An unusual manifestation of Wilson disease presenting with burning feet syndrome

J Rollnik, I Rost, C Marschall, P Wetzel

Background: Wilson disease is rarely associated with peripheral neuropathy. Case Report: We report on a 50 y old male with an unusual manifestation of Wilson disease. The patient presented with burning feet syndrome. Nerve conduction studies revealed a mild axonal and myelin damage. In genetic testing, a homozygous point mutation (c.3207C>A) on the ATP7B gene was found. Conclusions: Physicians should be aware that patients suffering from Wilson disease may present with a broad spectre of symptoms, including signs of polyneuropathy.

INTRODUCTION

Wilson disease is known to cause a variety of neurological and multisystemic manifestations. It may affect liver function, cognition, behaviour, motor and osseomuscular system [1]. Among symptoms of central nervous system involvement movement disorders, major depression, and psychotic symptoms are the most common [2]. An association of Wilson disease and damage of the peripheral nerve system has been observed very rarely [3-6]. In the case of a 17 y old Wilson patient reported by Jung and co-workers [3], deep tendon reflexes were decreased, distal muscles of upper and lower extremities were weak, and sensory examination was normal. Nerve biopsy revealed a mixed myelin and axonal damage [3]. Unfortunately, a genetic testing was not performed.

METHODS

DNA was extracted from EDTA blood with the NucleoSpin Blood Kit according to the protocol of the manufacturer (Macherey-Nagel, Düren, Germany). DNA was stored at 4°C. Exon 14 of the ATP7B gene was amplified using intronic primers (forward: TCCATCTGTATTGTGGTCAG and reverse: G GCCCTCTAGTGGGTTCCTCC).

For PCRs 50 ng DNA (1.2 µl) was added to PCR mixes (28.8 µl) containing 1.5 mM MgCl₂, 200 µM of each dNTP, 0.4 µM oligonucleotides, 0.5 U Taq DNA polymerase and 1 x PCR buffer (MBI Fermentas, St. Leon-Rot, Germany). PCRs were performed in Biometra T1 thermo cycler (Biometra, Göttingen, Germany). Thermo cycler profiles were: 1 cycle at 95°C for 4 min followed by 35 cycles at 94°C 20 sec, 54°C 20 sec followed by 72°C 20 sec and a final step of 72°C for 3 min. PCR products were cleaned using MultiScreen®-PCR 96-Well Filtration System (Millipore, Schwalbach, Germany) according to the recommendations of the manufacturer and controlled on 2% agarose geles stained with ethidium bromide. Cycle sequencing reactions (volume 10-20 µl) contained 1 µl PCR oligonucleotide, 1-3 µl PCR product and 2-4 µl terminator mix (BigDye Kit, Applied Biosystems, Weiterstadt, Germany). Thermo cycler profile consisted of 25 cycles 96°C 10 sec, 50°C 5 sec and 60°C 2-4 min. The DyeEx Spin Kit (Qiagen, Hilden, Germany) was used according to the protocol of the manufacturer to get rid of excess fluorescent terminatoreS. Sequence reactions were automatically analysed on a 3730 Genetic Analyser (Applied Biosystems, Weiterstadt, Germany).

CASE REPORT

We report on a 50 y old Caucasian male suffering from burning feet syndrome for two years (beginning of 2007). The patient’s brother already suffered from Wilson disease.
Elevated serum liver enzyme levels were reported 1½ years prior to diagnosis (August 2007: GPT (ALAT) 73 U/l, GGT 258 U/l). In November 2007, a first neurological examination (including nerve conduction studies) did not reveal any signs of peripheral neuropathy. A gastroenterologist diagnosed liver cirrhosis, portal hypertension, and splenomegaly in March 2008. Liver biopsy showed signs of a fatty liver disease, only. In April 2008, GGT was 316 U/l, GOT (ASAT) 52 U/l, and GPT (ALAT) 61 U/l. First examination of ceruloplasmin showed a low level of 15.0 mg/dl, but the diagnosis of Wilson disease was not taken into consideration. The patient was tested negative for infective or autoimmune hepatitis and hemochromatosis. In August 2008, the following lab results could be obtained: GGT 294 U/l, GOT 48 U/l, GPT 47 U/l, INR 1.38, CHE 3.73 kU/l, albumine 30 g/l. Ceruloplasmin level was low again (14.5 mg/dl), but Wilson disease was not diagnosed.

In December 2008, the patient presented with painful burning feet syndrome. In clinical examination the deep tendon reflexes were normal (only Achilles tendon reflex was disturbed), no palsies were observed. The patient suffered from burning sensations and plantar dysaesthesia. There were no symptoms of a movement disorder, neither any other sign of central nervous system affection. Nerve conduction studies confirmed a mild mixed axonal and myelin damage, Table 1, Fig. 1. Ceruloplasmin level was low (12.5 mg/dl), total serum copper was normal (79 µg/dl), but calculated free serum copper was increased (41.5 µg/dl). The ophthalmologist found no Kayser-Fleischer corneal rings.

We did a genetic testing for Wilson disease revealing a homozygous point mutation: c.3207C>A (His1069Gln, exon 14, ATP7B gene). Thus, Wilson disease was confirmed and a therapy with d-penicillamine was started. No other cause of polyneuropathy was found (no diabetes, no alcohol abuse, no inflammatory disease).

**Figure 1**
Table 1: Nerve conduction studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>amplitudes</th>
<th>conduction velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>right peroneal</td>
<td>↓ (1.6 mV)</td>
<td>normal</td>
</tr>
<tr>
<td>left peroneal</td>
<td>↓ (1.7 mV)</td>
<td>normal</td>
</tr>
<tr>
<td>left tibial</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>right tibial</td>
<td>↓ (33 m/s)</td>
<td>(40 m/s)</td>
</tr>
<tr>
<td>right sural</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>left sural</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>right sural</td>
<td>↓ (1 µV)</td>
<td>normal</td>
</tr>
</tbody>
</table>

**Figure 2**
Fig. 1: Nerve conduction study of the left peroneal nerve. There was a mild mixed axonal (reduced CMAP amplitudes, 1.7 mV) and myelin damage (reduced motor conduction velocity, 33 m/s).

**COMMENT**

Wilson disease rarely leads to an affection of the peripheral nerve system [3-6]. Like in a previous case (association of Wilson disease and polyneuropathy) [3], we confirmed a mild myelin and axonal polyneuropathy. The major symptom was a burning feet syndrome. Since liver diseases (e.g. hepatitis C) may lead to painful plantar sensations as well [7], the definite cause of burning feet in this particular case (abnormal copper metabolism vs. hepatopathy) cannot be determined. However, burning feet occurred before elevated serum liver enzymes were detected.

Many Wilson disease mutations are known [8], but their genotype/phenotype correlation remains uncertain. Unfortunately, in a previous case no genetic testing was performed [3], so it cannot be said whether both cases are caused by the same mutation in the ATP7B gene or not. The c.3207>A mutation found in this case accounts for at least 30% of the mutations found in patients of European descent.
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While Stapelbroek et al. [9] found this mutation to be associated with a late presentation of neurological symptoms, this correlation could not be confirmed by Vrabelova and co-workers [10]. On the contrary, they found a wide clinical spectrum in homozygote patients even in one and the same family. However, in line with previous findings [9], a late onset of neurological symptoms was present in our case, too.

An ongoing collection of detailed case reports together with an examination of the underlying genetic disturbance will be necessary to understand different phenotypes (peripheral vs. central nervous system involvement) and additional genetic or environmental factors that may influence the variable expression of known mutations in Wilson disease.

References

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