Pediatr Pol 2025; 100 (4): 370-375
DOI: https://doi.org/10.5114/polp.2025.156137
Submitted: 09.07.2025, Accepted: 30.10.2025, Published: 12.11.2025

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

CASE REPORT

Menkes disease – a rare disorder requiring interdisciplinary management

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ABSTRACT

Menkes disease is a rare, X-linked recessive neurodegenerative disorder caused by mutations in the *ATP7A* gene, resulting in defective copper transport. The clinical picture is dominated by early-onset neurological decline, connective tissue abnormalities, and characteristic hair shaft defects. The aim of this report was to present the case of a 4-year-old boy diagnosed with Menkes disease based on clinical features, biochemical analysis, trichoscopy, and whole exome sequencing, which revealed a novel pathogenic ATP7A variant. Dermatological signs, including brittle, depigmented, and twisted scalp hair, were among the earliest disease indicators. This case highlights the importance of early suspicion based on subtle cutaneous signs, especially in the neonatal period. This case highlights that a multidisciplinary diagnostic approach – including dermatological, neurological, radiological, and genetic assessment – is critical for timely diagnosis, a condition necessary for successful prevention of disease progression. Early treatment with copper histidine may improve outcomes but remains limited to selected patients with residual ATP7A function.

KEY WORDS:

Menkes disease, kinky hair syndrome, *ATP7A*, copper.

INTRODUCTION

Menkes disease (MD), also known as kinky hair syndrome or *trichopoliodystrophy*, is a rare and fatal neurodegenerative disorder caused by a genetically determined defect in cellular copper metabolism [1]. Due to the wide distribution and essential functions of copper-dependent enzymes throughout the human body, the disease manifests early in life with a broad spectrum of symptoms, including severe neurological impairment, skeletal abnormalities, and distinctive structural hair defects [2].

Currently, treatment with copper histidine may prevent irreversible organ damage, but its effectiveness is critically time-dependent and must begin within the first 3–4 weeks of life. At such an early stage, however, the classic clinical signs of MD are typically absent, rendering early identification of affected infants a significant diagnostic challenge [3].

This case report describes a 4-year-old boy diagnosed with MD in early infancy and highlights the importance of timely, interdisciplinary collaboration – particularly between pediatric neurologists and dermatologists – in

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achieving accurate diagnosis and delivering coordinated care for this rare multisystem disorder. Such approach is essential for timely introduction of treatment and prevention of irreversible complications of the disease.

CASE REPORT

The patient, a term male neonate, with uneventful pregnancy, the first child of nonconsanguineous parents, born naturally at the 38th week of gestation (body weight: 2500 g, length of the body: 53 cm, head circumference 34 cm, APGAR 10), presented with prolonged neonatal jaundice, bilateral subperiosteal hematomas, and generalized hypotonia requiring early physiotherapy. Feeding was normal, and the infant received formula milk.

From birth, the hair was abnormal – sparse, dull, light-colored, curly, and difficult to comb (Figure 1). Hypopigmented patches and flaccid, atrophic skin were noted in the axillae and neck.

At 5 months, the child developed focal seizures (eye deviation, eyelid blinking, oral clonia, tongue twitching). Neurological assessment revealed psychomotor delay, axial hypotonia, and asymmetrical tone. MRI showed bilateral white matter lesions, increased subcortical signal, tortuous arteries, and delayed myelination. Video-EEG revealed focal paroxysmal discharges (Figure 2).

Biochemical testing demonstrated markedly decreased serum copper and ceruloplasmin. A whole exome sequencing revealed in the patient a novel variant *c.3577del (p.Val1194SerfsTer6)*. At the age of 5 months the MD was confirmed.

A detected variant has not been submitted in human genetic databases (e.g. ClinVar) yet. Nevertheless, this is a frameshift variant, which leads to a production of a truncated protein. It is a very well-known mechanism in the pathogenesis of many monogenic diseases. Fortunately, the genetic tests based on DNA isolated from blood lymphocytes did not prove that a patient's mother is a carrier of MD. However, it was not possible to exclude a germinal mosaicism. That is why the patient's mother

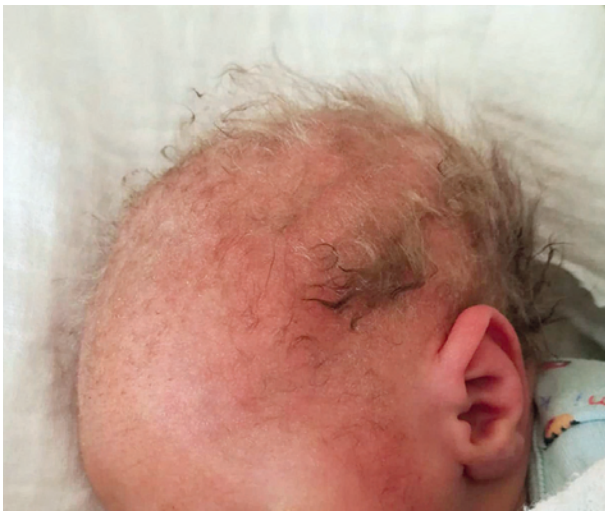

FIGURE 1. Sparse, dull, light-colored, short, curly scalp hair in a newborn with Menkes disease

was informed about a possibility of targeted invasive prenatal diagnosis in future pregnancies.

The patient was treated with phenobarbital and levetiracetam, achieving partial seizure control. Copper histidine injections were not applied due to late diagnosis and psychomotor retardation.

At the age of two, a percutaneous endoscopic gastrostomy was placed. By the age of three, abdominal ultrasound showed nephrolithiasis and bladder diverticula. The child's neurological condition (motor function and seizures control) during last two years was stable, but the gradual regression of cognitive functions was observed (poor response to visual and auditory stimuli).

Presently, at the age of four years, dermatologic consultation was sought due to erythematous, scaly scalp lesions (ultimately seborrheic dermatitis) and persistent hair abnormalities. Examination revealed discolored, coarse, brittle hair with patchy alopecia (Figures 3 A, B). Trichoscopy demonstrated woolly hair, *pili torti*, and *monilethrix* (Figures 3 C–F).

Additional dysmorphic features included a cherubic face (broad nasal tip, flat cheeks, ptosis, reduced expres-

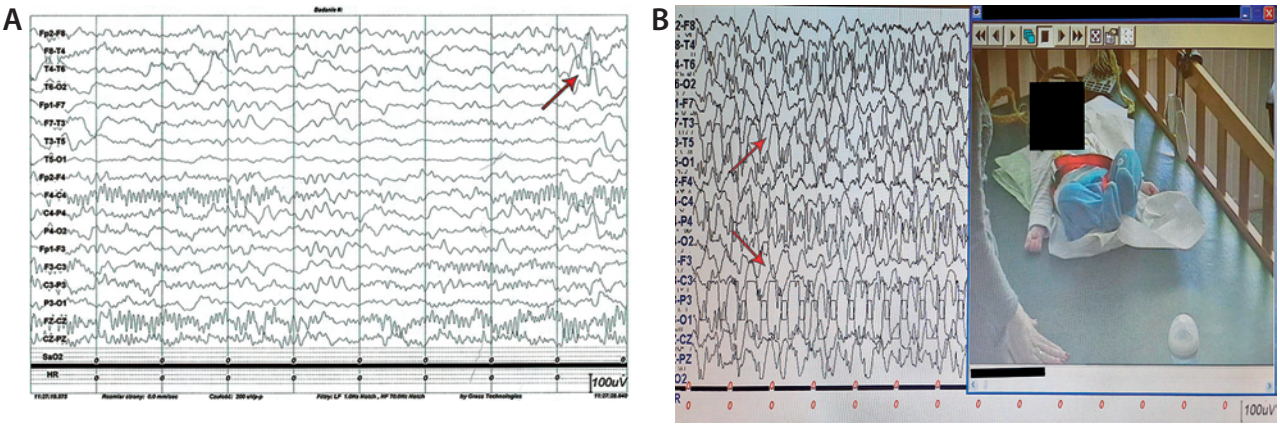

FIGURE 2. A) Inter-ictal Video-EEG during sleep with abnormal focal discharges in right temporal region. **B**) Ictal Video-EEG registration of eight minutes episode of clinical seizures (fixation of the eyes and elides blinking)

Arrows indicate epileptic discharges.

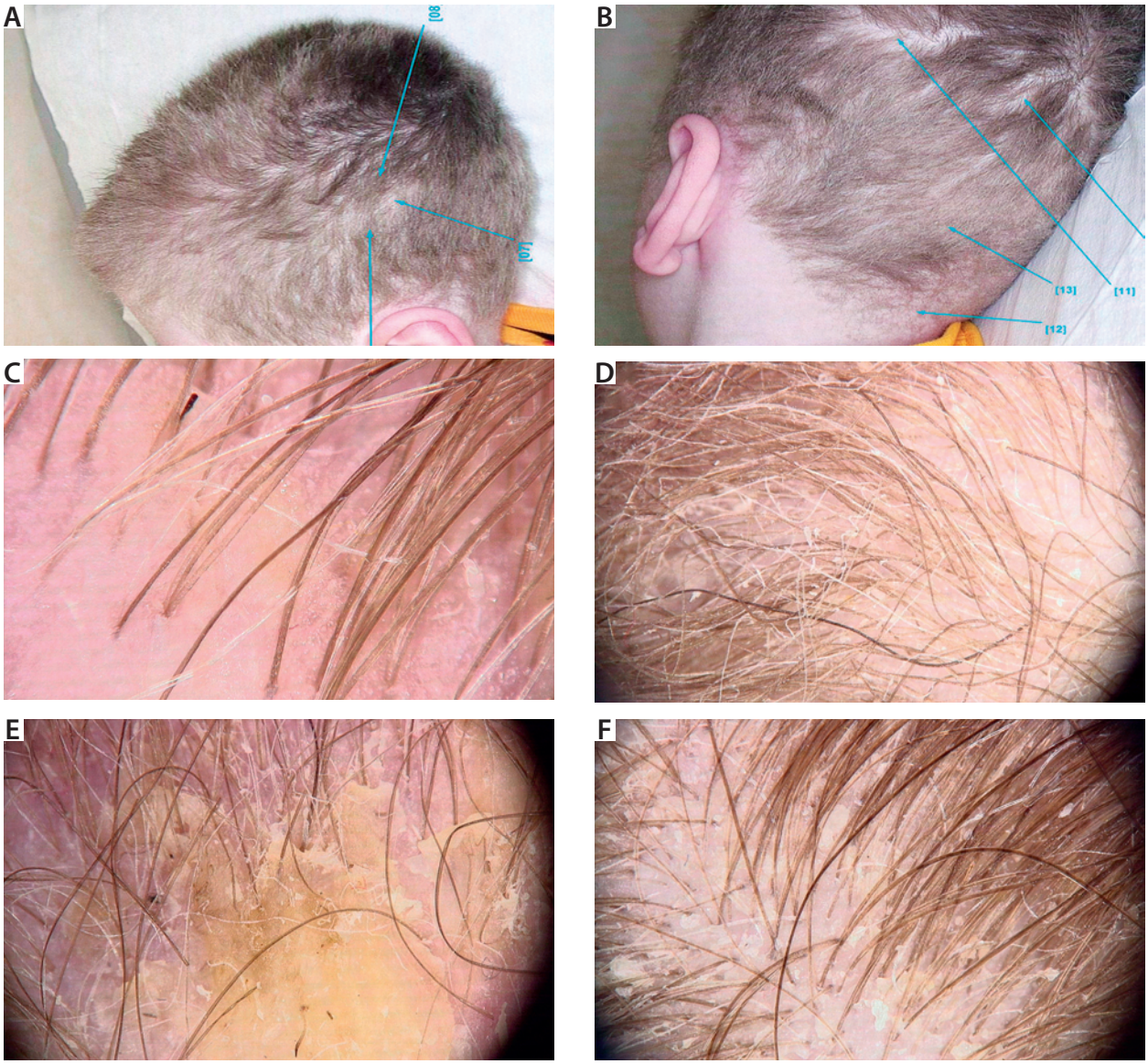

FIGURE 3. **A, B**) Discolored, coarse, brittle hair with areas of patchy alopecia. **C–F**) Trichoscopic findings showing structural hair shaft abnormalities, including bright woolly hair, pili torti, and monilethrix. Features of seborrheic dermatitis are also present

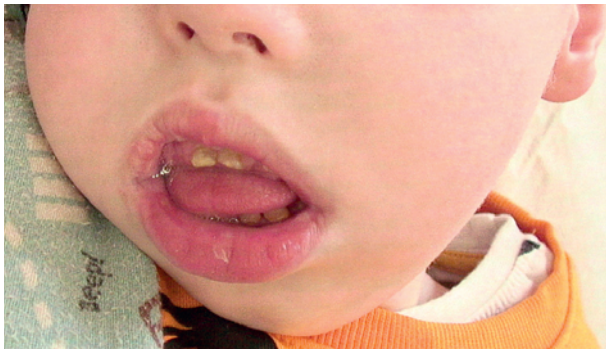

FIGURE 4. Dysmorphic features in a patient with Menkes disease, including a cherubic facial appearance (broad nasal tip, flat sagging cheeks, ptotic eyelids, and reduced facial expression) and a distinct "Cupid's bow" upper lip

sion), hypopigmented skin patches, and a "Cupid's bow" upper lip (Figure 4).

Current medications include valproic acid, levetiracetam, topiramate, phenobarbital, furazidine, magnesium citrate, and potassium citrate. The patient remains under multidisciplinary care (neurology, nephrology, rehabilitation, dentistry) within/in a home hospice setting.

DISCUSSION

Menkes disease was first described in 1962 by John Hans Menkes in a boy presenting with hypotonia, intractable seizures, and brittle, coarse hair. A familial pattern of early childhood deaths suggested a lethal X-linked recessive disorder. A decade later, David Danks identified a defect in copper metabolism as the underlying cause and introduced the term "steely hair disease" [4, 5].

Menkes disease results from mutations in the *ATP7A* gene (Xq13.3), which impair copper transport. Although incidence estimates vary from 1 in 40,000 to 1 in 350,000 live births [6], recent genetic analyses suggest it may be as frequent as 1 in 8,500 male births [7]. A third of cases arise de novo, complicating early diagnosis, especially in

TABLE 1. Relationship between copper-dependent enzymes and clinical symptoms in Menkes disease [1, 2, 6]

Enzyme	Mechanism	Clinical manifestations
Dopamine β-hydroxylase	Catalyzes hydroxylation of dopamine to norepinephrine in neurons and adrenal glands	Symptoms of catecholamine deficiency: hypothermia, hypoglycemia, ptosis, and other signs of sympathetic nervous system insufficiency
Cytochrome C oxidase (complex IV)	Mediates electron transfer to H+ which is required for the activity of proton pump in mitochondria, enabling ATP synthesis	Generalized cellular energy deficiency, affecting high-demand tissues: central nervous system degeneration, hypotonia, myopathy, delayed myelination, ataxia, seizures, hypothermia
Lysyl oxidase	Enables cross-linking of lysine residues in collagen and elastin *via* formation of Schiff bases	Connective tissue abnormalities: lax skin, joint hypermobility, skeletal deformities, and vascular fragility leading to aneurysms or dissections
Peptidylglycine α-amidating monooxygenase	Catalyzes initial hydroxylation preceding the amidation of neuropeptides at their C-terminus, required for activation	Decreased activity of several peptide hormones and neuropeptides: gastrin, VIP, ACTH, CCK, calcitonin, TRH, vasopressin – contributing to neuroendocrine dysregulation
Superoxide dismutase	Quenches superoxide radicals by converting them into hydrogen peroxide	Oxidative stress, particularly in metabolically active tissues: myelin degeneration, spasticity, seizures
Sulfhydryl oxidase	Catalyzes oxidation of sulfhydryl groups to form disulfide bonds in keratin	Hair shaft fragility and structural abnormalities: pili torti, monilethrix, woolly hair
Tyrosinase	Catalyzes oxidation of tyrosine and DOPA into dopaquinone, a key step in melanin biosynthesis	Reduced melanin synthesis resulting in hair depigmentation and low skin phototype

families without history. The broad spectrum of mutations – from large deletions to missense variants – contributes to clinical variability [6].

Copper is the third most abundant trace element in the human body and is essential for numerous enzymatic processes [2]. *ATP7A* is highly expressed in enterocytes, placenta, and brain – tissues crucial for copper distribution and neurodevelopment [6]. It shuttles copper to the trans-Golgi network for incorporation into cuproenzymes and to the plasma membrane for excretion when levels rise. Mutations in *ATP7A* disrupt both intracellular copper delivery and systemic export, leading to copper deficiency despite normal intake (Table 1).

Neurological decline in MD reflects copper deficiency within the central nervous system. Copper becomes sequestered at the blood-brain and cerebrospinal fluid barriers, impairing neuronal uptake [6]. Several pathogenic mechanisms are implicated: heightened excitability of NMDA receptors due to *ATP7A* dysfunction, mitochondrial damage from cytochrome c oxidase deficiency, and cerebral infarctions due to lysyl oxidase-related vascular instability [3].

The disease typically presents in infancy with neuroregression, refractory seizures, hypotonia, and connective tissue abnormalities [8]. The occipital horn syndrome is considered as milder variant of MD [3]. Classic MD leads to progressive deterioration and death by the age of 3–4 years [9]. Early symptoms may include prolonged jaundice, feeding difficulties, hypoglycemia, and fractures. Over time, affected children may develop fair skin, a cherubic face, lax joints, and soft, inelastic skin [1, 10]. A full overview of systemic manifestations is provided in Table 2.

The earliest specific sign of MD is abnormal scalp hair, resulting from deficiency of sulfhydryl oxidase (affecting keratin structure) and tyrosinase (affecting pigmentation) [8, 14]. Hair is typically sparse, short, dull, and depigmented, described as "steel wool". Trichoscopy reveals *pili torti*, woolly hair, *monilethrix*, *trichorrhexis nodosa*, *trichoptilosis*, and *trichoclasia* [15, 16].

Diagnosis is based on clinical features – particularly hair abnormalities – combined with low serum copper and ceruloplasmin [1, 8]. Imaging may show cerebral atrophy, delayed myelination, and tortuous vessels. However, classic signs may not be evident until after 3 months of age, delaying definitive diagnosis. Early suspicion should prompt trichoscopy and molecular testing for *ATP7A* mutations [17].

Biochemical testing of plasma and cerebrospinal fluid for neurochemical markers (dopamine, norepinephrine, DOPAC, DHPG) offers high sensitivity and specificity in neonates [18]. Prenatal diagnosis is possible through chorionic villus sampling and genetic analysis in known carriers. If the familial variant is unknown, functional testing in fetal fibroblasts may be considered [6].

Treatment relies on intravenous copper histidine, as oral forms are ineffective due to impaired absorption [14]. When initiated within the first 3–4 weeks of life – especially in patients with milder variants or partial *ATP7A* function – it can improve neurological outcomes, motor development, and quality of life [18]. However, response depends on the specific mutation and the protein's residual ability

TABLE 2. Extracutaneous manifestations of Menkes disease [1, 2, 6, 11–13]

Parameters	Manifestations
Osteoarticular system	Wormian bones of the skull, pectus excavatum, pectus carinatum, thoracolumbar kyphosis, scoliosis, osteopenia, fractures of long bones, epiphyses, ribs, and skull; joint hypermobility
Neurological	Neuroregression; seizures: focal clonic seizures, intractable infantile spasms, multifocal myoclonic seizures, tonic spasms
Cardiovascular	Tortuous blood vessels, internal jugular vein dilatation, phlebectasias, aneurysms, valvular dysfunction, congenital atrioventricular block
Visual system	Abnormal eyelash growth, strabismus, blue irides, reduced visual acuity (including blindness)
Autonomic nervous system	Syncope, orthostatic hypotension, chronic diarrhea
Gastrointestinal	Gastroesophageal reflux disease, progressive hiatal hernia, gastric polyps, colonic diverticula, hepatomegaly
Urinary and genital	Vesicoureteral reflux, hydronephrosis, bladder diverticula, spontaneous bladder rupture, renal parenchymal damage, cryptorchidism, recurrent urinary tract infections
Respiratory	Diffuse emphysema, cystic lung parenchymal changes, recurrent respiratory infections
Stomatognathic	Gingival overgrowth, delayed eruption of deciduous teeth, enamel hypoplasia, bicuspid incisors

to transport copper across the blood-brain barrier [2]. In severe forms, the treatment remains largely ineffective.

Other interventions – such as supplementation with vitamins C and E, carbamino acid derivatives (e.g., diethyldithiocarbamate), and gene therapy – are still under investigation and lack sufficient evidence for routine clinical use [18]. Clinical trials on gene therapy for MD are underway. A promising new therapeutic option appears to be the adeno-associated virus gene therapy approach to delivering working copies of a codon-optimized version of *ATP7A*. Preliminary studies in mouse models of the disease indicate the effectiveness of this approach, combined with copper histidine to improve outcomes. In the assumption, gene therapy for MD will be the most effective in asymptomatic or minimally symptomatic boys in the burdened families [19].

CONCLUSIONS

Although MD has been recognized in medicine for over five decades, recent advances have significantly expanded our understanding of its genetic basis, molecular pathomechanisms, and – most importantly – emerging therapeutic strategies. Menkes disease exemplifies a condition in which close collaboration between pediatric neurologists and dermatologists is essential for early diagnosis and effective clinical management. Such interdisciplinary cooperation is essential to offering new hope to affected children and preventing disease progression at its earliest stages – before irreversible damage to the central nervous system occurs.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: All the photos are presented with parent's permission.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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