

Noonan's syndrome diagnosed at second decade of life

Abstract

In 1963 Noonan and Ehmke described an autosomal dominant condition called Noonan syndrome in a group of patients with abnormal facial deformations, congenital heart diseases and various malformations. Its Incidence is 1 in 1000 to 2500 live births. One can miss the diagnosis in mildly affected cases as it usually depends on clinical features. We are presenting a case of a 24yr old Egyptian male, who was incidentally diagnosed to have Noonan's Syndrome by means of morphological, clinical and echocardiographic & magnetic resonance imaging (MRI) findings. This young patient had frequent spells of loss of consciousness. ECG showed runs of ventricular tachycardia with evidence of biventricular hypertrophy and severely impaired LV systolic function by ECHO. Treatment and prognosis varies from individual to individual according to its severity. Our patient was referred to electrophysiology department and underwent ICD implantation for secondary prevention of sudden cardiac death. This case report gives a clear cut management pathway when dealing with a newly identified adult Noonan. Most of the cases need multidisciplinary approach.

Keywords: noonan's syndrome, asymmetrical hypertrophy, hypertrophic cardiomyopathy

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Abbreviations: MRI, magnetic resonance imaging; ICD, international classification of diseases; LOC, loss of consciousness; EF, ejection fraction; RV, right ventricular; LV, left ventricular; IQ, intelligence quotient; GI, gastrointestinal

Introduction

Noonan syndrome is one of the commonest genetic disorders caused by RAS-MAPK signal pathway alteration characterized by various congenital malformations.^{1,2} The prevalence is estimated as 1 in every 1000 to 2500 live births.³ It usually presents with developmental delay, short stature, a broad and webbed neck, typical facial features, chest deformities, scoliosis, cryptorchidism, bleeding disorders, congenital heart disease, intellectual disability, neurological & lymphatic disorders.⁴

Case report

A 24year old Egyptian laborer, presented to our emergency room with complaints of loss of consciousness (LOC) lasting for about 1-2minutes during his work as a manual labor. He experienced several such occurrence of transient LOC during the past 30days prior to this episode. Last episode was preceded by palpitations for 1-2seconds. He is a known smoker with no history any drug abuse. He had history of cryptorchidism and underwent orchidopexy. No other past medical history. On general examination patient had facial dysmorphic features, webbed neck, high nasal bridge, short stature (5.38feet/164cm), pectus excavatum & scoliosis (Figure 1) (Figure 2). His heart rate was 70 beats per minute, blood pressure 120/80mmHg, respiratory rate 20 per minute, saturation 99% on room air. Jugular venous distention was noted with no evidence of pedal edema. Cardiomegaly was clinically evident and on auscultation wide split with loud S2 was noted. Chest air entry was bilaterally equal. Abdomen was soft and hepatomegaly was noted. Chest X-ray Figure 3 showed cardiac enlargement.

Electrocardiogram Figure 4 showed normal sinus rhythm with rate 70/min, P wave 120msec and 3mm, notching of P wave in II, bifid P in V1, PR 180msec, QRS 80msec, QR pattern in III&V1, V1 R/S=35/9, V5 R/S=25/10, S1 Q3 T3 pattern noted. Laboratory investigations showed: WBC=5.210⁹/L, Hb=14g/L, Platelet Count=16110⁹/L, GLU=4.5mmol/L, BUN=10.4mmol/L, Creatinine=80umol/L, Na+=136 mmol/L, K+=4.52 mmol/L, Trop-i=0.08ng/mL, CK=470ng/mL, CKMB=48ng/mL, Vit D Level=9.51nmol/L. Twenty-four hour Holter monitoring done was within normal limits. Ultrasound abdomen showed right grade 1 nephropathy and hepatomegaly. Transthoracic echocardiography showed Impaired left ventricular (LV) systolic function ejection fraction (EF) around 30-35% with a picture of hypertrophic cardiomyopathy with bi ventricular hypertrophy and bi-atrial dilatation. Cardiac MRI showed moderate to severe LV systolic dysfunction with EF of 32%, moderate right ventricular (RV) systolic dysfunction, bi-atrial enlargement, asymmetrical hypertrophic cardiomyopathy with left & right ventricular (mild RVH) involvement. Genetic screening done and was inconclusive as it require further analysis (Figure 5) (Figure 6).



Figure 1 Pectus excavatum & scoliosis.



Figure 2 Pectus excavatum & scoliosis.



Figure 3 Chest X-ray.

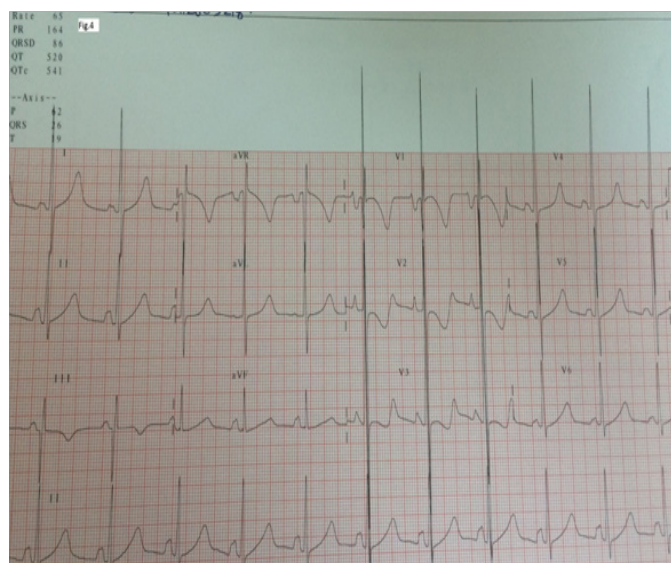


Figure 4 Electrocardiogram.

Cause of Referral: ?? Noonan syndrome

Specimen Type	Peripheral Blood
Number of cells counted and analyzed	20
Number of cells karyotyped	9
Banding	G + N.O.R.
Average band resolution	450
Analysis by	Visual and PSI Power Gene karyotyping system

Results
46,XY

Comments
The GTG and N.O.R banding analysis revealed the presence of apparently normal male complement.

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Figure 5 Cytogenetic laboratory report.

Clinical Diagnosis: Noonan Syndrome

Sample Type: DNA extracted from whole blood

Test: PCR-sequencing for exons 3, 4, 7, 8 & 13 of the *PTPN11*, ex. 4, 6, 10 of *SOS4* & ex. 2 of *KRSA* gene

Results:
Sequencing analysis of the patient's DNA showed that the patient **does not have any mutation** in the exons of genes mentioned above.

Comments and Recommendations:
Mutations in the *KRAS*, *SOS1* and *RAF1* gene were reported to cause Noonan syndrome (NS), in addition to *PTPN11* which is the first gene reported to cause NS. The *PTPN11* gene is a large gene having 15 exons, but the most common mutations reported were in exons 3, 4, 7, 8 & 13. Sequencing was done for these five exons; therefore, the results do not exclude the disease, as complete sequencing of the whole *PTPN11* gene and the other genes causing this syndrome is recommended.

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Figure 6 Molecular genetic laboratory report.

Discussion

In Noonan Syndrome we can observe a multi system involvement in regard to clinical presentation. Literature review shows that Noonan is a pan-ethnic syndrome and the incidence is similar in both males and females. It is very difficult to diagnose Noonan at childhood since the facial dysmorphology features will be more evident as the child grows. Delayed puberty is one of the commonest features seen in male Noonan. We are reporting an adult male Noonan case which was left undiagnosed till the age of 24years.

Majority of the patients have normal intelligence. Mental retardation with low *intelligence quotient* (IQ) and memory are seen in almost 25% of Noonan patients.⁵ In our case, patient had no signs of mental retardation. Short stature and delayed growth are seen in 50-70%.⁶ Our patient had a short stature with height (5.38feet/164cm). Scoliosis and spinal deformities are common findings in Noonan and 30% of the cases its evident.⁷ Scoliosis was evident in our case and was confirmed by chest X-ray.

Manifestations on skin differ from case to case. It may be in the form of lentigines, Keratosis pilaris, café au lait spots, pigmented nevi.⁷ There was no evidence of any kind of skin manifestations in our patient.

Facial dysmorphic features are characteristic of Noonan. Refractive errors Amblyopia & Strabismus are commonly seen in Noonan. Our patient had facial dysmorphic features but no refractory errors. Facial shape usually appears triangular. Head circumference will be non-proportionate to the face. Shape of the nose will be broad and short with high nasal bridge. Philtrum will be deeply grooved. Short neck with webbing is a classical feature. Low set ears, hypertelorism also seen in such patients.^{8,9} Our patient had a triangular face and short neck with webbing and large head.

Hearing defect of low and high frequency range can be seen 10% and 25% respectively.¹⁰ Dental malocclusion and micrognathia are seen in Noonan cases.⁴ Our patient had no hearing defect or dental malocclusion. Pectus excavatum and carniatum is also considered as a characteristic feature.³ Pectus excavatum was present in our case.

Cardiovascular manifestations/congenital heart diseases associated with Noonan syndrome are hypertrophic cardiomyopathy, pulmonary valve stenosis, atrial septal defect, ventricular septal defect, tetralogy of fallot and coarctation of aorta.¹¹ Our patient had a cardiac MRI which revealed asymmetric LVH with normal left ventricular volume. Moderate to severe LV systolic dysfunction EF=32% and markedly elevated myocardial mass in diastole 231g (147g/m²). A faint patchy enhancement noted at the inferior insertion point and mid lateral wall. Normal right ventricular (RV) volume and moderate right ventricular dysfunction EF=31%. Mild RV hypertrophy and hypertrabeculations noted. No SAM at rest. Batrial enlargement noted. Features are suggestive of asymmetric hypertrophic cardiomyopathy with RV involvement (Figure 7).

Gastrointestinal (GI) abnormalities are seen mainly during childhood. Hepatosplenomegaly is seen in almost 25% of the patients.¹² Our patient was free of any GI disorders. Delayed puberty and male gonadal dysfunction can be present in such cases. Cryptorchidism will be present around 80% of the Noonan patients.¹³ Our patient had unilateral cryptorchidism for which he underwent surgical correction. Juvenile myelomonocytic leukemia, myeloproliferative disease with coagulation defects and increased bleeding tendency are not uncommon.¹⁴ Our patient had no such manifestations.

Noonan Syndrome manifestations are mainly due to the mutation of genes in the RAS-MAPK signaling pathway alteration. Out of all PTPN11 is the commonest and 50% patients with cognitive dysfunction have *PTPN11* mutations, 13% patients with normal cognitive function have *SOS1* mutations, 5-17% patients with delayed puberty and hypertrophic cardiomyopathy have *RAF1* mutations and other mutations like NRAS, CBL, BRAF, KRAS, SHOC2, and MAP2K1 are not common.^{15,16} For our patient we performed only basic genetic study in view of financial constraints. Hence it was in conclusive.

Diagnosis of Noonan can be made easily by using the diagnostic criteria by Van der Burgt et al.⁵ (Table 1) Turners syndrome will mimic as Noonan in girls. Our patient had typical Noonan facial features with high nasal bridge, webbed neck, short stature, pectus excavatum, cryptorchidism, hypertrophic cardiomyopathy, kyphoscoliosis, hepatomegaly, mild renal dysfunction, delayed puberty. In all diagnosed noonan cases genetic counseling is vital as the risk of transmission to offspring in the coming generation is high as 50%.¹⁷ Multidisciplinary management strategy is required for Noonan syndrome treatment. Careful evaluation with clinical features and proper genetic study will help physicians to manage the cases properly.¹⁸ Our patient was referred to electrophysiology department and underwent ICD implantation for secondary prevention of sudden cardiac death.

Table 1 Diagnostic criteria by Van der Burgt⁵

Features	A = Major	B = Minor
1. Facial	Typical facial dysmorphology	Suggestive facial dysmorphology
2. Cardiac	Pulmonary Valve Stenosis, Hypertrophic Cardiomyopathy and or typical ECG changes	Other defects
3. Height	<3 rd percentile	<10 th percentile
4. Chest wall	Pectus carniatum/ excavatum	Broad thorax
5. Family History	First degree relative with definite Noonan syndrome	First degree relative with suggestive Noonan syndrome
6. Other Features	All of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia	One of the following: intellectual disability, cryptorchidism, or lymphatic vessel dysplasia

Noonan syndrome (NS) can be diagnosed if :

1. 1A Typical Facial dysmorphology + One major (Any one major feature from 2A to 6A) = NS.
2. 1A Typical Facial dysmorphology + Two minor (Any two minor feature from 2B to 6B) = NS.
3. 1B suggestive dysmorphology + Two major (Any two major feature from 2A to 6A) = NS.
4. 1B suggestive dysmorphology + Three minor (Any three minor feature from 2B to 6B) = NS.

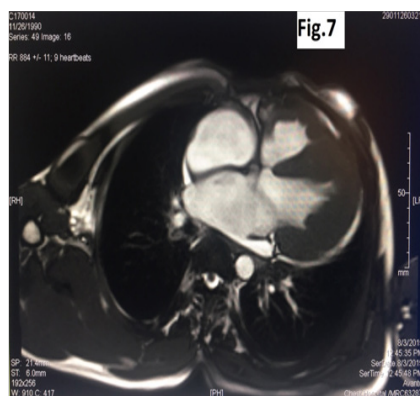


Figure 7 Asymmetric hypertrophic cardiomyopathy with RV involvement.

Conclusion

One should suspect Noonan Syndrome if the patient had typical facial dysmorphism, cardiac involvement, short stature, family history, delayed puberty, chest deformities and other features like low IQ and cryptorchidism. Type of associated congenital heart disease will influence the mortality and morbidity in Noonan. Multidisciplinary approach is mandatory as multiple systems were involved.

Limitations

In Kuwait genetic screening is not widely available and in most of the complicated cases samples are sent to UK and involve high cost. It's mostly done free for the citizens. For this patient we could manage to do few tests only. Our patient being an expat he was not financially sound enough to pay for further genetic screening.

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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