Unusual presentation of more common disease/injury

Severe congenital thrombocytopaenia – first clinical manifestation of Noonan syndrome

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Summary

This report focuses on a male infant, the first born of non-consanguineous parents diagnosed with polyhydramnios at 26 weeks of gestation. The newborn was admitted during the neonatal period with bleeding diathesis associated with a low platelet count at birth ($5 \times 10^9/l$). The authors registered a persistent low platelet count (9000–129 000/l) during the infants 1st year of life. Physical examination revealed a petechial rash, a dysmorphic face and bilateral cryptorchidism, in the absence of organomegaly. Additionally, cardiologic evaluation revealed an aortic valve dysplasia and an atrial septal defect, while bone marrow biopsy and aspiration were found normal. Throughout the investigation, the authors excluded congenital infection, alloimmune and familiar thrombocytopaenia, Fanconi anaemia and thrombocytopaenia absent radius syndrome. The cytogenetic analysis revealed a mutation in the PTPN11 gene associated with Noonan syndrome. Here the author highlights that severe neonatal thrombocytopaenia is a manifestation that should be considered in the diagnosis and clinical management of Noonan's syndrome.

BACKGROUND

Noonan syndrome (NS) is an autosomal dominant disorder comprising distinct craniofacial features, congenital heart defects, short stature, genital malformations, abnormalities of the lymphatic system, mild mental retardation and bleeding diathesis.^{1–3} Haematologic abnormalities in NS occur with an estimated frequency of 20–65%, including clotting factor deficiencies, von Willebrand disease, stem cell dysfunction, thrombocytopaenia and both abnormal platelet counts and function.^{2–8}

Despite the relative high frequency of haematologic abnormalities in NS patients, serious neonatal thrombocytopaenia has rarely been described as a clinical manifestation.

Thrombocytopaenia is a frequent platelet disorder occurring during the neonatal period. Accurate classification and clinical management of different forms of thrombocytopaenia constitutes a common clinical problem for paediatricians.

Early-onset thrombocytopaenia (in the first 72 h of life) is usually associated with infection, immune thrombocytopaenia, fetal hypoxia, fetal intrauterine growth restriction, chromosomal and non-chromosomal causes.⁹ In apparently healthy infants, the most common form of severe thrombocytopaenia in the immediate postnatal period is immune thrombocytopaenia, which is caused by the passage of antiplatelet antibodies from the mother to the fetus.¹⁰ The differential diagnosis between congenital or acquired platelet disorders relies on medical experience, assessment of personal and family history coupled with clinical examination.¹¹

CASE PRESENTATION

A Caucasian male, first born of healthy non-consanguineous parents, diagnosed at 26 weeks of gestation with a

polyhydramnios, during routine pregnancy check-ups. The mother tested negative during routine pregnancy screening for both TORCH infections (toxoplasmosis, others – syphilis, HIV, rubella, cytomegalovirus, herpes simplex) and vaginal Group B Streptococcus. At 39 weeks of gestation, a caesarean delivery was performed with an Apgar score of 3/5/9. The infant was born with birth weight of 2560 g P_{3–10}, and length 45 cm P_{<3}. The newborn was admitted immediately postpartum due to bleeding diathesis detected at delivery.

Physical examination revealed a non-septic appearing newborn, with generalised petechia and ecchymosis. Other clinical features included a dysmorphic face with hypertelorism, downslanting palpebral fissures, ptosis, low-set posteriorly rotated ears, high forehead, short neck, bilateral cryptorchidism and syndactylia of the fourth and fifth left foot fingers (figure 1). We found no organomegaly. On cardiac auscultation we heard a systolic cardiac murmur III/VI, which the transthoracic echocardiogram, revealed a dysplastic aortic valve with minimal insufficiency and an atrial sept defect.

A transfontanelar sonography excluded any intracranial malformations or haemorrhage. The karyotype analysis revealed the patient to be 46XY.

INVESTIGATIONS

The patient presented a platelet count at birth of $5 \times 10^9/l$ and both haemoglobin and leucocyte values were within the normal range, including differential white cell count. During the 1st month, due to persistent low platelet counts ($<29 \times 10^9/l$), the newborn remained in the hospital, and platelet transfusions were administered every 3 days with no new manifestations of cutaneous dyscrasia.

Figure 1 Caucasian male newborn diagnosed with Noonan syndrome. Note petechya and ecchymosis, dysmorphic face with hypertelorism, downsloping palpebral fissures, low-set posteriorly rotated ears, high forehead, and bilateral cryptorchidism.

Administration of immunoglobulin had no effect on platelet count. The prothrombin time (PT) and activated partial thromboplastin time (aPTT) remained within normal limits. Further analysis revealed normal levels of clotting factors VIII, XI and XII.

Both the bone marrow biopsy and aspiration showed normal haematopoiesis excluding megakaryocytic thrombocytopaenia or juvenile myelomonocytic leukemia (JMML). Likewise, no congenital infections (HIV, toxoplasmosis, rubella virus, hepatitis B virus, parvovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, cytomegalovirus) were detected. In addition, both haemoculture and uroculture tests performed were negative.

DIFFERENTIAL DIAGNOSIS

The diagnosis of neonatal alloimmune thrombocytopaenia was excluded due to the inexistence of immunisation against maternal platelets, more specifically; platelet antigens HPA1a, HPA5b and HPA15b were negative in mother, newborn and father.

Familiar thrombocytopaenia, Fanconi anaemia and thrombocytopaenia absent radius syndrome were additionally ruled out.

In conclusion, the cytogenetic analysis identified the mutation C.218C>T in exon 3 of the PTPN11 gene, which corroborated the hypothesis of NS.

OUTCOME AND FOLLOW-UP

The infant is currently 12 months old and remains asymptomatic; no bleeding diathesis has been recorded since the neonatal period. Initially, due to the persistent low platelet count ($9-28 \times 10^9/l$) platelet transfusions were carried out weekly and subsequently monthly (figure 2). After the 6th month, no further platelet transfusions were required.

The patient is growing above the 5th percentile for weight and length, and displays a mild developmental delay. The infant remains under evaluation and is being followed by a multi-disciplinary team which includes a haematologist, a geneticist, a cardiologist and a development specialist.

Figure 2 Evolution over the time of platelet counts, note the persistent thrombocytopenia.

DISCUSSION

There are several causes of neonatal severe thrombocytopenia. Thrombocytopenia in affected neonates is often due to underlying illnesses such as sepsis, disseminated intravascular coagulation, and respiratory distress syndrome or alternatively due to maternal factors such as pregnancy-induced hypertension and gestational diabetes.^{9 10}

Thrombocytopenia due to a congenital cause is often associated with characteristic features in physical examination, positive family history of thrombocytopenia, alterations in platelet morphology, persistent low platelet counts or with a lack of response to intravenous immunoglobulin.

The reported patient presented several physical features such as hypertelorism, low-set posteriorly rotated ears, short neck, bilateral cryptorchidism, hypotonia and short stature, which suggested that he could be affected by NS.

Pulmonary valvar stenosis, hypertrophic cardiomyopathy and atrial septal defect of ostium secundum type are common cardiac malformations associated with NS, whereas the dysplastic aortic valve defect, detected in our patient, has been very rarely described.¹²

The mechanism by which thrombocytopenia develops in patients with NS is not fully understood. It has been reported that it can be attributed to secondary to ineffective production (reduced or absent megakaryocytes in the bone marrow), or it may occur due to sequestration of platelets in an enlarged and/or myelodysplastic spleen. Our patient's thrombocytopenia is not explained by any of these hypotheses. The need for frequent transfusions in the first months of life suggests that platelet consumption occurred, however the patient presented a normal sized spleen.

Therefore, further studies are required in order to identify the causes and nature of thrombocytopenia in these patients.

Haematological findings in NS have been previously described in literature, some of them leading to life-threatening haemorrhage.⁵ The literature review on NS^{2 4 5 8} reveals multiple types of haemostatic abnormalities attributed to low clotting factor concentrations, in which factor XI is the most frequently described culprit, followed by factor XII and factor VIII.

The co-existence of various types of bleeding disorders is unusual in NS and would require further investigation. We screened for additional bleeding disorders in our patient and found no other except thrombocytopenia. In some cases, like ours, thrombocytopenia improves with time.¹

Germline PTPN11 mutations are responsible for approximately 50% of cases of NS. Importantly, PTPN11 proto-oncogene encodes Src-homology tyrosine phosphatase 2, a protein that plays a role in signal transduction and haematopoiesis. This in turn could lead to a predisposition to develop JMML and therefore, despite the rarity, this kind of disorder should always be considered in the follow-up of patients with NS.^{13 14} JMML could be a benign form of myelomonocytic leukemia with spontaneous resolution and/or prolonged survival or a malignant form that is lethal without therapy.¹⁴

In addition, periodic clinical and haematologic control should be maintained for several years, especially in patients with somatic mutations in exons 3 and 13 of PTPN11 gene, such as the reported patient.^{1 2 13 15}

Learning points

- Patients with NS should have an adequate haematologic follow-up and screening for a bleeding tendency.
- Paediatricians who are involved in the care of patients with NS need to be aware of the associated bleeding tendency and other haematologic problems, as these patients will often require surgical procedures.
- Further studies are required to identify the cause of thrombocytopenia in patients with NS.
- In patients with severe congenital haemorrhagic disorder and persistent thrombocytopenia, the medical history and a careful clinical examination are crucial for a correct diagnosis.

Competing interests None.

Patient consent Obtained.

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