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Case report

Noonan syndrome: cochlear implantation in the setting of cochlear nerve deficiency

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Abstract. *Background and aim:* Noonan syndrome (NS) is a congenital disorder characterized by a wide heterogeneity in clinical and genetic features. Hearing loss can frequently occur in NS, although not always mentioned in its diagnostic criteria. We are reporting on a child with an established NS who underwent bilateral cochlear implantation (CI) in the setting of cochlear nerve deficiency. *Case presentation:* We present the case of a child-girl affected by NS. Newborn hearing screening and audiological evaluations reveled an asymmetric sensorineural hearing loss (SNHL), profound at left ear and severe at right ear. Hearing aids were fitted at the age of six months. Brain magnetic resonance imaging showed hypoplastic cochlear nerves. Due to progressive worsening of the hearing thresholds and inappropriate speech development, at the age of 2 years she underwent a left-sided cochlear implantation. Four years later, right ear was also implanted. Six years after the first surgery, a partial extrusion of the electrode array was noticed. Explantation and reimplantation of a new device was performed, adopting a subtotal petrosectomy approach. The patient reached a score of 95% in open-set speech perception tests. *Conclusions:* Hearing loss is a frequent finding in patients with NS; however, its nature and severity are very heterogenous. In consideration of the possible progression of SNHL, audiological follow-up in NS patients must be carefully and periodically performed so as to early detect worsening of hearing threshold. If indicated, cochlear implantation should be considered, taking account of audiological and systemic features of this syndrome. (www.actabiomedica.it)

Key words: Noonan syndrome, hearing loss, cochlear nerve deficiency, sub-total petrosectomy, cochlear implantation

Introduction

Noonan syndrome (NS) is a relatively common genetic disorder with an estimated incidence of 1:1000 to 1:2500 live births (1). This syndrome was first described in 1963 by Jacqueline Noonan; it is characterized by wide heterogeneity in clinical and genetic features (2). NS is most commonly transmitted as an autosomal dominant trait with a high proportion of sporadic cases due to *de novo* mutations. PTPN11 gene mutation is the most common finding, being present in about 50% of individuals with NS (3,4).

NS is clinically characterized by short stature, a wide spectrum of congenital heart defects, and distinctive facial dysmorphism comprising broad forehead, short neck, hypertelorism, down-slanting palpebral fissures, and low-set posteriorly rotated ears. Other clinical characteristics as coagulation defects, chest deformity, cryptorchidism, learning difficulties, neurologic issues, cognitive impairments, as well as hearing loss could be heterogeneously observed (1,3,4).

Although hearing impairment is not mentioned as one of the clinical criteria for the diagnosis of NS (5), conductive, mixed or sensorineural hearing loss (SNHL) may be present in fair number of cases (9). Radiological and histopathological studies have revealed that NS patients may present temporal bone anomalies, including venous malformations, cochleo-vestibular dysplasia, and marked reduction of spiral ganglion cells (6,7). However, to the best of our knowledge, no cases

of cochlear nerve deficiency (CND) in NS have been previously described in the literature. In this present study, we report on a child with an established diagnosis of NS who underwent bilateral cochlear implantation (CI) in the setting of CND.

Case presentation

This case report was conducted according to the principles expressed in the Declaration of Helsinki. For case reports, no formal research ethics board approval was necessary and therefore no reference number was generated. Informed consent was obtained from the parents of the patient before any treatment. The patient was a full-term born girl, with a birth weight of 3200 gr. Clinical examination showed the characteristics facial dysmorphic phenotype of NS including epicanthal folds, low set and posteriorly rotated ears, down slanting palpebral fissures, ptosis and mild hypertelorism. Additionally, echocardiography revealed a stenosis of the peripheral pulmonary arteries. The genomic DNA analysis confirmed a missense mutation c.124A > G in PTPN11. At the age of 3,5 years, growth retardation was observed; a neurosecretory growth hormone dysfunction was demonstrated and treatment with growth factor was started. A neuro-psychiatric evaluation excluded intellectual disability. From an audiological point of view, neonatal screening with transitory evoked otoacoustic emissions showed no response. Bilateral sensorineural hearing loss (SNHL) was confirmed by auditory brainstem responses (ABR), which showed no responses at the left ear and a threshold of 70 dB at the right ear. Hearing aids were fitted at the age of six months. At the age of 9 months, age-appropriate audiologic evaluation showed a PTA of 90 dB HL at the left ear and 70 dB HL at the right ear. The visual reinforcement audiometry (VRA) revealed a PTA of 75 dB HL at the left ear and 40 dB HL at the right ear. Brain magnetic resonance imaging (MRI) revealed hypoplastic cochlear nerves with a normal diameter of internal auditory canals, in absence of anomalies of the labyrinth (Figure 1).

Therefore, according to Govaerts classification, a type IIb CND was diagnosed (8). Despite unambiguous responses to sounds with hearing aids, the patient

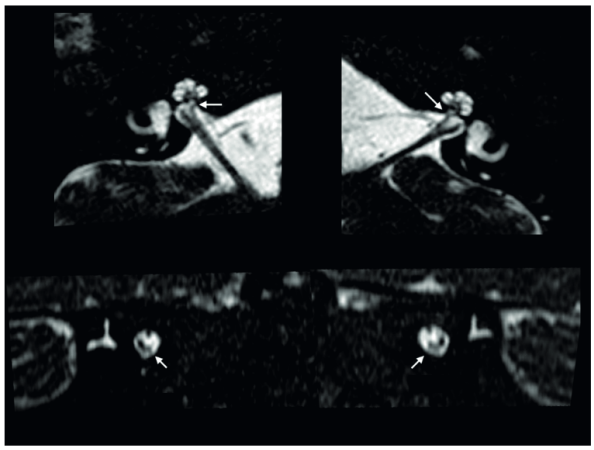

Figure 1. MRI findings of bilateral hypoplastic cochlear nerves: 3D axial DRIVE and reformatted parasagittal oblique images show within the antero-inferior aspect of the IAC fundus a hypoplastic cochlear nerve (white arrow) of smaller diameter than the facial nerve.

failed to make adequate signs of progress in terms of auditory performance and speech development during a trial period of amplification with intensive auditory training. The pre-operative speech perception category (SPC) was 2/6. Thus, at the age of 2 years, she underwent a left-side cochlear implant surgery; a perimodiolar electrode array (Nucleus Contour, Cochlear, Melbourne, Australia) was chosen. The operation was uneventful with full electrode insertion into the scala tympani. Two years after surgery, she showed a sound-field PTA threshold of 30 dB HL, which remained stable over time and the patient developed spoken language. The speech perception category increased to 5/6 after 12 months and 6/6 at 24 months. Successively, a progression of SNHL to profound level at the right ear (unaided PTA of 100 dB HL) became evident at the age of 6 years, when she underwent right-sided cochlear implantation using a Nucleus 24 RE (Cochlear, Melbourne, Australia) with full electrode insertion into the scala tympani. To note, the patient suffered of bilateral recurrent acute otitis media, both before and after CI. Six years after the first implantation, during annual routine examination, a defect of the bony posterior wall of the left external auditory canal with a partial extrusion of the electrode array was noticed (Figure 2).

This complication was well evident on temporal bone computed tomography (Figure 3).

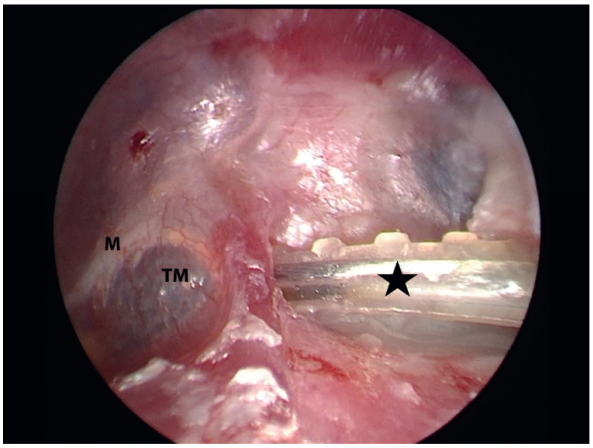

Figure 2. otoscopy showed a large defect of the bony posterior wall of the external auditory canal with a partial extrusion of the electrode array (black star); in the left-side of the image was evident an intact tympanic membrane (TM) and the malleus (M).

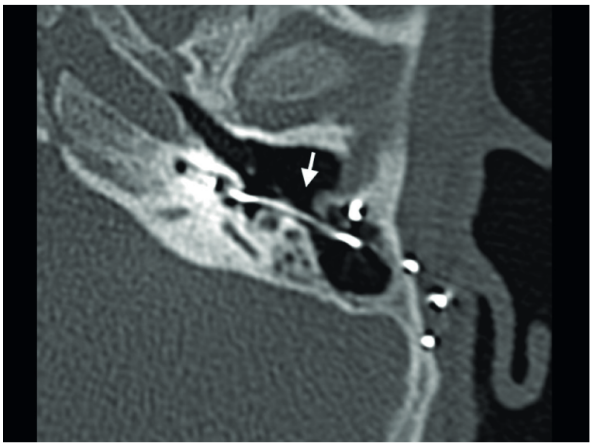

Figure 3. computer tomography scan, axial section of the left petrous temporal bone showed a defect of the bony posterior wall of the external auditory canal with a partial extrusion of the electrode array (white arrow).

For this reason, a subtotal petrosectomy (STP) with blind sac closure of the external auditory canal, Eustachian tube closure, and obliteration of the cavity with abdominal fat was performed. Despite good performance we decided to proceed with explantation and reimplantation of a new device because there were concerns about bacterial colonization of the implant. Reimplantation was uneventful and all electrodes were inserted into the scala tympani. Six months later vowels, bysillabic words, sentence and comprehension recognition scores were 100%, 90%, 100% and 90% respectively. The patient is still followed-up at our clinic, with stable performances.

Discussion

Hearing impairment has been reported in many patients affected by NS, most frequently as a result of otitis media. SNHL has been also described; moreover, its pathophysiology is not thoroughly known (3). Ziegler *et al.* hypothesized that in NS patients premature cell death of the inner ear cells may induce SNHL (9). While reviewing the literature, SHNL in NS is characterized by a great heterogeneity in clinical presentation and incidence. Qiu *et al.* examined 20 patients with NS; in 75% of the cases were reported a SNHL, while in 15-40% of the cases a conductive hearing loss due to otitis media was present (10). van Trier *et al.* found hearing impairment in 33 of 97 patients in their extensive study on hearing impairment in NS patients; SNHL was present in 9 out of 33 and varied between mild high-frequency and profound SNHL (11). Interestingly, SNHL progression over the years has been reported by several Authors (12,13); therefore, it was recommended that hearing thresholds of patients with NS should be followed periodically, even if their hearing sensitivity were within normal limits (12). Although not frequently, NS patients may be considered for and undergo CI. To our knowledge, there are three articles reporting on CI in NS (9,13,14). In 2009, Scheiber *et al.* described two patients, one with congenital profound SNHL and the other one born with a moderate SNHL that progressed to profound levels (14). Both children underwent bilateral sequential CI with remarkable benefit. In 2017, van Nierop *et al.* reported on cochlear implantation in 4 NS patients, 3 of which affected by congenital profound SNHL and the other one with severe to profound progression of SNHL (13). Surgery was associated with more than the usual diffuse hemorrhage in two patients out of four; actually, bleeding disorders have been reported in NS and have to be take into account in the work-up to CI (3,13). Despite good audiological results, including speech recognition, after CI, in all 4 patients there was language development, but, due to intellectual

disability, it was not age-appropriate (13). Still in 2017, Ziegler *et al.* reported on five patients presenting with profound SNHL and molecularly confirmed NS. SNHL was progressive in three cases and CI was performed in four patients. Unfortunately, no information about rehabilitative outcomes has been provided; CI was complicated by a hematoma in one patient consequently to coagulation defect (9).

A histopathological study of four temporal bone obtained from individuals with NS evidenced a striking reduction of spiral ganglion cell, with the mean population of spiral ganglion cells (15699 cells) being approximately half of those (32978 cells) in four age-matched control cases (6). It is noteworthy that CT scans and MRI did not evidence malformations of the cochlear nerve in any of implanted patients reported in the literature. Such was not our experience with the patient described in the present report. In our department, radiologic evaluation of pediatric candidates for CI included both temporal bone HRCT and brain MRI. Axial and sagittal oblique high T2 weighted reformatted images are obtained in planes perpendicular to the course of the seventh and eighth nerves in the internal auditory canal (IAC) and cerebellopontine angle to demonstrate if cochlear nerve is normal, hypoplastic or aplastic (15). CND is diagnosed if the diameter of cochlear nerve is smaller than that of the facial nerve or if there are less than four nerve bundles in the IAC (8). In our patient, comprehensive radiological study showed hypoplasia of the cochlear nerve associated with normal cochlea and normal diameter of IAC on both sides. Despite the presence of CND, our patient achieved good audiologic results, developed an age-appropriate spoken language and had an adequate daily average use (about 11 hours) of the cochlear implant, as shown by data logging evaluation.

Outcomes of CI in children with CND are extremely variable, ranging from sporadic cases in which open set speech perception and acquisition of a spoken language are achieved, to most cases in which only improved access to environmental sound develops (15-17). Exploration for potential prognostic factors that might be related to auditory performance outcome with a CI in patients with CND found that patients with hypoplastic cochlear nerves may be more likely to achieve speech discrimination than patients with

Unfortunately, six years after implantation, our patient developed resorption of the posterior wall of the external auditory canal with extrusion of the electrode array. Excessive thinning of posterior canal wall along with electrode array impinging on the bony canal was judged the cause of this complication. Furthermore, low bone mineralization, a frequent finding in NS, may have played a role in the resorption of the bony canal wall (19). The large size of the canal wall defect, along with the related risk of bacterial colonization of the implant and documented history of recurrent otitis media prompted us to proceed with STP instead of canal wall reconstruction.

Conclusions

Hearing loss is a frequent and heterogenous finding in patients with NS. In this case, degree and progression of the hearing impairment led to bilateral CI in order to allow proper speech development. Preoperative comprehensive radiological study is advisable in consideration of temporal bone and cochlear nerve anomalies often encountered in this syndrome. Notwithstanding, the presence of hypoplastic cochlear nerves did not affect the CI performances in this case. As regards indication for CI, no difference should be there from patients without NS and, when it is indicated, CI should be programmed as soon as possible. Due to the possible progression of SNHL, audiological follow-up of NS patients must be carefully and periodically performed so as to early detect worsening of hearing threshold.

Conflict of interest: Each author declares that she or he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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