Early diagnosis of Menkes disease

A rare condition that demands **rapid recognition and action**

Menkes International Association
Copper Rare Foundation

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What is Menkes disease?

Menkes disease is a genetic disorder caused by a variant in the ***ATP7A* gene on the X chromosome**. It primarily affects boys, although girls can also develop this disease.

ATP7A dysfunction disrupts the body's ability to absorb and distribute dietary copper. Copper is a micronutrient vital for brain development, connective tissue function, and normal metabolism.

Menkes disease results in a copper deficiency in the brain and key intracellular body compartments. As a result, essential copper–requiring enzymes do not function, leading to progressive neurological deterioration, structural abnormalities and life-threatening complications (Horn *et al*. 2021).

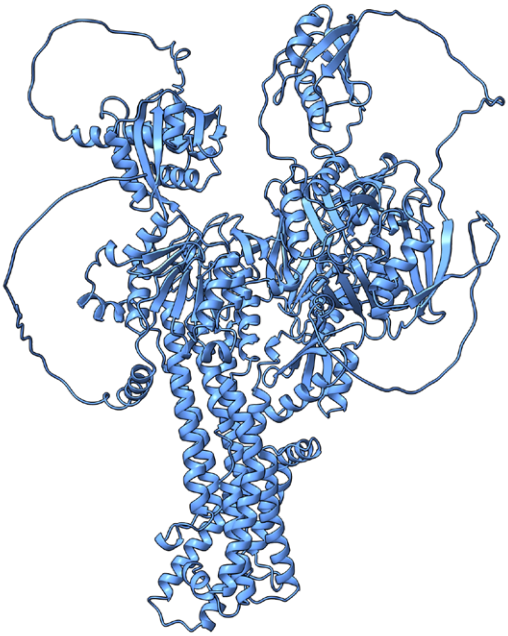


Figure 1: The predicted structure of *ATP7A* protein. The *ATP7A* copper transporter that is non-functional in Menkes disease. Publicly available model predicted by Alphafold. (www.uniprot.org/uniprotkb/Q04656/entry#structure)

Why act early?

Menkes disease is a rare, X–linked genetic disorder that disrupts copper transport. It can affect babies in any population. It is estimated to occur in 1 in 35,000 births.

Researchers consider this figure to be a considerable underestimate, since Menkes is likely underdiagnosed (Kaler *et al*. 2020).

Without early treatment, Menkes disease results in progressive neurological decline, which is often fatal by the age of three.

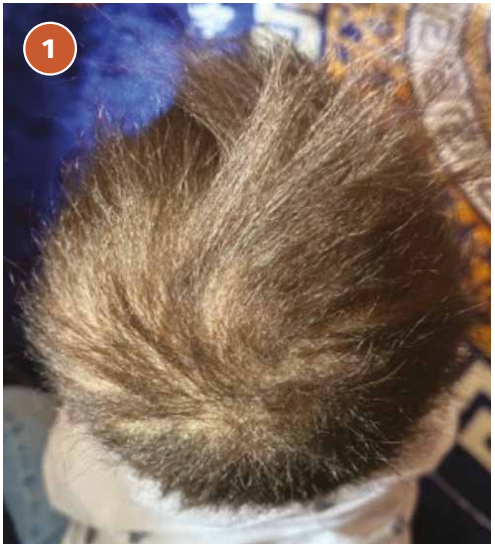
Early diagnosis – ideally at birth – is critical. Treatment started in the first weeks of life can prevent severe, irreversible brain damage.

Recognize early (warning) signs – then act

Menkes disease often presents subtly or mimics other conditions (Kaler *et al.*, 2008).
If you have any suspicion of Menkes, test immediately.

Consider Menkes disease if you observe:

- Loss of developmental milestones, seizures, failure to thrive in the first months of life;
- Any sign of an inborn error of metabolism;
- Low muscle tone (hypotonia) or feeding problems;
- Unexplained bruising, bleeding or pathological fractures;
- Subdural hemorrhage;
- Hair abnormalities (kinky or brittle hair);
- Low temperature (hypothermia);
- Low APGAR score or birth complications;
- Jaundice resistant to treatment;
- Lethargy or irritability.



1) Kinky hair.

2) Kinky hair / Microscopy: Trichorrhexis nodosa.

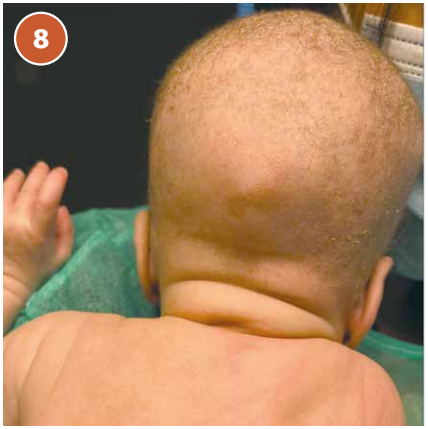
3) Kinky hair / Microscopy: Pili torti.

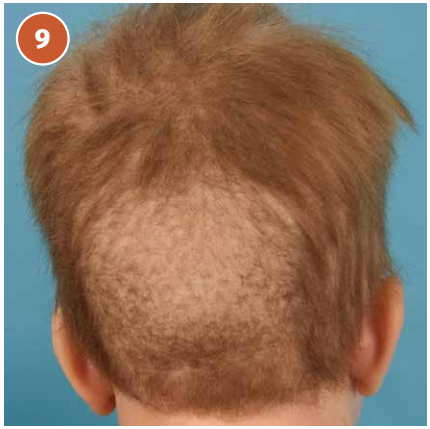
"Red Flags" for Menkes disease in newborns (first days to weeks)

- Preterm delivery (**4**);
- Poor feeding / Weak sucking reflex (**5**);
- Facial features in Menkes disease, such as broad nasal bridge, sagging cheeks, pale or loose skin, small chin (**6**-**7**).

Other "Red Flags" in newborns (first days to weeks)

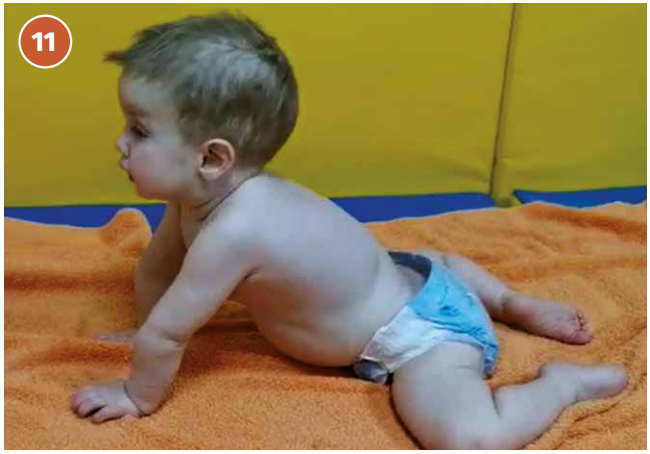
- Hair abnormalities are also characteristic of Menkes disease, **but do not wait, it will be too late**. The hair can become brittle and twisted (sometimes called "kinky"), producing hair loss or thinning where the scalp contacts the bed or pillow (**8**-**9**-**10**).



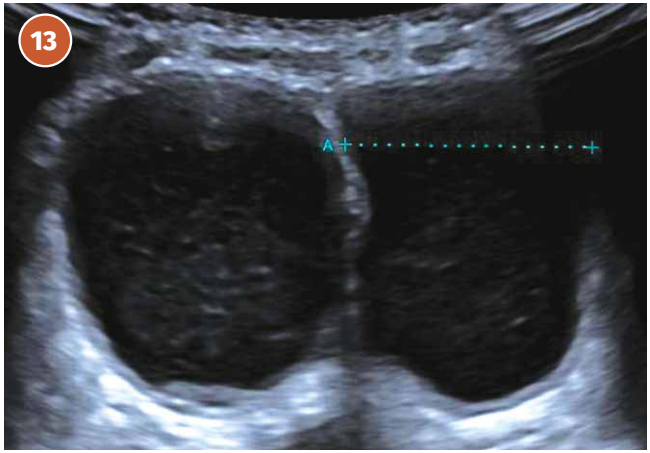


Infant Progression (weeks to months)

- Developmental delay or failure to achieve milestones;
- Seizures or abnormal movements;
- Hernias (inguinal or umbilical);
- Skeletal abnormalities (wormian bones on X-ray);
- Vasculopathy (vascular tortuosity (intracranial arterial tortuosity), aneurysms, vascular stenoses);
- Lung problems (e.g. emphysema or pneumonia);
- Kidney and urological problems (bladder diverticula, tubulopathy);
- Bone abnormalities (metaphyseal lesions, periosteal reactions);
- Chest Bone abnormalities (pectus carinatum or excavatum);
- Distinctive facial features of Menkes disease (include sparse, brittle, or “kinky” hair which is a hallmark sign, but mostly appears later, loose, sagging skin and pale complexion due to reduced pigmentation, jowly appearance with sagging cheeks, among others);
- Poor weight gain, persistent diarrhoea.



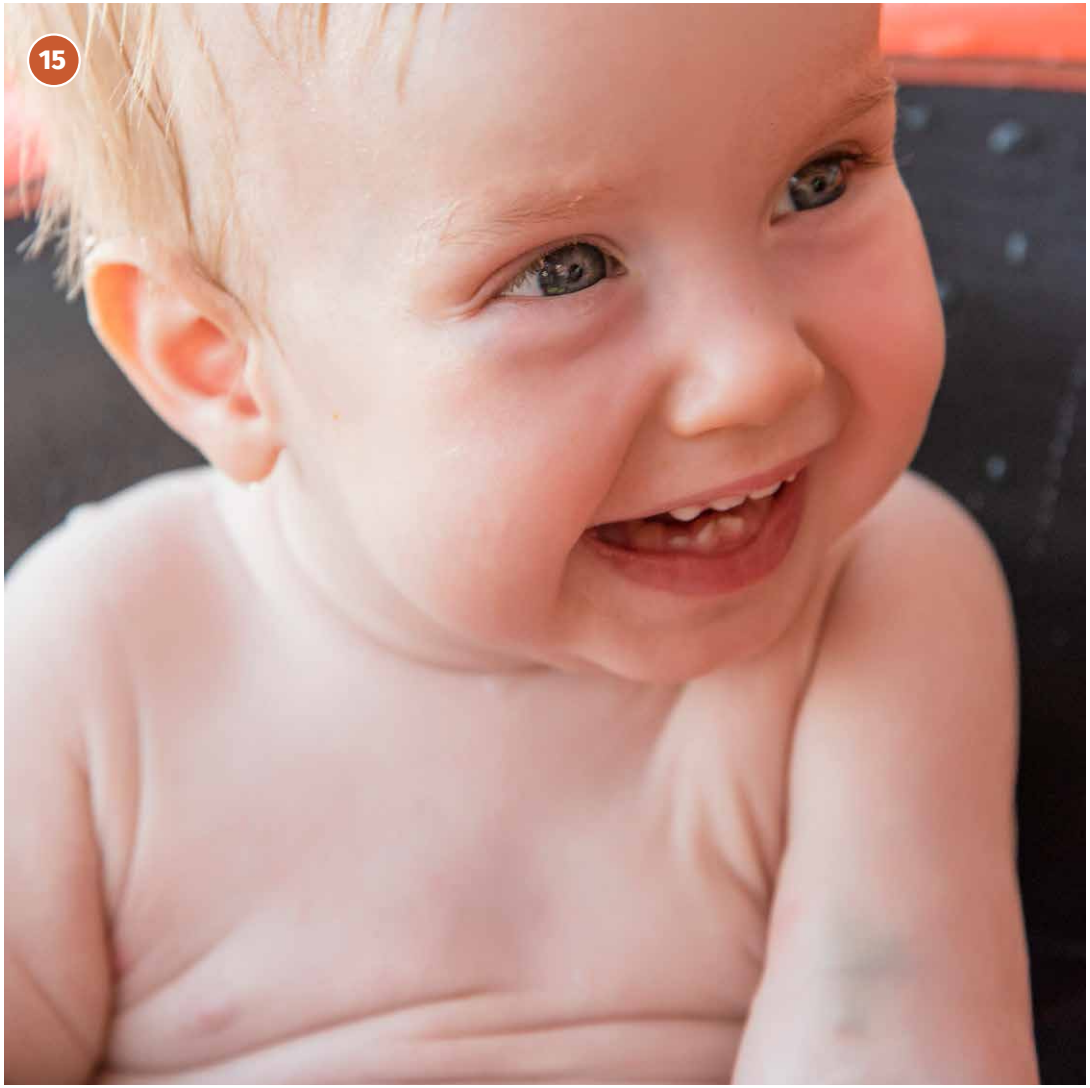
Joint laxity and limp lower body.
Hypotonia with an open book position.



Bladder diverticula.

Chest bone deformities (pectus carinatum).

Brittle hair, hypotonia, broad nasal bridge.



Hypotonia and sagging skin.

Menkes diagnosis

Rapid testing is available and essential.

Under suspicion, a blood and urine test should be performed. Plasma and urinary catecholamines can be a sensitive test, even in the first days of life, and can be performed in most hospitals.

Note, plasma copper levels and ceruloplasmin levels, are not reliable biomarkers of Menkes disease for diagnosis at birth, as they are naturally low in newborns. These biomarkers return significantly abnormal results only after two months of age–treatment should optimally begin well before this timepoint.

Biochemical Tests – Perform immediately upon suspicion

- Blood test: Dopamine (DA)/norepinephrine (NE) ratio greater than 0.8 is highly suggestive of Menkes disease (DA/NE) ratio > 0.8 (normal: ~0.1);
- Urine test: Homovanillic acid (HVA)/vanillylmandelic acid (VMA) ratio greater than 4: HVA/VMA ratio > 4 (strongly indicative of Menkes disease).

Genetic Testing – Confirmatory (Kansal R., 2025)

- *ATP7A* sequencing confirms diagnosis (either by Sanger DNA sequencing or exome/genome DNA sequencing).;
- Required for family screening and prenatal options;
- Carrier testing in female relatives, and prenatal testing in at-risk pregnancies are crucial;
- Preimplantation genetic diagnosis (PGD) for carriers is an option for *in vitro* fertilization (IVF);
- Family–based genetic counselling is essential in all cases.

Effective treatment is highly time-sensitive

Copper supplementation must begin in the first weeks of life to protect brain development.

Delayed treatment results in irreversible damage.

Elesclomol-copper: used in exceptional treatments facilitated by Menkes International with promising results. (Godoy-Molina *et al.* 2025, Gohil 2021, Guthrie *et al.* 2020)

Copper histidinate injections (standard of care).

Multidisciplinary Care Required (non-exhaustive list)

- Neonatology;
- Neurology;
- Clinical genetics;
- Metabolic & nutrition medicine;
- Nephrology & urology;
- Physiotherapy & rehabilitation;
- Family support groups (e.g. Menkes International).

Key messages

Recognize early-Menkes can mimic many conditions.

Act on suspicion; rapid testing is justified.

Do not wait for hair changes or test results to worsen.

Treat early; outcomes depend on timing.

Support families; offer genetic counselling.

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Menkes disease is a race against time!

Early recognition saves lives.

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Making Menkes disease history.

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