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The Rare Association of Noonan Syndrome with Tetralogy of Fallot

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Abstract

Background: Noonan syndrome is an autosomal dominant multisystem disorder characterized by short stature, distinctive facial features, congenital heart defects, and variable developmental delays. While pulmonary valve stenosis is the most common cardiac lesion, Tetralogy of Fallot is rarely reported in Noonan syndrome. To date, there are fewer than 60 documented cases of Noonan syndrome associated with Tetralogy of Fallot in the medical literature.

Objective: To report the third documented case of Noonan syndrome from Iraq, uniquely associated with repaired Tetralogy of Fallot, and review the two previously reported Iraqi cases with differing phenotypes.

Patients and Methods: A 16-year-old male with a history of surgically corrected Tetralogy of Fallot was evaluated for slow growth and subtle dysmorphic features.

Results: The patient demonstrated hallmark features of Noonan syndrome including short stature, broad forehead, hypertelorism, downslanting palpebral fissures, and mild learning difficulties. Echocardiography revealed residual cardiac abnormalities consistent with post-TOF repair. Diagnosis was made based on clinical criteria.

Conclusion: This case underscores the diagnostic importance of reassessing patients with repaired congenital heart disease for underlying syndromic conditions. Increased awareness of Noonan syndrome and its varied cardiac manifestations, including Tetralogy of Fallot, is essential for early diagnosis and comprehensive management, especially in resource-limited settings.

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Introduction

Noonan syndrome is a genetically heterogeneous congenital syndrome that can occur sporadically or inherited as an autosomal dominant disorder, and is associated with a wide spectrum of clinical manifestations that vary greatly in range and severity including facial dysmorphism, short stature, congenital heart defects, cryptorchidism in males, and learning difficulties.

The diagnosis of Noonan syndrome is entirely clinical as there is no specific diagnostic test available.

During the 1940s, 1950s, and early 1960s Noonan syndrome was considered to be Turner syndrome occurring in males. However, at the meeting of the Mid-Western Society for Pediatric Research in 1962, Jacqueline A. Noonan (Figure 1) presented nine patients who had growth retardation, hypertelorism syndrome of valvular pulmonary stenosis and other congenital abnormalities. In 1968, Jacqueline A. Noonan published reporting 19 patients including males and females. In 1971, Hellebusch called the condition Noonan syndrome.

We have previously reported the first and second documented cases of Noonan syndrome in Iraq [1, 2].

The first documented case from Iraq was a dysmorphic ten-month girl with the following features:

1. Poor feeding, and growth retardation.

2. Hypotonia with poor head control and delayed sitting.

3. Psychomotor retardation with poor awareness to the surrounding.

4. Craniofacial dysmorphism with low set ears, bulbous nose, thick upper eyelids, high arched

Figure 1: Jacqueline A. Noonan.

palate, and micrognathia.

5. Widely space nipples.

6. Nuchal folding and a low posterior hairline.

The parents were health and the case was sporadic.

Echocardiography showed normal finding and CT-scan showed ventriculopathy with evidence of brain atrophy.

Chromosomal analysis showed normal female karyotype.

Cerebral abnormalities have been rarely associated with Noonan syndrome. However, Heye and Dunne (1995) reported the association of Noonan syndrome with hydrocephalus, hindbrain herniation, and upper cervical intracord cyst.

Henn et al (1997) from Germany reported four patients from three subsequent generations of a family with autosomal dominant Noonan syndrome associated pulmonary valve stenosis, craniofacial dysplasia with marked hypertelorism and, a variable occurrence of progressive hydrocephalus.

Brasil et al (2010) from Bazil reported the association of Noonan syndrome with cerebral abnormalities including isolated ventriculomegaly, posterior fossa anomalies, and cerebral atrophy in infants.

Zarate et al (2014) from the USA reported a six-year-old boy with Noonan syndrome associated with Chiari malformation type I and cerebrovascular changes.

Spennato and colleagues (2019) from Italy reported a five-year old with boy an unusual association of Noonan syndrome and tetraventricular hydrocephalus, caused by fourth ventricle outlet obstruction. Magnetic resonance imaging showed a diverticular enlargement of the left foramen of Luschka, with compression of the facial nerve that resolved following treatment of hydrocephalus by endoscopic third ventriculostomy [1].

Therefore, the first documented case of Noonan syndrome in Iraq was associated with very rare association of CT-scan evidence of ventriculopathy and brain atrophy.

In many patients the syndrome characterized by craniofacial abnormalities including low set ears, hypertelorism, congenital heart defect, short stature, and undescended testes. Although pulmonary stenosis is the commonly associated congenital cardiac defects, a variety of cardiac defects may occur in this syndrome.

Atrial septal defect, and patent ductus arteriosus are other well-recognized cardiac defects of this syndrome.

The second documented case of Noonan syndrome from Iraq was ten month old boy who was referred to the pediatric neuropsychiatric clinic of the Children Teaching Hospital of Baghdad Medical City because of developmental delay associated with multiple congenital abnormalities was studied.

The boy was experiencing growth and developmental delay and was unable to sit. He had facial dysmorphic features consisting of low set ears, hypertelorism, and smooth philtrum. Examination of the heart suggested the presence of congenital heart disease and his testes were not palpable in the scrotum.

Echocardiography showed interatrial septum, small atrial septal defect and closing patent ductus arteriosus.

Abdominal ultrasound showed ectopic intra-abdominal testes located at the inlet of the inguinal, and both testes' measures 10 mm in diameter. Chromosomal analysis showed normal female karyotype. Parents were consanguineous and family history was negative for similar condition.

The second documented case of Noonan syndrome from Iraq was associated with unique cardiac defects. The previously reported 2 cases of Noonan syndrome from Iraq demonstrate the variability of the phenotype of this syndrome.

Tetralogy of Fallot is the most common cyanotic congenital heart defect, and while typically nonsyndromic, it can be associated with syndromes such as 22q11.2 deletion, Down syndrome, and Noonan syndrome [3, 4].

The aim of this paper reports the third documented case of Noonan syndrome from Iraq, uniquely associated with repaired Tetralogy of Fallot

Patients and Methods

A 16-year-old Iraqi male was referred for evaluation of slow growth and subtle facial dysmorphic features (Figure 2). His father reported a history of poor growth since early childhood. There were no significant developmental delays, though academic performance was slightly below average.

The patient had previously undergone complete surgical correction of tetralogy of Fallot in Turkey at the age of four. No genetic evaluation had been performed at the time. The surgical details were not fully available, but parental report and medical documents confirmed complete intracardiac repair.

At presentation, the patient displayed several mild but consistent dysmorphic features (Figure 2) including a broad forehead, hypertelorism, downslanting palpebral fissures, a high nasal bridge, and a flat philtrum. No webbing of the neck, pectus deformity, or scoliosis was noted.

No family history of congenital heart disease, short stature, or similar features was reported.

Results

A 16-year-old male presented with persistent slow growth and subtle dysmorphic features, including:

- Broad forehead
- Hypertelorism

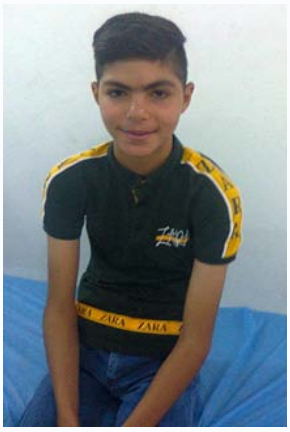

Figure 2: The patient displayed dysmorphic features including a broad forehead, hypertelorism, downslanting palpebral fissures, a high nasal bridge, and a flat philtrum.

- Downslanting palpebral fissures
- High nasal bridge
- Flat philtrum

Developmental history revealed mildly delayed milestones and below-average academic performance. There was no webbed neck, scoliosis, or chest wall deformity. Family history was negative for congenital heart disease or dysmorphic features.

The patient had undergone successful surgical repair of TOF in Turkey at age four. Current echocardiography revealed:

- Normal left ventricular systolic function (EF 62%)
- Mild right atrial and ventricular dilation
- Moderate pulmonary valve stenosis (peak gradient 28 mmHg)
- Mild pulmonary and aortic regurgitation
- No residual septal defects

Based on the constellation of clinical and cardiac findings, a clinical diagnosis of Noonan syndrome was made.

Discussion

This case underscores a frequently overlooked clinical scenario: adolescents with repaired congenital heart disease who may still harbor an undiagnosed genetic syndrome.

The patient's prior tetralogy of Fallot repair and subsequent medical stability may have masked the presence of a syndromic condition. However, ongoing growth failure and subtle dysmorphism prompted reevaluation, raising a strong suspicion for Noonan syndrome.

Although pulmonary valve stenosis is the most common cardiac lesion in Noonan syndrome, tetralogy of Fallot has rarely been associated [3, 4].

Notably, the study by Goodship et al. identified a common PTPN11 variant (rs11066320) associated with increased risk of nonsyndromic tetralogy of Fallot, suggesting a genetic continuum from isolated tetralogy of Fallot to overt Noonan syndrome. Our patient's phenotype could lie on this spectrum, possibly influenced by a hypomorphic variant with partial effect on the RAS-MAPK pathway [3].

A 2024 study from Uganda (Khainza et al.) found only 5.7% of tetralogy of Fallot patients were clinically recognized as syndromic, underscoring the global underdiagnosis of Noonan syndrome and similar conditions in low-resource settings. Early identification has practical implications: beyond cardiac monitoring, Noonan syndrome patients may benefit from growth hormone therapy, developmental support, and genetic counselling [4].

Slow growth in this patient may have been attributed to chronic illness or cardiac disease in early life. However, in Noonan syndrome, growth retardation often persists independently of cardiac status, and may benefit from tailored endocrinologic interventions.

Recognition of syndromic features may be overlooked when early surgical correction of cardiac defects leads to an assumption of isolated disease. This case report highlights the diagnostic relevance of post-surgical dysmorphology assessment and genetic re-evaluation in patients with repaired tetralogy of Fallot and unexplained growth abnormalities.

For many decades, the fields of clinical genetics and dysmorphology were largely absent from the Iraqi medical landscape.

There were no structured diagnostic pathways, no specialized centers for rare diseases, and minimal local literature to support genetic awareness or dysmorphic diagnosis. As a result, generations of patients with congenital abnormalities and inherited disorders remained undiagnosed or misclassified.

The transformation began with our early clinical observations in pediatric practice, which led to the recognition of patterns suggestive of specific syndromes. Gradually, through careful phenotyping, clinical photography, and correlating systemic findings with existing global data, we began to document and publish rare and very rare disorders observed among Iraqi children.

We have previously reported an uncountable number of the first described disorders in Iraq [1, 2, 5-9].

To date, there are fewer than 60 documented cases of Noonan syndrome associated with Tetralogy of Fallot in the medical literature.

In 2022, Baldo et al., analyzed 118 patients with confirmed Noonan syndrome. Only 2 patients (1.7%) had Tetralogy of Fallot, highlighting its rarity among the cardiac defects seen in Noonan syndrome. Most cardiac anomalies in the cohort were pulmonary valve stenosis and atrial septal defects, consistent with global trends. The study of Baldo et al. provided concrete epidemiologic evidence that Tetralogy of Fallot is uncommon in Noonan syndrome [10].

Conclusion

To date, there are fewer than 60 documented cases of Noonan syndrome associated with Tetralogy of Fallot in the medical literature.

In adolescents with a history of congenital heart disease and persistent slow growth or developmental issues, careful dysmorphologic evaluation remains essential. This case illustrates how syndromic diagnoses such as Noonan syndrome can be delayed or missed in patients who undergo early cardiac surgery. We advocate for genetic re-evaluation in all patients with repaired tetralogy of Fallot and additional suggestive features.

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