CLINICAL QUIZ (p126) ANSWER

The clinical features of this patient (dysmorphism, failure to thrive, pulmonary stenosis and pectus carinatum) were suggestive of Noonan syndrome (NS). He was seen by the clinical geneticist and blood test for *PTPN11* gene was performed. A heterozygous c.417G>C mutation in exon 4 of the *PTPN11* gene was detected and this mutation has been reported in patients with NS.[1] Therefore the clinical and molecular diagnosis of NS in this baby was substantiated.

NS is a clinical and genetic heterogeneous disease with multi-organ involvement. Most of them are sporadic due to *de novo* mutations. Its incidence was estimated to be between 1 in 1000 and 1 in 2500 live births.[2] NS can be diagnosed clinically by distinctive clinical features. Scoring system was developed for the clinical diagnosis (Table 1).[3, 4]

The facial features of NS would change with age, with the most striking features in the newborn period and mid-childhood, and more subtle in adulthood. The main features are hypertelorism with downward slanting palpebral fissures, epicanthic folds, thick or droopy eyelids and low set, posteriorly rotated ears with a thick helix. They may also have short, webbed neck and/or with low posterior hairline. For the detailed description of the facial features, one can refer to Allanson 1987.[2]

The most common congenital cardiac defect in patient with NS is pulmonary valve stenosis and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. They may also present with other congenital cardiac defects.

Apart from clinical features in the scoring system, other manifestations of NS included bleeding diathesis, urinary tract malformations, ectodermal abnormalities and juvenile myelocytic leukaemia.

Table 1 Scoring system for Noonan syndrome (NS)

Feature	A=Major	B=Minor
1. Facial	Typical face dysmorphology • Epicanthal folds • Ptosis • Down slanting palpebral fissures • Triangular facies • Low set and/or posteriorly rotated ears • Webbed neck	**Suggestive face dysmorphology**
2. Cardiac	**Pulmonary valve stenosis** Hypertrophic obstructive cardiomyopathy (HOCM) and / or ECG* typical of NS	Other cardiac defect
3. Height	**<3rd centile**	<10th centile
4. Chest wall	**Pectus carinatum**/excavatum	Broad thorax
5. Family history	First degree relative with definite NS	First degree relative with suggestive NS
6. Other	Intellectual disability, cryptorchidism AND lymphatic dysplasia	Intellectual disability, cryptorchidism OR lymphatic dysplasia
Definitive NS: 1'A' plus one other major sign or two other minor signs 1'B' plus two major signs or three other minor signs		

(Font in bold are present in our patient)

*ECG typical of NS consists of wide QRS complexes with a predominantly negative pattern in the left precordial leads. They also display left axis deviation and giant Q waves.[3]

PTPN11 encodes the non-receptor protein tyrosine phosphatase SHP-2 that positively modulates RAS/MAPK signaling pathway. There are other genes regulating this pathway, which are *SOS1*, *BRAF, RAF1, KRAS, RASA1, HRAS, NRAS, MAP2K1, MAP2K2, NF1* and *SPRED1*. Genetic syndromes, which are caused by mutations in genes regulating the RAS/ MAPK pathway, are called RASopathies. RASopathies include NS, Costello syndrome, cardio-facial-cutaneous syndrome, neurofibromatosis type 1 and Legius syndrome.

With the advancement of knowledge about the genetic causes of NS and the availability of genetic testing, molecular genetic testing can now be used to confirm or make the diagnosis of NS. Mutation in *PTPN11* gene is identified in approximately 50% of affected individuals. Mutation in other genes of RASopathy pathway, e.g. *SOS1, RAF1, KRAS, NRAS* and *BRAF etc.* have been reported in other patients with NS.[4, 5] Genotype-phenotype correlation has been reported, e.g. there was a statistically significant association with pulmonic stenosis in patients with *PTPN11* mutations while those without *PTPN11* mutation were more often associated with HOCM.[1]

Concerning the management of NS, some baseline investigations are recommended (Table 2).[6] Clinical guideline for the management of NS in different age groups is also available.[6]

As for our patient, he was referred for formal developmental assessment. Basel line investigations included USG kidney and coagulation profile were performed. His cardiac problem was continued to follow up by cardiologist and his growth was regularly monitored in Paediatrics clinic.

Table 2 Recommended baseline investigations in Noonan syndrome

Clinical features of NS	**Baseline investigations**
Congenital heart defects	Full cardiac evaluation at diagnosis.
Failure to thrive/slow growth rate/feeding problems Short stature	Monitor and plot growth on appropriate NS and age-based growth chart.
Developmental delay and neuropsychological/behavioural issues	Refer patient when child was older than 6 months old or at diagnosis for formal developmental assessment. Baseline neuropsychological assessment at primary school entry.
Minor renal anomalies	Refer for renal ultrasound at diagnosis.
Bleeding disorders	Baseline coagulation screening in patients aged 5+, or earlier if major procedure to be undertaken.
Visual problems (e.g. posterior segment ocular changes and anterior segment ocular abnormalities)	Refer to ophthalmologist for assessment at diagnosis.

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References

1. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet 2002;70:1555-63.
2. Allanson JE. Noonan syndrome. J Med Genet 1987;24:9-13.
3. van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007;2:4.
4. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. Best Pract Res Clin Endocrinol Metab 2011;25:161-79.
5. Allanson JE, Roberts AE. Noonan Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews(R). Seattle (WA): University of Washington, Seattle, 1993.
6. DYSCERNE - Noonan Syndrome Guideline Development Group. Management of Noonan syndrome: a clinical guideline. Available from: https://rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf.