A Case Report of Hypothyroidism in a Noonan Syndrome Patient: A Comprehensive Approach to Diagnosis and Management

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Introduction

Noonan syndrome is a multisystem, genetic, developmental disorder occurring with the incidence of 1 case per 1000 to 1 case per 2500 live births in the United -States. The condition occurs either in a sporadic or autosomal dominant manner and affects both males and females equally. [1] Ullrich (1930) and Turner (1938) described females with a syndrome of short stature, sexual infantilism, and a pattern of characteristic minor anomalies like pterygium colli. This syndrome originally named Ullrich-Turner syndrome was later called Noonan syndrome. It was first reported by Kobylinski (1883), but it was first recognized as a unique entity in 1963 when Pediatrician and Heart specialist Jacqueline Noonan and Ehmke described a series of patients with unusual facies and multiple malformations, including congenital heart defects. The characteristic abnormalities resemble those in Turner syndrome, which only affects females and so Noonan syndrome was used to be called "Male Turner syndrome". This term is no longer used because Noonan syndrome can affect females also. Noonan syndrome is also called Webbed neck syndrome, Pseudo-Ullrich Turner syndrome, Female Pseudo-Turner syndrome, or Turner-like syndrome.[2]

The condition is mainly characterized by facial dysmorphism, congenital heart defects, growth hormone deficiencies, webbed neck, wide space nipples, and musculoskeletal, renal, genital, and bleeding abnormalities. Mental retardation can also occur in about 25% of patients with Noonan syndrome. Facial abnormalities include hypertelorism, down-slanting eyes, webbed neck, eyelid abnormalities, and skin manifestations. Prenatally the presentation of Noonan syndrome is not unremarkable, however, some cases are often complicated by polyhydramnios, fetal edema, increased nuchal translucency, and cystic hygroma. [3,4,5]. Very little is known about the occurrence of hypothyroidism in patients with Noon syndrome, this case report highlights the concomitant occurrence of hypothyroidism in a patient with Noonan syndrome, and stresses that further research should be done to find the association of these two.

Case presentation : A 15 -year-old female patient was presented to the outpatient department of a tertiary care hospital for bilateral eye puffiness, easy fatiguability, and generalized body weakness. The patient's condition started 6 months back and it gradually worsened. On further inquiry, the patient has a history of constipation on and off which relieves with laxatives. The past medical history of the patient was significant for acute hepatitis A and COVID-19 infection 3 and 1 year back respectively. The patient was born through

a normal vaginal delivery at the hospital and she was the 7th child of his parents. The medical record of the patient showed that all the developmental milestones were up to date, and the patient received all the childhood vaccination. Family history was not significant for congenital heart defects, mental retardation, short stature, or unusual facial features. She was 135 cm tall and had 32 kg weight with vital signs of blood pressure of 100/70 mm Hg, pulse rate of 65 beats per minute, and respiratory rate of 15 breaths per minute. Examination revealed pale conjunctive, down slanting eyes, hypertelorism, webbed neck, shield chest with wide space nipple as shown in Figure.1. Systemic examination was unremarkable except for decreased muscles power in both upper and lower limb with a positive Gower's sign. The patient examination findings were suggestive of some congenital syndrome and initially both Turner's and Noonan were suspected. Karyotyping was done which showed normal 46 XX chromosomes as shown in Figure.2 A diagnosis of Noonan syndrome was made based on the clinical features and chromosomal analysis. The patient was further evaluated for recurrent eye puffiness and easy fatiguability and the laboratory results revealed anemia, hypothyroidism, and increased creatinine kinase as shown in Table. 1. A nerve conduction test and electromyography of both the upper and lower limb were done for progressive weakness that was consistent with mild myopathy, without evidence of spontaneous activity, mainly affecting the proximal muscles. A final diagnosis of Noonan syndrome with hypothyroidism that led to proximal myopathy was made. The patient was further evaluated for cardiac, ophthalmologic, hearing, renal and genital, and coagulation abnormalities that were all normal. The patient and her parents were counseled about the condition, she was started on levothyroxine 50mg OD, cap Iron sulfate 1 cap daily for two months, and tablet opendrine and paracetamol 35/450 mg SOS for muscular pain and weakness. She was referred to a pediatric endocrinologist for growth and development assessment and was instructed to do close follow-up with repeat thyroid function tests in 6 weeks and coagulation profile and echocardiography when symptoms develop.

Discussion

Phenotypically Noonan syndrome especially in female share similar features with Turner syndrome such as short stature, webbed neck, wide space nipple, mental retardation, urogenital and cardiac abnormalities, and craniofacial dysmorphism. Karyotyping is the only investigation on the basis of which we can differentiate between these two conditions. [5] Noonan syndrome is a genetic condition and the common mutations involve are PTPN11, SOS1, RAF1, KRAS, NRAS, and BRAF genes. Among these mutations, PTPN11 gene mutations account for about 50%, SOS1 gene mutation for 10%–15%, and RAF1 gene mutation for 5%–10% of Noonan syndrome. KRAS, NRAS, and BRAF genes account for a relatively small percentage of Noonan syndrome. [6, 7] Diagnosis of Noonan syndrome can be made either by genetic testing or clinical diagnostic criteria. Both are equally specific because 25 percent of the genetic testing for Noonan syndrome is nonconclusive. The scoring system for the diagnosis of Noonan syndrome was developed by Van der Burgt et al in 1997 which are made of 6 major features and 6 minor features. According to this criteria, Noonan syndrome can be diagnosed with typical facial features plus 1 major or 2 minor characteristics or suggestive facial features plus 2 major or 3 minor signs. [8] Our patient had typical facial features with 1 major criterion i.e. short stature (below 3rd percentile). The following shows table shows the scoring system for Noonan syndrome (Table.2)

Differential diagnoses of Noonan syndrome include Turner syndrome (45, XO), Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1), and LEOPARD syndrome. Syndromes that are characterized by facial dysmorphology, short stature, and cardiac defects may sometimes be difficult to differentiate from NS, notably Williams syndrome and Aarskog syndrome. As the syndrome has a wide spectrum of disorders, patients with Noonan syndrome have to undergo hematological investigations, karyotyping and mutation analysis cardiac investigations, and Assessment of development (IQ, Identifying any delays, mental retardation). [9,10]

Previously a study has shown the association between hypothyroidism and Noonan's syndrome although few studies report autoimmune thyroiditis the cause is unknown, but factors that may predispose to the condition include genetics, high iodine consumption, and age. Vesterhus P et al in a study showed thyroid antibodies were found to be more common in Noonan syndrome, but hypothyroidism is not more common

in Noonan syndrome compared to the general population. [11,12] There is no single treatment available for Noonan syndrome, a multidisciplinary approach is needed to address the patient's concerns and to treat the complications or associated conditions.

Conclusion

Noonan syndrome is a genetic developmental disorder that can affect any system of the body. Primary hypothyroidism in a patient with Noonan syndrome is a rare phenomenon that can occur either as a separate entity or might have an association with Noonan syndrome. Further research is needed to find the association between these two conditions. A multidisciplinary approach focused on patient concerns and treatment of associated conditions is needed for better outcomes.

Author's contributions

Q.A.K. and A.B. were responsible for data collection and acquisition of data. Y.L.C., A.N., R.K., A.Z.K., V.G., and M.A. performed the literature review and wrote the original manuscript. Q.A.K., A.B., and S.S. reviewed and critically revised the manuscript. All authors have approved the final manuscript.

Data availability statement: Data can be available on reasonable request to the corresponding author

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