CASE REPORT

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# Noonan Syndrome and Its Ophthalmic Implications: Insights from a Pediatric Case

Ali DAL[a], Murat ERDAĞ[b], Mehmet CANLEBLEBİCİ[c]

[a]Private Uğur Eye Hospital, Clinic of Ophthalmology, Kahramanmaraş, Türkiye
[b]Van Training and Research Hospital, Clinic of Ophthalmology, Van, Türkiye
[c]Kayseri State Hospital, Clinic of Ophthalmology, Kayseri, Türkiye

**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), initially documented by Noonan and Ehmke 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 cardiac problems, facial dysmorphology, and modest developmental delays are all characteristics of NS. Other symptoms include male cryptorchidism, ophthalmologic defect and chest wall abnormalities. Facial dysmorphisms encompass hypertelorism, epicanthal folds, and ptosis. It has been noted that NS can present with both external ophthalmologic problems and diseases affecting the anterior segment and retina.[4] Consequently, the International Noonan Syndrome Clinical Management Guidelines recommend that an ophthalmological evaluation be performed at the exact moment of diagnosis.[5] As part of our research, we describe a 7-years-old patient who was diagnosed with NS. Our objective is to analyze the ophthalmologic results within the framework of the current body of 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

**Correspondence:** Mehmet CANLEBLEBİCİ
Kayseri State Hospital, Clinic of Ophthalmology, Kayseri, Türkiye
**E-mail:** mehmetcl@hotmail.com

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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 genetic 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.

The measurements obtained from the NIDEK Tonoref III for Autoref/Kerato/Tono/Pachymetry revealed that the right eye had a refractive error of -0.75 (-0.25 axis 130), while the left eye had a refractive error of -2.00 (-0.50 axis 170). Additionally, the intraocular pressures were 12 mmHg in the right eye and 10 mmHg in the left eye. The keratometric readings were K1: 44.82 diopters (D) and K2: 45.17 D in the right eye, and K1: 44.25 D and K2: 44.87 D in the left eye. Furthermore, the central corneal thicknesses were 537 µm in the right eye and 543 µm in the left eye. With the Snellen chart, the best-corrected visual acuity was 0.8 in the right eye and 0.1 in the left eye. Cup-to-disc (C/D) ratios were 0.6 in the right eye and 0.8 in the left eye in the post-dilation fundus examination performed with 0.5% tropicamide administration (Figure 2). Peripapillary retinal nerve fiber layer (RNFL) thickness measurements were performed with optical coherence tomography (OCT). For the right eye, the measurements were 60 µm superior, 43 µm nasal, 74 µm inferior, and 48 µm temporal. On the other hand, for the left eye, the measurements were 56 µm superior, 49 µm nasal, 101 µm inferior, and 48 µm temporal. The patient demonstrated notably reduced optic disc areas, as measured using OCT; the right eye exhibited an area of 1.53 mm², and the left eye 1.41 mm² (Figure 3). The refractive errors following cycloplegic refraction were determined to be -1.50 (-0.25 axis 180) in the left eye and -0.25 (-0.25 axis 125) in the right. The patient, advised for refractive correction and occlusion therapy of the right eye for 3 hours daily, was followed up every 3 months for one year. At the final examination, the visual acuity of the right eye stayed unchanged at 0.8, while the visual acuity of the left eye improved to 0.2.

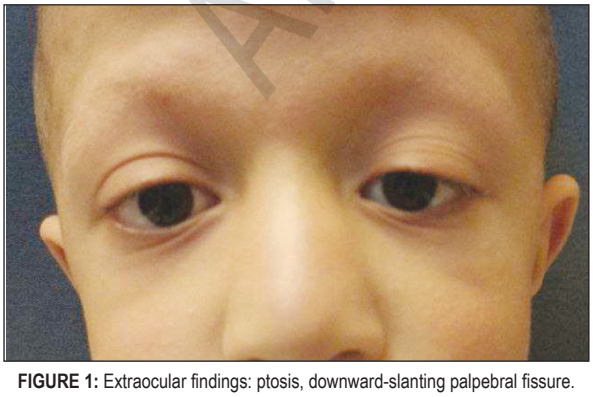

**FIGURE 1:** Extraocular findings: ptosis, downward-slanting palpebral fissure.

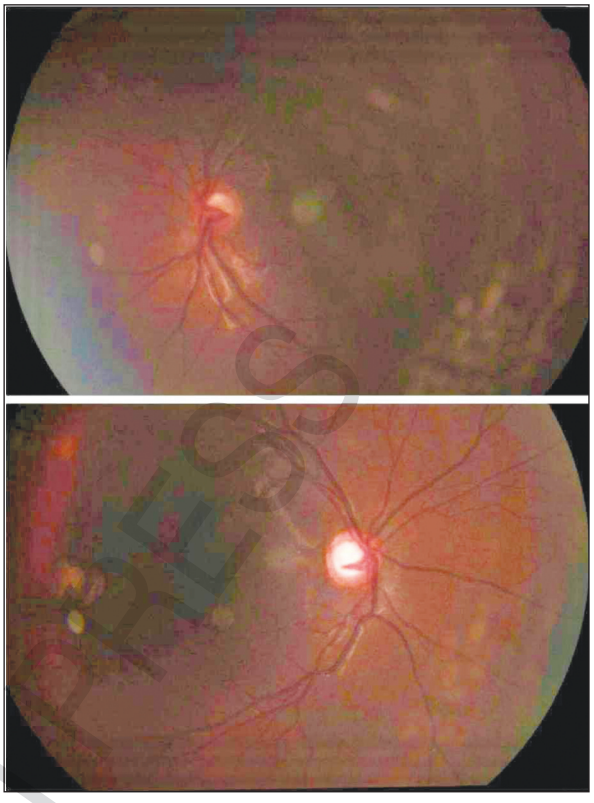

**FIGURE 2:** The upper image shows the fundus photograph of the right eye, and the lower image is of the left eye.

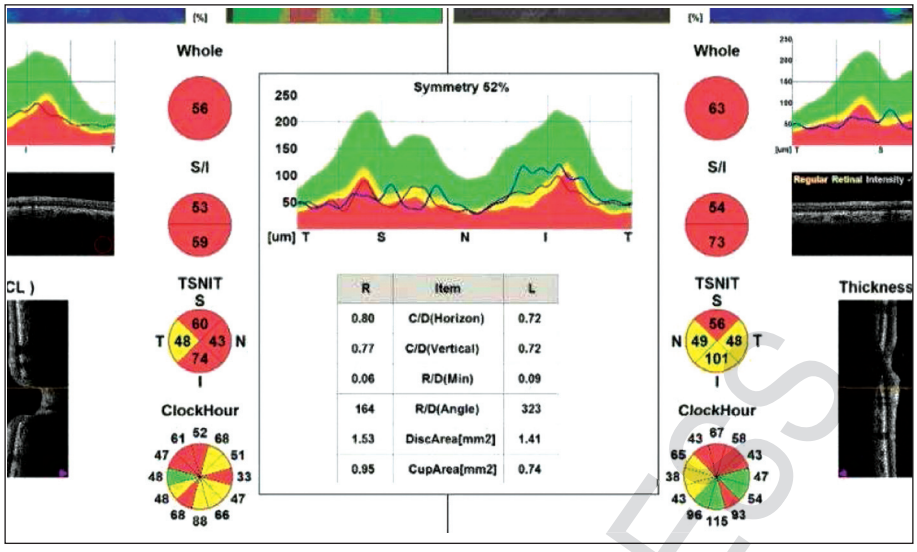


**FIGURE 3:** Peripapillary retinal nerve fiber layer for the right and left eyes.

## 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 ophthalmological 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.[12,13] 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 impair-

ments, 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 main reason for our patient's visual impairment, overshadowing the anisometropic amblyopia. Despite the delayed diagnosis a year prior and the amblyopia treatment received, the patient's vision only improved slightly from 0.1 to 0.2. This limited progress accentuates the critical role early detection plays in managing amblyopia, although the prognosis is constrained by the optic nerve condition. Another condition we observed in our case was that the posterior segment examination revealed an unbalanced C/D ratio and an elevated bilateral C/D ratio (right: 0.6, left: 0.8), despite the patient's normotensive state. Even in the absence of hypertension, studies have shown that the C/D ratio increases in 10% of patients.[12] Neither ocular hypertension nor glaucoma have been directly linked to NS in any research conducted so far. It is very important to do full neurological exams to find out if the observed thinning of the peripapillary RNFL and higher C/D ratio are signs of the wider neurodevelopmental and neurodegenerative spectrum linked to NS. These should encompass evaluations for cognitive deficits, learning difficulties, speech and language issues, motor dysfunctions, and other related symptoms as documented in the literature.[14,15]

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.


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***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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