SUNTEXT REVIEWS

SunText Review of Case Reports & Images
ISSN: 2766-4589

Open Access
Case Report
Volume 4:7

# Thrombocytopaenia and Down Syndrome – What about the Usual Suspects?

**Schmit Céline[1,*], Geurten Claire[2], Florkin Benoit[2] and Dresse Marie-Françoise[2]**

[1]*Department of Pediatrics, Centre Hospitalier Universitaire de Liege, University of Lige, Belgium*
[2]*Department of Pediatrics, division of Pediatric Hematology and Oncology, Centre Hospitalier Universitaire de Lige, University of Lige, Belgium*

[*]**Corresponding author:** Schmit Céline, CHR Citadelle – Department of pediatric hematology and oncology, Boulevard du Douzieme de Ligne 1 4000 Lige Belgium, Tel: +3243218739; E-mail: c.schmit@student.uliege.be

**Received date:** 22 August 2023; **Accepted date:** 01 September 2023; **Published date:** 04 September 2023

**Citation:** Schmit C, Geurten C, Florkin B, Dresse M-F (2023) Thrombocytopaenia and Down Syndrome – What about the Usual Suspects?. SunText Rev Case Rep Image 4(7): 201.

**DOI:** https://doi.org/10.51737/2766-4589.2023.101



## Abstract

Down syndrome is a chromosomal disorder renowned for conferring a predisposition to auto-immune and hematological conditions; hematological abnormalities in this population should prompt investigations to exclude malignancy, but comprehensive differential diagnosis should be broadened to other pathologies. A 15 months-old infant with Down syndrome presented with isolated moderate thrombocytopenia during an episode of upper respiratory tract infection. Clinical examination was unremarkable except for mild hepatomegaly and diffuse petechial rash. A bone marrow aspiration showed no malignant infiltration. Intravenous immunoglobulins showed little benefit over the course of the following 7 days. The patient secondarily developed hemolytic anemia. ADAMTS13 activity was undetectable, and plasmatic inhibitors were detected confirming the hypothesis of immune thrombotic thrombocytopenic purpura (TTP), triggered by an infection. Daily plasmapheresis were started with immediate but short-lived benefit, and TTP persistently recurred every 48h after interruption of exchanges, warranting initiation of treatment with Rituximab and enabling the achievement of long-term remission. Acquired TTP is an extremely rare entity in children below 9 years of age (<1/1.000.000), and can be life-threatening due to the formation of micro thrombi occluding terminal circulation leading to organ damage and dysfunction. Prompt recognition of this entity is important to avoid long-term damages. Altered IFN signaling in Down syndrome could theoretically predispose to immune TTP, although we couldn't find any other report of cases of immune TTP in patients with Down syndrome.

**Keywords:** Down syndrome; Thrombocytopenia; TTP; ADAMTS-13

## Introduction

Down syndrome (DS) is a chromosomal disorder characterized by specific facial features, learning difficulties and congenital heart disease. Hematological complications include abnormal complete blood count (neutrophilia, thrombocytopenia and polycythemia) at birth, and, in 10% of cases, transient peripheral blastosis in the setting of transient myeloproliferative disease, classically associated with somatic GATA-1 mutation. Patients with DS have a lifelong increased risk of developing myelodysplasic syndrome and acute lymphoblastic or myeloid leukemias, with a cumulative risk of 2,1% by the age of 5 [1,2]. These different conditions/disorders can present initially with thrombocytopenia and bone marrow aspiration should be promptly warranted in this subgroup of children to exclude malignant or pre-malignant conditions.

## Case Report

A 15 months-old infant with Down syndrome presented with isolated moderate thrombocytopenia (platelet count 66.000/mm$^3$, Hb 11.3 g/dL, and white cell count 6900/mm$^3$) during an episode of upper respiratory tract infection. Medical history included a recent episode of infectious mononucleosis and a mild interatrial communication. Clinical examination was unremarkable except for known dysmorphic features, mild hepatomegaly and diffuse

petechial rash. As thrombocytopenia worsened, the patient developed rectal bleeding, requiring initiation of treatment. Bone marrow aspiration was performed and showed preserved cellularity with no signs of dysplasia or marrow infiltration, in keeping with idiopathic thrombocytopenic purpura. Medullary caryotype was 47XY, +21c. No GATA-1, CEBPA, FLT3 and NPM1 mutations were detected. Intravenous immunoglobulins (IVIG) were selected as the first line of treatment to avoid masking any potential underlying malignancy with steroids. No hematological response was observed over the course of the following 7 days. Following IVIG infusion, the patient did however develop hemolytic anemia (Hb 7.8 g/dl, reticulocytes 217.0000/mm$^3$, haptoglobin <0.01mg/dL, schizocytes 54/mm$^3$). In consequence a course of prednisolone 4mg/kg/day was initiated. No improvement in platelet count or hemoglobin level was noted with steroids, but counts did improve following platelet transfusion. A repeat marrow with trephine confirmed the absence of malignant infiltration or dysplasia. Differential diagnosis at this stage included Evans' syndrome and thrombotic microangiopathy. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13) activity was undetectable (<0.2%), and plasmatic inhibitors were detected (4.25 U Bethesda), confirming the hypothesis of immune thrombotic thrombocytopenic purpura (TTP), triggered by an infection, or unravelled by passive transfer of antibodies through the IVIG administered earlier in the course of the disease. Daily plasmapheresis were started with immediate but short-lived benefit, as thrombocytopenia persistently recurred within 72 hours after plasma exchange, warranting initiation with Rituximab 375 mg/m$^2$ for 4 doses. This management has enabled sustained remission and the patient has not yet experienced recurrence at 12 months follow-up.

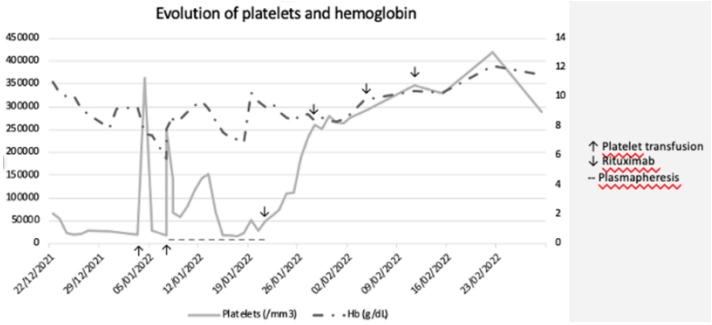


***Figure 1:*** *Evolution of platelet and hemoglobin count with time and different treatments.*

## Discussion

Down syndrome (DS) is a chromosomal disorder characterized by specific facial features, learning difficulties and congenital heart disease. Hematological complications include abnormal complete blood count (neutrophilia, thrombocytopenia and polycythaemia) at birth, and, in 10% of cases, transient peripheral blastosis in the setting of transient myeloproliferative disease, classically associated with somatic GATA-1 mutation. Patients with DS have a lifelong increased risk of developing myelodysplasic syndrome and acute lymphoblastic or myeloid leukemias, with a cumulative risk of 2,1% by the age of 5 [1,2]. These different conditions/disorders can present initially with thrombocytopenia and bone marrow aspiration should be promptly warranted in this subgroup of children to exclude malignant or pre-malignant conditions. Patients with DS also have a higher propensity to develop auto-immune conditions such as thyroiditis, celiac disease, type 1 diabetes, alopecia, vitiligo and rheumatoid arthritis. Recent studies have highlighted the role of higher circulating levels of pro-inflammatory cytokines and increased complement consumption suggesting prominent interferon signalling and dysregulation predisposing to auto-immunity in this population [3,4].

Idiopathic thrombocytopenic purpura (ITP) is the leading cause of acute-onset isolated thrombocytopenia in children. This condition is characterized by peripheral destruction of platelets mediated by auto-antibodies. It occurs in 1 per 10.000 children every year and hasn't been reported to be more prevalent in children with DS, probably because the pathophysiology of ITP, although not yet completely understood, isn't interferon related. Association of thrombocytopenia with hemolytic anemia broadens the differential diagnosis to the wide spectrum of thrombotic microangiopathy, comprising of ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif member 13) deficiencies (i.e. TTP or Moschowitz's purpura) whether hereditary or immune mediated, and inherited or secondary complement dysfunction (i.e. hemolytic uremic syndrome (HUS) or atypical HUS). In the absence of ADAMTS13, large and adhesive von Willebrand multimers lead to the formation of microthrombi [5-7], with the potential to occlude distal and terminal vasculature, causing life-threatening organ damage (stroke, renal insufficiency). Prompt recognition and early management are important factors to help prevent long-term damages. Deficit in ADAMTS13 can either be hereditary or acquired (i.e. immune-mediated). The presence of an inhibitor and an ADAMTS13 activity <30% confirms the diagnosis of immune TTP. While familial history of TTP and the absence of inhibitors pleads in favour of hereditary TTP [5]. See table 1 for the main differences between hereditary and acquired TTP (Table 1). The severity of the ADAMTS13 deficit is proportional to the clinical symptoms, as patients presenting with activity <5% at diagnosis have a threefold higher risk of recurrence [4]. Immune TTP is an extremely rare entity in children below 9, and accounts for 2/3 of Paediatric TTP cases. Delayed diagnosis and management significantly impact morbidity and mortality [6].

Before the advent of plasma exchange, over 90% of patients with TTP could not be saved.

***Table 1:*** *Comparison of clinical characteristics between hereditary and acquired Thrombotic Thrombocytopenic Purpura (TTP).*

| | **Hereditary TTP (Upshaw-Schulman syndrome)** | **Acquired TTP** |
|---|---|---|
| Etiology | ADAMTS13 biallelic mutations | Anti-ADAMTS13 autoantibodies |
| Prevalence | 0.8/1.000.000<br><br>1/3 of paediatric TTP cases | 1/1.000.000, more frequent in older children and females<br>2/3 of paediatric TTP cases |
| Clinical presentation | Neonatal hyperbilirubinemia<br>Thrombocytopaenia<br>TIA/stroke | Hemolytic anaemia<br>Thrombocytopaenia<br>Neurological signs (confusion, headache)<br>Autoimmune disease (common in older children) |
| Treatment | Plasma infusion<br>Factor VIII concentrates (BPL 8Y)<br>Future : recombinant ADAMTS13<br>Avoid platelet transfusion (life – threatening bleeding only) | Plasma exchange<br>Corticosteroids<br>Immunosuppression<br>Consider : Bortezomib, N-acetylcysteine<br>Future : Caplacizumab, immunosuppression without plasma exchange<br>Avoid platelet transfusion (life –threatening bleeding only) |

Currently first-line therapies for acquired TTP are plasma exchange (up to twice daily), corticosteroids, and rituximab [4-10]. They aim at eliminating circulating anti-ADAMTS13 auto-antibodies and simultaneously transfusing plasma containing normal levels of ADAMTS13 without inducing volemic changes. The objective of the treatment is to maintain platelet count above 150.000/mm$^3$ for at least 30 days. Monitoring ADAMTS13 activity can help identify the 20-50% of patients at risk of recurrence [4]. Treatment alternatives include cyclosporine, splenectomy, vincristine, cyclophosphamide, Bortezomib, Eculizumab, N-acetylcysteine [4-9]. Recently Caplacizumab, a human monoclonal anti-von Willebrand protein antibody that interferes with the interaction between the vWF and platelets, has shown interesting results [11,12]. Supportive care measures include avoidance of platelet transfusion, as platelet aggregation facilitate thrombotic complications. Their use should be limited to patient presenting life-threatening bleeding [4].

## Conclusion

The case described above illustrates the importance of assessing all potential causes in children with DS presenting with haematological abnormalities. Excluding malignancy is a priority, but enriching the differential diagnosis is crucial as these children are not devoid of risk to develop rarer conditions which can be life-threatening if treatment is not initiated early on. Patients with DS have a 4 to 6-fold higher risk of developing auto-immune conditions, mostly thyroid disorders, diabetes and coeliac disease, thought to stem from an innate T-cell dysfunction with overproduction and oversensitivity of cytokines associated with auto-immunity (IFN, IL17, etc) and resisting to Treg suppression. These immune alterations do not seem to confer an increased risk of developing ITP, but interferon as a drug is a known precipitating factor of immune TTP [13], suggesting altered IFN signalling in DS could theoretically predispose to immune TTP, although we couldn't find any other report of cases of immune TTP in patients with DS. In our patient's case we considered passive transfer of anti-ADAMTS13 antibodies through intravenous (IVIG) as hemolytic anemia developed after the infusion. TTP is a rare but serious condition associating thrombocytopenia and hemolytic anemia. Plasma exchange should be initiated promptly. Poorly sustained response to treatment should lead clinicians to suspect an underlying associated congenital deficit in ADAMTS13 or alternative diagnosis. New therapies such as Caplacizumab are being investigated, mostly in teenagers and adults.

## Statements and Declarations

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

### Patient consent

The patient's mother provided informed consent for the case publication.

## References

1. Xavier AC, Ge Y, Taub J. Unique clinical and biological features of leukemia in Down syndrome children. Expert Rev Hematol. 2010; 3: 175-186.
2. Bruwier A, Chantrain CF. Hematological disorders and leukemia in children with Down syndrome. Eur J Pediatr. 2012; 171: 1301-1307.

3. Sullivan KD, Evans D, Pandey A, Hraha TH, Smith KP, Markham N. Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation. Sci Rep. 2017; 7.
4. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012; 158: 323-335.
5. Loirat C, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura in children. Curr Opin Pediatr. 2013; 25: 216-224.
6. Grall M, Azoulay E, Galicier L, Provot F, Wynckel A, Poullin P. Thrombotic thrombocytopenic purpura misdiagnosed as autoimmune cytopenia: Causes of diagnostic errors and consequence on outcome. Experience of the French thrombotic microangiopathies reference centre. Am J Hematol. 2017; 92: 381-387.
7. Siddiqui A, Journeycake JM, Borogovac A, George JN. Recognizing and managing hereditary and acquired thrombotic thrombocytopenic purpura in infants and children. Pediatr Blood Cancer. 2021; 68.
8. Joly BS, Vanhoorelbeke K, Veyradier A. Understanding therapeutic targets in thrombotic thrombocytopenic purpura. Intensive Care Med. 2017; 43: 1398-1400.
9. Gomez-De Leon A, Villela-Martinez LM, Yanez-Reyes JM, Gomez-Almaguer D. Advances in the treatment of thrombotic thrombocytopenic purpura: repurposed drugs and novel agents. Expert Rev Hematol. 2020; 13: 461-470.
10. Jestin M, Benhamou Y, Schelpe AS, Roose E, Provot F, Galicier L, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. Blood. 2018; 132: 2143-2153.
11. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knobl P, Wu H, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016; 374: 511-522.
12. Scully M, Cataland SR, Peyvandi F, Coppo P, Knobl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019; 380: 335-346.
13. Kundra A, Andrei M, Wang JC. Interferon-induced thrombotic microangiopathy. In (Ed.), thrombocytopenia. Intech Open. 2018.