Thrombocytopenia in childhood: a practical guide for investigation

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Abstract

Platelets play a central role in haemostasis. A significant reduction in the platelet count, thrombocytopenia, and the investigation of a child prone to bleeding and bruising, are common reasons for referral to paediatric haematology physicians. This article offers a practical guide to investigation of the thrombocytopenic child. The varied aetiology of thrombocytopenia in childhood, including both acquired and congenital forms are summarised. Conditions characterised by defective platelet function are also discussed. Key themes include a focus on distinguishing the cause of thrombocytopenia from history and examination with an explanation of the tests used to confirm diagnoses in specialist centres.

Keywords platelet aggregation; platelet count; platelet function tests; platelets; thrombocytopenia

Introduction

Platelets and their interactions with their surroundings play an essential role in haemostasis thus a reduction in the circulating platelet number or dysregulation of platelet function can manifest with clinically significant bleeding. Severe platelet disorders present early in childhood with investigation of the underlying cause posing a challenge in young children due to the practicalities of venepuncture and the volumes of blood needed for assessment.

Thrombocytopenia is the term given to a low platelet count. The normal platelet count in childhood is between 150 and 300×10^9/litre. A sustained or acute reduction of platelets requires prompt investigation and the urgent management of associated bleeding symptoms. The platelet level at which bleeding manifests depends on the underlying process. For example, in immune thrombocytopenia (ITP), a common cause of a thrombocytopenia in childhood, the severity of thrombocytopenia doesn't always correlate with severity of bleeding. Some inherited platelet disorders, such as Glanzmann thrombasthenia, are characterised by having a severe bleeding phenotype in association with a normal platelet count.

The underlying aetiology of thrombocytopenia can be primary (congenital) or a secondary (acquired). A severe form of thrombocytopenia can be seen in neonates in association with circulating maternal antibodies targeted against neonatal human platelet antigens; a condition termed 'NAIT' (neonatal alloimmune immune thrombocytopenia). The characteristic presentation and investigation pathway is well cited and is therefore not included in detail in this discussion.

Platelet production, regulation and function

In order to understand why platelet number and function is essential in securing haemostasis, we need to understand the roles and interactions they perform.

Platelets are anucleate cells produced from budding from larger, immature cells made in the bone marrow, megakaryocytes. A platelet's life span in the circulation is approximately 10 days and regulation of platelet and megakaryocytic proliferation and maturation is via the hormone thrombopoietin. This hormone is synthesised mainly in the liver and acts upon the c-Mpl receptor on platelet and megakaryocyte cell membranes.

When we bleed, platelets respond by interacting with the damaged vascular endothelium. Collagen-bound von Willebrand factor (VWF), a glycoprotein essential for haemostasis, binds to the platelets by the GP1b/IX/V complex on the platelet surface, securing platelets to the site of injury. Pathways linked with thrombin release stimulate platelet activation, leading to a conformational change in platelet shape and degranulation of the platelet's stored granule contents. ADP is released and acts as a positive feedback mechanism accruing platelets and activating other platelets in the region. A platelet plug is formed at the site of injury, secured by the formation of a network of fibrin strands.

A low platelet count or production of dysfunctional platelets can therefore be seen in association with defects along this pathway including:

- Platelet production
- Platelet-endothelial interaction including glycoprotein receptors
- Release of platelet granules and platelet signalling
- Increased peripheral platelet consumption

Assessment of the thrombocytopenic child

History

Bleeding disorders relating to a low platelet count or suspected platelet disorders can be challenging to diagnose in young children from history alone due to a lack of haemostatic challenges (such as previous surgery) prior to presentation. Paediatric bleeding assessment tools aid bleeding evaluation.

Important points to focus on in the history (see Table 1) include bleeding at birth (such as intracranial bleeding associated with instrumental delivery) and prolonged bleeding with umbilical stump separation or circumcision. In addition to mucosal bleeding (e.g. epistaxis) and cutaneous bleeding (e.g. petechiae or bruising), excessive or atypical bleeding after surgery and dental extraction should be explored. Bleeding disorders may present at menarche therefore should be discussed as part of the history for post pubertal females.

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Summary of important points to include in the history

- Chronicity of symptoms
- Bleeding manifestations (noting severity and duration of bleeding):
  - At birth/neonatal period
  - Mucosal and cutaneous bleeding patterns including epistaxis and oral cavity bleeding (note if this prompted or spontaneous bleeding)
  - Response to haemostatic challenges (e.g. dental extraction or surgery)
  - Menstruation
- Other medical conditions (including renal, ocular, hearing and locomotor)
- Family history including bleeding history of first degree relatives
- Medications history including anti-inflammatory use
- Presence of 'B symptoms' (night sweats, lymphadenopathy, weight loss, fatigue)
- History of recent and/or prolonged bacterial, viral and fungal infections

Table 1

A family history is essential in the investigation of the thrombocytopenic child and may reveal a focus for investigation, such as a suspicion of von Willebrand disease. A personal or family history of locomotor, ocular, hearing, immunodeficiency or renal defects may point you towards an inherited platelet disorder (see Table 2).

Examination

The examination of the thrombocytopenic child is a full systems inspection dividing broadly into the distribution of bruising and bleeding and other associated features (see Table 2 for a summary of the significance of examination findings).

Whilst a detailed discussion of Non-Accidental Injury (NAI) is beyond the scope of this article, doctors should consider this possibility. NAI can occur in children with bleeding disorders and therefore if a diagnosis of thrombocytopenia or a platelet disorder is made, this does not exclude NAI if suspicion still exists.

Investigation of the thrombocytopenic child

Practicalities of investigation

Which investigations should be performed first?

Investigation should commence with a detailed assessment of the full blood count (FBC) parameters and morphology. Information gathered in the history, e.g. a family history of Bernard Soulier syndrome, may guide you to the relevant pathway for investigation. Furthermore, a classical history of primary ITP may not require investigations beyond the FBC, blood film, direct coombs test (DCT) and immunoglobulin levels. If the likely cause is ITP, local paediatric or paediatric haematology teams would be the most appropriate team for referral. Any child with thrombocytopenia and severe bleeding (defined as a haemoglobin drop of 20 g/litre, intracranial haemorrhage or active bleeding requiring surgical intervention) should be discussed urgently with a paediatric haematologist.

Inherited platelet disorders — summary of associated features

Region	Feature	Significance
Cutaneous	Eczema	Wiskott-Aldrich syndrome (classical phenotype)
	Albinism (including ocular)	Hermansky—Pudlak syndrome
		Chediak-Higashi syndrome
	Facial capillary haemangioma	TAR
Locomotor	Absence of radii	TAR
	Radioulnar synostosis	ATRUS
Splenomegaly		Gray Platelet syndrome
Infection	Bacterial/viral/fungal infection	Wiskott-Aldrich syndrome
	Severe immunodeficiency	Chediak-Higashi syndrome
	In association with neutropenia	Hermansky—Pudlak syndrome
Hearing disorders	Sensorineural hearing loss	May-Hegglin syndrome
		ATRUS
Ocular	Cataract	May-Hegglin syndrome
Renal	Glomerulonephritis	May-Hegglin syndrome
	Congenital malformation	TAR
Cardiorespiratory	Pulmonary fibrosis	Hermansky—Pudlak syndrome
	Cardiac anomalies	TAR

Abbreviations: TAR — Thrombocytopenia and absent radii, ATRUS — Amegakaryocytic Thrombocytopenia with Radioulnar synostosis.

Table 2

How old does the child need to be before we investigate?

There is no minimum age for investigation. The investigation for neonatal alloimmune thrombocytopenia (NAIT) in the thrombocytopenic neonate should be performed urgently (see below).

Investigations at specialist centres

The precise pathway for investigation is dependent on the age of the child as it relates to the volume of blood needed to perform the required tests. It is therefore common for a limited range of tests to be performed in young children with more extensive investigation reserved for when they are older. The first line investigations at our centre, after the initial assessment of the FBC and blood film, include platelet aggregometry and platelet-based flow cytometry studies. We do not routinely perform a platelet function assay (PFA-100), although a small quantity of blood is required to perform this test, the results obtained can lack specificity and further testing is still required.

Measuring the platelet count and further investigation

The full blood count and interpreting the parameters: the FBC is processed in the laboratory by an automated machine. The