

Peripheral neuropathy in Whipple's disease: A case report

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SUMMARY

Whipple's disease is a chronic multisystem inflammatory disease with predominantly gastrointestinal manifestations due to *Tropheryma whipplei* infection. Typical neurological abnormalities include dementia, eye movement abnormalities, hypothalamic dysfunction and oculomasticatory myorhythmias. The literature on peripheral neuropathy in Whipple's disease is sparse and the involvement of peripheral nerves in Whipple's disease has not been documented convincingly so far.

We present a case of Whipple's disease presenting by axonal peripheral neuropathy without gastrointestinal involvement. The diagnosis was confirmed by a sural nerve biopsy and consequent PCR of the sample. All clinical signs disappeared progressively during the antibiotic therapy. Two years after the *T. whipplei* infection, the patient developed dopa-sensitive Parkinson's disease, although these two events seem to be unrelated.

This case illustrates the value of peripheral nerve biopsy in cases of axonal neuropathy of unexplained origin and extends the clinical spectrum of Whipple's disease to a new modality.

Keywords: Whipple's disease – peripheral nerve – axonal neuropathy – polymerase chain reaction – electron microscopy

Periferní neuropatie u Whippleovy choroby: Popis případu

SOUHRN

Whippleova choroba je mutlisystémové onemocnění s převážně gastrointestinální manifestací, způsobné infekcí *Tropheryma whipplei*. Mezi typické neurologické poruchy patří u této choroby demence, oko-hybné poruchy, hypothalamická dysfunkce a okulomastikatorní myorhythmie. Postižení periferního nervu zatím nebylo u této choroby přesvědčivě zdokumentováno.

Popisujeme případ Whippleovy choroby, která se projevila periferní neuropatií axonálního typu bez postižení zažívacího traktu. Diagnóza byla potvrzena biopsií periferního nervu s následnou konfirmací pomocí PCR. Příznaky neuropatie vymizely během terapie antibiotiky. Dva roky poté se u pacienta rozvinula dopa-senzitivní Parkinsonova choroba; tyto dvě události se ale zdají být bez souvislosti. Náš případ dokumentuje přínos biopsie periferního nervu v případech axonálních neuropatií neznámé etiologie a rozšiřuje klinické spektrum symptomatologie Whippleovy choroby.

Klíčová slova: Whippleova choroba – periferní nerv – axonální neuropatie – PCR – elektronová mikroskopie

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Additional video file
is available at

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Whipple's disease (WD) is a rare chronic multisystem infection caused by *Tropheryma whipplei* (1). Most common presentations include fatigue, profound weight loss and various gastrointestinal signs from constipation to diarrhea. Fever, arthralgias and peripheral lymphadenopathy are also frequent. The clinical picture is often insidious and non-specific, which prolongs the time between the first signs and the diagnosis. Neurological manifestations of WD (Neuro-Whipple) are rare and usually central with cognitive

pairment, supranuclear ophthalmoplegia, psychiatric features, oculomasticatory myorhythmias, and hypothalamic dysfunction (2–4). The involvement of peripheral nerves in Whipple's disease is extremely rare and it has not been documented convincingly in the literature so far.

Here we present the first case of WD presenting by peripheral neuropathy without GIT involvement, confirmed by sural nerve biopsy and consequent PCR of the sample.

CASE REPORT

A 64-year old man with a history of arterial hypertension and mild depression developed over 6 months progressive, involuntary buccolingual and palpebral movements associated with increasing fatigability and nocturnal leg paresthesias. The patient did not complain about any gastrointestinal disturbances and he had no weight loss for the given period.

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On admission, incessant rhythmic protrusion and retraction of the tongue and palatine elevation and depression synchronized with eye blinking and convergent nystagmoid jerks were observed. These increased with emotional excitation and diminished during sleep. Occasionally, uvular myoclonus and postural tremor, with a frequency similar to facial movements, occurred.

Moreover, clinical examination revealed peroneal fasciculations, distal sensory loss and areflexia of both lower limbs suggesting symmetric peripheral neuropathy. The muscle tonus and voluntary movements on the extremities were normal, with no signs of pyramidal tract involvement. The patient had no extrapyramidal signs (rigidity, akinesia or resting tremor).

Laboratory analysis showed an elevated erythrocyte sedimentation rate (60 mm/h) and increased C reactive protein (153 mg/l); abnormal CSF with proteinorachia (0.694 g/l) and 6 mononuclear cells, and negative serology for HIV, Borrelia, neurolyses and anti-Hu antibodies.

We performed a detailed neurophysiological evaluation. Comparative needle EMGs of the mylohyoid and the orbicular ocular muscles (Fig. 1A) revealed irregular rhythmic spontaneous activity at 5 Hz, unsuppressed by voluntary actions. The tracing also confirmed that the two tested muscles contracted in near synchrony.

EMGs of the lower extremities showed decreased motor amplitudes (under 2 mV in the tibial and peroneal nerves) and absent sensory evoked responses. Motor conduction velocities were slight-

ly relatively slowed (25–30 ms) and distal latencies were prolonged. Needle EMG revealed a reduced pattern in the anterior tibial muscle with increased motor unit potential (MUP) amplitudes (3–5 mV) evoking regeneration patterns. On the upper extremities, EMG found no significant abnormalities in motor nerve fibers, whereas sensory evoked responses were absent. We finally concluded that there was distal symmetric axonal polyneuropathy.

A brain MRI found minimal nonspecific vascular white matter lesions. Neuropsychological assessment excluded any cognitive impairment.

Despite the absence of gastrointestinal symptoms, we suspected Whipple's disease presenting with purely neurological manifestations and performed a duodenal biopsy that turned out to be normal (specific PCR for *T. whipplei* was not available at that time).

Ultimately we concluded that it was a case of Whipple's disease having purely neurological manifestations and started treatment with parenteral penicillin and amikacin followed by oral co-trimoxazole.

Over six months, the fatigue and oculofacial myorhythmias regressed; however, the painful leg paresthesias worsened. The results of CSF and MRI investigations were comparable to the previous analysis. EMG found similar results in nerve conduction and needle studies even though MUP increased. Taking into consideration the axonal character of the polyneuropathy, we performed a *sural nerve biopsy*. Although only non-specific moderate axonal

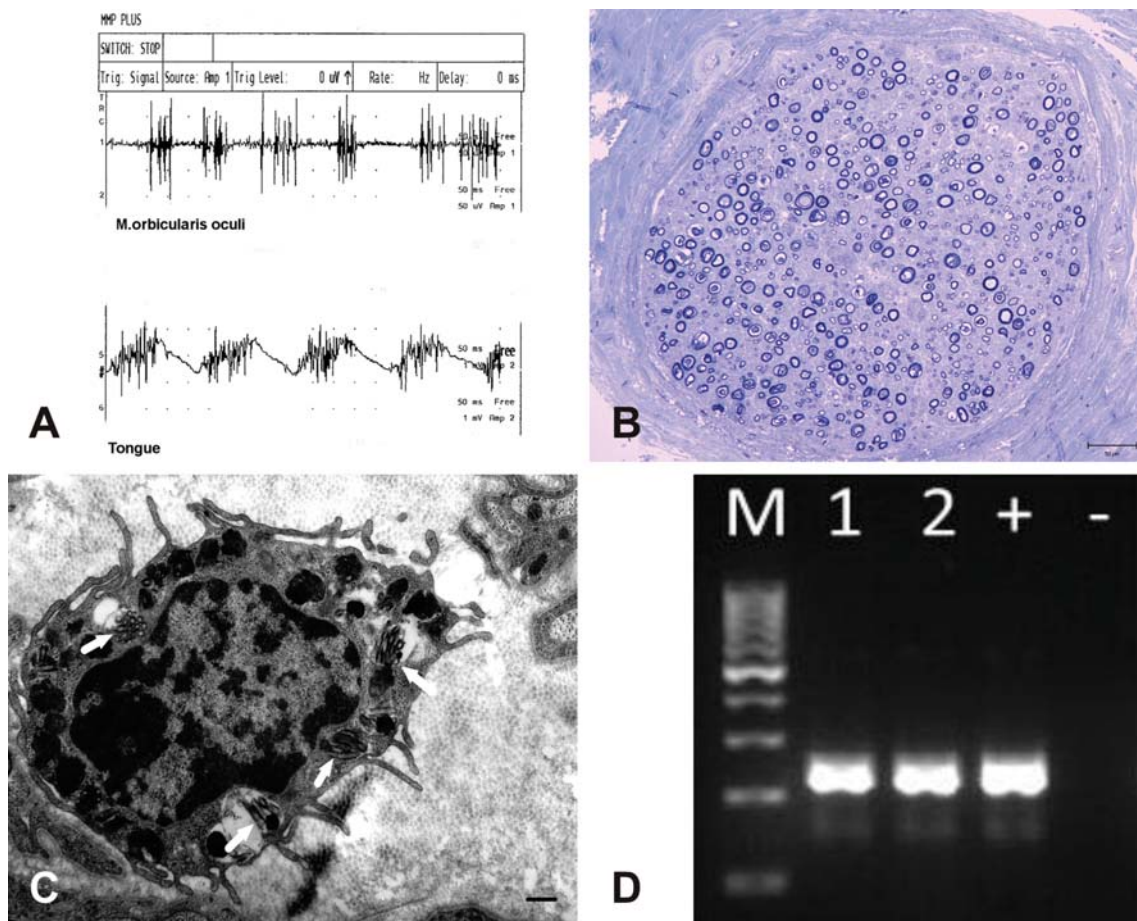


Fig. 1. A: Simultaneous recording from the mylohyoid and orbicular ocular muscles (needle EMG). Spontaneous activity in the mylohyoid muscle (below) at 5 Hz is followed by a corresponding tremor in the ocular orbicular muscle (upper record) that is less regular. **B:** Non-specific axonal neuropathy with mild to moderate loss of both myelinated and non-myelinated fibers. Toluidin blue, resin section. Bar = 50 μ m. **C:** Electron micrograph showing macrophage (localized in the endoneurium) containing numerous rod-shaped bacteria *T. whipplei* (arrows). Bar = 1 μ m. **D:** PCR detection of *Tropheryma whipplei*. M molecular weight marker, 1 archived sural nerve biopsy specimen, 2 CSF, + positive control, - non-template control.

Additional file - video (www.CSpatologie.cz): Incessant rhythmic movements of the tongue and the palate synchronized with eye blinking

neuropathy (Fig. 1B) without any inflammatory changes was observed at the microscopic examination of toluidin blue stained resin sections of the nerve, the electron microscopical analysis revealed rod-shaped bacteria characteristic of *T. whipplei* in a single macrophage localized in the endoneurium (Fig. 1C).

Thereafter, the treatment was adjusted to include gabapentin and two weeks of ceftriaxone infusions. Progressively, all clinical signs disappeared; the co-trimoxazole was continued for 12 months.

Two years later, progressive, extrapyramidal akinesia with rigidity and predominant left sided hand tremor developed; however, there was no indication of the previously described oculo-facial involuntary movements. Treatment with levodopa was started, leading rapidly to a significant improvement of the patient's movement symptoms. We concluded dopa-sensitive Parkinson's disease, which was probably unrelated to the previously diagnosed Whipple's disease.

The patient is still receiving levodopa treatment, parkinsonian features at the extremities are mild, gait is stable, and there are no ocular and/or oral spontaneous manifestations.

EMG studies two years later showed persistent signs of axonal neuropathy with moderately slowed conduction velocities and a severe decrease in amplitudes but without any signs of denervation. Clinically, the patient has only ankle areflexia and peripheral hypoaesthesia in the lower extremities together with mild paresthesias. Muscle strength is normal and there are no fasciculations confirming the absence of any progression in the patient's neuropathy.

Two years after the biopsy was performed, we analyzed retrospectively both the archived sural nerve biopsy specimen and the frozen CSF sample using PCR. Both tests were positive for *T. whipplei*, confirmed by PCR amplification and sequencing of the gene encoding 16S rRNA (Fig. 1D).

DISCUSSION

Whipple's disease, which is caused by *T. whipplei*, is a chronic inflammatory disease with predominantly gastrointestinal manifestations.

Neurological manifestations are classically associated with dementia, eye movement abnormalities and hypothalamic dysfunction. The oculomasticatory myorhythmias, considered to be a unique involuntary movement in Neuro-Whipple (4), are less frequent. When analysis was performed of primary Whipple's disease of the brain in cases confirmed histopathologically or by PCR (5), myorhythmia was found in only a small proportion of them (6).

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MRIs often show hyperintensities in the peri-aqueduct regions and hypothalamus. Cognitive impairment, if present, is often sub-cortical and may be partially reversible after prolonged antibiotic therapy, mainly co-trimoxazole (for up to 2 years).

Neurological impairment in Whipple's disease has been considered to be a result of chronic systemic inflammation. The literature on peripheral neuropathy in Whipple's disease is sparse and while there are cases described that associate neuropathy and Whipple's disease in the same patient, clear proof of a causal relationship was missing. Only one published study found peripheral nerve compression and proximal myopathy in a patient with Whipple's disease, but the relationship was unclear (7). Recently, a case with gait disturbance, supranuclear ophthalmoparesis, dysarthria, axonal neuropathy and PCR positivity for *T. whipplei*, was published (8).

Our observation shows that cases of "idiopathic" neuropathy may be caused by specific pathological conditions open to specific therapeutic options. In our patient, we initially considered the neuropathy as unrelated to Whipple's disease and ruled out most of the classic etiologies of axonal neuropathy (e.g. diabetes, alcohol, metabolic and systemic diseases, paraneoplastic conditions): finally, results of the nerve biopsy led us to reinforce and prolong the antibiotic therapy in our patient. Thus, this case study illustrates the need and usefulness of peripheral nerve biopsy in cases of axonal neuropathy of unexplained origin.

A peculiar aspect in our case was the development of dopa-sensitive extrapyramidal features, compatible with idiopathic Parkinson's disease, two years after the disappearance of the involuntary oculo-facial movements. It is important to emphasize, that the myorhythmias in our patient disappeared after antibiotic therapy (no levodopa was given at that time) and did not re-appear later. It could be argued that the tongue tremor was related to direct basal ganglia involvement by *T. whipplei* infection, but repeated MRI scans did not find brain tissue signal abnormalities. We consider the initial oculo-facial involuntary movements and the later onset of tremor-dominant Parkinsonism, as probably unrelated.

To our knowledge, this case is the first published observation of peripheral neuropathy directly related to Whipple's disease, confirmed by PCR and direct visualization of *T. whipplei* by electron microscopy in nerve biopsy, thus extending the clinical spectrum to a new modality.

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