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Hypertelorism in Charcot-Marie-Tooth disease 1A from the common PMP22 duplication: A Case Report

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Abstract

The 1.4Mb tandem-duplication in the PMP22 gene at 17p11.2 usually manifests as hereditary sensorimotor polyneuropathy with foot deformity, sensorineural hearing-loss, moderate developmental delay, and gait disturbance. Hypertelorism and marked phenotypic variability within a single family has not been reported. In a single family, the PMP22 tandem-duplication manifested as short stature, sensorimotor polyneuropathy, tremor, ataxia, sensorineural hearing-loss, and hypothyroidism in the 27 years-old index case, as mild facial dysmorphism, muscle cramps, tinnitus, intention tremor, bradydiadochokinesia, and sensorimotor polyneuropathy in the 31 year-old half-brother of the index-patient, and as sensorimotor polyneuropathy and foot-deformity in the father of the two. The half-brother additionally presented with hypertelorism, not previously reported in PMP22 tandem-duplication carriers. The presented cases show that the tandem-duplication 17p11.2 may present with marked intra-familial phenotype variability and that mild facial dysmorphism with stuck-out ears and hypertelorism may be a rare phenotypic feature of this mutation. The causal relation between facial dysmorphism and the PMP22 tandem-duplication, however, remains speculative.

Keywords: Hereditary neuropathy; Nerve conduction; Neuromuscular disorder; Peripheral nervous system.

Introduction

The autosomal-dominantly inherited 1.4Mb tandem duplication in the PMP22 gene at locus 17p11.2 most frequently manifests as hereditary demyelinating, sensorimotor polyneuropathy with weakness and wasting of the lower limbs, sensory disturbances, and foot deformity (HMSN-1A).[1] Rare clinical features include sensorineural hearing-loss, moderate (motor) developmental delay, or gait disturbance.[2] As disease severity may vary greatly; marked interfamilial and interfamilial phenotypic variability may be observed. Hypertelorism has rarely been reported.

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Case Report

The patient was a 31 year-old Caucasian male with an uneventful history until adulthood, who then developed recurrent sensory disturbances, when taking certain positions, which resolved upon changing of the limb position, muscle cramps of the thighs, and tinnitus. Psychomotor development was normal and motor milestones were reached at time. Clinical neurologic examination revealed mild facial dysmorphism, manifesting as stuck out ears and hypertelorism (Fig. 1), with an interorbital distance of 41 mm (normal: 18-35 mm),[3] an interpupillary distance of 86 mm, intention tremor, brady-diadochokinesia, reduced tendon reflexes, discrete weakness for foot extension and markedly reduced nerve conduction velocities, (Table 1). Cerebral MRI was normal. He was diagnosed as HMSN-1A after the disorder had been diagnosed before in his 27 year-old half-sister who presented with short stature (163 cm), sensorimotor polyneuropathy with distal quadruparesis, numbness of the distal limbs, tremor, ataxia, sensorineural hearing-loss, and hypothyroidism (Table 1). HMSN-1A was also diagnosed in the father of the two, who had developed sensorimotor deficits, gait disturbance, and foot deformity since age 30 years without other features as in his daughter or son, (Table 1). Psychomotor development and achievement of motor milestones were normal in both father and half-sister.

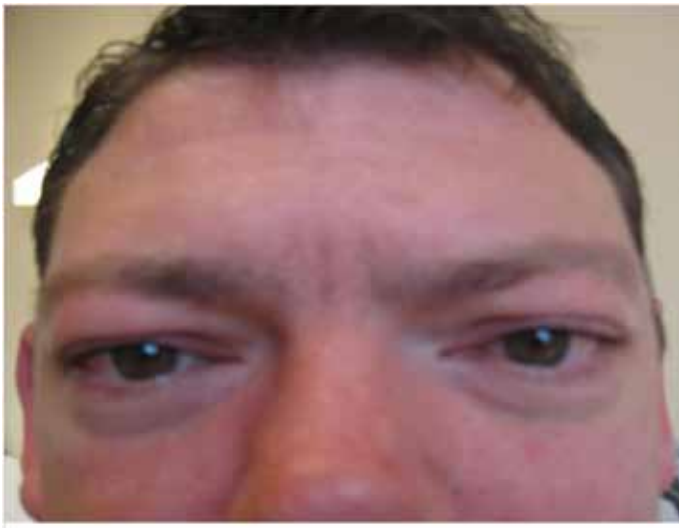

Figure 1: A 31 years-old Caucasian male carrying the common tandem duplication in the PMP22 gene locus showed hypertelorism and facial dysmorphism. He additionally presented with hereditary neuropathy (HMSN-1A) and liability to pressure palsies.

Table 1: Clinical and electrophysiological findings of the index patient, his half-sister and their father.

	Index patient	Half-sister	Father
Age at onset	23yrs	Childhood (deformed feet) 17yrs (gait disturbance)	30yrs (weakness)
Motor involvement	Yes	Yes	Yes
Sensory involvement	Yes	Yes	Yes
Tremor	Yes	Yes (discrete)	No
Impaired hearing	No	Yes	Yes
Foot deformity	No	Yes	Yes
Additional features	Hypertelorism, tinnitus	Hypothyrodism, prolonged VEPs	Transient diabetes, glaucoma, sleep apnea, foot drop after cast
Nerve conduction			
Motor			
Right median (NCV, ampl)	24m/s, 9.9mV	18.1m/s, 5mV	Abnormal
Left median (NCV, ampl)	NA	22.1m/s, 2.8mV	18m/s, 5.0mV
Left ulnar (NCV, ampl)	20m/s, 3.6mV	22.1m/s, 6.0mV	NA
Right tibial (NCV, ampl)	23m/s, 1.0mV	0 potential	NA
Left tibial	NA	0 potential	NA
Right peroneal	NA	0 potential	0 potential
Left peroneal	0 potential	0 potential	NA
Sensory			
Left sural	0 potential	0 potential	NA
EMG	Normal, neurogenic	Neurogenic	Neurogenic
Cerebral MRI	Normal	Normal	Falx meningeoma
Course	Slowly progressive	Slowly progressive	Slowly progressive

NCV: nerve conduction velocity, ampl: nerve action potential amplitude, EMG: electromyography, NA: not available, VEP: visually evoked potentials

The application of the microsatellite analysis according to Badano et al. 2001,[4] using the markers D17S2220, D17S2224, D17S2226, D17S2227, and D17S2230 revealed the common 1.4 Mb tandem duplication in the PMP22 gene at 17p11.2 in the father as well as in his two children. No flanking markers outside the commonly duplicated region were analysed.

Discussion

Dysmorphic features have only rarely been reported in patients with hereditary neuropathy. In a 4 months-old patient with the Charcot-Marie-Tooth (CMT) duplication on chromosome 17, coronal synostosis and club feet were described.[5] An 8 years-old girl carrying four submicroscopic interspersed 17p duplications presented with mental retardation, short stature, microcephaly, and mild dysmorphic features including mild hypertelorism.[5] Also, a 6 years-old boy carrying the de novo duplication 17p11.2p12, different from the usual 1.4Mb duplication in CMT1A, presented with behavioral deficits, moderate developmental delay, gait disturbance, autism, and mild dysmorphic features, including mild hypertelorism.[2] Facial dysmorphism has also been described in a subtype of CMT4 (autosomal-recessive HMSN), also known as congenital cataracts, facial dysmorphism, and neuropathy (CCFDN) syndrome,[6] which predominantly occurs in the European gypsy population. The CCFDN-syndrome may additionally present with microcornea, moderate cognitive deficit, pyramidal signs, mild chorea, short stature, or hypogonadotropic hypogonadism.[7-10] Facial dysmorphism was also reported in an 8 years-old boy with congenital insensitivity to pain and anhidrosis (CIPA, HSAN-IV). He additionally presented with severe swallowing disorder and a myogenic EMG.[11] The boy carried the c.C2011T mutation in exon 15 of the NTRK1 gene.[11] Hypotelorism and unusual skin folds and creases have recently been described as additional phenotypic features in hereditary neuralgic amyotrophy (HNA).[12] Dysmorphic features and neuropathy can also be found in peripheral neuropathy associated with agenesis of the corpus callosum (ACCPN) syndrome.[13] The ACCPN syndrome is a severe autosomal recessive sensorimotor neuropathy associated with mental retardation, dysmorphic features, and complete or partial agenesis of the corpus callosum.[13] ACCPN is due to mutations in the SLC12A6 gene on chromosome 15q, which encodes the K+-Cl- transporter KCC3.[13] Dysmorphic facial and digital features were also reported in a child with partial trisomy of the 17p12pter region and HMSN1.[14] In a 7 year-old

girl with CMT1A due to the duplication 17p10-p12 dysmorphic facial features, dislocation of hips, talipes, developmental delay, premature adrenarche, and deep palmar creases supplemented the phenotype.[15]

Hypertelorism in the presented patient could be a phenotypic manifestation of the PMP22 mutation but could also be explained by the involvement of contiguous genes that lie adjacent or distant to the PMP22 gene in the 17p11.2 region. In patients with the duplication dup(17)(p12+p11.2) mild cognitive impairment was associated with subtle dysmorphic features, including hypertelorism.[16,17] There has also been a report of a patient with mosaic trisomy 17 who presented with developmental delay and hypertelorism.[18] Hypertelorism in the presented patient could also be the manifestation of a collateral mutation in a gene outside the duplicated region inherited from the mother and distinct from PMP22. It is also conceivable that the presented family did not carry the common 1.4Mb duplication, which usually has the same size, but one that was larger in size. Due to the limitations of the applied method, the exact boundaries of the duplication were not determined. Additionally, it can be speculated that the family carried not only the 17p11.2 duplication but also an undetected 17p12.2 deletion, which may phenotypically manifest as Smith-Magenis syndrome. In single cases of Smith-Magenis syndrome, hypertelorism has been reported.[19] Since hypertelorism is frequently seen in many other genetic disorders, such as deletion 4p, 4q, 9p, 11q, or 13q; the occurance of hypertelorism in the presented patient is rather interpreted as coincidential than as casual. Though a second trouble can be assumed resulting in the coincidental occurrence of two independent phenotypes, it cannot be definitively excluded that hypertelorism was simply due to the PMP22 duplication. Assuming that hypertelorism resulted from the 17p11.2 duplication, it might be explained by a variant longer than the common 1.4Mb duplicated region, which also affected genes involved in the formation of the facial shape. Since flanking markers were not analysed, the size of the duplication might be longer than that of the common duplication.

To explain the phenotypic variability within the presented family, it can be speculated that additional polymorphisms or modifier genes influenced the variable phenotype. The phenotypic variability between the described family and the previously reported cases may be due to the same causes as the intra-familial variability. A single major anomaly can be found in 1.3% and a minor anomaly in 2% of the new-born babies.[20] However, this is of little concern since the frequency of major defects is not appreciably increased in this group. In both children, the onset of clinical manifestations was earlier than in their father and clinical manifestations were more severe; a phenomenon known as anticipation. Anticipation has particularly been reported in tri- and tetra-nucleotid expansion disorders, which were not diagnosed in the presented family, but appropriate analysis of the phenomenon usually requires large pedigrees. Anticipation has not been reported in hereditary neuropathies so far. Anticipation in the presented family and phenotypic heterogeneity between the family members suggests a weak phenotype-genotype correlation, which is usually closer in patients with other hereditary neuropathies.[21]

Coclusion

The presented cases show that the common duplication 17p11.2 may present with marked intra-familial phenotype variability and that mild facial dysmorphism with stuck out ears and hypertelorism may be a rare clinical feature of this mutation. However, hypertelorism could also be attributed to the involvement of contiguous genes or to mutations in genes distinct from PMP22.

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