CASE REPORT

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Noonan Syndrome in a Nigerian Neonate: A Case Report and Review of Literature

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Abstract

Noonan syndrome (NS) is a genetic condition with a heterogeneous phenotype and multi-systemic involvement. This condition has been linked to mutations in the RAS/MAPK pathway, which is involved in cell differentiation. Noonan syndrome has been associated with multiple anomalies, with complications arising from the cardiovascular system, and this has been recognized as the commonest cause of death. Across the world, there is an upsurge in the number of congenital malformations, especially in mineral and petroleum-producing African countries. The report describes a term male neonate who had features of Noonan syndrome, with the scoring system used in diagnosis and review of existing literature. There is a robust scoring system that has diagnostic value in NS, as used in this report. This report aims to create awareness about the scoring system used in diagnosing NS, especially in resource-limited settings where genetic testing may not be feasible.

Keywords: Congenital anomaly, Genetic disease, Noonan syndrome, Turner-like syndrome, Webbed-neck syndrome.

Introduction

Noonan syndrome (NS) is a heterogeneous, clinically recognizable, multiple congenital anomaly syndrome.[1,2] It mostly occurs on a sporadic basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission.[3,4] The *de-novo* PTPN11 mutation on chromosome 12 in sporadic NS cases is predominantly of paternal origin and accounts for 50% of cases.[5] However, there is evidence of a rare autosomal recessive form of NS.[6] Noonan syndrome is also known as" female pseudo-turner syndrome", "Turner-like syndrome", "Turner phenotype with normal karyotype" or "webbed neck syndrome".[7] It has an estimated incidence of 1/1000 to 1/2500 life birth.[8,9] This syndrome, though previously peculiar to males, shares some characteristic defects with Turner syndrome, which is exclusive to females. Hence, NS was previously labelled "male Turner syndrome".[7] However, NS has been found to affect both gender over time, with an equal male-to-female ratio. Noonan syndrome was first characterized by Jacqueline Noonan, who reported nine patients with cardiac and skeletal malformations, intellectual impairment, cryptorchidism, and other systemic defects.[8,9,10]

The medical literature has an abundance of studies on NS, but few are from the African continent. Little is known about phenotypic specificities and molecular characteristics of NS in Africa. There is a lack of studies done on

NS in Nigeria; however, there is a multicenter study involving over 20 countries, including Nigeria, and both the scoring system and facial analysis technology were used in diagnosing NS.[17] Phenotypically, short stature is present in 92% of cases, characteristic craniofacial defects combining wide-spaced eyes, a broad forehead, down-slanting palpebral fissures, low set ears posteriorly rotated, and a short and webbed neck.[1,11] Another characteristic clinical finding is the common presence of congenital heart defects in up to 95% of cases, and the commonest type is pulmonary stenosis (mainly pulmonary valve stenosis in 50-65% of cases) associated with hypertrophic cardiomyopathy (in 20%).[1-6] The phenotype often includes musculoskeletal defects (extremities, chest or spinal anomalies), ophthalmic problems in 85% of cases (strabismus, nystagmus, cataract), cryptorchidism in 80% of male cases, hepatic and renal malformations, oral anomalies (high arched palate, malocclusion, impacted teeth, reclined mandibular incisors), coagulation defects, hypogonadism.[1,6,7] Approximately 10% to 25% of the patients have hearing difficulties. The most affected persons have problems with learning capacities, and mental retardation is observed only in 25% of affected individuals. Findings in the prenatal period include increased nuchal translucency, polyhydramnios, fetal oedema, hydrops fetalis, short femur, and congenital heart defects.[7,12]

The diagnosis of NS is primarily based on clinical findings. Generally, classical facial features or atypical cardiac malformation trigger suspicions of NS. The facial features are less common in the neonate, but generalized oedema, excess nuchal fold, and congenital heart defect can suggest the diagnosis. In addition, a marked change of phenotype with age from the newborn period through infancy and adolescence to adulthood has been documented, resulting in a mild phenotype in adult patients.[1] All these facts can contribute to misdiagnosis, especially in patients without congenital heart disease, with mild forms, and at an older age.

The scoring system for the diagnosis of NS was developed by Van der Burgt, *et al*. in 1997.[13,15]

In recent studies, the Van der Burgt scoring system is the most used model to select patients for molecular studies.[4,5] In this scoring system, patients are first classified according to facial features broad forehead, hypertelorism, low-set posteriorly rotated ears with a thickened helix, micrognathia, short neck with excess nuchal skin and a low posterior hairline) as having typical or suggestive NS characteristics. A typical face and any other major or two minor signs establish the diagnosis of NS. In contrast, patients with suggestive NS facie need two major or three minor criteria to confirm the NS diagnosis.[15] Analyses of clinical features in NS patients, who had their diagnosis confirmed by the molecular study, demonstrated that no isolated clinical characteristic can ensure the diagnosis of NS; however, the van der Burgt, *et al.* criteria, which takes into account the facial features, growth pattern, chest deformity and cardiac defects, have been shown to be an accurate tool for the diagnosis of NS. [13,15]

This case report aims to improve clinicians' knowledge of clinical diagnosis of this rare genetic condition, create awareness, and cause physicians to have an index of suspicion when they encounter some features suggestive of NS. The report describes a term male neonate who had features of Noonan syndrome, with the scoring system used in diagnosis and a review of existing literature.

Case Presentation

Baby Q is a term male neonate born to a 34-year-old mother. The mother was a known patient with well-controlled diabetes mellitus. There was a history of two episodes of spontaneous first-trimester abortions before index pregnancy. There was no known family history of congenital defects or the birth of syndromic children. Antenatal ultrasound scans and anomaly scans done in the index pregnancy were reported as normal. The delivery was via

elective cesarean section at term. The baby was limp at birth but was successfully resuscitated (suctioning, bag and mask ventilation) with an Apgar score of 6 in 1 minute and 9 in 5 minutes and a birth weight of 3625g.

Table I: Scoring system for the diagnosis of Noonan syndrome (NS)[15]

Feature	A - Major	B – Minor
Facial	Typical face dysmorphology	Suggestive face dysmorphology
Cardiac	Pulmonary valve stenosis, HOCM, and or ECG features typical of NS	Other defects
Height	< 3rd centile for age	<10th centile for age
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First-degree relative with definitive NS	First-degree relative with suggestive NS
Others	Mental retardation, cryptorchidism, lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

HOCM: Hypertrophic Obstructive Cardiomyopathy

Definitive NS: **1A (typical face morphology) plus ONE other major sign (2A-6A) or TWO minor signs (2B-6B)**
1B (suggestive facial dysmorphology) plus TWO major signs (2A-6A) or THREE minor signs (2B-6B).

Some dysmorphic features were noted at birth (low set ears with a thickened helix, short webbed neck, low posterior hairline, broad forehead, increased nuchal skin fold, flattened occiput, and widely spaced nipples. At about 60 minutes of life, the child became dyspneic and tachypneic (Figures 1-3). On systemic examination, the baby had reduced muscle tone across all joints, with a negative response on ventral suspension. This grade 3/6 pansystolic murmur was loudest in the apical region, with a palpable 4cm liver below the right coastal margin, smooth, firm to touch, and non-tender. There was also a splenomegaly of about 3cm below the left costal margin and undescended testis. A diagnosis of term male neonate with respiratory distress unknown aetiology with features of Noonan syndrome was made. Baby Q was started on continuous positive airway pressure (CPAP) and intravenous fluids and was also placed on *nil per os*.

The Chest X-ray revealed a grossly enlarged cardiac silhouette with a multi-chambered configuration (cardiothoracic ratio of 0.66, features suggestive of congenital cardiomegaly. An abdominal scan revealed hepatosplenomegaly with an absent left kidney. The trans-fontanelle scan done was normal. Echocardiography showed dilated right atrium, right ventricle and pulmonary artery, intact interatrial and interventricular septum, mild to moderate tricuspid regurgitation, and decreased ventricular contractility with a diagnosis of cardiomyopathy. Following the investigation results, caregivers were counselled on the findings, possible complications, treatment options and prognosis. Further testing for genetic mutation was planned. However, the child succumbed to the illness at about 12 hours of life before further testing or intervention could be done.

Discussion

Noonan syndrome is a genetic multisystem disorder involving gene mutations encoding the proteins in the RAS-MAPK pathway.[2] Due to this shared RAS/MAPK dysregulation, there is an overlap in the clinical characteristics at presentation.

Figure 1: A thickened helix, increased nuchal skin fold, and low posterior hairline.

Figure 2: Widely spaced nipple with a broad chest, broad forehead and low set ears with thickened helix.

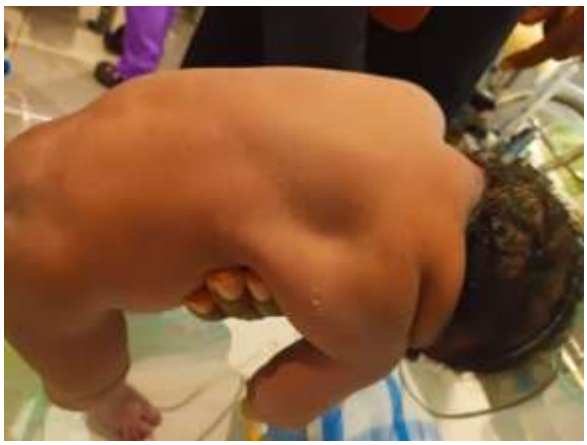

Figure 3: Loss of tone on ventral suspension.

Although it is an inherited disorder, the patient can be a newly diagnosed case of NS without a history of the disorder in other family members, and this is in keeping with our index patient.[2]

The mutation in PTP11, KRAS gene and several other genes are reported to cause NS. The index patient, who had typical clinical characteristics of NS, did not benefit from genetic testing due to early demise. However, while some studies reported a positive mutation in the PTP11 gene, others had a contrary report, though a negative mutation report did not rule out the presence of NS.[14]

According to the NS scoring system, the index child can be diagnosed with NS. This scoring system used in the diagnosis of NS was developed in 1997, with six major and six minor criteria.[13] The index patient had typical facial features, one significant criterion (cryptorchidism), and two minor criteria (other cardiac defects, broad thorax). Reports have shown that the commonest cardiac defects are hypertrophic obstructive cardiomyopathy (20%) and pulmonary valve stenosis (50-63%).[10,15] Olteanu *et al*. reported a 3-month-old female with features of NS whose cardiac findings varied from the typical heart defects seen in NS. This was also the case with the index child. Cryptorchidism, also found in baby Q, has been documented in 77% of those with NS[15], which was also reported by Kakizaki *et al.* This child's birth weight and length were normal, which is a common finding in those with NS.[15] In 26-51% of patients, hepatosplenomegaly is a common finding, and this was seen with the index child.[4,16] In 10% of those with NS, urinary tract anomalies have been reported, as observed in the index child who had an absent left kidney.[3]

It has been documented that individuals with NS from reports in African populations have the classic phenotype characteristics, including typical minor facial anomalies such as widely spaced eyes (31–100%), short stature (71–

100%), and congenital heart disease with pulmonary stenosis found in 24–100% of patients and this agrees with some of the findings in the index case.[17] Pokrowiecki *et al.*[16] reported cutaneous findings in addition to the features of NS; however, there was no apparent cutaneous manifestation in this index child. The clinical features of the index patient were not significantly different from those described in the literature in other populations affected by NS.[1,7,11-12] Management and care of cases of NS is multidisciplinary. There is variation in the expression, and the phenotype becomes less pronounced with age. Most authors state that children with NS can be raised with parental support alone, without any specialized intervention.[15] The most typical cause of death arises from a cardiac defect, and this may have contributed to the early demise of the index child.

One limitation of this case report is that PTPN11 and RAS-MAPK pathway protein gene mutation analyses were not performed. In addition, there could be overlapping of similar clinical features found in other syndromes.

Conclusion

Few studies characterizing NS have been reported in Africa. There may have been a lot of missed cases due to limited resources and facilities for testing in our environment, as well as the lack of awareness of the NS scoring system. Therefore, it has become important to enlighten health professionals about the scoring systems available for diagnosing NS while advocating for pocket-friendly genetic testing in our setting. In addition, it would be desirable to accumulate and analyze other cases diagnosed using the NS scoring system.

Because children with NS usually have diverse health challenges and require multidisciplinary care, a thorough examination, prompt and appropriate laboratory investigations, and adequate counselling are necessary. A good knowledge of clinical features and the use of a scoring system may be of great benefit in making a diagnosis of NS, especially in developing countries where genetic mutation testing may not be affordable.

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