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Autosomal dominant stapes fixation, syndactyly, and symphalangism in a family with *NOG* mutation: Long term follow-up on surgical treatment

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ABSTRACT

Objective: Evaluation of clinical findings and audiological outcome after surgery in a Danish family with autosomal dominant facio-audio-symphalangism syndrome with stapes fixation, syndactyly and symphalangism.
Methods: Retrospective report on eight affected family members in a Danish family. Clinical investigation included X-ray, audiology and in one case video-recorded surgery. Main outcome measure was audiologic results after stapedectomy. Sanger DNA sequencing of NOG was performed on peripheral blood.
Results: Audiologic analysis showed that seven of eight affected family members had bilateral conductive hearing loss. Three patients were treated with stapedectomy, on one or both ears, due to fixation of stapes. All the affected members had syndactyly and symphalangism. A not previously reported mutation in the NOG gene (c.688_699del, p.Cys230_Cys232delins11) was found to segregate with the stapes fixation, syndactyly, and symphalangism. p.Cys230_Cysdelins11 was classified as likely pathogenic according to guidelines from the American College of Medical Genetics and Genomics.
Conclusion: The clinical presentation of the reported mutation corresponds with previous case reports of families with *NOG* mutation. In this family, surgery with stapedectomy had lasting effect without renewed fixation of the stapes in a follow up period of 18 months–38 years.

1. Introduction

Syndromic congenital stapes fixation is rare, but can cause conductive hearing loss with early onset. In 1990, Teunissen and Cremers reported data on a family with conductive hearing loss caused by stapes ankyloses [1]. The affected family members had severe hyperopia, broad thumbs and first toes, brachytelephalangia and, in one case, symphalangism. The syndrome was reported within several other families and named Teunissen-Cremers syndrome [2,3]. Nine years later, genetic analysis found a mutation in the *NOG* gene to be responsible for the syndrome [4].

Since the first presentation of a mutation in the *NOG* gene, more than 35 mutations have been identified causing overlapping variations of the syndrome: Teunissen-Cremers syndrome [1–3], Proximal symphalangism [5–8], Multiple synostoses syndrome/facioaudiosymphalangism syndrome [6–12], Tarsal-carpal coalition syndrome [8] and Bradydactyly type B [13]. In addition to heterogeneity among the syndromes, there are inter- and intrafamilial variations in phenotypes [8,10,14,15]. Consequently, it can be difficult to distinguish between the syndromes and clinical diagnoses and an unifying term, *NOG*-related symphalangism spectrum disorder (*NOG*-SSD), has been introduced [16].

The *NOG* gene encodes the protein Noggin which inactivates bone morphogenetic proteins (BMPs). Absence of Noggin increase BMP-activity, resulting in recruitment of the cartilage cells, hyperplasia and bone growth [17]. Patients with stapes ankyloses caused by *NOG* mutation and morphological changes in Noggin may have an increased risk of refixation of stapes after surgery [18].

The aim of this study is to present long term audiological results after stapedectomy in a Danish family with a *NOG* mutation not earlier described.

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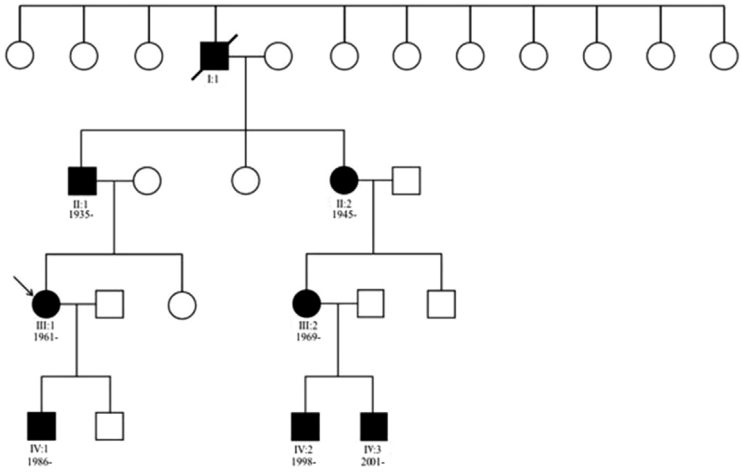

Fig. 1. Pedigree.

2. Material and method

2.1. Ethics

The study was conducted in accordance with the Danish law for scientific ethics committee and approved by the Danish Data Protection Agency. Informed consent was obtained from all included patients or from parents of the children.

2.2. Subjects

The family was presented by P. Vase et al., in 1975, where five family members had a syndrome with conductive hearing loss, syndactyly and symphalangism [19]. At this follow up study, there were eight affected family members in four generations. The pattern of inheritance was autosomal dominant as shown in the pedigree, Fig. 1.

Six of the seven living affected members gave consent to participate in the study, though one of the six patients did not consent to blood sample (patient IV:1). All available records, surgical reports, audiograms and imaging were reviewed. The individuals were examined by one of two otorhinolaryngologists with clinical examination, otomicroscopy and tympanometry. Audiologic examination consisted of pure tone audiometry (air and bone conduction) and speech audiometry with speech reception threshold (SRT) and discrimination score (DS). Patient III:1 and IV:1 underwent X-ray of hands and feet in connection to the study. X-ray was not repeated in patients were the diagnosis of symphalangism had been made with previous imaging.

2.3. Genetic analysis

A genetic analysis was performed on peripheral blood obtained from five of the six affected family members (patient III:1, II:2, III:2, IV:2 and IV:3). Genomic DNA was isolated from peripheral blood leucocytes. Sanger DNA sequencing of *NOG* was performed at Klinisch-Genetisch Centrum, Njmegen, KGCN, Nijmegen, Nederland. The familial mutation was analyzed by bidirectional sequencing using BigDye® Terminator v.3.2 cycle sequencing kit (Applied Biosystems, Denmark) and an AB13730XL capillary sequencer (Applied Biosystems, Denmark). Tertiary structure was evaluated based on the published structure of Noggin (1M4U).

3. Results

3.1. Otologic and audiologic findings

None of the individuals had a history of trauma or noise damage. Two of the affected patients (II:2 and IV:2) had an anamnesis with middle ear infections. Patient IV:2 had tubulation of both tympanic membranes at the age of 2 years. The tympanic membrane was healed at the time of examination and there was no suspicion of glue or infection in the middle ear. Three patients (III:1, IV:1 and III:2) had gone through stapedectomy on one or both ears at the time of examination. The ears (n = 5) who had gone through surgery had postoperative thickening of the tympanic membrane. The preoperative and early audiograms consisted only of pure tones (air and bone conduction) and data on speech reception threshold were not available. The audiologic results are shown in Table 1 in accordance to guidelines from Committee on Hearing and Equilibrium [20].

Patient 1, proband, III:1 (Fig. 1), 55 years of age at follow up, had a hearing loss documented at the age of 4 years. She underwent explorative tympanotomy at the age of 5 years, which revealed osseous fixation of stapes but no deformity of the bones of the middle ear. No further surgery was performed until bilateral stapedectomy at the age of 10 years. The preoperative audiograms at the age of 10 years showed bilateral conductive hearing loss of 50–60 dB. An improvement was obtained by stapedectomy and reduced the air-bone gap as shown in Table 1 and Fig. 2.

At the follow up, 38 years postoperatively, the hearing had declined and audiologic treatment with hearing aids was required. The air-bone gap was 10 dB, but the hearing threshold was increased to 20–40 dB (Fig. 2 and Table 1).

Patient 2, her son, IV:1, 30 years of age at follow up, was diagnosed with hearing loss at the same age as the mother. At the age of 10 years the audiogram showed severe bilateral conductive hearing loss with maximal air-bone gap, and he used bilateral hearing aids. After stapedectomy on the left ear (at the age of 14 years) and on the right ear (at the age of 15 years), hearing was improved and only a minor air-bone gap persisted in the audiogram 10 years after surgery (Table 1).

Patient 3, the paternal aunt of the proband, II:2, 71 years of age at follow up, had not gone through any ear surgery. She had hearing loss since childhood, mainly on the left ear. At the follow up the audiogram showed severe mixed conductive and sensorineural hearing loss and no stapedius reflexes. She used hearing aids on both ears.

Patient 4, her daughter, III:2, 47 years of age at follow up, had a conductive hearing loss of 40–50 dB since childhood. After