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Ocular Manifestations of Noonan Syndrome

A Prospective Clinical and Genetic Study of 25 Patients

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Purpose: To determine the full spectrum of ocular manifestations in patients with Noonan syndrome (NS).

Design: Prospective cross-sectional clinical and genetic study in a tertiary referral center.

Participants: Twenty-five patients with NS (mean age, 14 years; range, 8 months–25 years) clinically diagnosed by validated criteria.

Methods: All patients were examined by the same team following a detailed study protocol. Genetic analyses were performed in 23 patients.

Main Outcome Measures: Ocular abnormalities of vision and refraction, external ocular features, ocular position and motility, anterior segment, posterior segment, and intraocular pressure.

Results: Ocular features of vision and refraction were amblyopia (32%), myopia (40%), and astigmatism (52%). External ocular features were epicanthic folds (84%), hypertelorism (68%), ptosis (56%), high upper eyelid crease (64%), lower eyelid retraction (60%), abnormal upward slanting palpebral fissures (36%), downward slanting palpebral fissures (32%), and lagophthalmos (28%). Orthoptic abnormalities included strabismus (40%), abnormal stereopsis (44%), and limited ocular motility (40%). Anterior segment abnormalities included prominent corneal nerves (72%) and posterior embryotoxon (32%). Additional ocular features were found, including non-glaucomatous optic disc excavation (20%), relatively low (<10 mmHg) intraocular pressure (22%), and optic nerve hypoplasia (4%). Mutations were established in 22 patients: 19 *PTPN11* mutations (76%), 1 *SOS1* mutation, 1 *BRAF* mutation, and 1 *KRAS* mutation. The patient with the highest number of prominent corneal nerves had an *SOS1* mutation. The patient with the lowest visual acuity, associated with bilateral optic nerve hypoplasia, had a *BRAF* mutation. Patients with severe ptosis and nearly total absence of levator muscle function had *PTPN11* mutations. All patients showed at least 3 ocular features (range, 3–13; mean, 7), including at least 1 external ocular feature in more than 95% of the patients.

Conclusions: Noonan syndrome is a clinical diagnosis with multiple genetic bases associated with an extensive variety of congenital ocular abnormalities. Ocular features of NS are characterized by 1 or more developmental anomalies of the eyelids (involving the position, opening, and closure) associated with various other ocular abnormalities in childhood, including amblyopia, myopia, astigmatism, strabismus, limited ocular motility, prominent corneal nerves, and posterior embryotoxon. *Ophthalmology 2016;■:1–10 © 2016 by the American Academy of Ophthalmology.*

Noonan syndrome (NS), first described by Noonan and Ehmke in 1963,[1] is an autosomal dominant syndrome characterized by facial dysmorphism, short stature, and congenital heart defects.[2,3] Other distinctive abnormalities of NS include mild learning problems, hearing impairment, hematologic anomalies, cryptorchidism, and intrinsic ophthalmic abnormalities. There is a great diversity in the phenotypes. Incidence rates vary from 1:1000 to 1:2500 live births.[4,5]

The first gene discovered to be responsible for NS was *PTPN11* on chromosome 12q24.1. This gene encodes the nonreceptor-type tyrosine phosphatase SHP-2, which implicates dysfunction of several signal transduction pathways, and therefore influences various developmental processes. Approximately 50% of patients with NS have a *PTPN11* mutation.[6] SHP-2 is required for the function of the Ras/mitogen-activated protein kinase pathway and is essential in the response to growth factors, cell adhesion molecules, cytokines, and hormones.[7] Mutations in other coding genes of proteins that are associated with function of the Ras/mitogen-activated protein kinase pathway also are found. *KRAS* mutations were described in 2006,[8] and *SOS1* mutations were discovered in 2007.[9] Since then, studies have described *BRAF*, *RAF1*, *SHOC2*, *NRAS*, *MAP2K1*, *MAP2K2*, *SOS2*, and *RIT1* mutations in NS.[10–16]

In clinical reports, the main facial findings of NS are hypertelorism, downslanting palpebral fissures, and ptosis,[4,17] but few studies including in-depth ophthalmologic examinations have been performed. In 1992, a study of 58 patients showed at least 1 ophthalmologic abnormality in 95% of the patients.[18] In a more recent study, all 35 patients with NS showed at least 1 abnormality.[19] Although ocular

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abnormalities are described in up to 100% in all NS patients,[5,18] few studies have reported comprehensively about these features. Complete ophthalmologic examinations for both external and inner ocular abnormalities in NS are rare. The aim of this study was to determine prospectively the full spectrum of ocular manifestations in patients with NS and to link the phenotypes to the genotypes.

Methods

Protocol Setup

Twenty-five patients with NS from the Departments of Genetics and Pediatrics, Radboud University Medical Center, Nijmegen, The Netherlands, were referred for prospective and complete ophthalmologic examination in a detailed study protocol by a team of the Institute of Ophthalmology. The same team examined all the patients. Seventeen patients were male and 8 were female. They were clinically diagnosed by the criteria of van der Burgt et al,[20] including characteristic features in 6 categories (facial, cardiac, height, chest wall, family history, and other), with 2 alternatives (A and B) in each category. Definite NS was defined as 1A plus 1 of 2A through 6A or 2 of 2B through 6B, or 1B plus 2 of 2A through 6A or 3 of 2B through 6B. Age at ocular examination ranged from 8 months to 25 years, with a mean age of 14 years. The cohort included 23 white persons, 1 Turkish person, and 1 Hindustani person. Two brother and sister pairs were included.

The ophthalmologic study protocol included a detailed ocular history and measurements in 6 ophthalmic categories: (1) vision and refraction, using subjective and objective methods; (2) external ocular features, including anthropometry and photography; (3) ocular position and motility, including full orthoptic testing; (4) anterior segment, including slit-lamp biomicroscopy; (5) posterior segment, including ophthalmoscopy; and (6) intraocular pressure, including tonometry.

The study adhered to the tenets of the Declaration of Helsinki, and local ethics committee approval was obtained. All participants or their parents gave fully informed consent for performing the study and for publication of data, tables, and photography of eye strips.

Ocular Examination

A full ophthalmologic examination was performed. Best-corrected visual acuity was assessed with Snellen optotypes at 6 m after subjective and objective refraction measurements, including keratometry. Refractive errors were defined to be clinically significant if the spherical equivalent of ametropia (SEA) was 1.00 diopters (D) or more. They were classified as hyperopia (positive SEA; absolute value of SEA, $\geq$1.00 D), myopia (negative SEA; absolute value of SEA, $\geq$1.00 D), or astigmatism (absolute value of astigmatism, $\geq$1.00 D). Furthermore, Amsler grid tests and Donders tests were performed.

Subjective scoring of the external ocular features was performed according to the methods of Farkas,[21] and for the definition of ptosis, we used the criteria of Small et al.[22] Levator function tests were performed with a ruler. Anthropometry was used for 3 objective measurements: the inner canthal distance, the outer canthal distance, and the interpupillary distance. Photogrammetric evaluation was performed to complete the physical measurements and facial findings. In anthropometry and photogrammetry, standard landmarks were used for measuring distances and angles based on the literature of Farkas.[21] For facial photography (Olympus Co., Tokyo, Japan), patients were positioned in a standard ophthalmic headrest with an adjustable chin rest and forehead strap to ensure stable head position. Photographs were obtained with the eyes in the primary position of gaze, with fixation of the camera lens at 3 m. The indices were based on those of Stengel-Rutkowski et al.[23] Finally, Hertel exophthalmometry (Oculus Optikgeräte GmbH, Wetzlar, Germany) was performed.

The orthoptic examination included examination of ocular alignment with cover tests, with the patient fixated on an accommodative target at near (30 cm) and distance (2.5 m and 6 m). Ocular motility was tested by checking the ocular ductions in the cardinal directions of gaze. Binocular vision tests were performed at 30 cm (prism test, Titmus stereotest), at 2.5 m (Bagolini test), and 6 m (Worth 4-dot test).

Ocular examinations were completed with testing of pupillary reactions, slit-lamp biomicroscopy (Haag-Streit AG, Bern, Switzerland), and measurement of intraocular pressure using noncontact tonometry (children) and applanation tonometry (adults). Ophthalmoscopy (indirect and direct) was performed after mydriasis. For children, the refraction was performed under cycloplegia after topical administration of cyclopentolate 1%. In a selected case, we performed digital color fundus photography (Topcon, Tokyo, Japan) and spectral-domain optical coherence tomography (SD OCT; Heidelberg Engineering, Heidelberg, Germany). Ocular features of NS were defined as major ocular features (prevalence, >50%), minor ocular features (prevalence, 25%−50%), and additional ocular features (prevalence, <25%).

Genetic Analysis

Genetic analyses were performed in 23 patients by Sanger sequence analysis in a routine DNA diagnostic setting for mutations in the coding regions of the genes known for NS. For primer sequences and PCR conditions, we refer to previous studies from our medical center.[24] Descriptive statistics with percentages were used for analyzing the results. We compared the ocular manifestations of our 25 patients with those of other cohort studies of NS.[18,19,25,26]

Results

The individual ocular manifestations and genetic findings of the 25 patients with NS are summarized in Table 1. The ocular features of the present cohort are compared with those of other cohort studies in Table 2, which shows differences in the prevalence of ocular features and new findings.

Ophthalmologic History

Eighteen patients (72%) had been examined by an ophthalmologist before their participation in this study. Eight patients (32%) had a history of occlusion therapy for amblyopia because of congenital blepharoptosis or infantile strabismus. Three patients (12%) had a history of ptosis surgery, and 3 other patients (12%) had undergone strabismus surgery. Thirteen patients (52%) used glasses for refractive errors.

Vision and Refraction

Visual acuity measurements were performed in 24 patients; 1 patient was too young for reliable results. This patient without measurement showed no signs of visual impairment. Twenty-three patients had normal to near-normal corrected visual acuity. One patient who was visually impaired (patient 19) had binocular best-corrected visual acuity of 0.3. Ophthalmologic examination revealed 3 ocular anomalies with a prevalence of more than 25%: treated and untreated amblyopia in 8 patients (32%), myopia in 10 patients (40%), and astigmatism in 13 patients (52%).