Arq Neuropsiquiatr 2007;65(1):157-160

MENKES´ DISEASE

Case report

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ABSTRACT - Menkes' disease is a rare neurodegenerative disorder due to an intracellular defect of a copper transport protein. We describe a 7 months male patient who presented with seizures, hypoactivity and absence of visual contact. The investigation disclosed *pilli torti* and *thrycorrexis nodosa* in the hair, low serum levels of both copper and ceruloplasmin, brain magnetic resonance study showed atrophy and white matter hypointensities on T1-weighted images, electroencephalogram reveals moderate background activity disorganization and epileptiform activity, and muscle biopsy with type 2 fiber atrophy. The clinical, laboratorial, genetic, muscle biopsy and neurophysiological findings in Menkes' disease are discussed.

KEY WORDS: Menkes' disease, copper, ceruloplasmin.

Doença de Menkes: relato de caso

RESUMO - A doença de Menkes é uma rara desordem neurodegenerativa causada por defeito intracelular na proteína transportadora do cobre. Descrevemos um paciente de 7 meses, masculino, com crises convulsivas, hipoatividade e ausência de contato visual. A investigação demonstrou *pilli torti* e *thrycorrexis nodosa;* níveis séricos baixos de ceruloplasmina e cobre; RNM de crânio com atrofia e redução de sinal da substância branca (imagens em T1); eletroencefalograma com moderada desorganização da atividade de base e atividade irritativa; e biópsia muscular com atrofia de fibras do tipo 2. As características clínicas, laboratoriais, genéticas, biópsia muscular e estudo neurofisiológico na doença de Menkes são discutidas.

PALAVRAS-CHAVE: doença de Menkes, cobre, ceruloplasmina.

Menkes' disease (MD) is a degenerative disease, with an X-linked recessive inheritance, characterized by involvement of the nervous system due to an intracellular defect of the copper transport protein[1-5]. Clinical diagnosis can be confirmed by quantifying serum and urinary levels of copper, serum ceruloplasmin level and genetic study[5]. Nevertheless, neurophysiological studies and muscle biopsy can be used to helping in the diagnosis[6].

We describe the characteristics on patient with MD, because only few cases have been described since the first report of the disease.

CASE

A 7-months-old, white, male patient presented with a history of clonic seizures compromising only the left upper-limb, along with hypoactivity and absent visual contact since 2 months-old. At three months seizures evolved to a more wide-spread compromise, with clonic movements of right upper-limb and lower-limb, along with blinking movements and he was started on phenobarbital 4 mg/kg qid and sodium valproate 30 mg/kg qid, obtaining a partial control of seizures. The patient had been born at term, vaginal delivery, without any sort of complication; his parents were not related and prior to his admission he had had 5 episodes of pneumonia.

Physical examination showed a pale, hydrated boy, somewhat little active, tough reactive to examination, with bilateral inguinal hernias. Facial features included epicanthus, thin, brittle hair with a metallic gray tone (Fig 1A). He also had a generalized increase in subcutaneous fat with loose, thin skin. Neurological examination revealed a hypoactive baby, without social grinning, who could not maintain visual contact nor follow objects, with compromised sucking reflex. Fundoscopic images were normal. He was also hypotrophic, with diminished muscle tone in the axial muscles, unable to head sustain, but with an increase in muscle tone of the extremities. Muscle strength was slightly diminished, deep tendon reflexes were increased with extension plantar reflex response.

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Received 19 June 2006, received in final form 8 August 2006. Accepted 9 October 2006.

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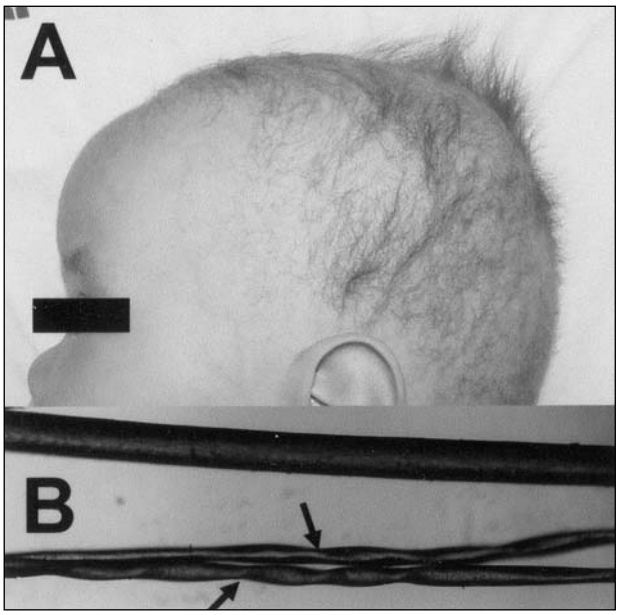

Fig 1. (A) Typical facial features of MD patients include epicanthus, thin and breakable metallic gray hair strands. (B) Microscopic examination of hair showed abnormal torsion of hair strands along their own axis (arrow: pilli torti) when compared to normal hair strands.

The investigation showed cerebrospinal fluid, red and white blood cell count, platelet count, sodium, potassium, creatinine, alkaline phosphatase, gamma-GT, alanine and aspartate aminotransferases, creatine kinase, bilirubins, lactate, albumin, thyroid hormones and panel for inborn metabolic errors all normal. The serum ceruloplasmin level (82 mg/L; normal value >200 mg/L) and serum copper level (<0.1 μg/L; normal value: 0.7 to 1.3 μg/L) were decreased. The X-ray of long bones presented epiphyseal fragmentation in the distal extremities of humerus and femurs. Optic microscopy of a hair sample disclosed *pilli torti* with nodular thickening at the fracture points *(thrycorrexis nodosa)* (Fig 1B).

Magnetic resonance imaging (MRI) showed at two months of age abnormalities of signal intensity in the white matter of both cerebral hemispheres, more evident over the right temporal region (Fig 2A). After 5 moths a new MRI study disclosed diffuse brain atrophy, dural thickening and large subdural and epidural collections, suggestive of chronic blood clots in different stages (Fig 2B).

On the electroencephalogram (EEG) there was an abnormally disorganized background activity without any predominance of side, intermingled with highly active epileptic activity, mostly over the parieto-rolandic areas bilaterally, which was immediately followed by diffuse voltage depression. Sensitive nerve conduction of median and ulnar nerves and motor nerve conduction were normal. Needle electromyography (EMG) disclosed low amplitude, short motor unit potentials, a great density of short polyphasic potentials and increased muscle recruitment (biceps, tibialis anterior and quadriceps muscles). Muscle biopsy analysis, according to standard procedures (hematoxylin-eosin, modified Gomori-trichrome, oil red O, PAS, cresyl violet, siryus red, ATPases, NADH, nonspecific esterase, myophosphorylase, acid phosphatase, alkaline phosphatase, succinate dehydrogenase, cytochrome-C oxidase and adenylate deaminase)[6], showed only marked atrophy of type 2 muscle fibers.

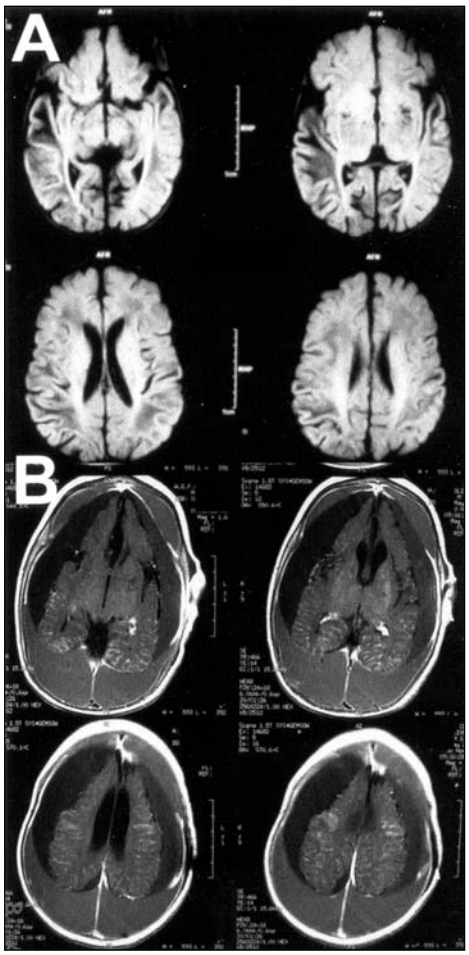

Fig 2. MRI, with axial slices revealed that: (A) at two months of age showed hypointensities of white matter, with higher signal intensity over right temporal lobe; and (B) at seven months of age T1-weighted slices showed hematomas ranging from isointense to moderate hypointense signal over the subdural and epidural regions, with marked atrophy of the whole brain.

All studies were done following informed consent of parents.

DISCUSSION

Menkes' disease main clinical features make a triad of developmental delay, neurological degeneration and hair abnormalities found only in this disease[1]. The incidence is of one case for every 100,000 to 250,000 births; its unique features can be found early in the first few months after birth and include

skin, hair and connective tissue abnormalities, early onset seizures and decreased muscle tone with progressive deterioration[1-3]. MD was first described in 1962 by Menkes et al. who reported the affected subjects, all of them male and from the same family[4]. The genetic mutation responsible for the disease was first identified in 1993, leading to a defect in the production of an intracellular protein involved in copper transport[7,8]. Copper is a key cofactor of several different enzymes and it's absence can secondarily impair the action of other enzymes such as cytochrome C oxidase, superoxide-dismutase, tyrosinase and lisine oxidase, which then leads to a multisystemic compromise, especially the central nervous system[1,9,10].

The classical form of MD comprises a neurological degenerative syndrome (cognitive compromise, ataxia, seizures, retarded neurological development), arterial abnormalities, bony changes like osteoporosis, bladder diverticulum , changes of connective tissue and skin and hair abnormalities *(pili torti, monilethrix and trichorrhexis nodosa)*[1-5]. Over time neurological symptoms and arterial anomalies of abdominal and cranial arteries become more severe, with symptoms suggestive of symptomatic West's syndrome, or conversely a drug-resistant progressive epileptic syndrome[5,11,12]. Bilateral inguinal hernias in MD had previously been described in mild forms of the disease, like the occipital horn syndrome (mild variant form of DM), although they can also be found in the classical presentation; they are probably due to structural abnormalities of connective tissue[5,13].

Early diagnosis is uncommon, as the first signs can be somewhat unspecific, with more prominent features (like the unique hair abnormalities) developing over time, sometimes at the same time as neurological compromise[14]. Serum levels of copper and ceruloplasmin should be measured after the third week (because as they can be low in normal children during this time-window) and low levels of both are needed to confirm the diagnosis[5]. X-rays can be helpful in disclosing epiphysary hairlines in the extremities of long bones, whereas bone densitometry can show mild to severe osteoporosis in the majority of patients[5].

MRI abnormalities correspond to neuronal loss and range from isolated cerebral or cerebellar atrophy or both combinations, subdural collections and cerebral hemorrhage[15-17]. Those evolve over time and are associated with a poor prognosis[15,16]. Vessel-wall compromise might be the pathological change responsible the majority of these abnormalities, especially when subdural and epidural collections are found[17-20]. Severe atrophy and subdural and epidural collections are the end-stage abnormalities found late in the evolution of the disease, such as in our case.

The first report of the EEG changes in MD included four patients with multifocal spike-and-wave activity[15]. Jayawant et al reported a rapidly progressive and unfavorable evolution with drug-resistant seizures and status epilepticus[11]. Other abnormal EEG patterns have been described in association with the disease, like hypsarhythmia and background activity changes[11,12,15]. Normal background activity without epileptiform activity was reported in 9 children followed over 27 months in a study of the prognosis of the disease, suggesting that the EEG changes might correspond to physiopathological changes in expression biochemistry of copper in brain[15].

The EMG pattern has not yet been established in MD because exist few studies focus on the electrophysiological abnormalities in this disorder. Nevertheless, we believe that EMG findings vary according to the time when the study is performed and the severity of the disease. In early cases EMG can be normal, whereas in those patients in late stages of the disease an EMG study can show abnormalities suggestive of myopathic compromise. This pattern can be found if MD is associated with mitochondrial myopathy, with abnormal motor unit potentials with reduced amplitude and duration, an increase in the density of short polyphasic potentials and increased motor unit recruitment[16,21].

The pathophysiological basis of these electrophysiological changes can either be due to changes in nerve and muscle excitability, or to abnormalities in the transmission of nerve impulses caused by the impaired copper metabolism, somewhat similar to what is found in other diseases affecting copper metabolism like Wilson's disease[22].

Additionally, the findings in muscle biopsy can range from mild changes found in a myriad of other disease, like an increase of variability of muscle fiber size, atrophy of type I and II muscle fibers, lack of fiber predominance, with mostly normal histological findings in muscle fibers[18,19]. However, in those patients in late stages of MD mitochondrial compromise (oxidase c cytochrome complex) ragged red fibers can be found, similar to those found in mitochondrial myopathies[18,19]. The lack of copper may result in these changes, as copper is a key cofactor in the mitochondrial respiratory chain[18,19].

The treatment options are limited because the brain-blood barrier acts as an obstacle to copper delivery without the transporter protein[1,2,5,16,17]. Also, copper is poorly absorbed by the gastrointestinal tract, without attaining an adequate serum level, mainly as copper histidine by parenteral reposition (200-1000 μg/day), might be beneficial in some cases when given early in the course of the disease[2,5,16,17]. There is no evidence, at present, of benefit of parenteral administration of copper associated with D-penicillamine or vitamin E[5]. Treatment of MD patients must also include, when needed, anti-convulsive drugs[12,15].

Acknowledgments – The authors would like to thank Dr. Francisco M.B. Germiniani by english review of the manuscript.

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