shafts of (A) scalp and (C) eyebrows with pili torti, showing hair shaft with sharp bending (*black arrow*) at irregular intervals. Dermoscopy of (B) scalp and (D) eyebrows, showing trichorrhexis nodosa with white nodules (*black arrow*) along affected hair shafts as well as fractured and frayed ends with brush-like appearance (*black arrow*.)

recurrent seizures, failure to thrive, and abnormal hair, a diagnosis of MD was strongly suspected; thus, metabolic and genetic workups were recommended. Further blood analysis results, including serum copper and ceruloplasmin levels, were unremarkable. The patient and his mother both underwent sequence analysis and deletion/duplication testing. In both cases, 1 pathogenic variant was identified in the ATP7A gene (c. 2186G > A), confirming the diagnosis of MD. However, due to the influence of X-inactivation, the mother was an asymptomatic carrier.

Although there is no cure for the disease, we treated our patient with copper histidine to prevent neurologic deteriorations. Follow-up information was attained via virtual visit 6 months after hospital discharge. Substantial hair growth was observed in the scalp and eyebrow areas. In addition, it was

reported that the seizure episodes decreased in frequency. The patient remains on copper histidine treatment and continues to be monitored by a pediatric neurologist.

DISCUSSION

MD is a rare genetic disease, typically manifesting in early infancy. Patients usually exhibit severe clinical disease followed by death during early childhood.⁵ The diagnosis of MD is typically suggested by the presence of characteristic clinical manifestations, though in early disease, the symptoms are often nonspecific, representing a diagnostic challenge.

In many cases, the presenting symptoms are often neurologic, with intractable myoclonic seizures being the most common. Hair findings may precede or present during the onset of neurologic symptoms,

highlighting the importance of having a high index of suspicion in male patients with brittle hair and new-onset intractable seizures. Most neonates who develop MD have normal-appearing hair at birth, and after shedding of the newborn hair, the characteristic hypopigmented, kinky, and unruly hair develops. In our case, the hair shaft abnormalities had been present since birth, which may have been related to the severity of the patient's disease.

The most important dermatologic signs of MD, present in all cases, are the structural hair shaft abnormalities (PT, TN, monilethrix) that result in the characteristic brittle, steely, kinky hair appearance. Structural hair shaft abnormalities can be confirmed by LM of the hair shafts or by such noninvasive modalities as dermoscopy. PT is most commonly associated with hair shaft disorders, with some authors suggesting that it is a marker of MD in the appropriate clinical context. Monilethrix and TN have also been reported in cases of MD, though not consistently; whether or not they are truly associated with MD is still controversial. Our patient had concomitant findings of PT and TN affecting his scalp, eyebrows, and eyelashes, as confirmed by LM and dermoscopy. To our knowledge, our case is novel in that it includes dermoscopy of the hair shaft of a patient with MD.

In a given patient, the constellation of hair findings (brittle, steely, kinky hair), the LM findings of PT and TN, and low serum copper and ceruloplasmin levels are all highly suggestive of MD. However, serum copper and ceruloplasmin levels may be normal during early disease and, thus, are not completely reliable in early cases such as ours.^{6,7} In such cases, hair and LM findings alone are highly suggestive of disease and support early treatment initiation while waiting for confirmatory molecular genetic studies.^{8,9} Given that prompt treatment with copper histidine may prevent some neurologic sequelae,⁴ recognizing the hair-related clinical manifestations as indicative of MD early in the disease

process is of vital importance and highlights the potentially significant role of dermatology in aiding rapid diagnosis and treatment initiation.

This case was unusual in that the patient experienced hair-related (scalp, eyebrows, eyelashes) clinical manifestations of MD earlier than is the norm. In this case, the combination of characteristic hair findings and the history of new-onset, intractable seizures was highly suggestive of MD, highlighting the importance of a multidisciplinary approach in such cases to prevent delays in treatment of what is a rare, usually fatal, disease.⁴

Conflict of interest

None disclosed.

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