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Clinical Record

Cochlear implantation in a patient with deafness induced by Charcot–Marie–Tooth disease (hereditary motor and sensory neuropathies)

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Abstract

Charcot–Marie–Tooth disease (CMT), also named hereditary motor and sensory neuropathies (HMSN), comprises a clinically and genetically heterogeneous group of disorders affecting the peripheral nervous system. Deafness induced by CMT is clinically distinct among the genetically heterogeneous group of CMT disorders. Deafness in CMT patients is associated with point mutations or deletions in the transmembrane domain in the peripheral myelin gene (PMP) 22, which are in close proximity to the extracellular component of this gene. We present a patient with deafness induced by CMT type 1A, undergoing cochlear implantation. Prior investigations showed good results due to replacing a synchronous impulse by means of cochlear implantation in patients with auditory neuropathy.

Key words: Hereditary Motor and Sensory Neuropathies; Cochlear Nerve; Cochlear Implants

Introduction

In this paper, we present a woman with sensorineural deafness induced by hereditary motor and sensory neuropathies (HMSN), also known as Charcot–Marie–Tooth disease (CMT), undergoing cochlear implantation. Charcot–Marie–Tooth disease comprises a clinically and genetically heterogeneous group of disorders affecting the peripheral nervous system. Depending upon clinical, electrophysiological and pathological features, CMT is usually subdivided into demyelinating (CMT 1) or axonal (CMT 2) disorders.[1] Due to recent advances in the genetics of these disorders, this classification has been refined based on the underlying discrete genetic defects. Most CMT disorders are characterized by a combination of progressive muscle weakness and atrophy with a distally pronounced sensory dysfunction.[2] The severity of disability varies considerably between the different subclasses of CMT.

Charcot–Marie–Tooth disease with deafness is a rare entity but has been described in some autosomal dominant families. De Weerdt and Heerspink reported in 1974 an autosomal dominant neuropathy with deafness in an autosomal family.[3] Boltshauer *et al*. described in 1989 a combination of motor-sensory neuropathy, vocal fold paralysis and sensorineural hearing loss in three patients in a large, three-generation family.[4] Deafness has been reported within five different types of CMT, namely: CMT 1; CMT 2; an X-linked dominant type of CMT; hereditary motor and sensory neuropathy-Lom; and Dejeine–Sottas disease.[5–9] In our patient's case, CMT with deafness was attributed to the most common type of CMT (accounting for 50 per cent of CMT patients), CMT type 1A. In most cases, CMT type 1A is caused by a 1.5 Mb deoxyribonucleic acid (DNA) duplication on chromosome 17, but these individuals do not suffer sensorineural deafness. Charcot–Marie–Tooth disease with deafness is only associated with point mutations or deletions in the peripheral myelin protein (PMP) 22 gene, which is the gene product of chromosome 17p11.2–12.[10] The role of the PMP22 gene is the regulation of myelination and myelin maintenance. The pathogenesis of deafness in patients suffering CMT type 1A is uncertain. It is considered that point mutations or deletions in particularly areas of the PMP22 gene are associated with demyelination of the acoustic nerve. Because of the neural character of the hearing loss, the question remains whether cochlear implantation is feasible or not.

We present the results of cochlear implantation in a patient with HMSN type 1A.

Case report

A 53-year-old woman presented to our cochlear implantation team with a bilateral sensorineural hearing loss induced by HMSN type 1A. She had developed a progressive, bilateral hearing loss since approximately eight years of age. At the age of 29 years, she started to use conventional hearing aids and also developed a continuous, severe balance disorder. Initially, the hearing aids were used unilaterally, but when her hearing capacity deteriorated hearing aids were used bilaterally. When her hearing deteriorated further, she sought advice as to whether cochlear implantation was feasible.

ENT examination

A routine ENT examination revealed no abnormalities. A pure tone audiogram showed severe, bilateral sensorineural hearing loss. Unaided pure tone average thresholds were 95 dB for the left ear and 92.5 dB for the right ear.

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Stapedial reflexes were absent in both ears. The maximal discrimination scores were 30 per cent at 75 dB in the left ear and 50 per cent at 75 dB in the right ear. Transiently evoked otoacoustic emissions were absent in both ears. Click-evoked auditory brainstem responses showed no repeatable waveforms. Auditory brainstem response threshold audiometry revealed a threshold of 100 dB and 90 dB in the right and left ears, respectively. Both ears showed a type A tympanogram. Balance investigation revealed a drastic decline in vestibular function. Caloric stimulation of the semicircular canals showed areflexia of the horizontal semicircular canal. Computed tomography and magnetic resonance imaging scans of the temporal bone were normal.

An Advanced Bionics HIRes 90K R cochlear implant (Advanced Bionics, Sylmar, California (CA)) was implanted in the right ear. During surgery, full insertion of the electrodes was achieved and post-operative complications did not occur. Speech recognition assessment was repeated six months after surgery, showing maximal discrimination scores of 59 per cent at 60 dB in the implanted ear. Pure tone audiography showed an average threshold for the right ear of 30 dB.

Neurological examination

Neurologically, our patient developed an intention tremor at 17 years of age. Over the years, the amplitude of the tremor declined gradually. At the age of 27 years, she noticed gait difficulties, causing her to injure her leg, sprain her ankle and to stumble continuously over obstacles. She noticed an increase of sensory loss in her fingertips when she attempted to pick up fine objects.

A recent physical examination revealed no deviations of the cranial nerves apart from the hearing loss. Further examination revealed a loss of vibratory sense in both legs distally, hand and distal leg atrophy ('stork legs'), scoliosis, high arches and pes calcaneovarus. All these symptoms were attributed to HMSN type 1A. Electrophysiologic studies suggested that the primary pathology was a diffuse demyelinating process with secondary axonal loss, evident in many motor nerves. At the age of 53 years, this patient developed an infarction of the right hemisphere of the brain, without unresolved complaints of the infarction.

Genetic analysis

The patient's grandniece suffered HMSN type 1A, detected by isolating DNA from a blood sample to test for the presence of duplication on chromosome 17. This individual was the only other family member suffering HMSN type 1A. Surprisingly, genetic analysis in our patient showed a substitution (G → T exchange) at nucleotide 193 in exon 3 of the PMP22 gene. This novel mutation resulted in a heterozygous valine to phenylalanine substitution at codon 65 (Val65Phe).

Discussion

In this paper, we describe a rare association of a demyelinating neuropathy and a sensorineural deafness induced by a mutation in the PMP22 gene. In our patient, this mutation was attributed to a heterozygous valine to phenylalanine substitution at codon 65 (Val65Phe). This mutation was described by Huehne *et al.* in 2002.[11] Amino acid 65 represents the first amino acid of the second transmembrane domain of the PMP22 protein.[11] Apart from the mutation discovered by Sambuughin *et al.*, all mutations associated with this phenotype affect amino acids in the first two transmembrane domains of the protein.[10] Sambuughin *et al.* described a novel 12-basepair in-frame deletion in the PMP22 gene in the third transmembrane domain of the protein. A literature review revealed five cases of deafness associated with a point mutation or deletion in the PMP22 gene. All these mutations of the PMP22 gene associated with deafness were located at the border of the transmembrane domains and the adjacent extracellular component of the PMP22-gene.

Regarding the mechanism of deafness, mutations at this site cause defective interactions with other proteins in Schwann cells, which may result in hypo- or demyelination of the peripheral nerves, including the auditory nerve.[12] Contrarily, hypermyelination due to an excess of PMP22 in the myelin sheath has been found in cases of PMP22 duplication.[13] Both mutations at the borders of the transmembrane domains and the induced hypo- or demyelination might be potential factors in causing auditory neuropathy. Furthermore, simultaneous duplication and a point mutation of the PMP22 gene in one family is extremely rare. To date, this unique situation has never been reported in the literature.

Prior studies have shown good post-operative audiometric results for patients with auditory neuropathy who have undergone cochlear implantation.[14] Due to significant temporal processing dysfunction, patients suffering auditory neuropathy generally receive little or no benefit from conventional hearing aids. In most cases, speech discrimination improves significantly after cochlear implantation. In our patient, post-operative audiometric results were in keeping with those of previous studies reporting the audiological outcome of cochlear implantation in patients with auditory neuropathy. In the case of CMT type 1A, the site of the lesion is the myelin sheath of the auditory nerve. Auditory neuropathy is caused by disruption of the synchronous activity of the auditory nerve. By means of supraphysiological electrical stimulation of the auditory nerve, the absent synchronous neural activity is reintroduced.[15]

We recommend cochlear implantation for children and adults suffering auditory neuropathy who do not benefit from conventional hearing aids.

- **Deafness induced by hereditary motor and sensory neuropathies type 1A, also known as Charcot–Marie–Tooth disease type 1A, is associated with particularly mutations in the PMP22 gene**
- **Mutations at this site cause defective interactions with other proteins in Schwann cells, which may result in hypo- or demyelination of the peripheral nerves, including the auditory nerve**
- **Previous studies have shown good audiometric results in adults and children with auditory neuropathy using cochlear implantation. This paper reports optimistic post-operative results for a patient with auditory neuropathy undergoing cochlear implantation**

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Dr J T F Postelmans takes responsibility for the integrity of the content of the paper.
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