Familial Progressive Vestibulocochlear Dysfunction Caused by a COCH Mutation (DFNA9)

Wim I. M. Verhagen, MD, PhD; Steven J. H. Bom, MD; Patrick L. M. Huygen, PhD; Erik Fransen, PhD; Guy Van Camp, PhD; Cor W. R. J. Cremers, MD, PhD

Objective: To describe the decline of vestibulocochlear function in a man with vestibulocochlear dysfunction caused by a Pro51Ser mutation within the COCH gene on chromosome 14q12-13 (DFNA9).

Methods: A follow-up of more than 15 years was performed in a single case. Clinical investigations were supplemented by oculomotor, vestibular, and auditory tests.

Results: A 50-year-old man had had progressive sensorineural hearing loss and dysequilibrium for 15 years; he had been asymptomatic at the age of 35 years. He suffered from instability in the dark, head movement–dependent oscillopsia, paroxysmal positional vertigo, and vertigo with and without nausea. Hearing impairment started unilaterally, predominantly in the high frequencies. He also reported tinnitus. Disease progressed to severe bilateral high-frequency hearing impairment and vestibular areflexia. Fluctuation of vestibulocochlear function was documented and mentioned by the patient.

Conclusions: Our patient proved to suffer from an autosomal dominant vestibulocochlear disorder caused by a COCH gene mutation. The remarkable medical history has some features in common with Ménière disease; however, there are also different clinical and neurophysiological features. In the family, phenotypic variability is present.

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Several years ago, we described a family with autosomal dominant progressive vestibulocochlear dysfunction resulting in sensorineural hearing loss and vestibular areflexia.1,2 The patients reported vague dizziness, blurred vision, dysequilibrium in the dark, and progressive hearing impairment. Symptoms seemed to start at about age 40 years.1,2 In 1991, Khetarpal et al3 described 2 families with progressive autosomal dominant hearing impairment and vestibular symptoms. Linkage analysis in one of these kindreds showed cosegregation of the disease with a 9-cM interval on chromosome 14q12-13, which locus was designated DFNA9.4

We were able to follow up an initially asymptomatic member of our family in whom a Pro51Ser mutation of the COCH gene within the DFNA locus was recently detected (Figure 1).5

REPORT OF A CASE

At the first examination, in 1983, a 35-year-old man (Figure 1, case IV-11 on pedigree)4 had no complaints. His audiogram and results of oculomotor and vestibular function tests were normal. Follow-up 2 and 3 years later disclosed a vestibulocochlear reflex with a long time constant, but the patient had no complaints (Table). Six years later, he had developed instability, especially in the dark. On a few occasions, he had vertigo, sometimes with nausea, lasting for several days, and he noticed head movement–dependent oscillopsia. He also reported slowly progressive hearing impairment in the right ear. The vestibulocular reflex showed a long time constant and a low gain (Table). Audigrams only showed minor high-frequency sensorineural hearing loss: about 10 to 40 dB hearing loss at 1 to 8 kHz.

In 1995, we saw the patient again because of benign paroxysmal positional vertigo during positioning on the left side, which was confirmed by a positive Dix-Hallpike test. He also noticed episodic vertigo, not related to positioning, that lasted for several weeks. Initially, nausea and vomiting were present. During these episodes, he did not experience more pronounced hearing impairment or tinnitus.

Early in 1998, at the age of 50 years, the patient had another episode of vertigo, nausea, and vomiting, combined with head movement–dependent oscillopsia. In the meantime, hearing impairment symptoms had become more prominent, affecting the left ear as well as the right. At that time, he also mentioned having had tinnitus on both sides for about a year. Vestibular testing showed hyporeflexia with...
METHODS

Saccades, smooth pursuit, and horizontal optokinetic nystagmus responses were elicited and analyzed as reported previously. For velocity-step tests (performed with electromyostigmatography in complete darkness, with eyes open, by suddenly stopping from constant rotation at 90°/s velocity), a rotatory chair (Toennies GmbH, Freiburg im Breisgau, Germany) was used. The nystagmus response was analyzed with a computer method. The cervico-ocular reflex was elicited in the dark by applying sinusoidal stimulation to the body with the head fixed. Bithermal (30°C and 44°C) caloric stimulation was applied to both ears. Pure-tone audiograms (air and bone conduction levels) were obtained in a sound-treated room according to common clinical standards and International Organization of Standardization norms. We used linear regression analysis of longitudinal threshold-on-age data to analyze progression in hearing impairment. Progression was considered significant if the slope—designated as annual threshold increase and expressed in decibels per year—was significantly greater than 0. We tested whether y-intercepts (extrapolated threshold at age 0) differed significantly from 0. Onset age (x at y = 0) was calculated for the lines with a negative y-intercept. Regression lines were pooled where possible, following F tests between the separate slopes and intercepts (Prism program, PC version 2.0; GraphPad, San Diego, Calif).

unilateral caloric weakness of the left labyrinth (slow-phase velocity at culmination of caloric nystagmus response of 15°/s to 30°C stimulation and 5°/s to 44°C), combined with a hyperactive response to hot-water caloric testing (71°/s vs cold-water response of 10°/s) of the right ear. A few months later, he had a similar episode. Two months later, our tests disclosed vestibular areflexia and increased sensorineural hearing impairment: about 10 to 60 dB hearing loss downsloping from 1 to 8 kHz bilaterally. The patient had a well-developed cervico-ocular reflex and optokinetic nystagmus response level (gain near unity at 20°/s and 40°/s stimulation); optokinetic after nystagmus could not be elicited. Six months later, he stated that his complaints had not changed, but he had no more episodes of vertigo or nausea.

Clear threshold fluctuation only at 4 kHz was seen in the left ear between the ages of 35 and 38 years. Longitudinal analysis disclosed significant progression at 0.5, 4, and 8 kHz; significant (negative) y-intercepts were detected at 4 and 8 kHz. The pooled regression lines for 0.5 to 2 kHz and 4 to 8 kHz showed a common onset at age 28 years, and annual threshold increases were 0.9 dB/y and 2.3 dB/y, respectively (Figure 2).

COMMENT

Our patient showed progressive sensorineural hearing loss with at least 1 instance of (partial) threshold fluctuation. Vestibular function showed some fluctuation between the ages of 35 and 38 years, but without complaints. Vestibular function gradually deteriorated at a more advanced age and was completely lost in the 50th year of life. Vestibular symptoms clearly developed from the age of 38 years onward and consisted of episodic and paroxysmal vertigo, followed by instability, especially in the dark, combined with head movement–dependent os-
ciliospia. We were able to confirm by longitudinal observation that the progressive vestibulocochlear dysfunction, with predominantly high-frequency hearing impairment and, finally, vestibular areflexia, in the other affected members of the patient’s family developed from about 40 years of age. Clearly enhanced cervico-ocular reflex and optokinetic nystagmus, as well as absent optokinetic after nystagmus at the time of vestibular areflexia, were in line with earlier observations. The cervico-ocular reflex and optokinetic nystagmus are compensatory for the vestibulo-ocular reflex loss.8,10

A similar progressive hearing impairment was described by Khetarpal et al11 in 3 cases from 2 kindreds; the first kindred showed an onset in the early part of the third decade, while the other kindred showed an onset at about 40 years. Only in 1 case (case IV-3, kindred 2)3 was vestibular function tested, showing a vestibular function loss at about 50 years of age.

The disorder in this family was genetically linked to a locus on chromosome 14q12-13, designated DFNA9.4 In the family described by Manolis et al,4 as well as 1 of the 2 kindreds described by Khetarpal et al,3 Robertson and colleagues11 described missense mutations in the human COCH gene. In a large Dutch family with DFNA9, a new Pro51Ser mutation in the COCH gene was found. The onset of hearing impairment ranged from 36 to 62 years of age, starting at the high frequencies. Several cases showed vestibular areflexia.12 In a large Belgian family with the same mutation, hearing loss and vestibular symptoms started between 20 and 56 years of age. The same mutation in the COCH gene was found in the present case as well as cases IV-9 and IV-10 (see Figure 1 and the pedigree).3

The cause of the dysfunction is still unclear. Khetarpal et al11 discovered an acidophyllic mucopolysaccharide-containing substance, especially in cochleas, maculas, and crista of patients with DFNA9, as well as severe degeneration of vestibular and cochlear sensory axons and dendrites. These areas correspond with areas in the chicken inner ear that show high levels of COCH expression.15 It was suggested that the mucopolysaccharide deposit could cause strangulation of nerve endings.3

Such strangulation might result in aberrant stimulation, ephaptic transmission, or triggering of primary vestibular afferent nerve fibers, giving rise to release from inhibition at the beginning of the disease, followed by vestibular hyporeflexia developing into complete areflexia because of nerve fiber degeneration. It also seems possible that an initial release from inhibition is caused by predominant involvement of efferent vestibular nerve endings, which is later followed by deafferentation when the afferent nerve endings are involved. The peculiar caloric response findings were similar to those previously reported as being associated with Ménière disease. These signs can be interpreted as being caused by release from contralateral inhibition.13 In one other family linked to DFNA9, fluctuating hearing loss was documented.2 In the same family, some patients reported periodic vertigo, sometimes with nausea. Our family showed phenotypic variability also. The father, grandfather, and oldest brother of the patient described herein (II-7, III-16, and IV-9; see Figure 1 and the pedigree)3 had no fluctuations or Ménière-like symptoms, but his sister (IV-10) mentioned unilateral tinnitus and an episode of vertigo.1 The cause of the phenotypic variability and the gene product are unknown. It may be that some patients who are suspected to suffer from Ménière disease in fact have DFNA9, a possibility that may now be assessed by screening for COCH mutations.3

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Corresponding author: Wim I. M. Verhagen, MD, PhD, Department of Neurology, Canisius-Wilhelmina Hospital, PO Box 9015, 6500 GS, Nijmegen, the Netherlands (e-mail: knf@cwz.nl).

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