PHE 84 DELETION OF PMP22 GENE ASSOCIATED WITH HMSN III WITH MULTIPLE CRANIAL NEUROPATHY: CLINICAL, NEUROPHYSIOLOGICAL AND MRI FINDINGS*

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ÖZET

Herediter motor ve duysal nöropati (HMSN) klinik, elektrofizyolojik ve nöropatolojik bulgulara dayanarak tam konan heterojen bir periferik nöropati grubudur. Hipertrofik demiyelinizan nöropatiler arasında HMSN III (Dejerine Sottas Hastalığı) en ağır olanıdır. Çoğunlukla periferik myelin proteinlerini kodlayan genlerde novo mutasyonlar sonucu gelişir. Periferik sinir hipertrofisi HMSN III'de beklenen bir bulguysa da kranyal sinir hipertrofisi alışılmadık bir bulgudur. Bu yazıda, manyetik rezonans görüntülemede kranyal sinir hipertrofisi izlenen, aile öyküsü olmaksızın infantil başlangıçlı sensori-motor nöropatisi olan 19 yaşındaki bir erkek hastada PMP22 geninde saptanan bir mutasyon ve hastanın klinik, elektrofizyolojik bulgularından söz edilmiştir.

Anahtar sözcükler: *Dejerine Sottas, Kranyal nöropati, HMSN III, genetik*

SUMMARY

Hereditary motor and sensory neuropathy (HMSN) is a heterogenous group of peripheral neuropathies which are diagnosed on the basis of clinical, electrophysiological and neuropathological findings. Among the hypertrophic demyelinating neuropathies, HMSN III is the most severe. It is often associated with de novo mutations in the genes encoding for peripheral myelin proteins. Even though peripheral nerve hypertrophy is an expected finding in HMSN III, cranial nerve hypertrophy is exceptional. Here we describe a mutation in PMP22 gene in a 19 years old male patient with infantile onset sensory motor polyneuropathy without family history and multiple cranial nerve hypertrophy seen in his cranial magnetic resonance imaging.

Key words: *Dejerine Sottas, Cranial neuropathy, HMSN III, genetics*

Hereditary motor and sensory neuropathy (HMSN) comprises a heterogenous group of peripheral neuropathies which are classified on the basis of clinical, electrophysiological and neuropathological findings (1). HMSN III (Dejerine Sottas disease: DSD) is a hypertrophic and demyelinating neuropathy with markedly reduced NCV (nerve conduction velocity), an early onset and variable mode of inheritance. It is usually considered to be inherited in an autosomal recessive manner. However, de novo mutations in autosomal dominant genes such as peripheral myelin protein 22 (PMP22) or P0 have been described (2,3). More recently, the occurrence of a recessive transmission of a mutation in PMP22 gene has been demonstrated in a Turkish family of DSD (4). Even though peripheral nerve hypertrophy is essential in the HMSN diagnosis, cranial nerve

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hypertrophy or neuropathy is very rarely seen (6,7). Here, we present a genetically proven, sporadic case of DSD with multiple cranial nerve hypertrophy shown with magnetic resonance imaging.

CASE

A nineteen years old, Turkish male was hospitalized with the complaints of unsteadiness, walking difficulty and feet deformity. His problems dated back to the age of 2 when he started to walk awkardly with thinning of the distal parts of legs, stepping on sides of his feet. He was operated for his feet deformities when he was 15 years old in 1992. He was diagnosed with DSD. His investigations at that time included slow motor and sensory NCV, less than 4 m/sec. Sural nerve biopsy showed hypertrophic neuropathy findings, decrease in myelinated fibrils, increase in intrafascicular area, proliferation in Schwann cells, increase in fibroblasts. In reticulin stain, nerve fibres were decreased. CSF contained high level of protein (400 mg/dl) with no cells. He was admitted to our Neurology clinic in 1996 for worsening of his gait and ataxia. On admission, he was intact mentally and able to work full time in a private laboratory as a technician despite his ataxia.

Neurological examination found muscle atrophy of his legs, forearms and hands with clubfeet deformity. Bilateral oral and orbicular muscles seemed mildly atrophic with thick lipped appearence. All other cranial nerve findings were unremarkable. Fundoscopic examination and audiometry were normal. Deep tendon reflexes were absent with no pathological reflexes. The distal parts of all extremities showed sensory disturbances of all modalities. Hypertrophy of small cutaneous nerve trunks such as great auricular nerve was palpable. He had decreased muscle strength on the distal parts of extremities, positive Romberg sign, and ataxic gait. His laboratory investigations included blood count, ESR, creatine kinase, serum immune globulins, thyroid function tests, serum ASO, C-reactive protein, rheumatoid factor, antinuclear antibodies, serologic tests for brucellosis, syphilis and HIV which were all normal.

His EMG showed denervation activity in distal muscles of extremities, extremely slow NCV of median and ulnar nerves, less than 4 m/sec, with no sural nerve response. Facial NCV was also slow with velocity of 25 m/sec with very late blink responses. Somatosensory evoked potentials could not be obtained, brainstem auditory evoked potential (BAEP) responses showed abnormality in cochlear nerve level.

His cranial MRI revealed symmetric hypertrophy of oculomotor, trigeminal, facial, vestibulocochlear and hypoglossal cranial nerves (Figure 1a,b,c,d,e,f). Bilateral Meckel caves and cavernous sinuses were enlarged with smooth margins, had isointense signal with gray matter on T1 weighted images and high signal intensity on T2 weighted images homogenously. The ophthalmic, maxillar and mandibular divisions of trigeminal nerve, oculomotor and hypoglossal nerves were hypertrophic on both sides. In the canalicular portion of the facial and vestibulo-cochlear nerves, symmetrical nodular hypertrophy were imaged bilaterally. After Gd-DTPA injection the hypertrophic cranial nerves showed diffuse

homogenous enhancement on fat saturated T1 weighted images. Multiple enlarged nerve roots in cauda equina were seen with the same signal intensity as the spinal cord on T1 and T2 weighted images.

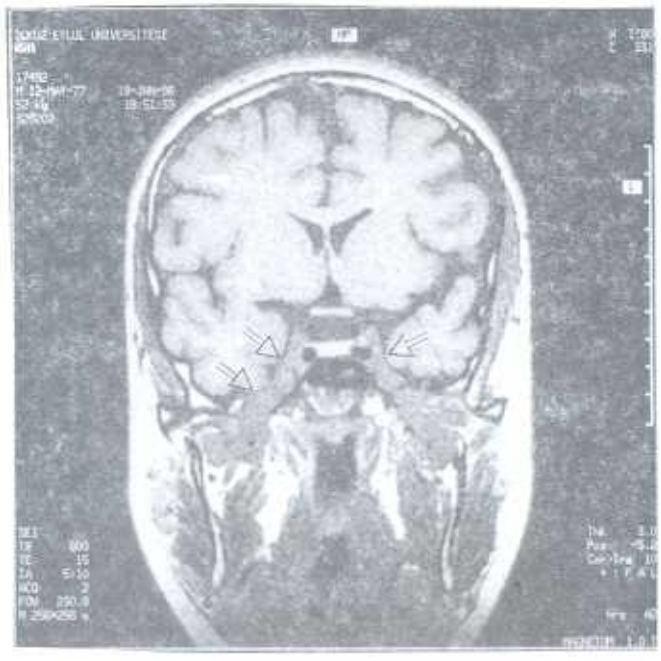

Figure 1a. The mandibular division of trigeminal nerve on T1 weighted non-contrast image.

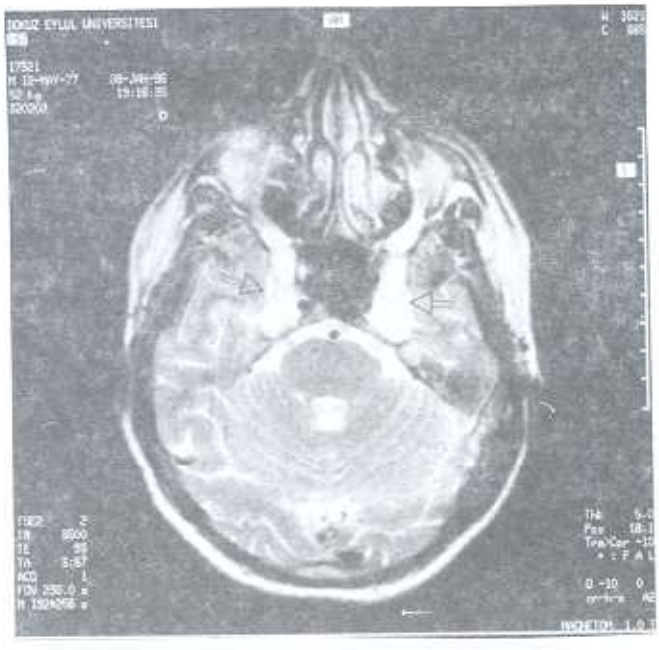

Figure 1b. Bilateral symmetrical enlargement of Meckel caves indicating trigeminal nerve hypertrophy on spin echo T2 weighted image.

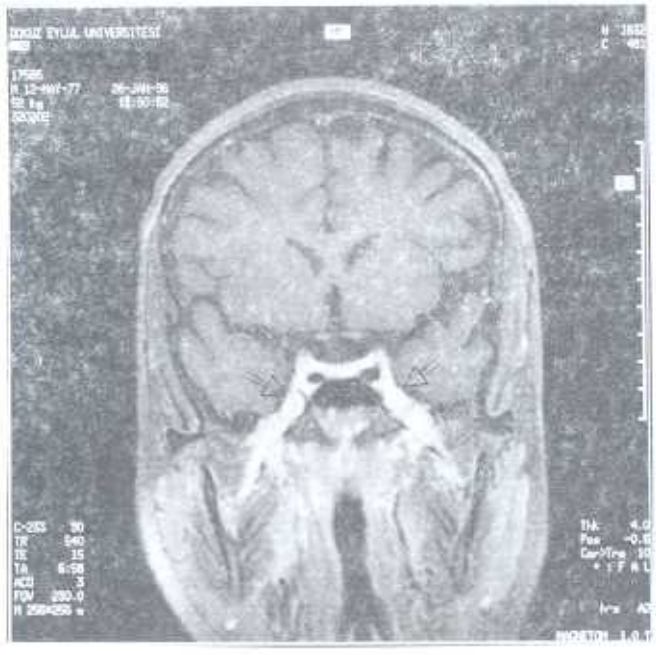

Figure 1c. The mandibular division of trigeminal nerve on fat saturated, contrast enhanced image.

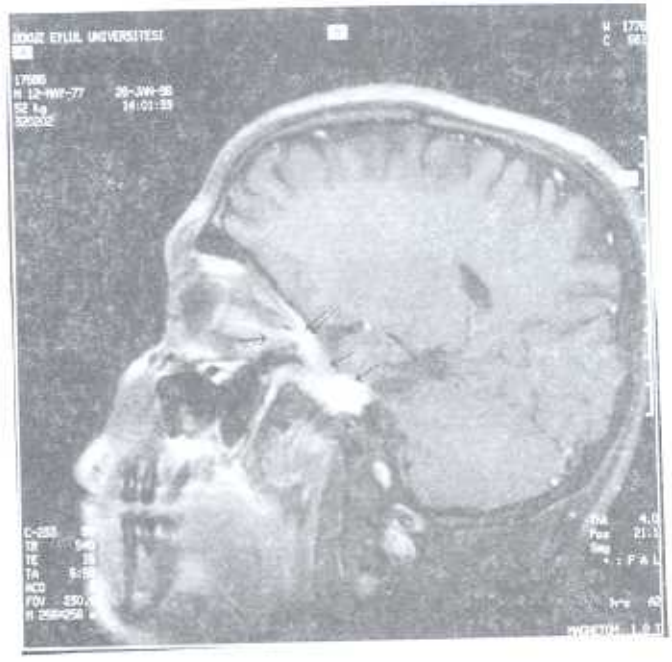

Figure 1d. The maxillary and ophthalmic divisions of trigeminal nerve on fat saturated, contrast enhanced image.

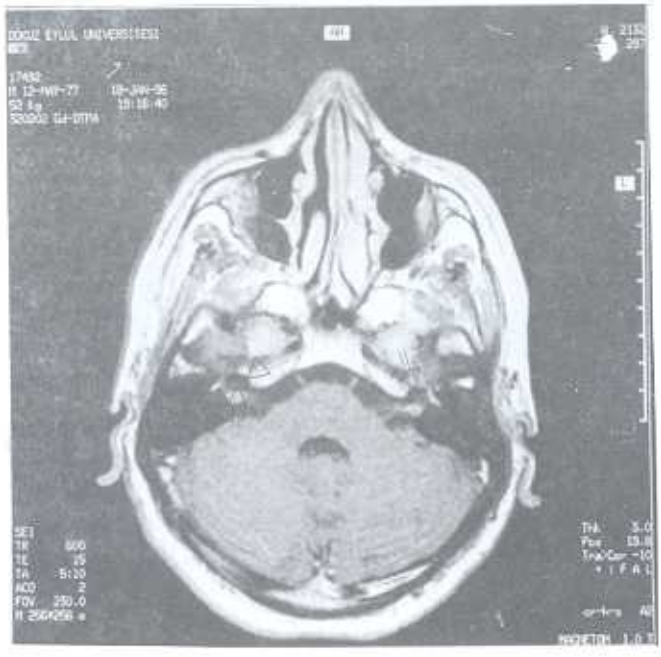

Figure 1e. Bilateral contrast enhancement of facial and vestibulo-cochlear nerves on T1 weighted image.

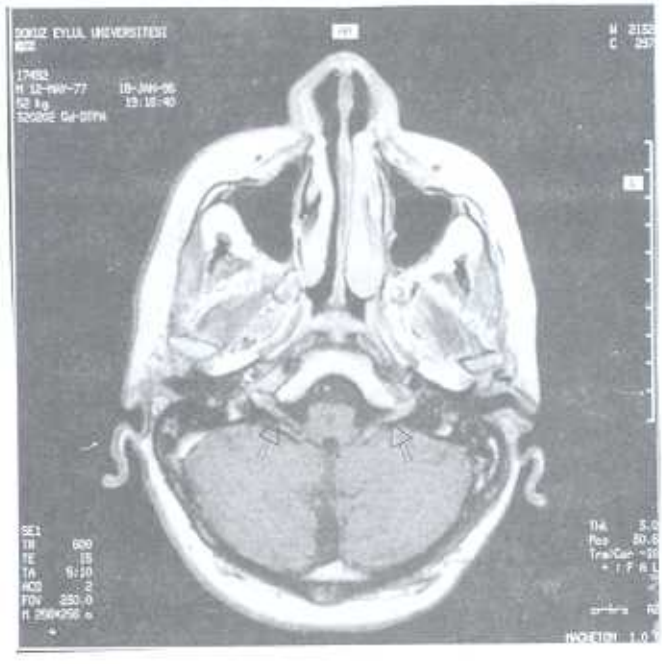

Figure 1f. Bilateral contrast enhancement of hypoglossal nerves on T1 weighted image.

For the molecular genetic study, genomic DNA was obtained from peripheral blood of the patient, his parents and 3 unaffected relatives. Analysis of the microsatellites RM11GT, D17S921, D17S839 and D17S955 excluded the 17p11.2 duplication (8,9). Mutation screening of PMP22 and P0 genes was conducted after amplification of the coding regions (2,3) by direct genomic sequencing of the PCR products on a 373A sequencer (Applied Biosystems Foster City CA, USA). Double strand sequencing was systematically performed. Nucleotide numbering of the PMP22 sequence was according to Patel (10). Sequence analysis revealed a heterozygous $T_{300}CT$ deletion in the third exon of the PMP22 gene which yielded a deletion of a phenylalanine in position 84 (delPhe 84) within the second transmembran domain of the protein. The deletion was found in both strands. Analysis of other coding regions of the PMP22 and P0 genes revealed normal sequences. The parents and other unaffected members of the family were found to carry normal alleles. The deletion was not found in 5 healthy unrelated controls indicating that it is unlikely to be a polymorphism.

DISCUSSION

Here we describe a patient with infantile age onset sensorymotor polyneuropathy with multiple symmetric hypertrophic cranial nerves in addition to the usual findings. His family history was negative for neurological diseases. He was diagnosed with DSD based on he had infantile age onset sensory-motor polyneuropathy with NCV less than 4 m/sec (11), palpable hypertrophic peripheral nerves and a positive sural nerve biopsy (1, 12). We have found a de novo mutation in the third exon of the PMP22 gene. This mutation (delPhe 84) is likely to be involved in the pathology since it has not been found in 50 healthy unrelated subjects and unaffected family members. Moreover, its location in the second transmembrane domain can induce a bad folding of the protein in the membrane. Most of the mutations previously described are indeed located in this domain. In addition, the same mutation has been reported very recently in a Finnish sporadic case of Dejerine Sottas disease (13).

In a study of hypertrophic forms of HMSN comparing HMSN I and DSD (HMSN III), there was greater incidence of ataxia, areflexia, and cranial nerve enlargement in DSD and higher CSF protein levels more than 100 mg/dl (12). Ouvrier et al (1987) summarized the clinical features for DSD in their 6 patients as delayed walking beyond the age 2 with abnormal coordination, ataxia, proximal weakness, clinical hypertrophy of peripheral nerves, facial weakness or unusual thick-lipped appearence of the face and very slow median NCV being less than 12 m/sec. All of the features mentioned above were found in our patient along with positive sural nerve biopsy and a mutation in PMP22 gene. His additional signs included multiple symmetric hypertrophic cranial nerves seen in MRI, also supported by prolonged cochlear nerve complex latency in BAEPs (14) and slowed facial NCV.

There is only one autopsy case of HMSN I associated with cranial neuropathy (7) and several reports stating cranial nerve neuropathy in HMSN (5, 6). Thus cranial nerve involvement in HMSN has already been reported. This is, however the

first genetically proven case of DSD with multiple cranial neuropathy in the literature. Multiple cranial hypertrophic neuropathy in our case of DSD was associated with a de novo mutation on PMP22 gene. This finding may help to enlighten a genetic locus related to cranial nerve myelination disorder.

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