

## MENKES DISEASE

### Case report of an uncommon presentation with white matter lesions

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**ABSTRACT** - Menkes disease is a rare X-linked disorder related to a defect in the copper metabolism. According to the current literature, the most frequent neuroimaging findings are cortical atrophy, chronic subdural effusion or hygroma, and vascular abnormalities. White matter lesions may be present before other features of the disease and may evolve into atrophy. We hereby report a case of Menkes disease with typical history and progression, and an early phase imaging study with important white matter abnormalities, which could have lead to diagnostic difficulties.

**KEY WORDS:** Menkes disease, neuroimaging.

#### **Doença de Menkes: relato de caso com comprometimento da substância branca cerebral**

**RESUMO** - A doença de Menkes é patologia ligada ao X relacionada a defeito no metabolismo de cobre. De acordo com literatura atual, os achados mais frequentes em exames de neuroimagem são atrofia cortical, efusão de subdural crônica ou higroma, e alterações vasculares. Lesões em substância branca podem estar presentes antes das alterações clínicas da doença e podem evoluir para atrofia. Apresentamos relato de caso da doença de Menkes com história e evolução típica, descrevendo os achados de neuroimagem na fase inicial da doença que revelaram sinais importantes de comprometimento da substância branca que poderiam conduzir a dúvidas diagnósticas.

**PALAVRAS-CHAVE:** doença de Menkes, neuroimagem.

Menkes disease is a neurological progressive disorder characterized by psychomotor deterioration, drug-treatment refractory epilepsy, and phenotypic characteristics such as thin and brittle hair, hypopigmented, and scattered eyebrows. The hair microscope study shows fragile and brittle filaments curled up in their own axis, which are called pili torti<sup>1-4</sup>. The disease is caused by a defect in intracellular copper transport. It is a disease related to the X located in the Xg 13.3 area. The responsible gene is organized into 23 exons and the mRNA transcript encodes a copper-transporting P-type ATPase and is expressed in all tissues. The clinical picture is due to a deficiency of copper, resulting in defects of key copper dependent enzymes, including lysyl oxidase, cytochrome c oxidase, dopamine  $\beta$ -hydroxylase, tyrosinase, and superoxide dismutase. The pathogenic mechanism is not entirely explained. Depigmentation of hair and

skin pallor are due to tyrosinase deficiency, hypothermia is due cytochrome c oxidase deficiency and lysyl oxidase deficiency causes tortuous arteries in brain with irregular lumen and a frayed and split intimal lining<sup>2,5-7</sup>.

The clinical spectrum of Menkes disease encompasses several distinct variants. Individuals with the mild variant are developmentally delayed with cerebellar ataxia, dysarthria and pili torti, and no seizures. Jankov et al.<sup>8</sup> described a neonatal form with multiple fractures and extensive vascular disease with early death. The occipital horn syndrome is considered Menkes disease variant. Skeletal dysplasia, soft bruisable skin, hyper-extensible joints, diarrhea, and occipital exostoses<sup>6,8-10</sup> characterize it.

Image alterations that were found in more advanced stages of the disease correspond to atrophy sequela lesions and vascular alterations. The early

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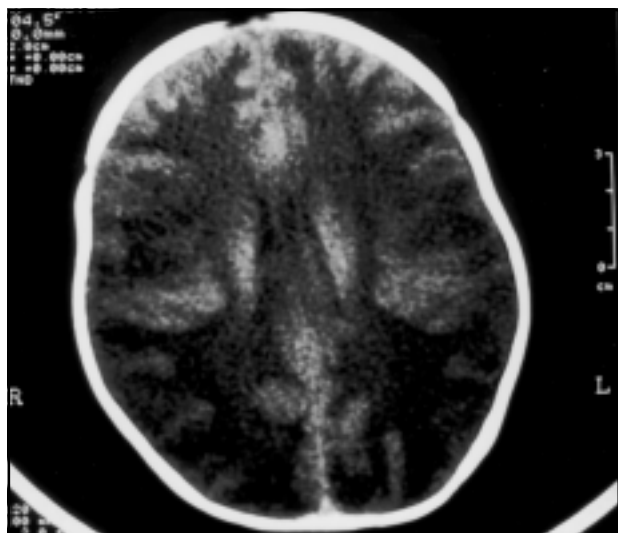


Fig 1. Skull tomography at two months of age displayed hypoattenuation of front-parietal bilateral white matter, more evident to the right and minor in occipital areas.

neuroimaging record shows extensive lesions in white matter that seem secondary to a progressive brain destruction and collapse of the myelination process<sup>1,2,12,13</sup>. We report a case of Menkes disease with neuroimaging study first conducted at two and then at four months of life, with substantial white matter lesion and vascular alterations.

### CASE

LMR, 8 months-old, white male with non-consanguineous parents. Early delivered at 8 months, after pregnancy with no interurrences. At two months of life epileptic manifestation began with various types of crisis, and frequency and intensity progressive aggravation despite the drug-oriented treatment. After crisis onset, the child remained hypoactive, poorly responsive to stimuli, and recurrent hypothermia. During the exam the child presented rectified and hypopigmented eyebrows,



Fig 2. Brain magnetic resonance at four months showed intense bilateral damaging of white matter and tortuosity of medium brain arteries.

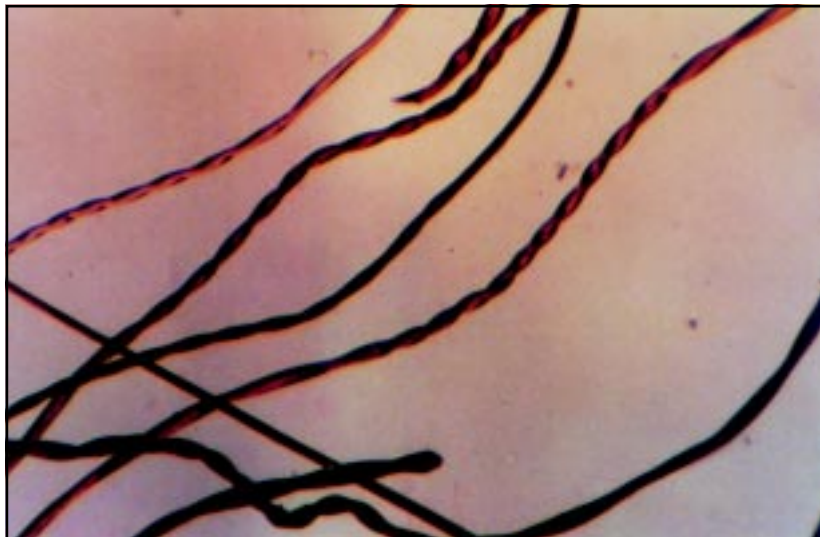


Fig 3. Pili Torti with monoletrix.

micrognathia and scattered thin and brittle hair. Laboratory exams confirmed the Menkes disease diagnostic hypothesis, with copper dosage of 24mg/dl (normal values 70 to 140 mg/dl), and ceruloplasmin of 7 mg/dl (normal values between 20 and 40 mg/dl). The skull tomography at two months of age displayed hypoattenuation of front-parietal bilateral white matter, more evident to the right, and minor damage, in occipital areas (Fig 1). The brain magnetic resonance at four months showed intense bilateral damaging of the white matter, with mild cortical atrophy and vascular alterations, and dilation and tortuosity of the medium brain arteries (Fig 2). The hair microscope analysis showed pili torti and monoletrix (Fig 3).

## DISCUSSION

The pathology of the case at issue has a very suggestive clinical history, confirmed by the copper and ceruloplasmin serum dosage and hair analysis. The skull tomography displayed considerable white matter lesion at two months of life, and included a differential diagnosis regarding other leukodystrophies. Brain magnetic resonance at four months showed intense bilateral damaging of white matter, very similar to diseases primarily affecting white matter. Usually radiological studies of patients with Menkes disease show cerebral atrophy, large subdural collections, and tortuosity of cerebral blood vessels. The neuroimaging study using brain magnetic resonance shows local hypodensity areas, atrophy, necrosis, and gliosis of white matter that may be identified before the phenotypic alterations<sup>1,11,12</sup>. In cases with diffuse and intense damaging of white matter, the arteriopathy with vascular insufficiency probably leads to a deficient myelination process, mainly in semi-oval centers and long tracts<sup>2</sup>. The angiographic alterations are better visualized after three months of age.

Although the pathogenic mechanism of the Menkes disease has not yet been established, we know there is a flaw in the copper absorption by the gastrointestinal tract, and that this element ends up being poorly distributed in the tissues and very reduced in the brain, liver and white cells. Copper histidine is naturally present in normal human serum, histidine was shown to enhance the uptake of copper in human trophoblast cells in the presence of serum, and

this is considered to be due the release of copper bound to albumin. Treatment with copper histidine had been described. In the mild variations copper histidine treatment led to normalization of plasma copper and ceruloplasmin with marked reduction of epileptic discharges, improved muscular tone and increased motor activity. The classical Menkes disease therapy is not effective and the parenteral reposition during the first weeks of life raises the copper serum level but not that of ceruloplasmin, thus not preventing neurological deterioration<sup>2,5,7,13</sup>.

The early diagnosis is mainly required for genetic counseling, X-linked inheritance with a recurrence risk of 50% for son's affected and 50% of daughters to be carriers. Less aggressive forms of the disease with compatible laboratory exams have also been described<sup>2,11</sup>. The intra-uterus diagnosis can be performed through amniocentesis both using copper dosages in culture of amniotic liquid cells and chorionic villi cells; however, false negatives may occur as pregnancy age progresses<sup>11</sup>.

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