International Journal of Pediatric Otorhinolaryngology 79 (2015) 874–878

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

External ear anomalies and hearing impairment in Noonan Syndrome

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ARTICLE INFO

Article history:
Received 11 December 2014
Received in revised form 23 March 2015
Accepted 24 March 2015
Available online 1 April 2015

Keywords:
Noonan Syndrome
Hearing impairment
Genotype–phenotype correlation
Dysmorphic ear anomalies

ABSTRACT

Objective: This is the first cohort in which hearing impairment and external ear anomalies in Noonan Syndrome are described extensively.
Methods: Retrospective analysis of the otorhinolaryngological and clinical genetic data from 97 Noonan Syndrome (NS) patients. Forty-four NS patients were seen by an otorhinolaryngologist for the analysis of hearing impairment. In our cohort 80 of the 97 patients were genetically tested. In 71 of these mutations were found: in 48 patients a mutation in *PTPN11*, in 10 patients in *SOS1*, in 5 patients in *SHOC2*, in 5 patients in *RAF1*, in 1 patient in *MAP2K2*, in 1 patient in *KRAS* and in 1 patient in *A2ML1*.
Results: External ear anomalies were reported in 75 NS patients (77%). In 69 patients the ears were low-set, 28 patients had posteriorly rotated ears, 14 patients showed protruding ears and 18 had thickened helices. Hearing impairment was detected in 34 NS patients. Nine patients had sensorineural hearing impairment, two a permanent conductive hearing impairment, two other patients had mixed hearing impairment and 20 patients had conductive hearing impairment in the past, caused by otitis media with effusion. Their temporary conductive hearing impairment resolved between the ages of 2 and 18 years. Sensorineural hearing impairment varied between mild high-frequency hearing impairment and profound (uni- and bilateral) hearing impairment and was progressive in three patients. Four NS patients received cochlear implants for their severe sensorineural hearing impairment. The cohort is small for genotype–phenotype correlations, but sensorineural hearing impairment, especially the bilateral severe hearing impairment, was only seen in patients with a *PTPN11* mutation.
Conclusion: NS is characterized by dysmorphic external ear anomalies and both sensorineural and conductive hearing impairment. Audiological examinations are recommended in all patients with Noonan Syndrome.

1. Introduction

Noonan Syndrome (NS) was first described by Noonan and Ehmke in 1963 [1]. A broad spectrum of features is seen and multiple abnormalities are characterizing NS. Common features include congenital heart anomalies, short stature and facial dysmorphism consisting of hypertelorism, short neck, low set ears and downslanting palpebral fissures. Other characteristics comprise chest deformity, cryptorchidism, learning difficulties and hearing impairment (HI) [2]. NS is an autosomal dominant disorder with an estimated incidence between 1:1000 and 1:2500 live births [2].

In the literature there are several studies describing NS patients with HI. HI is not mentioned as one of the clinical criteria for the diagnosis of NS [3]. However, it has been linked to NS since 1976 when it was described by Cremers [4]. External ear anomalies are described as well, mainly as part of facial dysmorphism [2,5]. Sharland et al. [6] described HI in 40% of the 146 NS patients. Qiu et al. [7] also studied data of HI in Noonan patients and they found sensorineural hearing impairment (SNHI) in 50% of the 40 ears without describing further information of the inclusion of NS patients.

In 2001 the first gene responsible for NS was discovered and mapped on chromosome 12q24.1 [8]. An activating missense

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http://dx.doi.org/10.1016/j.ijporl.2015.03.021
0165-5876/

mutation in the *PTPN11* gene accounts for approximately 50% of the Noonan patients. *PTPN11* influences the RAS-MAPK pathway. Also other genes of this pathway are involved in NS. *KRAS* was described in 2006 [9], *SOS1* in 2007 [10] and also other genes such as *BRAF* [11], *RAF1* [12] and *SHOC2* [13] are involved in NS.

In this study, we present data on hearing impairment, external ear anomalies, and molecular findings of 97 NS patients. We will compare our results with those in the literature and we will give an overview of the genotype–phenotype correlations for HI. To the best of our knowledge, this is the first time a large cohort of NS with these symptoms is presented with genotype–phenotype correlations.

2. Methods and patients

We collected retrospective data from 97 NS patients, 49 of them were males and 48 females. All these patients were seen in our medical center at the human genetic department and NS was clinically diagnosed by using the validated criteria of van der Burgt [3]. In most patients DNA analysis was available. Because most of the patients were seen by otorhinolaryngologists, speech and hearing centers and pediatricians elsewhere, data were collected on both external ear anomalies and hearing impairment after written informed consent. Clinical geneticists, pediatricians or otorhinolaryngologists described the external ear anomalies. Forty-four patients were seen by an otorhinolaryngologist and in 38 of them audiological tests were performed. The other six patients were seen by otorhinolaryngologists with complaints of otitis media and other otorhinolaryngological complaints. In this group no audiological tests were done because they had no complaints of hearing impairment. We included 97 patients for the analysis of external ear anomalies and the 44 patients seen by an otorhinolaryngologist for the analysis of HI. HI is defined as a high-frequency pure tone average (PTA) (average of 1, 2 and 4 kHz) of more than 20 dB. In most patients with HI analysis, pure-tone audiometry and speech audiometry were performed. In children, depending on the age, pure-tone audiometry, visual reinforcement audiometry (VRA), Brainstem Evoked Response Audiometry (BERA), Auditory Steady State Responses (ASSR), and/or impedance audiometry were used for audiological evaluation. The results of the hearing tests were collected retrospectively and were performed in different medical centers. In the Netherlands audiological investigations are performed in Speech and Hearing Centers and in otorhinolaryngology departments and 44 patients went to these centers and departments. We assume that in the six patients without audiological examinations, there were no clinical signs of HI.

3. Results

3.1. Genotype

NS was clinically diagnosed and DNA analysis was performed in 80 patients. Mutations were found in 71 patients. In 48 patients a mutation was found in *PTPN11*, in 10 patients in *SOS1*, in five patients in *RAF1* and in a further five patients in *SHOC2*. Unusually, we found KRAS in one patient, MAP2K2 in another patient and A2ML1 in a further patient. In nine patients DNA analysis was performed and no mutation was found. All of them were screened for the *PTPN11* gene and six of them were screened for other NS gene mutations. In our cohort of 97 patients, in 71 (73%) a mutation in one of the NS-genes confirmed the diagnosis of NS. The exact genotypes and the number of patients with HI are summarized in Table 1.

Table 1
Genotype and hearing impairment in 71 patients.

Gene	Nucleotide change	Amino acid change	*n*	SNHI	MHI	PCHI	THI
PTPN11	c.5C>T	p.Thr2Ile	1				
	c.124A>G	P.Thr42Ala	3	2			
	c.179 G>C	p.Gly60Asp	1				1
	c.181G>A	p.Asp61Asn	3			1	2
	c.181A>G	p.Gln79Arg	1				
	c.182A>G	p.Asp61Gly	2			1	
	c.184T>G	p.Tyr62Asp	1				
	c.186A>G	p.Tyr63Cys	1				1
	c.188A>G	p.Tyr63Cys	2				
	c.205G>C	p.Glu69Gly	1				
	c.228G>T	p.Glu76Cys	1				
	c.236A>G	p.Gln79Arg	4				1
	c.317A>C	p.Asp106Ala	1				
	c.417G>C	p.Glu139Asp	1				1
	c.794G>A	p.Arg265Glu	3		1		1
	c. 854T>C	p.Phe285Ser	1				
	c.922A>G	p.Asn308Asp	12	2			2
	c.923A>G	p.Asn308Ser	1				1
	c.1472C>T	p.Pro491Leu	1				
	c.1504T>A	p.Ser502Thr	1				1
	c.1507G>A	p.Gly503Arg	1				
	c.1508G>A	p.Gly503Glu	1				
	c.1510A>G	p.Met504Val	4	1			
SOS1	c.286G>T	p.Trp729Leu	1	1			
	c.508A>G	p.Lys170Glu	1				1
	c.742C>T	p.Arg248Cys	1	1			
	c.806T>C	p.Met269Thr	1				
	c.806T>G	p.Met269Arg	1				
	c.1656G>C	p.Arg552Ser	1				
	c.2104T>C	p.Tyr702His	1				
	c.2536G>A	p.Glu846Lys	1				1
	c.3134C>G	p.Pro1045Arg	2				
RAF1	c.770C>T	p.Ser257Leu	1				1
	c.782C>G	p.Pro261Arg	1	1			
	c.1457A>G	p.Asp486Gly	2				
	c.1837C>G	p.Leu613Val	1				
SHOC2	c.4A>G	p.Ser2Gly	5				3
KRAS	c.40G>A	p.Val14Ile	1				1
MAP2K2	c.401A>G	p.Tyr134Cys	1				1
A2ML1	c.4061+1G>A		1				

SNHI = sensorineural hearing impairment, MHI = mixed hearing impairment, PCHI = permanent conductive hearing impairment, THI = temporary hearing impairment.

3.2. External ear anomalies

Information of the external ear anomalies was obtained from retrospective descriptions during visits to the clinical genetics, otorhinolaryngology and pediatric departments. External ear anomalies were described in 75 patients out of the total cohort of 97 patients (77%). These are summarized in Table 2. Low-set ears are the most frequent external anomaly, described in 69 patients (71%), followed by posteriorly rotated ears in 28 patients (29%), thickened helices in 18 patients (19%), protruding ears in 14 patients (14%) and dysplastic ears in 4 patients (4%). In 22 patients no external ear anomalies were described.

3.3. Hearing impairment

In total 44 patients had visited an otorhinolaryngology department (Table 3). SNHI was found in nine patients (20%, age 0–47 years). Four of the nine patients had severe congenital HI and in three patients progression of the HI was seen (Table 4). HI and mutation analysis of the patients with both SNHI and mixed HI (MHI) is shown in Table 4. Permanent conductive hearing impairment was measured in two patients with a *PTPN11* mutation (age 11 and 17). They both had tympanic membrane perforation. It was noted that after tympanoplasty their conductive HI persisted.