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www.commprac.com
ISSN 1462 2815

ISOLATED THROMBOCYTOPENIA IN CHILDREN; IT IS NOT ALWAYS IMMUNE THROMBOCYTOPENIA

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DOI: 10.17605/OSF.IO/N6ERU

Abstract

Introductıon: Childhood immune thrombocytopenia (ITP) remains a diagnosis of exclusion when isolated thrombocytopenia is not part of another disease process. The diagnosis of ITP can only be confirmed when thrombocytopenia resolves or is excluded after the recognition of a primary cause. **Methods:** The records of 110 children with isolated thrombocytopenia seen over a Four-year Period in a Government paediatric haematology centre were reviewed retrospectively. Children in whom a primary cause was eventually found were the subjects of a further descriptive study. **Results:** 11 (10%) children with isolated thrombocytopenia were not diagnosed with ITP because a primary disease was found. Of these Eleven cases, four had thrombocytopenia because of Wiskott Aldrich syndrome, three patients with Platelet function disorder presented as moderate thrombocytopenia. Two more patients had inherited thrombocytopenia due to MPL gene mutation and SLFN14 gene mutation. One patient had myelodysplastic syndrome and one patient had portal vein agenesis. **Conclusıon:** Secondary thrombocytopenia is not uncommon in a tertiary paediatric specialty practice with adequate evaluation. Chronic Thrombocytopenia and failure of steroid and immunoglobulin therapy are predictive of secondary cases.

INTRODUCTION

Immune thrombocytopenia (ITP) is a relatively common childhood illness, with an annual incidence of 1.9–6.4 per 100,000 children (1). A diagnosis of ITP can be made when isolated thrombocytopenia (platelet count < 100 × 109/L) occurs in the absence of identifiable and specific precipitants (2). All current clinical practice guidelines have recommended a minimum evaluative process to look for secondary causes of thrombocytopenia before a diagnosis of ITP is made (2,3) Medical literature has numerous examples of ITP mimics of infectious (4), immune (5), haematologic (6), endocrine (7), neoplastic (8) and other disorders (9). In practice, however, the frequency of secondary thrombocytopenia has not been systematically reported, as cases of secondary ITP and nonimmune thrombocytopenia (non-IT) are generally difficult to recognize in a timely fashion. Red flags that raise the suspicion of secondary ITP and other nonimmune causes of thrombocytopenia have been proposed in the last few years and include positive family history, older age (adolescence), chronic ITP, platelet size either above or below the normal range, moderate (instead of severe) thrombocytopenia at first presentation, nonresponse to first-line treatments, and new symptoms or laboratory abnormalities during the disease course(10). Despite growing awareness of the differential diagnosis of primary ITP, secondary ITP and non-IT seem to be frequently identified with considerable delay, and thus the diagnostic workflow may benefit from better definition and validation.

METHODS

This retrospective chart review studied children from1-month to 18-years of age who were attending Department of paediatrics of Government Medical College-Srinagar in state of Jammu and Kashmir, northern India from March-2018 to March-2022. The Hospital received patients from all over state on an inpatient or outpatient basis. The Hospital database registered all children as having isolated thrombocytopenia (platelet count < 100 × 109 /L) when they presented with bleeding symptoms associated with thrombocytopenia or when they were referred for evaluation of isolated thrombocytopenia. Children with mild iron deficiency anaemia ([Hb] > 9.0 g/dL) or due to recent blood loss as well as children with leucocytosis concurrent with a febrile illness, were included. Cases were excluded if laboratory had suspected an alternative diagnosis, such as leukaemia or if there was anaemia with Hb ≤ 9.0 g/dL or leukopenia. All neonates with thrombocytopenia were excluded from the study as sepsis was one of the common causes of neonatal thrombocytopenia. All patients were evaluated with a thorough history taking, including familial predispositions, physical examination with particular attention to organ enlargements, and full blood counts with examination of the peripheral blood smear by a haematologist. The microscopic examination followed a checklist for isolated thrombocytopenia: red cell changes e.g. schistocytes and leucocyte changes (blasts, atypical lymphocytes and Pelger-Huët anomaly) and platelet changes (small platelets, giant platelets and platelet clumps). Secondary thrombocytopenia was diagnosed when the isolated thrombocytopenia was determined to be part of another disease process. Children with isolated thrombocytopenia formed the subjects of a descriptive study.

RESULTS

During the study period, 110 children presenting with isolated thrombocytopenia were diagnosed with ITP. 69 (62.7%) of the 110 children had acute ITP with resolution of thrombocytopenia within three months of diagnosis, 21 (19.09 %) had persistent ITP with disease resolution 3–12 months after diagnosis, and 20 (18.1%) had chronic thrombocytopenia lasting over 12 months. Secondary thrombocytopenia was diagnosed in 11 (10%) among these 20 chronic thrombocytopenia patients. Their clinical features are summarised in Table I. A Thirteen -year-old girl with mild thrombocytopenia with no family history was found to have Glanzmann's Thrombasthenia on platelet aggregometry. Two female siblings Five year and three-year-old with chronic mild thrombocytopenia failed to respond to prednisolone therapy prescribed by her primary physician were found to have Bernaud Soleur syndrome on platelet aggregometry and genetic testing. One Eight -year-old girl presented with a history of persistent thrombocytopenia of Three years duration with no response to steroids and IVIG and a small palpable spleen was the only positive sign on examination. In this case portal vein agenesis was confirmed on radiological imaging. Four male patients presented with isolated chronic thrombocytopenia and on genetic testing were found to have WAS-gene mutation diagnostic of Wiskott Aldrich syndrome. Among these two siblings had eczema as well and both of these died on follow up. Other two males (four year and Thirteen years) with diagnosis of Wiskott Aldrich syndrome had only thrombocytopenia without eczema and no history recurrent infections. Another patient (Five Months Male) had MPL mutation positive on genetic testing favouring congenital amegakaryocytic thrombocytopenia. One 8-year male child had chronic moderate thrombocytopenia with recurrent epistaxis and mutation

positive for SLFN14 heterozygous Platelet type bleeding disorder. Another patient 5-year Downs syndrome had chronic thrombocytopenia of three-year duration with bone marrow showing significant megakaryocyte dysplasia and managed as myelodysplastic syndrome, because of financial constraints Molecular and genetic testing could not be done in this case but he is under follow-up of our department.

Table I: Summary of the cases of secondary thrombocytopenia

Serial	Gender	Age	Platelet count	Previous treatment	Diagnosis
1	Male	1 years	3000	Nil	WAS
2	Male	3 years	7000	Nil	WAS
3	Male	11 years	64000	Nil	WAS
4	Male	5 years	12000	Steroids, Immunoglobulins	WAS
5	Female	13 years	83000	Steroids	Glanzmann thrombasthenia
6	Female	5 years	43000	Immunoglobulins	Bernaud soleur syndrome
7	Female	3 years	72000	Nil	Bernaud soleur syndrome
8	Female	8 years	88000	Steroids	Splenic vein agenesis
9	Male	1.5 year	8000	Nil	MPL mutation
10	Male	8 years	72000		SLFN14 heterozygous Platelet type bleeding disorder 20.
11	Male	5 years	32000	Nil	Myelodysplasia

DISCUSSION

In an unselected series of isolated thrombocytopenia ITP remains the most frequent diagnosis in the great majority of cases after thorough evaluation. However, secondary thrombocytopenia is not uncommon and accounts for 10% of the cases in this series. Hence, clinicians following up with children who have isolated thrombocytopenia should be alert for alternative diagnoses other than ITP until the disease remits. The importance of enquiring for a familial history of bleeding or thrombocytopenic disorder cannot be overemphasised.

A history of chronic ITP in a first-degree relative may be an important clue, as misdiagnosis of familial thrombocytopenia is common. As clinical practice guidelines (2,3) and an abundance of case reports (4-9) have highlighted, when ordering additional tests and diagnostic procedures to look for other causes of thrombocytopenia, it is important to take note of atypical events from the patient's history and abnormal signs other than bruises on physical examination.

In this respect failure to respond to prednisolone or immunoglobulin therapy can be another warning sign of non-immune causes of isolated thrombocytopenia. Examination of the peripheral blood smear is an important procedure in the evaluation as platelet size can be an important pointer to find the aetiology of isolated thrombocytopenia.

Box 1. Causes of childhood thrombocytopenia that mimic immune thrombocytopenia.

1. **Constitutional bone marrow failure syndromes/congenital disorders**
    - Congenital amegakaryocytic thrombocytopenia
    - Fanconi anaemia
    - Wiskott-Aldrich syndrome
    - X-linked thrombocytopenia
    - Myosin heavy chain 9-related disorders
2. **Consumptive thrombocytopenia**
    - Hypersplenism
    - Thrombotic microangiopathies
3. **Acquired bone marrow failure**
    - Aplastic anaemia
    - Leukaemia and other malignancies with marrow infiltration
4. **Specific infections**
    - Dengue fever
    - Malaria
    - Human immunodeficiency virus infection
5. **Systemic lupus erythematosus**
6. **Primary immune deficiencies**
7. **Autoimmune lymphoproliferative disorder**

In case of Wiskott Aldrich Syndrome, two cases were atypical without skin manifestations and were initially treated as Immune thrombocytopenia. All patient with thrombasthenia had moderate thrombocytopenia but bleeding symptoms were disproportionate to platelet count with presence of large platelets on smear (Fig-1) therefore needing platelet function assays and geniting testing. This paper emphasises the need of genetic testing as inherited thrombocytopenia can be wrongly labelled as Immune thrombocytopenia which can progress to marrow failure and can be treated with stem cell transplant. Correct diagnosis is important, as these patients are not responsive to corticosteroid or immune-based therapies. As alluded to earlier, it is unclear if the patients diagnosed with chronic ITP truly have immune thrombocytopenia, because the disease does not have a specific laboratory marker. In conclusion, secondary thrombocytopenia is not an uncommon diagnosis among children presenting with isolated thrombocytopenia and should be looked out for at the initial diagnosis and during the subsequent follow-up until thrombocytopenia resolves.

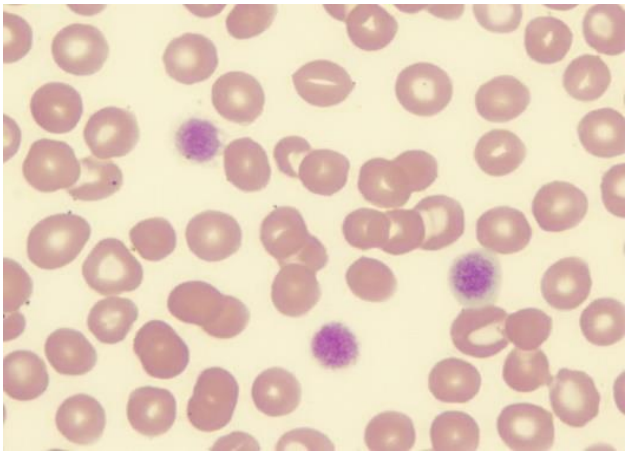

Fig 1: Peripheral blood film of patient with Beraud solieur syndrome showing large Platelets

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