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Usefulness of Trichoscopy in Menkes Disease: A Case Series study

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Abstract | **Case Report**

Background: Menkes disease is a rare X-linked recessive neurocutaneous disorder caused by mutations in the ATP7A gene, leading to impaired copper transport and multisystemic involvement. ***Objective:*** To describe the dermatological, neurological, and genetic features of Menkes disease through the report of three siblings, highlighting the role of dermatologists in early diagnosis. ***Methods:*** We report three siblings from the same family who presented with characteristic hair and skin abnormalities. Clinical, dermoscopic, neurological, and genetic evaluations were performed. ***Results:*** All patients exhibited pili torti, hair rarefaction, hypopigmented and hyperlax skin, associated with growth retardation and progressive neurological deterioration. Molecular analysis confirmed pathogenic mutations in the ATP7A gene. ***Conclusion:*** Dermatological findings, especially hair shaft abnormalities, represent key early diagnostic clues in Menkes disease. Early recognition is essential for prompt genetic confirmation, initiation of copper therapy, and family counseling.

Keywords: Menkes disease, ATP7A gene, Pili torti, Copper deficiency, X-linked recessive inheritance, Neurocutaneous disorder.

INTRODUCTION

Menkes disease (MD), commonly referred to as kinky hair disease, is a rare neurocutaneous disorder with X-linked recessive inheritance, resulting from pathogenic variants of the ATP7A gene encoding a copper-transporting ATPase [1,2]. Impaired function of this transporter leads to abnormal copper distribution to peripheral tissues, causing a generalized copper deficiency that predominantly involves the central nervous system, skin, and connective tissues [1,3]. Patients usually exhibit a severe clinical course with death in early childhood [1,4].

The disease usually presents in early infancy and is characterized by progressive neurological deterioration, delayed growth, seizures, and connective tissue anomalies [2,3]. Cutaneous and hair abnormalities represent some of the earliest and most distinctive clinical signs [5].

The present report describes the clinical, dermatological characteristics observed in three affected siblings, emphasizing the crucial contribution of dermatologists to early detection, diagnostic orientation, and coordinated multidisciplinary care of this rare yet life-threatening condition.

CASE PRESENTATION

We report the cases of three siblings two brothers aged five and two months, and one sister aged three years born to non-consanguineous parents after poorly monitored pregnancies. All three children were referred to the Dermatology Department for evaluation of hair abnormalities noted since early infancy particulary in the male children.

Clinical examination revealed marked rarefaction of scalp hair and eyelashes in all patients. **(Figure 1,2,3)**. Dermoscopic evaluation showed characteristic pili torti, with flattened and twisted hair shafts occurring at irregular intervals. **(Figure 4)** Cutaneous findings included generalized hypopigmentation, skin hyperlaxity consistent with cutis laxa, and increased skin fragility with easy bruising.

Systemic evaluation demonstrated growth retardation and progressive neurological deterioration, including hypotonia and delayed psychomotor development. Seizures were observed in the male siblings. Serum copper and ceruloplasmin levels were within the normal range. Molecular genetic analysis confirmed pathogenic partial mutations in the ATP7A gene in all three patients, establishing the diagnosis of Menkes disease.

Supportive management was initiated, including anticonvulsant therapy and nutritional support. The family was referred for genetic counseling. Copper replacement therapy was considered; however, delayed diagnosis limited its potential neurological benefit.

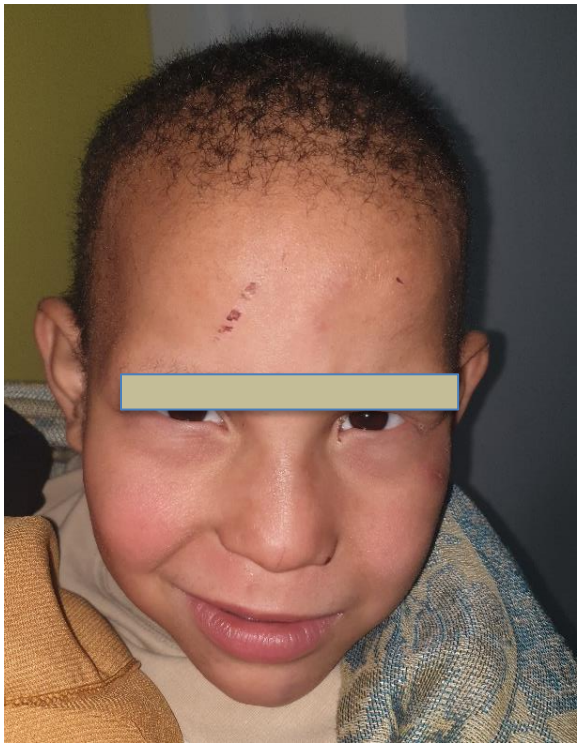

Figure 1: Patient 1: Hair eyebrows and eyelashes rarefaction

Figure 2: Patient 2: Hair eyebrows and eyelashes rarefaction

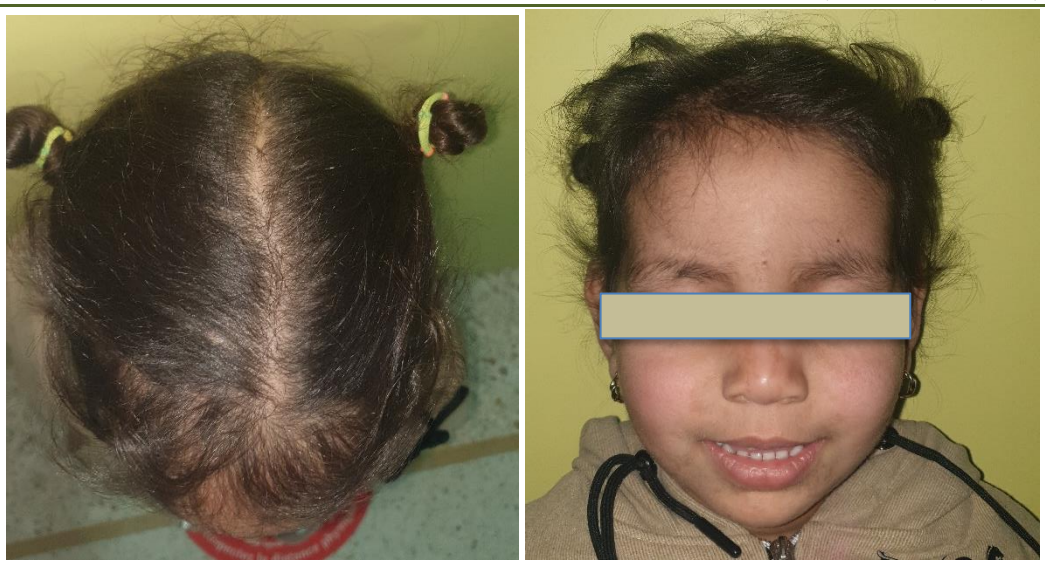

Figure 3: Patient 3: Tiny hair and rarefaction of eyelashes

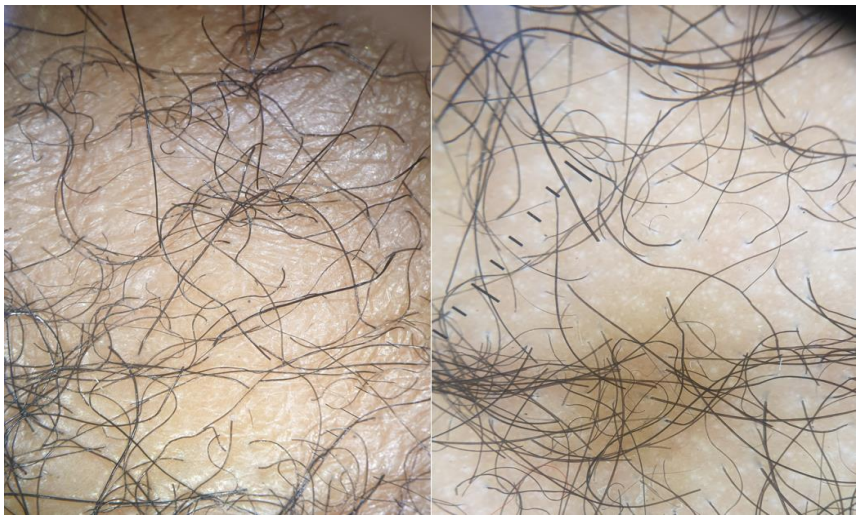

Figure 4: Thermoscopic evaluation showed characteristic pili torti, with flattened and twisted hair shafts occurring at irregular intervals

DISCUSSION

Menkes disease (MD) is a rare X-linked recessive disorder of copper metabolism caused by pathogenic variants in the ATP7A gene, which encodes a copper-transporting P-type ATPase [1,2]. This transporter plays a dual role in intracellular copper homeostasis by mediating copper delivery to copper-dependent enzymes within the secretory pathway and facilitating copper efflux from cells [2,4]. Dysfunction of ATP7A results in impaired copper distribution, leading to generalized copper deficiency in peripheral tissues, particularly affecting the central nervous system, skin, and connective tissues [1,3].

Copper is an essential trace element involved in numerous biological processes, including mitochondrial respiration (cytochrome-c oxidase), neurotransmitter synthesis (dopamine β-hydroxylase), connective tissue cross-linking (lysyl oxidase), keratin and hair shaft formation (sulfhydryl oxidase), and melanin production (tyrosinase) [3,6]. Consequently, disruption of copper homeostasis explains the multisystemic clinical spectrum of MD, combining progressive neurodegeneration, connective tissue fragility, and characteristic dermatological manifestations [3,6].

Cutaneous and hair abnormalities are among the earliest and most distinctive features of Menkes disease and may precede overt neurological deterioration [5]. Structural hair shaft defects, particularly pili torti, represent a hallmark finding and are considered highly suggestive of the diagnosis [5]. These abnormalities reflect impaired copper-dependent keratin cross-linking and abnormal hair shaft formation [3,6]. Additional dermatological signs, such as hypopigmentation, skin hyperlaxity, cutis laxa–like features, and increased skin fragility, are consistent with defective collagen and elastin maturation secondary to reduced lysyl oxidase activity [3,6]. These features were prominently observed in all three siblings in our series, reinforcing the concept

of MD as a neurocutaneous disorder in which dermatological findings may serve as critical early diagnostic clues.

Classically, diagnosis of MD is supported by reduced serum copper and ceruloplasmin levels [3]. However, as emphasized in previous studies, these biochemical markers are physiologically low in healthy neonates and young infants, limiting their diagnostic reliability during early life [2]. In our patients, serum copper and ceruloplasmin levels were within the normal range. Molecular confirmation through identification of pathogenic ATP7A variants therefore remains the diagnostic gold standard [2].

The clinical spectrum of Menkes disease is heterogeneous, ranging from the severe classical form with early death to milder phenotypes such as occipital horn syndrome and intermediate presentations [10]. Notably, genotype–phenotype correlations are imperfect, and significant intra-familial variability has been reported, even among individuals carrying identical ATP7A mutations [7]. The occurrence of three affected siblings in our report illustrates both the familial recurrence of the disease and the importance of early recognition in families at risk.

Early therapeutic intervention with parenteral copper-histidinate has been shown to partially modify disease progression, especially when initiated during the neonatal period and in patients with residual ATP7A function (8,9). Treated patients may exhibit improved neurological outcomes, reduced seizure frequency, and increased survival, although connective tissue abnormalities often persist [8,9].

Overall, this case series emphasizes the pivotal role of dermatologists in the early identification of Menkes disease. Recognition of characteristic hair and skin abnormalities should prompt immediate multidisciplinary evaluation, including genetic testing and metabolic assessment, even in the presence of normal copper parameters. Early diagnosis enables timely therapeutic intervention, informed genetic counseling, and appropriate prenatal assessment in future pregnancies.

CONCLUSION

Menkes disease remains a devastating neurocutaneous disorder with a generally poor prognosis [1,4]. Skin and hair abnormalities, particularly the presence of pili torti, frequently represent the earliest clinical signs and should alert clinicians to the diagnosis [5]. Early recognition by dermatologists is therefore pivotal for guiding genetic confirmation, initiating appropriate therapeutic strategies, and providing genetic counseling [2,8]. Improving awareness of this rare condition may facilitate earlier diagnosis and ultimately lead to better patient outcomes.

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