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*Full title* : ATP7A mutation with occipital horns and distal motor Neuropathy: a continuum.

*Short title* : Occipital Horn Syndrome and distal motor Neuropathy: a continuum.

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Abstract :

*ATP7A*-related copper transport disorders are classically separated in three pathologies according to their severity, all inherited in an X-linked recessive manner: Menkes disease (MD, OMIM #309400) which represent more than 90% of cases; occipital Horn Syndrome (OHS, OMIM #304150) and *ATP7A*-related distal motor neuropathy also named X-linked distal spinal muscular atrophy-3 (SMAX3, OMIM #300489) (1). Although there is no clear cut correlation between Cu and ceruloplasmin levels in *ATP7A* related disorders, these three entities probably represent a continuum partly depending on residual functional *ATP7A* protein (2). Thus far OHS and SMAX3 only partially overlap. In fact patients with OHS usually have no distal motor neuropathy signs but, on the other hand, occipital horns, which are the main sign of OHS, have not been described in SMAX3 patient. We describe here a patient bearing a missense *ATP7A* mutation with associated signs of distal motor neuropathy as well as occipital horns, confirming that OHS and SMAX3 are a continuum.

Keywords:

*ATP7A*

Menkes disease

Occipital Horn Syndrome

X-linked distal spinal muscular atrophy-3

Dysautonomia

## Introduction :

Copper metabolism defects were first described in their most severe form named Menkes disease (MD) (3). MD is a neurodegenerative disorder starting in infancy and often leading to death in early childhood. Serum copper and ceruloplasmin levels are very low, and some patients respond to parenteral copper histidine treatment (4–6). Diagnosis is based on suggestive clinical findings, and confirmed by biological results and presence of a pathogenic variant in *ATP7A* gene. Apart from neurodevelopmental regression, seizures and temperature instability have been noted. Extra-neurological symptoms, among others, include skeletal changes such as osteoporosis, abnormal hair (pili torti), intracerebral hemorrhages, bladder diverticulae, diarrhea, cutis laxa and hyperextensible joints. Occipital horns have not been described in the neonatal period in MD patients, but may be present after 2 years of disease evolution (7) or in long term surviving patients who receive parenteral copper histidine (8). Interestingly, not all treated patients develop occipital horns (9). Some children have been described as surviving beyond childhood (10,11). They share some features with classical Menkes disease especially cutis laxa, pili torti and milder developmental delay but they also show ataxia which is not a prominent feature of classical MD. Occipital horns are described in some of these patients which therefore show overlapping symptoms of classical MD, mild MD and Occipital Horn Syndrome (OHS).

OHS prominent features are skeletal abnormalities including occipital horns and dysautonomia. The latter manifests through chronic diarrhea, syncopes and orthostatic hypotension. Intelligence is normal to subnormal. Other features include bladder

diverticulae and hyperextensible joints and skin enlightening the fact it was previously known as type IX Ehlers Danlos Syndrome (11,12,14). When described, electroneuromyography in these patients is normal, showing no signs of motor neuropathy (12,15). Serum copper and ceruloplasmin are decreased and can be as low as in classical MD patients. (16,17)

*ATP7A*-related distal motor neuropathy (SMAX3) may start in childhood but it is usually diagnosed in adulthood as it is very slowly progressive. The main symptoms are distal lower limb weakness and gait instability. Clinical findings include distal muscle wasting and foot deformity with normal, reduced or absent deep tendon reflexes, but hands may subsequently be affected. Electrophysiological studies show decreased motor action potentials with normal or slightly reduced motor conduction velocity and normal sensory nerve conduction. The few patients described in literature do not exhibit skeletal features such as occipital horns. Skin and joints are described as normal, and dysautonomic signs have been reported once (18). Serum copper can be in normal range (1) or slightly low (18).

In 1993 *ATP7A* was identified as the causal gene for Menkes disease. (19–21) In 1995 mutations were observed in two Occipital Horn Syndrome patient (22). More recently SMAX3 was also associated with *ATP7A* mutations (1,23). All three are inherited in an X-linked recessive manner.

We describe here a patient bearing a missense *ATP7A* mutation exhibiting associated signs of distal motor neuropathy as well as occipital horns and dysautonomia. The aim of this report is to improve knowledge on two rare diseases and confirm that OHS and SMAX3 are part of a continuum.

## Clinical report and diagnostic tests:

The patient has no familial medical history. He noted the first symptoms in childhood with chronic diarrhea but medical investigations started in adulthood due to progressive worsening. The only noticeable event in childhood was inguinal hernia surgery. Since the age of 20 he suffered from daily syncope, erectile dysfunction, progressive gait instability with lower limb muscle weakness. He also described cold-induced acrocyanosis and heat-induced acral erythema. In the most recent years he describes pollakisuria. He remained active as a restaurant chef but described asthenia and envisaged a career change.

At the age of 42, one of his syncope led to a brachial plexic injury. Electrophysiological studies confirmed the plexic injury, but also showed a more diffuse neuropathy with subnormal nerve conduction velocities and compound muscle action potential amplitude but prolonged distal latency on the four limbs, and no sensory involvement but signs of chronic denervation on the two lower limbs and fasciculations (figure 1). Echocardiograph did not show arterial tortuosity, electrocardiography evidenced isolated bradycardia and supine/standing positions showed orthostatic hypotension with blood pressure measured from 130/65 to 65/40 associated with tachycardia and fainting. Vesical ultrasound showed no bladder diverticulum. Cranial CTscan without contrast was considered normal.

At clinical examination the patient was 1.64m (5<sup>o</sup> percentile), and weighted 51 kg (<5<sup>o</sup> percentile). OFC was 56.5 cm (50<sup>o</sup> percentile). He showed a slight joint laxity and had experienced several sprains of both ankles. His skin seemed slightly thin with very visible venous network, but was otherwise normal. Subcutaneous fat seemed

decreased giving cheeks and eyes a sunken appearance. He showed highly arched but otherwise normal palate. Neurological examination showed asymmetric calf muscles wasting whereas thigh muscles seemed hypertrophic. The patient described fasciculations of both upper and lower limbs. His feet also showed muscle wasting (figure 2). No muscle weakness or sensitive impairment was observed. Upper limb deep tendon reflexes were normal but patellar reflexes were very brisk and Achilles heel deep tendon reflexes were abolished. There was no Babinski sign. Subsequent Fludrocortisone treatment slightly improved his orthostatic hypotension.

Genetic exams were then initiated and led to the discovery of an *ATP7A* mutation. Reinterpretation of the CTscan showed occipital horns (figure 3). Subsequent serum copper level and ceruloplasmin were slightly decreased at 11 $\mu$ mol/l (reference value over 12.5 $\mu$ mol/l) and 1.61  $\mu$ mol/l (reference value 2  $\mu$ mol/l) and could not be controlled before death.

At 46 years old, the patient suddenly died in his room. There was no autopsy to our knowledge.

#### Material and Methods:

Informed consent was obtained from the patient as required. Genomic DNA was extracted by standard methods. NGS strategy was performed using an 89-genes-CMT-custom panel prepared by Ampliseq and sequenced on Proton (Life technologies); Sequences were mapped on hg19/GHCh37. Pathogenic variants were verified by Sanger sequencing. Variants were evaluated with Alamut-Mutation-Interpretation Software (Interactive-Biosoftware, Rouen, France).

#### Results:

DNA analysis showed a pathogenic variant in the *ATP7A* gene : NM\_000052.7: c.2576A>G ; NP\_000043.4: p.(Asp859Gly). The affected amino acid is highly conserved across species. It is located in the actuator domain of the protein, next to a potential p97/VCP binding site (24). The pathogenic variant was not found in several databases (GnomAD, Ensembl, ClinVar, dbSNP). It was predicted deleterious by four softwares (SIFT, Polyphen, UMDP, GERP). Familial segregation showed that the pathogenic variant was not present in the asymptomatic sister of the patient, but as both of his parents were dead familial analyses could not be pursued. 2015 ACMG criteria for variant classification are: PM1, PM2, PM3, PM6, PP3, PP4. Classification of the variant is 4: likely pathogenic.

Data are available upon request. Sequence traces are available in supplementary figure.

#### Discussion:

Pathogenic variants in *ATP7A* cause MD, OHS or SMAX3. Proof has already been given that MD and OHS overlap. OHS and SMAX3 were recently shown to overlap as a patient with SMAX3 and dysautonomia signs was described (23). This patient, bearing a novel missense pathogenic variant in *ATP7A* shows signs of OHS including the classical radiological aspects and dysautonomia but he also had a distal motor neuropathy. These features confirm that OHS and SMAX3 overlap.

Dysautonomia was the main symptom of our patient and *ATP7A* pathogenic variants should be considered as a possible diagnosis in such case. Since the clinical findings are quite unspecific, the diagnostic odyssey may be prolonged. Indeed, signs of peripheral neuropathy can easily go unnoticed by the patient and deep tendon reflexes can be preserved. Serum copper and ceruloplasmin can be normal or subnormal. Diagnosis then relies on a series of arguments including radiological changes such as

pathognomonic occipital horns, and electrophysiological studies showing signs of peripheral neuropathy.

Even though the cause of death was not determined in this case, early onset follow-up for dysautonomia seems important as it may induce severe consequences such as a severe head trauma, making it is a very important symptom to detect and to treat, although it can be only partially responsive to treatment. Muscle weakness follow-up must not be overlooked and appropriate management is often helpful.

Finally, as this is an X-linked disorder, it has a familial impact with the potential of carrier female testing giving a possibility of adapted genetic counselling.

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Legends:

Figure 1:

Electroneuromyographic studies showing right upper limb plexic injury and right carpal tunnel syndrome, diffuse neuropathy with subnormal conduction velocities and compound muscle action potential amplitude but prolonged distal latency on the four limbs, and no sensory involvement but signs of chronic denervation.

Figure 2:

Photographs of the patient showing decreased subcutaneous fat, calf and feet muscle wasting.

Figure 3:

Cranial CT scan showing occipital horns.

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