Subacute neuronopathy in a young man: a possible association with tetracycline treatment

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Abstract

A young man with subacute neuronopathy following tetracycline treatment is described. The symptoms started as a sensory dorsal root affection but by time also involved motor nerves. He developed a severe sensory ataxia with pseudoathetotic movements. Other possible aetiologies were scrutinized and excluded. Tetracycline induced neuronopathy is hitherto not reported in the literature. We propose a possible association between treatment with tetracycline and the development of sensory neuronopathy in this patient.

Introduction

Sensory neuropathy has been reported in patients treated with other antibiotics *e.g.* penicillin or a semisynthetic derivate,[1] chloramphenicol,[2] and metronidazole.[3] Nitrofurantoin treatment has caused sensory-motor neuropathy[4] and dapsone treatment has caused motor neuropathy.[5] A topical tetracycline induced neuritis has been reported in one patient,[6] otherwise no reports of an association between neuropathy and orally taken tetracycline has been published, to our knowledge.

Case Report

This 25-year old previously healthy man with no hereditary neuromuscular diseases experienced paresthesias in the whole body except the face two weeks after starting tetracycline treatment (100 mg daily, p.o.) because of acne. He stopped taking tetracycline after two months. When examined 4 months after the debut of symptoms he also complained of clumsiness in hands and feet. Examination revealed absent reflexes and a marked decrease in position sense and elevated vibratory thresholds in hands and feet. The gait was slightly ataxic. Testing for touch, cold and pinprick sensation were intact throughout. Motor power was normal. Blood tests including cobalamine, folic acid, thyroxine, plasma-electrophoresis, fasting-glucose, creatinine, liver-enzymes, anti-nuclear antibodies (ANA including SS-A and SS-B) and HIV-test were normal. Cerebrospinal fluid (CSF) analysis revealed normal white cell count, albumin-ratio, IgG-index and no oligoclonal bands. Serology for Borrelia was normal in the CSF and peripheral blood. Nerve conduction study results were normal including sensory nerve testing (Table 1) as was the electromyography (EMG). Sensory evoked potentials (SEP) were, however, not elictable from the right median and tibial nerve and were of low amplitude from the left side. Quantitative sensory testing (QST) showed a marked decrease in vibratory sensibility in all extremities and a slight decrease in touch and temperature sensibility in the hands. Magnetic resonance imaging (MRI) of the brain and cervical spine was normal. Biopsy of the sural nerve showed a slight loss of finecaliber myelinated sensory nerve fibers but no inflammation. Muscle biopsy of the anterior tibial muscle was normal. Treatment with high-dose intravenous steroids did not have any effect on the condition. His symptoms continued to worsen and on examination one year after the debut he showed a marked sensory ataxia with pseudoathetotic movements. Position sense and vibratory thresholds were unobtainable from hands and feet. Touch and pinprick sensibility were markedly decreased in the hands and absent in the feet. Muscle power was slightly decreased in the hands but was otherwise normal. Nerve conduction studies 26 months after debut of symptoms showed decreased motor velocities and decreasing amplitudes in the median nerves and prolonged F-wave latencies in all nerves except the left peroneal. Sensory results were still normal (Table 1). EMG showed denervation potentials in the right tibial, left vastus and in the left dorsal interosseus muscle and decreased interference pattern in all muscles. SEP in the median and tibial nerves bilaterally did not give any reproducible responses. On clinical examination eight years after the initial symptoms he could walk 5 meters with help. He showed muscle atrophies in the arms and legs, absent vibratory thresholds throughout the body, areflexia, and decreased touch and pin-prick sensibility in the arms, legs and in the distribution of the trigeminal nerve. During the last year his symptoms had been fairly stable and muscle strength even increased in hands and feet.

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Discussion

Our patient resembles the cases described by Sternman *et al.*[1] because of relative rapid development of profound sensory loss, ataxia and areflexia. After some time he also developed slight motor weakness in the upper limbs. Electrophysiological investigation including neurography, EMG and SEP and nerve-biopsy indicated that the lesion was most prominent in the dorsal and by time also ventral nerve roots. These findings are in agreement with those found in patients treated with nitrofurantoin in which the investigators found degeneration of posterior and to a lesser degree anterior nerve roots and ganglion cells on post-mortem examination.[7] There was no recovery and the patient experienced great difficulty in proprioceptive tasks. The pronounced decrease in position sensibility points to a damage of the sensory nerve roots compatible with a toxic neuronopathy. Toxic causes of neuronopathy have previously been described.[8] We found dissociation between relatively preserved neurography results and by time completely absent SEP responses in arms and legs, also pointing towards a sensory dorsal root injury. On the third nerve conduction investigation we found prolonged F-wave latencies in all except one nerve indicating also a proximal motor nerve root involvement. Motor nerve roots may be more resistant to toxic agents than the dorsal root ganglia. The dorsal root ganglion cells are vulnerable to exogenous agents as the blood-brain barrier is incomplete at these sites. This would explain why toxic agents *i.e.* doxorubicin and pyridoxine are especially toxic to dorsal root ganglion cells. There was no occult neoplasm on follow-up, we found no MAG-reactive monoclonal gammopa-

Table 1. Neurography findings in the patient with possible tetracycline induced neuronopathy.

Investigation done after debut of symptoms	CV	Amp	DL	F-w	CV	Amp	DL	F-w	CV	Amp	DL	F-w
	4 months				14 months				26 months			
Motor nerves												
Median dx	55	18	3.1	ND	52	9	3.3	ND	41*	4	3.8	56*
Median sin	57	14	3.2	ND	52	9	3.1	ND	44	6	3.6	42*
Ulnar dx	ND	ND	ND	ND	ND	ND	ND	ND	52	11	3.0	32*
Ulnar sin	ND	ND	ND	ND	ND	ND	ND	ND	51	10	3.1	NR*
Peroneal dx	45	14	4.0	ND	44	13	4.2	ND	39	8	4.5	61*
Peroneal sin	46	12	4.8	ND	48	13	4.9	ND	41	5	4.9	49
Sensory nerves												
Median dx	59	12	2.5	-	54	12	2.8	-	62	7	ND	
Median sin	55	12	2.6	-	53	12	2.8	-	58	10	ND	
UInar dx	ND	ND	ND	-	ND	ND	ND	-	51	7	ND	
Ulnar sin	ND	ND	ND	-	ND	ND	ND	-	57	7	ND	
Sural dx	41	5	3.8	-	42	6	3.2	-	40	5	ND	
Sural sin	43	6	3.3	-	ND	ND	ND[a]	-	NR*	NR*	NRa*	

ND, Not Done; NR, No Response; CV, conduction velocity (m/sec); Amp, amplitude (motor nerves in mV and in sensory nerves in μV); DL, distal latency (msec); F-w, F-wave (msec). a. Nerve biopsy was performed on the left sural nerve. *NR and mean values ±2SD.

thy, no laboratory or clinical evidence of Sjögren´s syndrome and there was no preceding infection as has been reported in cases with sensory neuronopathy.[9,10] Our patient fulfils the criteria for probable neuronopathy as proposed by Camdessanché *et al.*[11]

Several factors are suggestive of a toxic effect of tetracycline on the peripheral nervous system in our patient. There is a time association between development of neuronopathy and the tetracycline treatment. No obvious other cause of the neuronopathy was found despite extensive evaluation. He is a young man, usually not prone to develop neuropathy if hereditary causes and the Guillain-Barré syndrome are excluded. This patient had no family history of neuromuscular disorders and no clinical or laboratory findings supportive of the Guillain-Barré syndrome. After several years of worsening the condition seemed to stabilize and even improve concerning his muscle strength. An immunological reaction against dorsal nerve roots elicited by tetracycline cannot be ruled out, however. A few case reports on neuropathy as an adverse event of minocycline (a synthetic tetracycline antibiotic) treatment have been published; one ulnar neuropathy, one carpal tunnel syndrome, one vasculitic neuropathy and one axonal sensory neuropathy.[12-15] The case described by Graham and Bell[14] presents a 16-year-old girl developing acute polyarthritis and a peripheral neuropathy after taking minocycline because of acne, in part resembling our patient. In the World Health Organization (WHO) register of Global Individual Case Safety Report (ICSR) database, VigiBase (www.who-umc.org) of adverse drug reactions (ADR), there are 15 reports of neuropathy in association with tetracycline treatment (11 peripheral neuropathies, one of which was sensory in type, 3 neuritis and one nerve compression). The occurrence of neuropathy in association with tetracycline treatment must be rare bearing in mind that only a few medical case reports have been published, to our knowledge. In experimental studies on rat sciatic nerves minocycline was shown to have an inhibiting effect on regeneration of peripheral nerves, also implicating an impact of constructive events after nerve injury.[16] In conclusion we propose a possible association between treatment with tetracycline and the development of sensory neuronopathy in this patient.

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