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# NOONAN SYNDROME – CASE REPORT

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Noonan Syndrome is a rare, autosomal dominant disorder characterized by short stature, facial abnormalities, congenital heart defects and urogenital malformations. Ocular changes occur in 95% of patients and usually include hypertelorism, ptosis, refractive errors, strabismus, amblyopia, rarely nystagmus, colobomas, cataracts, optic nerve drusen.

Case report: We present a case of a boy, 10 months old, referred by the pediatrician because of strabismus. During the general examination of the head and face, we noted that the ears were low-set, and the lower jaw was slightly smaller. Ophthalmological examination revealed hypertelorism, left eye esotropia, hyperopia, and optic disc pit. Other associated malformations were: dilatation of both pyelons, cryptorchidism, pulmonary stenosis. Genetic analysis confirmed the diagnosis of Noonan syndrome.

The variety of clinical manifestations of this syndrome indicates that a multidisciplinary approach is necessary for diagnosis, treatment, and follow-up of these patients. *Acta Medica Medianae 2014;53(2):54-56.*

***Key words:*** *congenital anomalies, ocular manifestations, systemic manifestations*

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## Introduction

Noonan Syndrome (NS) is a rare autosomal dominant inherited disorder. It was known under various names such as male Turner's syndrome, Turner-like syndrome or Turner syndrome with normal karyotype, when in 1963 Dr. Jacqueline Noonan defined these changes as a specific syndrome which was named after her (1). The incidence of NS is different and ranges from 1/1000 to 1/2500 live births (2,3).

The disease is characterized by short statue, facial abnormalities, congenital heart defects and urogenital malformations. Less frequently the disease may be accompanied by delayed psycho-motor development. Also, in these patients, especially in childhood, disorders of coagulation factors (VIII, XI, XII) and thrombocytopenia are common. The hearing loss may also occur. In a small percentage of subjects, pigmentation disorders such as naevi, cafe-au-lait spots and lentigo occur. It is of great importance to mention that in these patients, there is a high incidence of lesions of the eye, usually hypertelorism, down-slanting palpebral fissures, epicanthic folds, ptosis, refractive errors, strabismus, amblyopia, nystagmus, and rarely cataract, colobomas, and keratoconus (4-6).

We present a case of a boy, 10 months old, sent by the pediatrician because of strabismus. Ophthalmological examination showed: hyper-telorism, down-slanting palpebral fissures, left eye esotropia (angle of deviation 15 Δd). Ocular motility, as well as convergence, were preserved in all directions. The child followed a toy and a light source in all directions (Figure 1). Anterior segment examination was normal and the value of intraocular pressure/IOP was 10mmHg. After performing the indirect ophthalmoscopy (indirect ophthalmoscope-Heine 500, Germany) we found that retinal blood vessel network was completely developed and the bilateral presence of optic disc pits was diagnosed. During cycloplegia, achieved by topical administration of Sol. Atropin 0,25%, mild hypermetropia (+1,0Dsph) was found. Ultrasound examination of the eyes was performed. (Ultrasound A/ B Scanner UD-6000, Tomey, A-scan, 10MHz, 5.3 mm). Axial length (Lax) was measured on both eyes, 20.95 mm right eye and OS 20.98 mm left eye. Ultrasound B-scan confirmed the presence of optic disc pit (Figure 2 and 3). Visual evoked potential in the right eye was normal, but on the left it was less defined, with prolonged latency and lower amplitude.

*Figure 1.*

*Table 1.* Scoring system for diagnosis of NS

| Present changes | A=major | B=minor |
|---|---|---|
| Face | Typical face dysmorphology | Suggestive face dysmorphology |
| Heart | Pulmonary valve stenosis, cardiomiopathy | Other defect |
| Body height | <P3* | <P10* |
| Thorax | Pectus carinatun/excavatum | Broad thorax |
| Family history | First degree relative with definite NS | First degree relative with suggestive NS |
| Other | Mental retardation, cryptorchidism and lymphatic dysplasia | Milder forms of these changes |

* P3 and P10-related measures height by age (normal range P3-P97)
Definitive NS: 1 "A" plus other major sign or two minor signs; 1 "B" plus two major signs or three minor signs

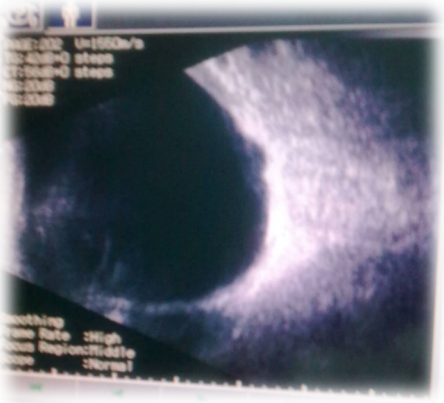

*Figure 2. Eho OD (Ultrasound A / B Scanner UD-6000, Tomey, A-scan, 10MHz, 5.3 mm)*

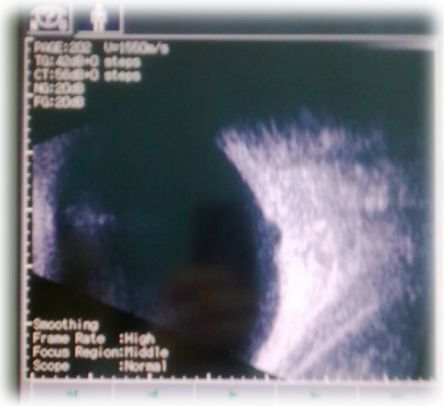


*Figure 3. Eho OS (Ultrasound A / B Scanner UD-6000, Tomey, A-scan, 10MHz, 5.3 mm)*

General examination of the head and neck showed that the ears were low-set, irregularly shaped, posteriorly rotated, with a thick helix, high arched palate, micrognathia.

From the child's medical documentation on the previous treatment we found out that it was a premature child (GS 36 weeks, TM 2500g) which suffered from respiratory distress syndrome, intracranial hemorrhage of the first degree, dilatation of both renal pyelons, migratory testis, and stenosis a. pulmonalis. Because of hypotonia, the child was prescribed an adequate physical treatment by a physiatrist.

However, due to all these changes, the child was referred to a geneticist. A normal male karyotype type (46 XY) was determined, but the clinical examination of the child pointed to Noonan syndrome. Genetic testing of the child and parents confirmed PTPN11 gene mutation on chromosome 12.

**Discussion**

Syndrome Noonan includes a very heterogeneous group of multiple congenital anomalies, which are easy to recognize clinically. However, due to a various degree of manifestations of these changes, a scoring system was created to help the diagnostic process (Table 1) (7).

This scoring system is very important for early recognition of this syndrome and appropriate treatment of numerous anomalies.

As the child grows, the clinical diagnosis is more and more difficult as the changes are not easily noticed, and the risk of consequences of untreated anomalies such as cardiac anomaly, cryptorchidism, chest wall deformities, coagulation disorders, slow psychomotor development, strabismus and amblyopic increase during the growth.

The ocular abnormalities in Noonan syndrome are very common and are found in about 95% of cases (6,8). The most common are refractive errors (61%), strabismus (48-63%), and amblyopia (33%) (5,8). Coloboma and other malformations of the retina occur very rarely (10%) and are usually associated with PTPN11 gene mutations (8,9). Given such a high incidence of ocular changes, the ophthalmologist can be a very important link in the diagnostic chain, as was the case with the patient we presented.

Even though the diagnosis of Noonan syndrome can be established on the basis of the clinical picture, it is important to do genetic testing whenever possible. In approximately 50% of these patients there is a mutation of PTPN11 gene on chromosome 12. This gene is responsible for the synthesis of the enzyme tyrosine phosphatase SHP-2. It is an intracellular signal for initiating a cascade reaction growth factor receptor, cytokines and hormones that regulate the processes of growth and development (10,11). Noonan syndrome mostly occurs on a sporadic

basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission (11,12). De novo mutation of PTPN11 is possible in sporadic cases of Noonan syndrome and is predominantly of paternal origin, as was the case in the present patient. However, there is evidence for a rare autosomal recessive form of the disease (12).

## Conclusion

This rare syndrome is characterized by a very heterogeneous group of changes in various organs, which further requires a multidisciplinary approach in order to provide early diagnosis and treatment of numerous malformations in these patients.

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# SYNDROMA NOONAN – PRIKAZ BOLESNIKA

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Nunanov sindrom je retka autozomalno dominantno nasledna bolest, koja se karakteriše niskim rastom, abnormalnostima lica, urođenim promenama na srcu i urogenitalnom traktu. Promene na oku javljaju se kod 95% ovih bolesnika i najčešće su to hipertelorizam, ptoza, refrakcione anomalije, strabizam, ambliopija, ređe nistagmus, kolobomi, katarakta, druze papile vidnog živca.

Prikazujemo slučaj dečaka starog 10 meseci, upućenog od strane pedijatra zbog skretanja levog oka. Opštim pregledom glave i lica primećeno je da su uši niže postavljene, a donja vilica nešto manja. Oftalmološkim pregledom nađen je hipertelorizam, esotropija levog oka, hipermetropija, anomalija optičkog diska po tipu jamice. Pregledom dokumentacije deteta saznajemo da se radi o prevremeno rođenom detetu, koje je imalo respiratorni distres sindrom, intrakranijalne hemoragije, dilataciju oba pijelona, migratorni testis, stenozu a.pulmonalis. Konsultativnim pregledom genetičara potvrđena je dijagnoza sindroma Noonan.

Raznolikost kliničkih manifestacija ovog sindroma ukazuje na neophodnost multidisciplinarnog pristupa kako u otkrivanju tako i u kasnijem lečenju i praćenju ovih bolesnika. *Acta Medica Medianae 2014;53(2):54-56.*

***Ključne reči:*** *kongenitalne anomalije, očne manifestacije, sistemske manifestacije*

 