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Hereditary Motor and Sensory Neuropathy (HMSN) and Optic Atrophy (HMSN Type VI, Vizioli)*

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Summary. Clinical and electrophysiological findings are described in three patients with hereditary motor and sensory neuropathy in association with optic atrophy (HMSN VI). The optic atrophy was of the Leber type in a 15-year-old boy. In a 70-year-old patient, as in three members of his family, optic atrophy was associated with tapetoretinal degeneration. In addition to HMSN and optic atrophy a 20-year-old man suffered from sensorineural deafness. Electrophysiological studies indicated a neuronal form of neuropathy, as in HMSN II. Brainstem auditory evoked potentials also revealed subclinical involvement of the central auditory pathways in the patients without hearing defects.

Key words: Hereditary motor and sensory neuropathy – Leber optic atrophy – Electrophysiology

Introduction

Heredodegenerative diseases of the nervous system are frequently associated with ophthalmological disorders. This holds true mainly for cerebellar ataxia. The association of hereditary motor and sensory neuropathies (HMSN) with optic atrophy however, is very rare but has given rise to a subclassification of HMSN type VI according to Dyck et al. [8]. No thorough electrophysiological and only a few histological studies have been done in such cases [2, 10, 11, 14, 17].

We report three patients with HMSN and optic atrophy (HMSN type VI). A young boy with HMSN had hereditary Leber's optic atrophy. Another young man with HMSN and sensorineural deafness developed marked reduction of visual acuity and optic atrophy. In a 70-year-old patient with HMSN, as well as in three members of his family, optic atrophy was associated with tapetoretinal degeneration.

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Case Reports

Case 1. Three months before admission a 15-year-old boy noticed "blurred" vision in the right eye, which remained poor over the next 2 months. Then the patient omit experienced episodes of blurred vision on the left. Over the past few years he had noticed clumsiness in walking and running and had suffered from aching of the leg muscles after activity and from pain in the feet. Pes cavus deformity had developed at the age of 12 years.

On examination there was pes cavus deformity on both sides, atrophy of the lower limb muscles and weakness of dorsiflection of the feet. The ankle jerk was absent on the right. Pallaesthesia was 4/8 at the toes. MRI was normal.

Ophthalmological examination disclosed reduction of visual acuity below 1/10 on both sides. There was severe impairment of colour vision and a large caecocentral scotoma on both sides. Fundoscopy revealed a hyperaemic, slightly congested disc on the left with some peripapillary teleangiectasia and increased tortuosity of vessels around the disc. On the right the retinal nerve fibre had an opaque appearance; disc pallor was pronounced temporally. Fluorescein angiography revealed no leakage from the discs or peripapillary region.

Nerve conduction velocity (NCV) was slightly slower than in normals only in the lower limbs (Table 1). Distal latencies and F-wave latencies of the median nerve were normal. Compound muscle action potentials (CMAPs) in muscles of the lower limbs were reduced in amplitude. No CMAP could be obtained from the extensor digitorum brevis muscle upon stimulation of the deep peroneal nerve. There were pseudomyotonic bursts and fibrillations at various sites in the anterior tibial muscle.

N20 components of the median nerve somatosensory evoked potentials (SEPs) were normal in latency but of low amplitude; the N35 component was absent (Fig. 1). Peroneal nerve SEPs after stimulation at the head of the fibula were delayed. Sural nerve SEPs were even more delayed. Interpeak latencies I-III of the brain-stem auditory evoked potentials (BAEPs) were increased. The amplitude of wave V on the left side was smaller than that of wave I and not detectable on the right side. A loss of perception of low frequencies, which may eventually lead to a simular pattern, was excluded by a normal audiogram.

With flash or after pattern reversal stimulation no visual evoked potentials (VEPs) could be recorded.

Table 1. Nerve conduction velocity (NCV) studies and electromyography in the three patients

	Right sural nerve NCV (m/s) SNAP	Left peroneal nerve NCV (m/s) CMAP	Right tibial nerve NCV (m/s) CMAP	Left median nerve NCV (m/s) CMAP F-wave	Electromyography of left anterior tibial muscle
Case 1	42 7 μV	Ø < 0.1 mV	36.6 1 mV	57.1 13 mV 23 ms[a]	Fibrillations, pseudomyotonic bursts
Case 2	44 5 μV	41 9 mV	42 11 mV	49 14 mV 35 ms[b]	Fibrillations +
Case 3	46 2 μV	44 3.5 mV	43 11.5 mV	48 15 mV 30 ms[b]	Fibrillations ++ increased rate of polyphasic potentials prolonged mean potential duration

Only Motor NCV of the legs in case 1 were delayed. In this case CMAP and SNAP were reduced in amplitude. F-wave latency of median nerve was delayed in case 2

CMAP, Compound muscle action potiential; SNAP, sensory nerve action potential

[a] F-wave, stimulation at elbow

[b] F-wave, stimulaiton at the wrist

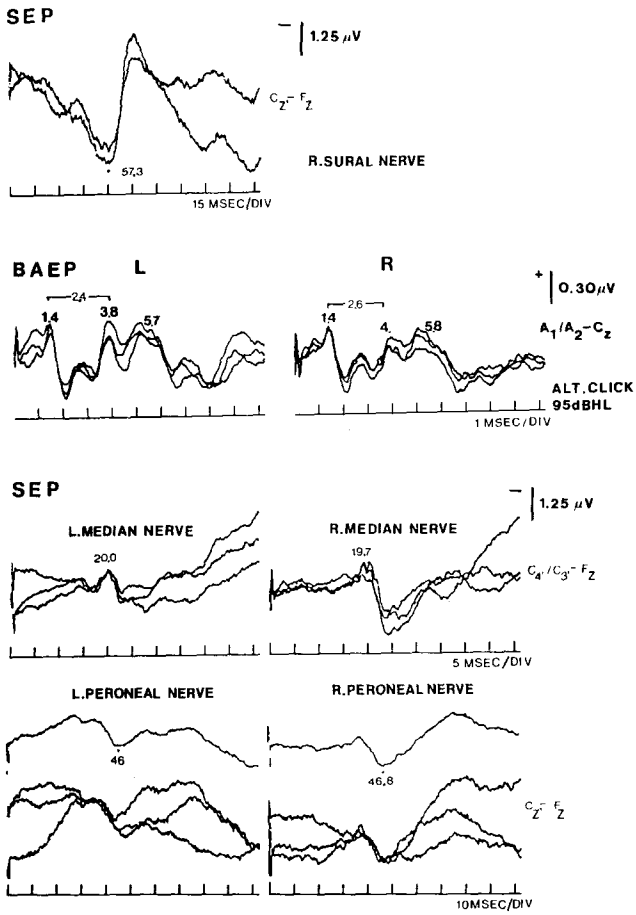

Fig. 1. Evoked potential studies in case 1. Amplitude of left median nerve somtosensory evoked potential *(SEP)* is reduced. N35 component is lacking. Peroneal (head of fibula) and sural nerve SEP are delayed. With brain-stem auditory evoked potentials *(BAEP)* interpeak latencies I-III are delayed. Wave V is reduced in amplitude with an amplitude ratio V/I of < 1

Over a follow-up period of 1 year, walking became worse. The patient had episodes of visual improvement lasting for minutes, but without sustained visual change. At this time both optic discs were completely pale.

The patient's father and his sister have pes cavus deformity. Neurological and ophthalmological examination, EMG, NCV and evoked potentials of this sister, another brother and the patient's mother showed no abnormality. The father of the propositus, aged 47, suffered from sone clumsiness in walking and cramps in the calves. NCVs were just within the lower limits of normals. Electromyography showed fibrillations and positive sharp waves in the left tibial muscle. SSEPs, VEPs and BAEPs were normal.

Case 2. At the age of 6 years, a 20-year-old man developed sensorineural deafness on the right and to a lesser degree on the left, which was not further investigated at that time. From the age of 10 he had pes cavus deformity on both sides. Pain in the feet and numbness in the legs developed gradually. He had had convergent strabismus since his childhood. Two years before admission, visual acuity declined rapidly on the right and 2 months later on the left. The patient was not able to give any information about his family history.

There was pes cavus deformity on both sides; ankle jerks were absent. Pallaesthesia was reduced to 5/8 at the toes. Visual acuity was markedly reduced to 3/10 on the right and 5/10 on the left. The optic discs were excavated and totally pale. There was a centrocaecal scotoma on both sides.

NCVs were normal (Table 1). Amplitudes of the CMAP were not significantly reduced. F-wave latency of the median nerve was delayed. The left anterior tibial muscle showed fibrillations at three sites.

VEPs were not detectable on the right and normal in latency on the left. Tibialis nerve SEPs were normal. Median nerve SEPs were not detectable on the left; no peaks after N20 could be distinguished on the right. BAEPs could not be reproduced because of artefacts.

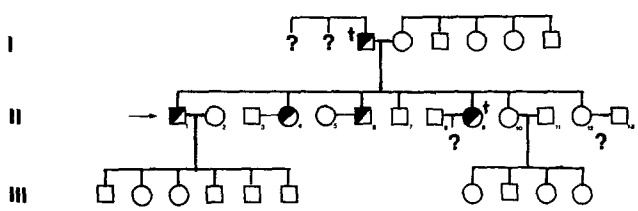

Fig. 2. Family tree of case 3 (→). ◩ ◐, HMSM and tapetoretinal degeneration. II4 and II6 were only examined clinically. Two patients were no longer alive at the time of examination. Relatives of the last generation were in general under the age of 30

Case 3. A 70-year-old man and his family are reported. Five members (3 men, 2 women) had HMSN and optic atrophy with tapetoretinal degeneration (Fig. 2). Symptoms of HMSN developed in the second to third decade, leading to disability after the age of 50. The propositus (III) had an operation for pes cavus at the age of 29. He and his sister (II4) have been confined to wheelchairs for several years.

The same five members of the family were affected by blindness. The age at onset of reduced visual acuity ranged from 19 to

30 years and visual failure progressed slowly, leading to blindness between the ages of 40 and 58 years.

We were able to examine the affected siblings of the patient (who are still alive), his brother (II6, now 80 years old) and his sister (II4, 77 years). All three had pes cavus deformity. Distal wasting was marked in the lower and minor in the upper limb. No fasciculations were seen. Moderate pallhypaesthesia was evident in the lower limbs.

The patient (II1) was blind in the right eye, with only faint residual vision in the left. He had no perception of green objects and little of red. His sister was completely blind; his brother could distinguish light and dark with his left eye. The optic discs were excavated and pale; there was pronounced temporal and peripheral tapetoretinal degeneration with pigmented modifications of the macula in the patient and the two siblings.

NCVs were normal in the patient (Table 1), as were distal latencies and F-wave latency. Electromyography of the anterior tibial muscle disclosed fibrillations and an increased rate of polyphasic motor unit potentials (MUPs) and a prolonged mean MUP duration.

Neither VEPs nor an electroretinogram could be obtained. Peroneal nerve SEPs from the head of the fibula were delayed. No muscle response could be elicited after stimulation of the deep peroneal nerve at the ankle. Median nerve SEPs were normal.

Interpeak latencies I/V of BAEPs were prolonged on both sides. On the right side, this was the result of I-III prolongation.

CT, CSF and other laboratory examinations including phytanic acid blood level were normal in all the patients described.

Muscle and nerve biopsy specimens of the three cases showed chronic neuropathy of the neuronal/axonal type with little, presumably secondary demyelination and will be dealt with separately [24].

Discussion

All three patients have the clinical, electrophysiological and histopathological features of slowly progressive, chronic neuropathy of the neuronal type with only a minor demyelinating component. SEPs as well as nerve conduction studies showed dominant involvement of the lower extremities, more severe in the distal part of the nerve, as usually seen in HMSN II [4, 7, 8].

Additionally, the central nervous system (CNS) is involved in all three cases. HMSN is associated with two eye problems: optic neuropathy (in case 1 of Leber's type) and retinal pigmentary degeneration. The central auditory pathway is also involved in these patients.

Subclinical involvement of the visual pathways in HMSN is well known [1, 5, 25]. There have also been several reports of HMSN associated with optic nerve atrophy since the first description by Vizioli in 1889 ([15, 21, 23, 27]; for further references see [2, 3, 7, 9, 13, 14]).

In the majority of these cases a detailed clinical description is lacking, so that reports on certain examples of HMSN and Leber's optic atrophy [16] are rare [2, 3, 9, 13, 14, 17, 21, 23]. Out of the 25 cases reviewed by Brihaye et al. [2], only two fulfil the criteria of Leber's optic atrophy.

McLeod et al. [14] reported a family with this association and assumed an independent inheritance of HMSN and Leber's optic atrophy. In the sporadic case of McCluskey et al. [13] a genetic inter-relationship was postulated. They did not give any electrophysiological or histopathological findings to confirm the supposed diagnosis of Charcot-Marie-Tooth disease. Unfortunately, this holds true for the majority of reports on HMSN VI. Some cases are of the demyelinating form of neuropathy [11, 14, 15, 23]. Others, like ours, are of the neuronal type [2, 9, 17].

In our case 3, HMSN and optic atrophy are combined with hereditary tapetoretinal degeneration. This condition has been described in more than 200 cases of heredodegenerative diseases, mainly cerebellar ataxia, more seldom associated with HMSN [11, 12, 20].

The triad of HMSN, optic atrophy and neural deafness of case 2 resembles that in the two cases of Iwashita et al. [10]. In other patients reported with this triad, the disease has had a different clinical course [19, 26]. Neural deafness without optic atrophy has also been described in HMSN [6]. A subclinical involvement of the acoustic system has been demonstrated by pathological BAEPs in our cases 1 and 3. Increased interpeak latencies I/III in these patients are in concordance with the findings of Satya-Murti and Cacace [22] in four cases of HMSN I. The amplitude reduction of wave V in our case 1 is highly suggestive of a central lesion. In contrast, Pierelli et al. [18] found normal BAEPs in three patients wiht HMSN type I and in two patients with HMSN type II.

Our findings suggests the possibility of a severe involvement of the optic nerve in some cases of HMSN. This may be true in cases with the neuronal as well as in cases with the neural variant. At least sometimes, this might not be a coincidental occurrence of two independent diseases. The optic atrophy may be the most prominent feature of CNS involvement, but BAEPs may indicate a further involvement of other central pathways as well. From the phenomenological point of view a subclassification of these cases of HMSN seems justified. Whether this corresponds to a different underlying pathogenetic mechanism remains to be clarified.

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