CASE REPORT

DOI: 10.5336/caserep.2023-100613

Noonan Syndrome and its Ophthalmic Implications: Insights from a Pediatric Case

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ABSTRACT Noonan syndrome (NS) is a rare genetic disorder and may present with extraocular findings such as ptosis, telecanthus, and downward-slanting palpebral fissures, as well as ocular signs including refractive errors, amblyopia, nystagmus, and optic atrophy. We present, a 7-year-old patient diagnosed with NS a year ago who was referred for ophthalmological evaluation. The patient had ptosis, nystagmus, esotropia, myopia, astigmatism and optic nerve hypoplasia. The best-corrected visual acuity, was 0.8 in the right eye and 0.1 in the left eye. He was prescribed spectacles and advised occlusion therapy for the right eye for 3 hours per day. At the one-year follow-up, the visual acuity in the right eye remained unchanged, whereas the visual acuity in the left eye improved to 0.2. Factors contributing to vision impairment in NS include ptosis, anisometropic amblyopia, and cataract. Early ophthalmological assessment is crucial for NS; because intervention for these conditions during childhood can lead to improvements in visual acuity.

Keywords: Noonan syndrome; ptosis; amblyopia; optic nerve hypoplasia

Noonan Syndrome (NS), first documented in 1963, is estimated to affect between 1 in 1,000 and 1 in 2,500 live births.[1] Around 50% of the instances are sporadic in nature, whereas a considerable proportion of the residual cases demonstrate autosomal dominant inheritance.[2] To date, over 14 genes have been identified as responsible for NS, with the most common being PTPN11 (accounting for about 50% of cases) and SOS1 (10-13%), while others are less frequently observed.[3]

Short stature, congenital heart issues, facial dysmorphology, and developmental delays typify NS, along with male cryptorchidism, ophthalmologic defects, and chest deformities. Facial features include hypertelorism, epicanthal folds, and ptosis. NS may involve external eye issues and internal segment and retinal diseases.[4] Hence, the International NS Clinical Management Guidelines mandate immediate ophthalmological evaluation upon diagnosis.[5] Our study focuses on a 7-year-old diagnosed with NS, aiming to analyze the ophthalmologic outcomes in light of existing literature.

CASE REPORT

A 7 years old male patient diagnosed with NS who was being monitored in the pediatric endocrinology section was referred to our clinic for an ophthalmological evaluation. Written consent was obtained from his family to use the patient's test results and images for scientific purposes. According to the medical history, there is no known history of eye problems or genetic disorders in the family. Additionally, due to limitations in technical equipment, it was not possible to conduct a detailed investigation into ge-

TO CITE THIS ARTICLE:
Dal A, Erdağ M, Canleblebici M. Noonan syndrome and its ophthalmic implications: Insights from a pediatric case. Turkiye Klinikleri J Case Rep. 2024;32(2):36-9.

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Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 04 Dec 2023 ***Accepted:*** 14 Mar 2024 ***Available online:*** 19 Mar 2024

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netic mutation subtypes. During the ophthalmological examination, bilateral ptosis and downward-slanting palpebral fissures were noted (Figure 1). The eyelid aperture in the right eye measured 7 millimeters, while in the left eye it was 6 millimeters. In the right eye, the levator function was 10 millimeters, while in the left eye, it was 8 millimeters. The margin-reflex distances were 1 millimeter and 0.5 millimeters, respectively in the right and left eyes. Direct and indirect light reflexes and pupil diameters were normal. Rotary nystagmus was observed, and a cover-uncover test revealed an esotropia of eight prism diopters. Biomicroscopy of the anterior segment revealed no pathological findings.

Measurements from the NIDEK Tonoref III (NIDEK, Japan) for Autoref/Kerato/Tono/Pachymetry showed the right eye had a refractive error of -0.75 (-0.25 axis 130), and the left eye -2.00 (-0.50 axis 170). Intraocular pressures were 12mmHg right and 10mmHg left. Keratometric readings were K1: 44.82D and K2: 45.17D right, and K1: 44.25D and K2: 44.87D left. Central corneal thicknesses were 537 µm right and 543 µm left. Best-corrected visual acuity via Snellen chart was 0.8 right and 0.1 left. Post-dilation fundus examination showed C/D ratios of 0.6 right and 0.8 left using 0.5% Tropicamide (Figure 2). OCT revealed RNFL thicknesses of 60 µm superior, 43 µm nasal, 74 µm inferior, and 48 µm temporal in the right eye; and 56 µm superior, 49 µm nasal, 101 µm inferior, and 48 µm temporal in the left. Optic disc areas were 1.53 mm² right and 1.41 mm² left (Figure 3). After cycloplegic refraction, refractive errors were corrected to -1.50 (-0.25 axis 180) left and -0.25 (-0.25 axis 125) right. The patient underwent refractive correction and daily occlusion therapy of the right eye for 3 hours, with follow-ups every three months. After one year, visual acuity was stable at 0.8 in the right eye and improved to 0.2 in the left.

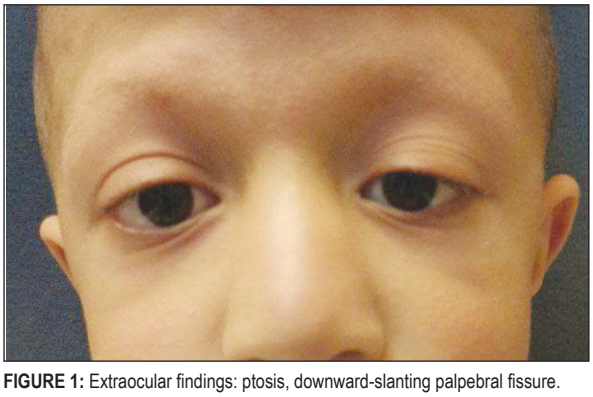

FIGURE 1: Extraocular findings: ptosis, downward-slanting palpebral fissure.

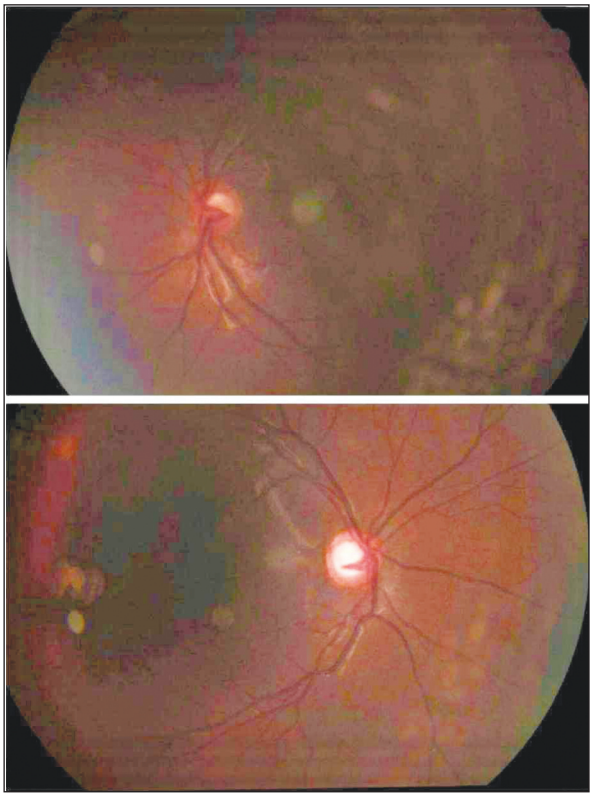

FIGURE 2: The upper image shows the fundus photograph of the right eye, and the lower image is of the left eye.

DISCUSSION

In patients diagnosed with NS, ocular symptoms vary, but it has been reported that at least one ocular sign is present in 95% of cases.[6] Despite the prevalence of ocular problems in NS patients, there can be delays in ophthalmological evaluations. Possible reasons for these delays include the presence of serious life-threatening conditions associated with NS, which may overshadow ocular findings.[7] NS is linked to serious cardiac abnormalities, specifically intractable cyothorax and hypertrophic cardiomyopathy, which can ultimately result in mortality.[8] Furthermore, it has been recorded that NS is linked to renal problems, and a young patient with NS suffered an awful outcome following a kidney transplantation.[9] Early oph-

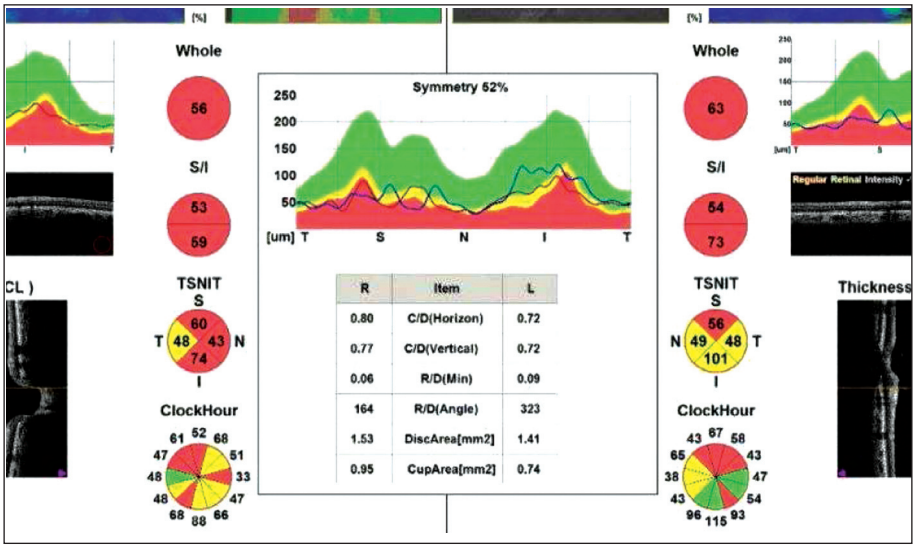

FIGURE 3: Peripapillary retinal nerve fiber layer for the right and left eyes.

thalmological evaluation is crucial in NS due to the potential accompanying pathologies that can cause vision loss. Current NS guidelines emphasize the necessity of a detailed ophthalmological assessment at the time of diagnosis. Post-diagnosis follow-ups, although varying according to ophthalmologists' recommendations, typically suggest a comprehensive ophthalmological evaluation every two years.[5]

Both extraocular findings and ocular problems are reported in NS patients.[10] Common signs outside the eye include minor occurrences of epicanthal folds, hypertelorism, ptosis, a prominent crease on the upper eyelid, and retraction of the lower eyelid.[11] Ptosis is usually symmetric in both eyes, though asymmetrical cases have been reported.[12] Another common issue in NS patients is ocular motility disorders, such as esotropia, exotropia, and nystagmus.[7] In our case, minimal esotropia and non-axis-obscuring ptosis and rotatory nystagmus were observed in both eyes.

According to reports, most vision disorders are frequently caused by congenital or developmental anomalies of the optic nerve.[7] These diseases often occur alongside optic nerve atrophy and hypoplasia. Patients with these conditions typically experience symptoms like nystagmus or strabismus, which may be connected to BRAF mutations.[7] The study by van Trier et al. documented a variety of genetic alterations (SHOC2, KRAS, and RAF1) in seven instances of visual impairment.[7] Lee et al. were the initial researchers to document visual impairments in individuals with NS, but their work did not incorporate genetic analysis.[6] This issue was not addressed in the publications of Alfieri et al. and Marin et al.[4,12] Amblyopia caused by visual deprivation can be another factor contributing to vision loss throughout early childhood, including conditions such as cataracts or ptosis. In order to prevent long-lasting visual impairments, it is crucial to promptly address these variables that can cause amblyopia. Undoubtedly, a thorough eye examination can aid in the early detection of any vision-endangering problems and enable the implementation of suitable treatment. Optic nerve hypoplasia and anisometropia were identified as the likely causes for the decreased level of vision in our instance. The limited improvement in visual acuity following treatment for anisometropic amblyopia suggests that other factors, beyond anisometropia, play a more significant role in the underlying causes of the observed reduction in vision, possibly implicating optic nerve hypoplasia as a more critical factor.

In a study by Van Trier et al., myopia and astigmatism were frequently observed in NS patients, hyperopia was less common, and significant anisometropia exceeding 1D was also common.[7]

Conversely, a study by Lee et al. reported a frequent occurrence of hyperopia as well.[6] Optic nerve hypoplasia was the primary cause of our patient's visual impairment, more significant than anisometropic amblyopia. Despite treatment starting a year after diagnosis, vision improved only marginally from 0.1 to 0.2. This emphasizes the significance of early detection in managing amblyopia, though the underlying optic nerve condition limits outcomes. Additionally, our examination showed an unbalanced cup-to-disc (C/D) ratio with elevated values (right: 0.6, left: 0.8) without hypertension. Studies indicate that a higher C/D ratio occurs in 10% of patients regardless of hypertension, with no direct links to ocular hypertension or glaucoma found in NS-related research.[12] It is very important to do full neurological exams to find out if the higher C/D ratio and thinning of the peripapillary RNFL are signs of more serious neurodevelopmental and neurodegenerative problems linked to NS, such as problems with learning, speaking, moving, and thinking.[13,14]

In conclusion, NS is a rare syndrome that can be accompanied by life-threatening conditions. Besides, ocular findings are commonly associated with NS. Conditions such as ptosis obscuring the visual axis, strabismus, and anisometropic amblyopia can accompany the syndrome, and early intervention can lead to gains in vision. Therefore, a detailed ophthalmological examination should not be overlooked when NS is suspected.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ali Dal, Murat Erdağ;* ***Design:*** *Murat Erdağ, Mehmet Canleblebici;* ***Control/Supervision:*** *Ali Dal, Mehmet Canleblebici;* ***Data Collection and/or Processing:*** *Murat Erdağ;* ***Analysis and/or Interpretation:*** *Mehmet Canleblebici, Ali Dal;* ***Literature Review:*** *Murat Erdağ, Mehmet Canleblebici;* ***Writing the Article:*** *Murat Erdağ, Ali Dal;* ***Critical Review:*** *Ali Dal, Mehmet Canleblebici;* ***References and Fundings:*** *Murat Erdağ;* ***Materials:*** *Murat Erdağ.*

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