CASE REPORT

Learning from errors: when a low platelet count in neonate excludes immune thrombocytopenic purpura in mother

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Abstract: This paper reviews the most common causes of thrombocytopenia in the newborn. It mentions few classification schemes that clearly characterize the most common causes, diagnosis and treatment approaches for neonatal thrombocytopenia. Particular attention is paid to inborn macrothrombocytopenia without congenital anomalies. They represent a rare group of diseases, often captured randomly or during routine examinations. An attention is paid on congenital macrothrombocytopenia variants with mutations in the MYH9 gene. If they are not associated with other disorders (deafness, presenile cataracts, nephritis or renal failure), they may be mistakenly diagnosed as the acquired immune thrombocytopenic purpura (ITP). This distinguishing is essential to avoid potentially harmful and unnecessary treatment. The listed case report points to a situation where a detection of the root causes of neonatal thrombocytopenia led to a review of misdiagnosed ITP in the mother. A platelet size evaluation by both an appropriate cell counter and blood film examination is useful for differentiating a heterogeneous group of rare inherited macrothrombocytopenias. A healthy twin supported autosomal dominant inheritance. The results of investigations of twins and mother confirmed the congenital/inherited macrothrombocytopenia from the group of MYH9-related diseases (Tab. 5, Fig. 2, Ref. 21).

Key words: neonatal thrombocytopenia, immune thrombocytopenia, congenital/inherited thrombocytopenia, MYH9-related disease.

Thrombocytopenia is the most common haematological abnormality detected in foetus or neonate. The incidence of significant thrombocytopenia at birth (platelet count <50 x 10⁹/L) is 0.1 to 0.5 % and the incidence of severe neonatal thrombocytopenia (platelet count <20 x 10⁹/L) is 0.04 %. Neonates with severe thrombocytopenia may have bleeding that leads to lifelong residual defects (e.g., intracranial haemorrhage) or death (1).

Commonly cited causes of neonatal thrombocytopenia (e.g. immunological disorders, congenital and perinatal infections, and disseminated intravascular coagulation) account for only a minority of these early-onset cases. The vast majority of the remaining patients are preterm neonates born following pregnancies complicated by placental insufficiency or foetal hypoxia. In these infants, the incidence of thrombocytopenia is as high as 15% and it is most severe several days after a delivery. The diagnosis is usually straightforward because the thrombocytopenia is accompanied by other characteristic haematological features seen on routine blood smears (2).

Late-onset neonatal thrombocytopenia (more that 72 hours of age) is mostly caused by late-onset sepsis or necrotizing enterocolitis. Thrombocytopenia is often severe (platelet count <50 x 10⁹/L), prolonged and prompts treatment by platelet transfusion (3, 4).

As majority of other forms of thrombocytopenia would have been resolved by this time, the likely causes of prolonged thrombocytopenia are immune thrombocytopenias, congenital infections, and congenital/ inherited thrombocytopenias. The Table 1 shows the most common causes of neonatal thrombocytopenia by age at presentation (2).

A well neonate presenting with clinical signs of severe thrombocytopenia (e.g. haemorrhage or purpura) is uncommon. However, it represents a neonatal emergency to avoid the potential for severe haemorrhage. In practice, the usual cause is neonatal isolate immune thrombocytopenia. The Table 2 shows the most common causes of neonatal immune thrombocytopenia (1).

Neonatal autoimmune thrombocytopenia (NITP) is an unexpected condition. Maternal platelet autoantibodies complicate a number of conditions. The most frequent cause is principally immune thrombocytopenic purpura /ITP/ in a mother, although...
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Because these antibodies can interfere with normal platelet aggregation, a qualitative defect may be present in those platelets that are yet not destroyed by the antibody. This functional platelet defect may explain why the incidence of serious bleeding is higher in infants with NAIT than in NITP infants.

NAIT usually presents in otherwise well term neonates with unexplained bruising and purpura. The platelet count is usually <30 x 10^9/L. Up to 20 % of affected infants will suffer serious bleeding ICH. This occurs in utero in 25 to 50 % of cases and is associated with long-term neurodevelopmental sequelae in 20 % of survivors (7).

The incidence is approximately 1:1000 live births, although approximately 25 % of cases may be clinically silent (5, 6). In 50 % of cases, first-born offspring is affected, suggesting that antigenic exposure can occur during the early course of pregnancy.

Laboratory confirmation is difficult but important with the reference to future pregnancies. A diagnosis of NATP is often inferential. The usual criteria include: normal maternal platelet count and negative history of maternal ITP, and no evidence of systemic disease, infections, malignancy, or haemangioma. The laboratory diagnosis of NAIT is made by demonstrating antiplatelet antibodies (usually anti-HPA-1a antibodies) in maternal serum, which are directed against paternal antigens and by platelet genotyping usually by polymerase chain reaction (6).

Treatment of mildly affected babies is not required, although the platelet count should be monitored for the first 5 days after delivery. By contrast, severely affected infants with NAIT (platelet count <30 x10^9/L and/or ICH or other major bleeding) should be promptly transfused with HPA-compatible platelets or washed maternal platelets. If severe thrombocytopenia persist, IVIG is often useful ameliorating the thrombocytopenia until a spontaneous recovery occurs 1 to 6 weeks after birth (2, 5–7).

Congenital/hereditary thrombocytopenias are a heterogeneous group of rare disorders both dominant and recessive forms of pure thrombocytopenia. Distribution is not uniform due to different clas-
sification criteria. In majority of neonates, but not in all, there are associated congenital anomalies that are useful in guiding investigation and establishing the diagnosis (Tab. 3) (1). Difficulties in the diagnosis cause mainly trombocytopenia without striking somatic abnormality. Platelet size evaluation by both an appropriate cell counter and blood film examination is useful for differentiating the heterogeneous group of rare disorders, inherited macrothrombocytopenias. This is characterized by abnormal giant platelets, thrombocytopenia and bleeding tendency with variable severity (8). Bone marrow examination demonstrates normal or increased numbers of megakaryocytes (9). The most frequent constitutional disorders with a macrothrombocytopenia are in Table 4 (10, 11).

Case report

Our patient was a boy, first of binovular twins, in whom at the day of birth a significant thrombocytopenia was found. In the second twin – girl, thrombocytopenia was not confirmed. Twins came from the second, high risk pregnancy (first one was interrupted by abortion). Mother was from the age of 17 years treated for severe thrombocytopenia accidentally trapped. Despite the long term serious platelets decline <30 x 10^9/L she had no significant bleeding difficulties. She has undergone various therapy within 6 years (IVIG, high dose methyl-prednisolone, prednisone), without a significant effect.

Refractoriness of the disease led to a re-investigation of bone marrow hemopoiesis, without changing the diagnosis. After 2 years of treatment she underwent splenectomy without affecting the platelet amount. At the age of 23 she became pregnant for the second time. During pregnancy, platelet count was critically low (platelet count 3–4 x 10^9/L), but without bleeding manifestations. She was not treated due to any other disease, she had no handicap (e.g. hearing or visual impairment, kidney disease). In the 35th gestational week, after a preparation (combination therapy: IVIG 1 g/kg/days for 2 days and corticosteroids and thrombocyte concentrate), pregnancy was terminated by the Caesar section. The mildly immature twins were somatically healthy, without bleeding or other signs of significant adjustment difficulties. Thrombocytopenia was confirmed on the day of delivery, but surprisingly only in a boy (platelet count 41 x 10^9/L). The girl had normal platelet counts. The boy was treated with IVIG (1 g/kg/day for 2 days). Monitoring of platelet count in the next three weeks confirmed a nonlinear variation in platelet counts between 43 and 111 x 10^9/L. The boy had asymptomatic thrombocytopenia, which persisted and varied in other months of life (platelet counts from 71 to 127 x 10^9/L). An unique situation has given rise to questions:

1. Can a mother with severe ITP give birth to twins – one with thrombocytopenia requiring treatment and the second one healthy?
2. What kind of thrombocytopenia has the child, when it persists beyond the neonatal period?
3. Could the mother be incorrectly diagnosed?

The microscopic evaluation of peripheral blood smear of the boy surprisingly confirmed a higher platelet count (platelet count 121 x 10^9/L) than the count obtained by an automat blood analyzer (platelet count 71 x 10^9/L). The difference was caused by large populations of giant platelets, which the automat blood analyzer evaluated incorrectly as other blood cells. In the blood smear, anisocytosis of platelets was remarkable with a shift to large forms and giant-forms (about 25 %). The platelet aggregates were not present in the blood smear and so the EDTA-dependent pseudothrombocytopenia was excluded. In the population of leukocytes (neutrophils, monocytes, eosinophils), basophilic Döhle-like inclusions (90 % granulocytes) were pres-
ent (Fig. 1). A coagulogram was appropriate for the age. The results raised a suspicion of inherited macrothrombocytopenia. Mother received a combination therapy with high-dose IVIG, corticosteroids, and transfusion with compatible platelets before delivery. Despite the treatment, an unchanged and critical platelet count persisted, but the patient did not bleed. At the time of examination of the children, the 3-a liner romiplostim treatment was recommended to the mother.

For a strong suspicion on familiar macrothrombocytopenia, the mother was asked to be examined after the agreement. The microscopic findings were similar to the child: mild thrombocytopenia was confirmed (platelet count 111 x 10^9/L), with a predominance of large and giant platelets (up to 70 %, the “giant platelets” 20 %), platelets of appropriate size were a minor population. The automat blood analyzer counted only platelets with physiological size and settled a false thrombocytopenia (platelet count 6 x 10^9/L). In all granulocytes, the basophilic Döhle-like inclusions were present (Fig 2). Mother did not suffer in adult from hearing or visual impairment or kidney disease. In mother’s parents, disorder also did not occur.

Discussion

The fact that the mother with ITP gives birth to twins, of which only one had thrombocytopenia, was very suspicious and could not be explained. The child had no signs of bleeding in the skin or mucous membranes. The choice of treatment of thrombocytopenia in the newborn resulted from the assumption of its deepening in the postnatal period. Mother on the combined treatment of ITP before and after delivery had no bleeding complications and at 6-year history of refractory ITP with severe decrease in platelets she did not overcome an unexpected severe bleeding episode. The second healthy twin unfixed the diagnosis of ITP in the mother.

When doesn’t a low platelet count mean ITP? The cases of constitutional/inherited macrothrombocytopenia that have been reported, were mistakes for the immune-mediated thrombocytopenia for years (12). The automated blood cell counters in the routine clinical use usually miss giant platelets and underestimate the mean platelet volume (13). A distinguishing between the acquired (secondary) thrombocytopenia, especially immune thrombocytopenia purpura (ITP), and the inherited (primary) thrombocytopenia is essential to avoid an unnecessary and potentially harmful treatment (12, 14). In the patient and his mother, macrothrombocytopenia was present, the healthy girl supported an autosomal dominant inheritance. The presence of basophilic Döhle-like inclusions in leukocytes narrowed suspected myosin heavy chain 9 (MYH9)-related platelet disorders (15–21).

There are autosomal dominant disorders caused by the mutations of MYH9 gene. The MYH9 gene encodes the nonmuscle myosin heavy chain IIa (NMMHC-IIa), cytoskeletal contractile protein that has been identified in the long arm of chromosome 22 (22q12.3–q13.2) (15, 17). Several mutations in the MYH9 gene lead to premature release of platelets from the bone marrow, macrothrombocytopenia, and cytoplasmic inclusion bodies within leukocyte (19).

This category encompasses a spectrum of independently described disorders: Epstein syndrome, Fechner syndrome, May Hegglin anomaly and Sebastian syndrome. There are autosomal dominant disorders caused by mutations of MYH9 (Tab. 5) (8, 14, 15).

Clinically, patients may present at birth with macrothrombocytopenia and basophilic Döhle-like inclusions in leukocytes. In childhood or adult life, patients may develop sensorineural hearing loss, cataracts, and glomerulonephritis that may progress to severe renal failure. In May Hegglin anomaly or Sebastian syndrome, the patients classically have macrothrombocytopenia with leukocyte inclusions (the difference being only in subtle ultrastructural change in the leukocyte inclusions) (17). Patients with the other associated features were classified as the Fechtner syndrome or Epstein syndrome based on the presence or absence of leukocyte inclusions (Tab. 5). Thrombocytopenia is usually noted incidentally or on routine screening and does not usually cause a symptomatic bleeding diathesis, although a few patients may have severe bleeding. On laboratory evaluation, patients present with variable thrombocytopenia with platelet counts ranging from 10 to 150 x 10^9/L. However, macrothrombocytes are always present, but to a variable degree. Platelets larger than red cell can vary from 3 % to 45 % of all platelets. A variable phenotypic expression in this disorder is seen in those with the same mutation and even within the same family. Platelet survival is normal although bone marrow examination sometimes shows an increased number of megalocytes (2, 15, 20).

In the baby within 1 year of clinical following, no organ disability was found. In the mother, only haematological changes were identified, at the age of 24 years she had not proven renal disease or sensory deficit. Similarly, also mother’s parents did not suffer from these diseases. Both underwent surgical procedures without bleeding complications. The triad of symptoms: thrombocytopenia, large platelets and characteristic basophilic Döhle-like inclusions in leukocytes, and autosomal dominant inheritance (mother and one of the twins) indicated MYH9-related disease. Most likely, the variant of the disease is so far May Hegglin anomaly or Sebastian syndrome. An accurate classification requires a long-term monitoring and in case of organ involvement may lead to a review of disorder in the MYH9-related disease of platelets.

<table>
<thead>
<tr>
<th>Type of syndrome</th>
<th>Thrombocytopenia</th>
<th>Döhle inclusions</th>
<th>Nephritis</th>
<th>Hearing loss</th>
<th>Cataract</th>
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<tbody>
<tr>
<td>May Hegglin</td>
<td>+</td>
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<td>Sebastian</td>
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<td>Fechterer</td>
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<td>Epstein</td>
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Tab. 5. Four overlapping syndromes of MYH9-related disease (8, 14, 15).
**Conclusion**

Pregnant women with ITP are at a 50% risk for delivering thrombocytopenic infants, whether or not the mother is thrombocytopenic during pregnancy or at the time of delivery (1). Thrombocytopenia in only one child of the twins has led to a review of mother’s diagnosis. The distinguishing of inherited thrombocytopenias from immune thrombocytopenia (ITP) can be difficult, and patients are therefore at risk of misdiagnosis and inappropriate treatments. Although it is known that the most common inherited forms of thrombocytopenia without congenital anomalies are characterized by an increased platelet size, the diagnostic power of this feature has never been investigated. The platelet size evaluation by both an appropriate cell counter and blood film examination is useful for the differentiating of inherited macrothrombocytopenias from ITP. This simple approach and accident of thrombocytopenic during pregnancy or at the time of delivery (1). Thrombocytopenia in only one child of the twins has led to a review of mother’s diagnosis. The distinguishing of inherited thrombocytopenias from immune thrombocytopenia (ITP) can be difficult, and patients are therefore at risk of misdiagnosis and inappropriate treatments.

**References**


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