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Case Report

Thrombocytopenia as a Clue for the Diagnosis of 22q11.2 Deletion Syndrome: A Case Report

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Abstract

Background: 22q11.2 Deletion Syndrome (22q11.2DS), also known as DiGeorge syndrome, is one of the most common chromosomal microdeletions, characterized by highly variable clinical manifestations. Diagnosis is often delayed, particularly in the absence of classic features such as conotruncal heart defects, hypocalcemia, and severe immunodeficiency.

Case Presentation: We report the case of a male patient initially referred at 3 years and 6 months of age due to global developmental delay. Clinical evaluation revealed mild dysmorphic features, speech delay, and a history of recurrent respiratory infections. Initial metabolic and genetic investigations were inconclusive. At the age of 10 years, the patient developed mild intermittent thrombocytopenia (101–154 $\times 10^9$/L) with macroplatelets. Further hematological evaluation showed partial deficiency of platelet glycoprotein Ib/IX (50%) and reduced ristocetin-induced aggregation. Immunological assessment revealed hypogammaglobulinemia (including IgG subclasses) and mild T and NK lymphopenia. Fluorescence in situ hybridization (FISH) confirmed a 22q11.2 deletion.

Conclusion: Macrothrombocytopenia may represent an early hematological marker of 22q11.2DS due to GP1BB haploinsufficiency. In patients with nonspecific clinical features, such findings should prompt further investigation. Early genetic diagnosis is essential for appropriate multidisciplinary follow-up and family counseling.

Keywords: 22q11.2 deletion syndrome; DiGeorge syndrome; Thrombocytopenia; Macroplatelets; Immunodeficiency; Case report

Introduction

22q11.2 Deletion Syndrome (22q11.2DS) is a genetic disorder caused by a microdeletion on chromosome 22q11.2, with an estimated incidence of 1:4,000 to 1:6,000 live births. It presents with a broad and heterogeneous clinical spectrum, including cardiac, immunological, endocrine, neurological, and psychiatric manifestations. The classic triad—conotruncal cardiac anomalies, thymic hypoplasia, and hypocalcemia—is not present in all patients, contributing to frequent underdiagnosis [1].

In recent years, hematological abnormalities, particularly macrothrombocytopenia, have been increasingly recognized in association with 22q11.2DS. This finding is attributed to haploinsufficiency of the GP1BB gene, located within the deleted region, and may serve as a diagnostic clue in atypical presentations.

Case Presentation

Initial Clinical History

A 3-year-6-month-old male child was referred for evaluation of global developmental delay.

Developmental milestones included:

- Head control: 7 months
- Independent walking: 20 months
- First words: 2 years
- Sentence formation: 3 years

Past medical history:

- Acute bronchiolitis (3 months)
- Community-acquired pneumonia (6 months)
- Congenital torticollis under physiotherapy
- Recurrent upper respiratory tract infections and otitis

Physical examination revealed mild dysmorphic features, including prominent ears, prognathism, mouth breathing, and high-arched palate. Neurological examination was unremarkable [2].

Initial Investigations

Metabolic screening and genetic studies (karyotype 46, XY; Fragile X testing) were normal.

At 10 years of age, routine blood analysis revealed mild intermittent thrombocytopenia without additional cytopenias. Mean platelet volume was increased (13.9 fL), consistent with macroplatelets.

Immunological studies showed reduced IgG levels and subclasses, particularly IgG4.

Platelet aggregation studies demonstrated:

- Partial deficiency (~50%) of glycoprotein Ib/IX
- Reduced response to ristocetin

Diagnostic Workup

Further immunological evaluation revealed:

- Mild T and NK lymphopenia
- Polyclonal B lymphocytosis
- Reduced switched and non-switched memory B cells

Given the combination of developmental delay, dysmorphic features, hypogammaglobulinemia, and macrothrombocytopenia, targeted genetic testing was performed.

Fluorescence in situ hybridization (FISH) confirmed a 22q11.2 deletion, establishing the diagnosis of DiGeorge syndrome [3].

Family screening (parents and sibling) was negative, consistent with a de novo mutation.

Additional Investigations

- Abdominal and renal ultrasound: normal
- Brain CT: normal
- Cardiology: bicuspid aortic valve
- ENT: bilateral conductive hearing loss with anatomical abnormalities
- Endocrinology: normal calcium and parathyroid hormone levels

Discussion

This case highlights the diagnostic value of mild thrombocytopenia as a potential early marker of 22q11.2DS. Macrothrombocytopenia in this condition is associated with deletion of the GP1BB gene, which encodes the β-subunit of the GPIb-V-IX complex, essential for platelet adhesion to von Willebrand factor. Haploinsufficiency results in enlarged and functionally impaired platelets, explaining increased mean platelet volume and mild bleeding tendency [4,5].

Concomitant immunological abnormalities, including hypogammaglobulinemia and mild T-cell lymphopenia, reflect partial thymic hypoplasia, a hallmark of the syndrome. The absence of classical features explains the delayed diagnosis, which is common in patients with milder phenotypes.

Early recognition is crucial to:

- Ensure appropriate multidisciplinary follow-up
- Provide genetic counseling
- Monitor for psychiatric and cognitive complications in later life

Conclusion

Macrothrombocytopenia may be an early and underrecognized feature of 22q11.2 Deletion Syndrome.

A systematic and multidisciplinary diagnostic approach is essential in patients presenting with persistent hematological abnormalities and developmental delay. Early genetic diagnosis enables tailored clinical management and prevention of long-term complications.

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