



Case Report

Noonan Syndrome with Hepatomegaly and Persistently Elevated Liver Enzymes: A Case Report

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Abstract

Noonan's syndrome is a polymorphic disorder with some facial features, congenital heart defects, cryptorchidism, etc., and also associated with some autoimmune diseases, lymphatic dysplasias. Here we are reporting a nine years old boy with Noonan's syndrome who has hepatomegaly with persistently raised hepatic enzymes, which remained unexplained.

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Introduction

Noonan syndrome is characterized by variable physical features like short stature, congenital heart defects, skeletal abnormalities like broad or webbed neck, chest abnormalities like pectus carinatum and pectus excavatum, developmental delay, cryptorchidism, and typical facies. Also, there are some coagulation defects and lymphatic dysplasias. It is a common autosomal dominant disorder. Mutations in several genes of the RasMAPK signaling pathway, e.g., PTPN11, SOS1, RAF1, and K.R.A.S., are known to be responsible for Noonan syndrome, and some genotypic phenotype correlations are reported.¹

incidence is between 1 in 1000 and 1 in 2000.² Mode of inheritance is autosomal dominant, but mostly Denovo mutations. Patients can be diagnosed on the basis of clinical features, but mild cases are commonly overlooked. Most patients with Noonan's syndrome are intellectually normal as adults.³

Jacqueline Noonan, a Pediatric Cardiologist early in her career, recognized that several children with valvular pulmonary stenosis had similar facial features. Dr. Noonan described the clinical characteristics of this condition, including short stature, hypertelorism, mild mental retardation, cryptorchidism, and some skeletal deformities.⁴ At the Midwest Society for Pediatric Research in 1962, she presented nine cases with congenital heart disease with some noncardiac phenotypic features compatible with Turner's syndrome. But the notable issue was the valvular lesion was pulmonary stenosis. She realized this could be a new syndrome because of its occurrence in both sexes, normal chromosomes, and associated congenital cardiac defect, which could be inherited.⁵

Further reportings of more cases of Noonan Syndrome led to the development of clinical criteria for the diagnosis. Subsequently, genetic causes were identified (like ptpn11 and other genes) for Noonan syndrome and the related Rasopathies.⁴

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The eponym, Noonan syndrome, was first used by Dr. John Opitz in 1965 in his publication "Noonan Syndrome in Girls: A Genocopy of the Ullrich-Turner syndrome." Some other cases were reported by different authors, including Dr. Noonan. They described the cases as "Turner phenotype:" Finally, in 1972, Dr. Noonan used the term Noonan syndrome at a conference. But a number of authors consider the first reported Noonan syndrome, as now called was a 20-year-old male reported by Kobylinski in 1883. An eight-year-old girl with similar features was written by Ulrich in 1930. In 1938 Turner reported seven older females with similar facies, like short stature and sexual infantilism. In 1943 Flavell introduced the term "male Turner syndrome." Ullrich reported similarities between his patients and mice bred by Bonnevie (a mouse geneticist who had bred a mutant strain of mice with webbed neck and swelling of the limbs). The term Bonnevie-Ullrich syndrome was then being used in Europe. The clinical features of those children match well with Noonan syndrome or Turner syndrome. However, there was a lot of effort to discover chromosomal abnormality in those so-called "male Turner syndrome," but chromosomal studies showed no exception. From a review of the literature now, we realize that these "male Turner syndrome" cases formed a heterogeneous group of

patients, and definitely some but not all would be considered Noonan syndrome today.⁵

The association of RASopathies and autoimmune disorders is not too common. The clinical and laboratory parameters were studied in 42 RASopathy patients in one study. Six patients (14%) had the clinical criteria for autoimmune diseases like systemic lupus erythematosus, autoimmune hepatitis, etc., and autoimmune antibodies in 52% of the patients. Three (7%) of the patients had specific gastrointestinal and liver autoantibodies, but there was no clinical finding. Physicians dealing with Rasopathies should be alert for the presence of autoimmune disease.⁶

In March 2015, Italia Loddo et al. reported a six-year-old female with Noonan syndrome with autoimmune hepatitis (Type1). George et al. studied 44 patients with Noonan syndrome with upper abdominal ultrasound and found six patients with hepatomegaly, also with splenomegaly (23,53%), renal abnormalities (11,5%), and some other abnormalities.⁷

Here we are reporting a Noonan syndrome who has hepatomegaly and elevated liver enzymes, which initially was thought to result from autoimmune hepatitis, but autoantibodies and immunoglobulins were negative, and the patient didn't respond to steroids.

Case Report:



Fig1: facies of the patient (printed with permission)

Fahim, a 9 years old boy, was brought by his mother to Rajshahi medical college hospital OPD with complaints of anorexia poor effort tolerance. The mother produced some papers showing some hepatomegaly ultrasound reports and persistently raised liver enzymes for about four years. On query, the mother admitted poor school performance.

He was short-statured; there was convincing evidence for pulmonary stenosis on auscultation of precordium. In addition, firm non-tender hepatomegaly was found at 15 cm on the right midclavicular line. The scrotum was empty.



Fig: short stature

Echocardiography showed severe pulmonary stenosis. Ultrasonography of the abdomen revealed both testes in inguinal regions, hepatomegaly. Screening for Hepatitis B and C was negative. Serum ferritin and caeruloplasmin were normal. Both SGPT and ALP were raised (445U/L against <45U/l and 663 U/L against 100-200 U/L, respectively). Bilirubin was normal. Considering the association of Rasopathies with autoimmune diseases, we performed we did antinuclear antibody, extractable nuclear antigen, serum immunoglobulins. But all were normal except elevated IgE, but no correlation with Noonan's is known.

We advised the patient to go to BSMMU for Liver biopsy and proper management for pulmonary stenosis and cryptorchidism.

Discussion

Valvular pulmonary stenosis is the most frequent finding as a cardiac abnormality, and in Turner's syndrome, left-sided lesions are common.⁵

Diagnostic criteria for diagnosis of Noonan syndrome⁸ have been established. Considering the diagnostic criteria here, we find two A criteria (pulmonary stenosis, short stature) and one B criteria (mental retardation, cryptorchidism, lymphatic dysplasia).

Hepatomegaly with persistently elevated liver enzymes is a rare finding in Noonan's syndrome unless it is due to autoimmune hepatitis, which is also rare. Liver biopsy findings may lead to further

thinking and evolution of a new unrecognized aspect of this rare disease.

Conclusion

Noonan's syndrome with hepatomegaly and the persistently elevated liver enzyme is an uncommon entity that needs further evaluation and management.

References

1. Noonan Syndrome, in Cassidy and Allanson's Management of Genetic Syndromes. p. 651-669.
2. Michael, B., et al., Cardiac abnormalities in Noonan syndrome: Phenotypic diagnosis and echocardiographic assessment of 118 patients. Journal of the American College of Cardiology, 1993. 22(4): p. 1189-1192.

3. Bhambhani, V. and M. Muenke, Noonan syndrome. Am Fam Physician. 2014 Jan 1;89(1):37-43.
4. Miller, B.S., The History of Noonan Syndrome. *Pediatr Endocrinol Rev.* 2019 May; 16(Suppl 2):424-427. doi: 10.17458/per.vol16.2019.m.historynoonan.
5. Noonan, J., Noonan syndrome a historical perspective. *Heart Views*, 2002. 3(2): p. 13-13.
6. Quaino, C.R.D.C., et al., Autoimmune disease and multiple autoantibodies in 42 patients with RASopathies. *American Journal of Medical Genetics Part A.* 158A (5): p. 1077-1082.
7. George, C.D., et al., Abdominal ultrasound in Noonan syndrome: A study of 44 patients. *Pediatric Radiology*, 1993. 23(4): p. 316-318.
8. van der Burgt, I., Noonan syndrome. *Orphanet Journal of Rare Diseases*, 2007. 2(1): p. 4.

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