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CASE REPORT

# Mitochondrial Disorders May Mimic Amyotrophic Lateral Sclerosis at Onset

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# اضطرابات المايتوكندريا قد تحاكي التصلب الجانبي الضموري في بداياته

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**ABSTRACT:** Similarities between a mitochondrial disorder (MID) and amyotrophic lateral sclerosis (ALS) fade with disease progression and the development of mitochondrial multiple organ dysfunction syndrome (MIMODS). However, with mild MIMODS, a MID may still be misinterpreted as ALS. We report a 48-year-old male who presented to the Neurological Hospital Rosenhügel, Vienna, Austria, in February 2001 with slowly progressive weakness, wasting and left upper limb fasciculations which spread to the shoulder girdle and lower limbs. Additionally, he developed tetraspasticity and bulbar involvement. He had been diagnosed with ALS a year previously due to electrophysiological investigations indicative of a chronic neurogenic lesion. However, a muscle biopsy revealed morphological features of a MID and a combined complex-II/III defect. Nerve conduction studies were performed over subsequent years until February 2011. This case demonstrates that MIDs may mimic ALS at onset and begin as a mono-organ disorder but develop into a multi-organ disease with long-term progression. A combined complex II/III defect may manifest with bulbar involvement.

***Keywords:*** Motor Neuron Disease; Mitochondrial Disorders; Amyotrophic Lateral Sclerosis; mtDNA; Oxidative Phosphorylation; Case Report; Austria.

**الملخص:** يختفي تدريجيا التشابه بين اضطرابات المتقدرة (MID) والتصلب الجانبي الضموري (ALS) مع تقدم المرض، ومع ظهور متلازمة الاختلال المتعدد الأعضاء المتقدري (MIMODS). غير أنه في حالات MIMODS المعتدلة، فقد يشخص MID على أنه ALS عن طريق الخطأ. ونعرض هنا لحالة رجل عمره 48 عاما في مستشفى روزنهيقل للأمراض العصبية في مدينة فيينا بالنمسا في فبراير من عام 2001م كان يشكو من ضعف تدريجي، وهزال، وارتجاف حزمي في الطرف العلوي الأيسر، امتد لاحقا إلى حزام الكتف والأطراف السفلى. ثم أظهر المريض شناجا رباعيا مع اكتناف بصلي. وكانت حالة المريض قد شخصت قبل عام على أنها ALS بناء على فحوصات كهربية–فيزيولوجية أشارت إلى آفة مزمنة عصبية المنشأ. إلا أن فحص خزعة من العضل أوضح أن خصائص مورفولوجية دلت على الإصابة بـ MID، متزامنة مع عيب في مركب – II/III. وأجريت دراسات حول النقل العصبي بعد سنوات من الفحوصات السابقة حتى عام 2011م. توضح هذه الحالة إلى أن حالات الـ MID قد تحاكي ALS في بداية المرض، وتبدأ في عضو واحد، ولكنها تتطور إلى أن تصبح اختلالا متدرجا في عدد من الأعضاء. وقد يحدث عيب في مركب – II/III مع اكتناف بصلي.

**مفتاح الكلمات:** مرض العصبون الحركي؛ اضطرابات المتقدرة؛ التصلب الجانبي الضموري؛ الحمض الريبي النووي منزوع الأكسجين؛ فسفرة تأكسدية؛ تقرير حالة؛ النمسا.

It is well established that mitochondrial disorders (MIDs) may phenotypically mimic motor neuron disease.[1–3] These similarities fade with disease progression and the development of mitochondrial multiple organ dysfunction syndrome (MIMODS).[4,5] However, if progression is slow and MIMODS is mild, a MID may still be misinterpreted as amyotrophic lateral sclerosis (ALS), as with the case presented below.

## Case Report

A 48-year-old Caucasian male presented to the Neurological Hospital Rosenhügel, Vienna, Austria, in February 2001. The patient had first noticed occasional weakness of the left brachial biceps muscle at 36 years of age. Four years later, fasciculations occurred for the first time in the shoulder girdle muscles which spread bilaterally to other muscles and the lower limbs during the following years. By the age of 46 years, the patient's muscle weakness had spread to the left intrinsic hand muscles, particularly those of the left thumb and fifth finger. The muscle weakness increased when it was cold and led to involuntary muscle contractions. He was an amateur cyclist, regularly cycling 4,000 km per year. After cycling, he often experienced aching of the neck extensor muscles which prevented him from sleeping. Previous creatine kinase values for the patient were unavailable.

One year before presentation, the patient was diagnosed with ALS by a neurologist based on clinical and electrophysiological findings. There was

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slight wasting of the shoulder girdle muscles and diffuse wasting of the left upper limb muscles with predominance of the left intrinsic hand muscles. Fasciculations were seen in all muscles of the left upper limb and the shoulder girdle, tendon reflexes were exaggerated and pyramidal signs were bilaterally positive. Cerebral magnetic resonance imaging (MRI) was normal and an MRI scan of the cervical spine showed only mild degenerative alterations. The diagnosis of ALS was confirmed by other neurologists. The patient was prescribed riluzole and high-dose vitamin D without effect. Immunoglobulins were prescribed without rationale or beneficial effect. Following the initiation of riluzole treatment, the patient developed muscle cramps in the distal lower limb muscles and his resting pulse occasionally reached 130 beats/minute. Although levothyroxine was prescribed by endocrinologists to prevent growth of diffuse multinodular goitres, the patient was non-compliant with the treatment.

At presentation to the Neurological Hospital Rosenhügel, the patient had developed liquid dysphagia and chewing difficulties. He had often complained of hyperhidrosis over the preceding years. Additionally, his history was positive for hyperlipidaemia and there was a family history of hypoacusis and *gibbus* deformity from his paternal grandfather. Re-examination of the patient revealed wasting of the tongue edges, frequent fasciculations of the tongue, distal weakness with left-sided predominance, diffuse wasting, exaggerated tendon reflexes, positional tremors with left-sided predominance, fasciculations in all muscles and positive pyramidal signs for the upper limbs. With regards to the lower limbs, there was weakness of the left foot extensors (grade M5-), exaggerated tendon reflexes and bilateral positive pyramidal signs.

The results of multiple nerve conduction studies performed over the following years are shown in Table 1. Needle electromyography of the right brachial biceps muscle showed fibrillations and fasciculations with bizarre morphology at 20/20 sites, increased mean motor unit action potential duration, increased *polyphasia* and satellite potentials and a reduced interference pattern at maximal voluntary contractions. His creatine kinase levels were slightly elevated (maximal value: 97 U/L; normal value: <70 U/L) and he had hypercholesterolaemia. However, the results of a lactate stress test were normal. Transcranial magnetic stimulation revealed increased central motor conduction time (CMCT) of the C8 motor neuron on the right side, normal CMCT of the C8 motor neuron on the left side and normal CMCT of the S1 nerve root bilaterally. Ganglioside GM1 antibodies were normal. An abdominal ultrasound revealed a double kidney on the right side.

Based on the patient's history and the existence of atypical clinical features—including hyperhidrosis, goitre and hyperlipidaemia—MIMODS involving the central nervous system, the peripheral motor, sensory and vegetative nerves, the endocrine system and the skeletal muscles was suspected. A muscle biopsy from the lateral *vastus* muscle showed neurogenic features with grouped atrophic fibres and a fibre-type grouping; however, the biopsy also showed indications for a MID, including a coarsening of the mitochondrial pattern on oxidative enzyme and Gomori trichrome stains. Immunohistochemistry revealed cytochrome c oxidase-hyporeactive/negative fibres and electron microscopy indicated the subsarcolemmal accumulation of abnormally-shaped mitochondria. Biochemical investigations of the muscle homogenate revealed a combined complex-II/III defect consisting of succinate cytochrome c-oxidoreductase related to non-collagen protein and citrate synthase. No tests for coenzyme-Q activity were carried out. Screening for common mitochondrial DNA (mtDNA) mutations causing the following conditions was non-informative: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; myoclonic epilepsy with red-ragged fibres; chronic progressive external ophthalmoplegia; Leber hereditary optic neuropathy; neuropathy, *ataxia* and retinitis *pigmentosa*; maternally-inherited Leigh syndrome; non-syndromic myopathy; cardiomyopathy; dementia; diabetes; or encephalopathy. Despite repeated attempts to contact the patient for further investigations, he was subsequently lost to follow-up.

## Discussion

Misinterpretation of a MID as ALS may occur with mild or unnoticeable MIMODS or when the MID starts primarily with motor manifestations and spasticity due to additional cerebral involvement.[4–6] In the presented case, the implications of the thyroid dysfunction, hyperhidrosis, hyperlipidaemia and autonomic and sensory involvement were neglected. In order to avoid misdiagnosis, clinical manifestations should not be ignored and a common cause of seemingly unrelated manifestations should not be excluded. Under these circumstances, patients with suspected ALS should be investigated for a MID. Since most MIDs develop into MIMODS during the disease course, it is usually just a matter of time before MIMODS becomes evident.[4,5]

Nevertheless, it is important to note that ALS may also show morphological evidence of a mitochondrial defect. Hirano *et al.* reported a 65-year-old ALS patient whose muscle biopsy showed 10% ragged-

**Table 1:** Nerve conduction study results of a patient with a mitochondrial disorder mimicking amyotrophic lateral sclerosis at onset

| Nerve | | May 2009 | | August 2009 | | October 2009 | | January 2010 | | November 2010 | | February 2011 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | L | R | L | R | L | R | L | R | L | R | L | R |
| Median | **Motor** | | | | | | | | | | | | |
| | dL in ms | 4.8 | NP | 6.3 | 4.4 | 4.8 | 4.3 | 6.0 | 4.6 | NP | 6.3 | 5.9 | NP |
| | CMAP in mV | 3.0 | NP | 0.9 | 4.2 | 1.8 | 4.6 | 0.8 | 3.2 | NP | 1.5 | 1.3 | NP |
| | NCV in m/s | 48.0 | NP | 41/52* | 49/51 | 52.0 | 59.0 | 41.0 | 56.0 | NP | 57.0 | 41.2 | NP |
| | **Sensory** | | | | | | | | | | | | |
| | SNAP in µV | 40.0 | NP | NP | NP | 28.8 | 15.5 | 55.0 | 40.0 | NP | 34.0 | NP | NP |
| | NCV in m/s | 56.0 | NP | NP | NP | 59.0 | 60.0 | 63.0 | 56.0 | NP | 50.0 | NP | NP |
| | F-wave persistence | NP | NP | NP | NP | 0/10 | 1/10 | NP | NP | NP | NP | 0/10 | NP |
| Ulnar | **Motor** | | | | | | | | | | | | |
| | dL in ms | 3.3 | NP | 3.8 | 3.2 | 2.3 | 3.4 | 3.8 | 3.3 | 4.2 | 4.0 | NP | NP |
| | CMAP in mV | 3.0 | NP | 2.8 | 3.2 | 6.2 | 8.3 | 2.7 | 2.9 | 0.9 | 1.9 | NP | NP |
| | NCV in m/s | 59/43* | NP | 56/45 | 53/58 | 62/51 | 43/41 | 60/33 | 47/53 | 48/38 | 46/28 | NP | NP |
| | **Sensory** | | | | | | | | | | | | |
| | SNAP in µV | 20.0 | NP | 20.0 | 5.0 | 18.8 | 9.5 | 11.0 | NP | NP | NP | NP | NP |
| | NCV in m/s | 61.0 | NP | 55.0 | NP | 51.0 | 54.0 | 48.0 | NP | NP | 30.0 | NP | NP |
| | F-wave persistence | NP | NP | NP | NP | 9/10 | 9/10 | NP | NP | NP | NP | NP | NP |
| Peroneal | **Motor** | | | | | | | | | | | | |
| | dL in ms | NP | NP | NP | 5.5 | 4.5 | 4.0 | 4.5 | 5.1 | 4.8 | NP | NP | NP |
| | CMAP in mV | NP | NP | NP | 4.0 | 8.9 | 10.1 | NP | 3.0 | 3.0 | NP | NP | NP |
| | NCV in m/s | NP | NP | NP | NP | 50.0 | 46.0 | NP | NP | NP | 44.0 | NP | NP |
| Tibial | **Motor** | | | | | | | | | | | | |
| | dL in ms | NP | NP | NP | NP | 3.9 | 3.4 | NP | NP | NP | 4.8 | NP | NP |
| | CMAP in mV | NP | NP | NP | NP | 18.5 | 12.7 | NP | NP | NP | 6.8 | NP | NP |
| | NCV in m/s | NP | NP | NP | NP | 50.0 | 46.0 | NP | NP | NP | 44.0 | NP | NP |
| Sural | **Sensory** | | | | | | | | | | | | |
| | SNAP in µV | NP | NP | NP | 5.5 | NP | 6.1 | 2.0 | 6.0 | NP | NP | NP | NP |
| | NCV in m/s | NP | NP | NP | 40.0 | NP | 42.0 | 43.0 | 38.0 | NP | NP | NP | NP |

*L = left; R = right; dL = distal latency; ms = milliseconds; CMAP = compound muscle action potential; mV = millivolt; NCV = nerve conduction velocity; m/s = metres per second; SNAP = sensory nerve action potential; µV = microvolts; NP = not performed.*

**Values represent the distal and proximal measurements.*

red fibres and 3% cytochrome c oxidase-negative fibres.[7] However, contrary to the present case, no biochemical abnormalities were detected.[7] A number of other reports have described mitochondrial dysfunction in ALS, including decreased complex-I activity, decreased superoxide dismutase 1 function and energy production, increased *apoptosis*, abnormal calcium homeostasis, impaired axonal transport of mitochondria, respiratory chain dysfunction and alterations of the mitochondrial genome and transcriptome.[8–14] There are also indications that mtDNA deletions are more common in individuals with sporadic ALS as compared to healthy controls.[15] Mitochondrial dysfunction in ALS is often regarded as secondary following the exposure of mtDNA to increased oxidative stress.[16]

In the current case, the diagnosis of ALS was eventually excluded due to the long duration of

the clinical course, the multisystemic nature of the phenotype (MIMODS), the muscle biopsy findings, the normal cerebral MRI scan and the biochemical findings. The strongest arguments in favour of a diagnosis of a primary mitochondrial defect were the multi-organ phenotype and the presence of a complex II/III defect. On the other hand, the histochemical findings did not match the biochemical findings. Since no mtDNA mutations could be detected, the complex II/III defect may have instead been due to a mutation in a nuclear DNA-located gene rather than a mtDNA-located gene. However, the precise genetic defect still requires confirmation.

Another point of interest with regards to the current case is the late onset of the disease and its slow progression. The frequency and severity of MIDs are usually increased in children and the disease usually progresses slowly in adults.[17,18] Often, only a single organ is initially affected and other organs are consecutively affected after long periods of time.[19] There is no consistent pattern of organ involvement and no regular sequence among the organs which are affected. Factors which drive the pattern of organ involvement and the speed of progression may include the type of mutation (e.g. protein, transfer/ribosomal ribonucleic acid, helicase or polymerase mutations) or modifying genes and the heteroplasmy rate or the threshold effect in the case of mtDNA mutations.[20]

## Conclusion

This case suggests that a MID can mimic ALS at the onset of the disease and that it may start as a mono-organ disorder and subsequently turn into a multi-organ disease after slow progression over a prolonged period of time. The exclusion of ALS may indicate the presence of a MID and a complex II/III defect may manifest with bulbar involvement. Patients with apparent ALS should be investigated for a MID if atypical manifestations have been noted.

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