Phenotype Variant of the Common Duplication at 17p11.2

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Dear Sir,

The autosomal-dominantly inherited 1.5-Mb tandem duplication in the PMP22 gene at 17p11.2 usually manifests as hereditary sensorimotor polyneuropathy with foot deformity (HMSNIA) [1, 2]. In single cases, however, it has been found in association with additional features, such as sensorineural hearing loss, moderate developmental delay, gait disturbance, autism-related disorder, mild dysmorphic features, or growth factor deficiency [3]. The coexistence of sensorimotor polyneuropathy with tremor, ataxia, sensorineural hearing loss, hypothyroidism, short stature, and papilledema has not been reported.

The patient is a 27-year-old HIV-negative woman, height 163 cm, weight 73 kg, who had peculiarly walked tiptoe since childhood and had pes cavus. Since the age of 17 years she additionally developed slowly progressive gait disturbance, easy fatigability, and numbness of the distal upper and lower limbs. She had to walk with all her concentration not to stumble. Motor deficits in the lower limbs resulted in inability to climb stairs, difficulties when walking or running, and to get up from the floor without assistance. Diagnostic work-up at the age of 20 years revealed distal weakness of all four extremities with right-sided and lower limb predominance, reduced tendon reflexes, muscular hypotonia, and endpoint ataxia. Blood work was normal. Biopsy of the right sural nerve was

not utilizable. Biopsy of the right gastrocnemius muscle revealed a chronic neurogenic pattern. Since the age of 22 years she noted impaired hearing on the right side. At the age of 26 years, hypothyroidism was diagnosed and levothyroxin prescribed.

At the age of 27 years she started to take phentermine to reduce her overweight. Eight weeks later she additionally received nandrolone to compensate for progressive wasting. Three weeks later she stopped phentermine and nandrolone at 100 mg/week after she had developed blurred vision of the right eye. Ophthalmologic investigation revealed right-sided reduced vision and a papilledema. Clinical neurologic examination revealed distal weakness in all four limbs, with lower limb predominance, and reduced respectively absent deep tendon reflexes. Blood work and CSF investigations were non-informative. Nerve conduction velocities were 18–22 m/s. Visually-evoked-potentials initially revealed an absent response upon stimulation of the right eye and later on prolongation of the P100 latencies bilaterally. Cerebral MRI was normal. Under corticosteroids, papilledema continuously resolved over weeks. Molecular genetic analysis revealed a common tandem duplication in the PMP22 gene at 17p11.2. HMSNIA was also diagnosed in her father, who had developed sensorimotor deficits and foot deformity without other features as in his daughter since the age of

35 years and her brother who presented with tremor, reduced tendon reflexes, and markedly reduced nerve conduction velocities.

Tremor has been rarely described together with HMSN1 [4] but is a frequent feature of Roussy-Levy syndrome [1]. Hearing loss has been rarely reported in association with a duplication at 17p11.2 [2] but has been more frequently found together with point mutations in the PMP22 gene [2, 5–8]. Hypothyroidism has been reported once in a single patient with non-genetically defined Charcot-Marie-Tooth disease [9]. Short stature is also no typical feature of HMSNIA, but has been occasionally described in other types of hereditary neuropathy [10]. Blurred vision due to optic atrophy has not been reported in association with the duplication 17p11.2, but together with other types of hereditary neuropathy [11, 12]. Whether papilledema, which is an atypical feature of hereditary neuropathies, represents a side effect of phentermine or nandrolone remains speculative. An argument against phentermine is the fact that blurred vision occurred not earlier than 2 months after initiation of the drug and that it persisted despite discontinuation of the drug. An argument for a causal relation between the mutation and the phenotype is that single features of this phenotype had been reported earlier [1, 2, 9–12]. It cannot be excluded, however, that the described patient

suffered from a double trouble, whereby the second trouble needs to be a disorder associated with endocrine disturbances.

The presented case shows that the duplication 17p11.2 may be associated with tremor, sensorineural hearing loss, unilateral papilledema, hypothyroidism, short stature in addition to the classical manifestations distal weakness of all four limbs sensory disturbances in the upper and lower limbs, and foot deformity. The causal relationship between these manifestations and the mutation remains to be elucidated.

References

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