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Indian Journal of Pathology and Oncology

Journal homepage: www.innovativepublication.com

Review Article

Clinico-hematological profile of inherited macrothrombocytopenia

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ARTICLE INFO

Article history:
Received 25-11-2019
Accepted 17-01-2020
Available online 25-05-2020

Keywords:
Inherited
Pubmed
Articles
Asymptomatic
Macrothrombocytopenia

ABSTRACT

Inherited macrothrombocytopenia is a common condition. The aim of the review was focussing on different aspects of inherited macrohtrmbocytopenia with particular reference to India. A pubmed search of articles between January 2000 to October 2019 with keywords macrothrombocytopenia, asymptomatic macrothrombocytopenia, syndromic macrothrombocytopenia and megakaryopoeisis were searched. A total of 210 articles were found, out of which 58 articles were found related to our topic.

1. Introduction

Platelets derived from megakaryocytes are involved in primary hemostasis.[1] Macrothrombocytopenia is defined as reduced platelet count (less than 1.5 lacs/cumm) with significant increase in platelet size (more than 12fl).[2] It can be acquired or inherited with acquired cases comprising the majority. Inherited macrothrombocytopenia (IMTP) are rare clinical conditions showing an increasing trend of occurrence affecting 2.7 per 1 lac individuals with mild to absent bleeding manifestations.[3] Indian population especially the eastern and north eastern side are more prone to suffer from such conditions.[4]

2. Materials and Methods

A Pubmed search of articles with keywords like macrothrombocytopenia, asymptomatic macrothrombocytopenia, syndromic macrothrombocytopenia, platelet disorders was done from January 2000 to October 2019. Reviewed articles provided additional references. Recent reviews in high impact journals and those decibing Indian population were given extra weightage. Out of total 210 articles, 58 articles were shortlisted and read.

In IMTP more than 12 genes have been found to be involved. These genetic mutations can be further categorised according to their mode of inheritance like autosomal dominant (AD), autosomal recessive (AR) and X-linked.

2.1. Autosomal dominant IMTP

Most common gene involved is Myosin heavy chain 9 (MYH9) gene leading to premature release of platelets from bone marrow causing macrothrombocytopenia and cytoplasmic inclusions in leucocytes.[5] MYH9 gene was discovered back in 1909.[6] May and Hegglin discovered an AD IMTP known as May -Hegglin anomaly (MHA) that decribes a triad of thrombocytopenia, giant platelets and leucocyte inclusion bodies.[7] This syndrome occurs due to deletion in region 11 of the long arm of chromosome 22. Other syndromes like MHA, Epstein syndrome, Fechtner syndrome and Sebastian syndrome are also associated with MYH9 gene.[8]

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https://doi.org/10.18231/j.ijpo.2020.039

2.1.1. Di George syndrome

This syndrome manifests due to deletion in region 11 of long arm of chromosome 22 in which platelet count is decreased, Mean platelet volume (MPV) is increased and there is reduced expression of platelet surface GP1b/IXb required for platelet adhesion.[9,10]

2.2. Autosomal recessive IMPTs

2.2.1. Bernard Soulier syndrome (BSS)

It was discovered by Bernard and Soulier as inherited bleeding disorder associated with platelet dysfunction.[11] There is absent to decreased expression of Von Willebrand factor (VWF) on platelets resulting in platelet dysfuctioning in the form of defective platelet adhesion. VWF receptors are GP1b-α, GP1b-β, GPV and GP IX.[12]

2.2.2. Gray platelet syndrome

It occurs due to inability of megakaryocytes to pack endogenously synthesized secretory proteins into developing α granules. As a result granules deficient platelet is decreased leading to thrombocytopenia.

2.3. X linked IMPT

It occurs due to mutations in GATA1 and ACTN1 genes. The GATA1 gene is responsible for megakaryocyte and erythroid development. Due to this mutation there is interference with the association of GATA1 with teanscriptional factor FOG1.[13–15]

ACTN1 mutation interferes with platelet and megakaryocyte cytoskeleton organisation.

Other less common mutations are TPM4, PRKACG, FLNA etc.[16–20] Many other mutations are still unknown which prevents proper diagnosis and treatment.

2.3.1. Clinical features

Majority of the patients are either symptomatic or have minor bleeding symptoms. In most cases it is just an incidental discovery. In other IMTPs association with other phenotypic abnormalities contribute to early diagnosis.

2.3.2. Diagnsotic modalities

1. Investigations should start with detailed bleeding history, family history, past history, drug and nutritional history.
2. Complete hemogram including MPV, Platelet distribution width (PDW) should be included.
3. Immature platelet fraction, platelet scatter plot and platelet histogram should be taken into account.
4. Peripheral smear examination to confirm thrombocytopenia and presence of megathrombocytes.
5. Platelet function studies.
6. Flow cytometry to detect lack of GP1B/IX.
7. SDS PAGE for diagnosis BSS, GPS and other X linked IMPTs.
8. Electron microscopy, DNA analysis and Next generation sequencing.

Ali et al. reported over 112 cases of macrothrombocytopenia having low platelet counts, high MPV and showed presence of giant platelets without any inclusion bodies in peripheral smear.[21]

Kakkar et al. detected macrothrombocytopenia in 75 patients having MPV ranging from 10.9 to 23.3.[22]

Naina et al. screened 203 blood donors to analyse platelet and RBC indices. Among 101 donors were form northern India and rest from Southern India. A significant difference was observed between platelet count among northern and southern population.[23]

3. Conclusion

IMTPs are not uncommon conditions but their subtle manifestations and lack of specialised diagnostic tools have led to under reporting of such disorders. Not much is known about its exact prevalence in India. Limited studies from India have shown increased frequency in Bengali and Kashmiri population. There is a real need of exploring its prevalence in different parts of India. A major challenge is diagnosing asymptomatic IMPTs and these should be differentiated from Immune thrombocytopenia as treatment modality of both these diverse group is different.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Cite this article: Jamal I. Clinico-hematological profile of inherited macrothrombocytopenia. *Indian J Pathol Oncol* 2020;7(2):204-206.