

INCIDENCE (PREVALENCE) AND CAUSES OF THROMBOCYTOPENIA AT A TERTIARY HEALTH CARE CENTRE, OXFORD MEDICAL COLLEGE HOSPITAL, ATTIBELE, ANEKAL, RURAL PART OF BANGALORE

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ABSTRACT

BACKGROUND

Thrombocytopenia is one of the relatively common finding in haematological investigation. The causes of this varies from mild cases, viral fever to malignant conditions like leukaemia. Though abnormal platelet count is detected by automatic haematology analyser, confirmation is always done by peripheral smear examination.

METHODS

2156 patients' blood samples from OPD and inpatients are collected in CBC tubes and subjected to automatic haematology analyser (SYSMEX KX-21) and the results were analysed. In all these cases of low platelet count, repeat analysis was done with suitable anticoagulant 3.8% sodium citrate, finally smear examination was done as a confirmatory evidence.

RESULTS

256 cases of thrombocytopenia were encountered out of 2156 patients' samples. It accounted for 11.8% of blood samples that were run on the analyser. Age varied from 0-75 years with peak incidence in 15-30 years. It is seen more among males than females. In our study, viral infection, dengue fever formed the commonest cause and seen with peak incidence in rainy season from June to October. Rarer cases seen were leukaemia, hypersplenism and massive blood transfusion. Majority of the cases were presented with mild-to-moderate thrombocytopenia. Only 19% cases presented with severe thrombocytopenia (counts less than 40,000 cells per cu. mm).

CONCLUSION

An important approach to the diagnosis and successful treatment of thrombocytopenia is understanding the underlying pathophysiological process in the development of disease. Prompt investigations and identification may be crucial and sometimes lifesaving as in TTP, HIT or severe ITP.

Notable progress has been made in the recent years in developing new treatment option for thrombocytopenia like ITP. Early diagnosis, treatment, vector control, community awareness are essential to decrease the incidence thrombocytopenia.

KEYWORDS

Platelets, Thrombocytopenia, Dengue fever, Viral fever.

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INTRODUCTION: Thrombocytopenia is relatively common in many clinical conditions. Viral fever is the commonest cause followed by Dengue, Haemorrhagic fever, spurious thrombocytopenia, Drug-induced Thrombocytopenia, Idiopathic Thrombocytopenia and Liver Disease.

It is one of the common cause of bleeding. Clinically, it remains in asymptomatic state to bleeding manifestation like purpura or ecchymosis. Thrombocytopenia is more common in paediatric age group and young adults. Males are more affected than females.

Present study determines the commonest cause of thrombocytopenia (incidence) with relation to age and sex at Oxford Medical College Hospital, Attibele, Anekal, Rural Part of Bangalore.

MATERIALS & METHODS: This is a prospective study involving all OPD and inpatients at Oxford Medical College Hospital, from January 2015 to January 2016. CBC samples are collected in EDTA sample tubes (Violet topped) and proper mixing by electric rotator and was subjected to automatic 3 part differential cell counter. Any abnormal platelet counts are repeated 2-3 times and smears are made for confirmation of count and morphology. This study utilises platelet histogram, L-J curves, platelet distribution width (PDW) and platelet crit (PCT).

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RESULTS: Thrombocytopenia is one of the common haematological findings seen in CBC results. There are many causes of thrombocytopenia in our study. Viral fever, spurious (pseudo thrombocytopenia), dengue fever, drug induced, chronic alcoholism, ITP are common causes. Less common causes are liver diseases, massive blood transfusion and leukaemias.

In this study for the period of 1 year, 2150 CBC samples are run of which 256 cases of thrombocytopenia were encountered of which viral fever, dengue fever, pseudo (spurious thrombocytopenia), drug induced, ITP formed the commonest causes.

All the outpatients and admitted patients were enrolled on structural protocol which include symptoms, signs, diagnosis and complications. Investigations like platelet count (CBC), viral screen, dengue, NS antigen, IgM & IgG dengue antibodies by ELISA techniques, LFT, proper drug history. Liver function test, serum Vit B₁₂/folate levels are done in appropriate cases.

Age	Male	Female	No. of cases	Percentage
0-14 yrs.	40	31	71	27.7%
15-29 yrs.	51	30	81	31.6%
30-45 yrs.	45	20	65	25.3%
46-60 yrs.	15	10.6	25.6	10%
61-75 yrs.	8.8	4	12.8	05%
Total	160	96	256	100%

Age and sex pattern of thrombocytopenia

Mild	62 Cases	(1.25 Lakh-4 Lakh/cu.mm)
Moderate	175 Cases	(40000 to 125000/cu.mm)
Severe	19 Cases	(<40,000/cu.mm)

Severity of thrombocytopenia

DISCUSSION: A total of 256 cases encountered out of 2156 patient samples during the period from Jan 2015 to Jan 2016. They were statistically analysed. Among 256 cases study prevalence of thrombocytopenia with reference to sex, majority of thrombocytopenia were seen in males as compared to females. Among the different age groups, majority of thrombocytopenia were observed in the age group of 15 to 29 years followed by age group between 0 - 14 years of age. All the cases were subjected for platelets count by automated haematology analyser and confirmed by peripheral smear examination. Relevant data was entered in proforma and analysed.

Diseases	Total cases	%
Viral Fever	129	(50.3%)
Dengue Haemorrhagic fever	56	(21.81%)
Spurious (Pseudo) Thrombocytopenia	26	(10.11%)
Drug-Induced Thrombocytopenia	18	(7%)
ITP	8	(3.1%)
Liver Disease	6	(2.3%)

Incidence of thrombocytopenia: Total cases 256

Diseases	Total cases	%
Megaloblastic Anaemia	3	(1.1%)
Hypersplenism	3	(1.1%)
Heparin-Induced Thrombocytopenia	3	(1.1%)
Leukaemia	2	(0.78%)
Massive Blood Transfusion	2	(0.78%)

Less common causes

Age and sex specific distribution among thrombocytopenia patients: Number of Patients.

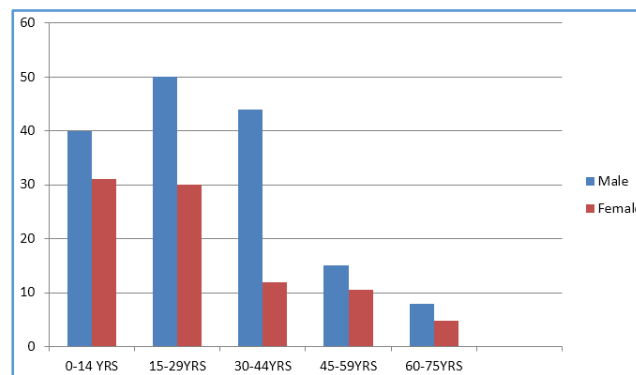


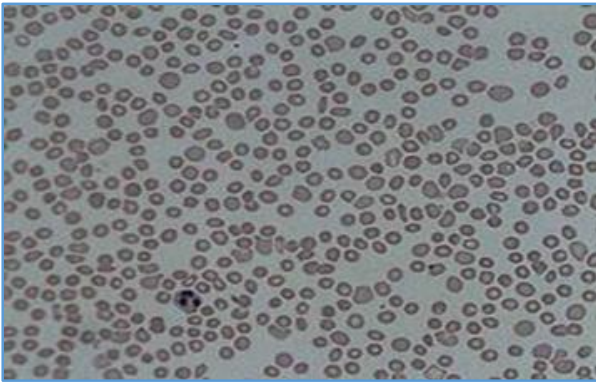
Figure 1: Age (years)

Similar pattern of age and sex and incidence is seen in a study by Shankar et al¹ and Tamil Selvan et al.²

Regarding aetiology of thrombocytopenia, viral infection is the commonest cause in our study. These patients presented with flu like symptoms with common cold, moderate-to-severe fever, nasal stuffiness, sore throat, headache and generalised body pain of one to two weeks duration. CBC was done in all the cases. There was neutropenia and thrombocytopenia in majority of cases and thrombocytopenia in all the cases. This is contrast to study by Tamil Selvan² where dengue fever was commonest cause encountered.

Peripheral smear study shows atypical lymphocytes (Downy type I) in nearly 50% cases. All patients showed good improvement with symptomatic treatment (antipyretics, antihistamines and antibiotics in some cases to prevent secondary bacterial infection). In 10% (28 cases), repeat CBC was done as followup procedure. At that time platelet count was normal. Other patients did not come for followup.

There were many viruses implicated in flu like illness. Commonest are Adenovirus, Coxsackie, Influenza, Herpes virus and Hepatitis A and B. Most of the infection are self-limited and can subside without treatment and may relapse.³



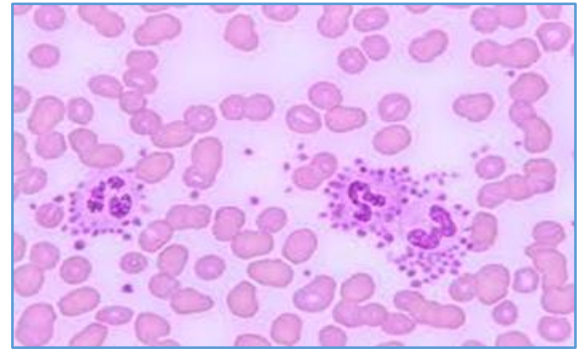
Patient of Viral Fever Showing Thrombocytopenia

Dengue haemorrhagic fever is the second common cause accounting for 56 cases (21.8%) similar incidence is seen in a study by L. Kabilan et al⁴ and also study by Shankar et al.¹

Dengue is a mosquito borne viral disease with four serotypes, also known as break bone disease which was first described by Benjamin Rush in 1780. It causes severe dengue fever, dengue with warning signs and without warning signs. Severity of thrombocytopenia was mild-to-moderate as the study by Tamil Selvan et al.² Mortality was nil. This could be due to community awareness, early diagnosis, management and vector control. Bleeding manifestation due to thrombocytopenia was seen in 4 cases. Similar to study by Buchanan GR.⁵

This fever is manifested in children due to outdoor activities, where the chances of getting bitten with mosquitoes are more. In all these cases, dengue was confirmed positive by IgG and IgM antibodies by ELISA.

Spurious thrombocytopenia is seen in 26 cases. Blood sample was collected in EDTA sample mixed properly on blood mixer and it was subjected for analysis by 3 part differential analyser. There was mild-to-moderate thrombocytopenia. All samples with thrombocytopenia were repeated 2 to 3 times with analyser and finally smears are made and stained with Leishman's stain and examined microscopically for confirmation, but found adequate on smear examination. Now it is concluded, it was due to pseudothrombocytopenia due to EDTA agglutinins to agglutinate platelets to cause platelet satellitism, which will not get counted by cell counter resulting in false value.⁶ And also because small extraneous particles in the preparation may be mistaken for platelets³. Correction studies done when sample was collected in 3.8% Sodium citrate sample as anticoagulant (blue topped) instead of EDTA sample (violet topped). No such decreased platelets counts or platelet satellitism observed.⁷



Picture Showing Aggregation of Platelet around Neutrophils (Platelet Satellitism)

Another important factor in preventing pseudothrombocytopenia is thorough mixing of blood in blood mixer for the minimum period of 10-15 mins.⁸

It is well known that some drugs used therapeutically causes decreased platelet count. In our study, quinidine, Septran and Amiodarone are the drugs which caused mild thrombocytopenia.

Quinidine is used as antiarrhythmic drug in ventricular and atrial arrhythmias. Septran (cotrimoxazole) used in resistant cause of urinary tract infection, respiratory tract infection caused by Gram-positive cocci and H. Influenza. Bacterial diarrhoea or dysentery due to resistant strain of E. coli, Shigella, salmonella and in Chancroid due to H. Ducreyi. Amiodarone used in supraventricular arrhythmias produces mild-to-moderate thrombocytopenia.⁹

All these cause mild-to-moderate thrombocytopenia. Drug-induced immune thrombocytopenia (DITP) should be considered in all the patients with thrombocytopenia not explained by other causes. Similar study in encountered in study by Bollinger Le et al.¹⁰ Thrombocytopenia is a potential serious adverse reaction to many drugs.^{9,11} Drug induced thrombocytopenia is important as it gives clinical and haematological picture indistinguishable from idiopathic thrombocytopenia.³

First step in the evaluation and management of patient with DITP is to discontinue the drugs that is most likely to cause thrombocytopenia for a minimum period of one to three weeks. Then recheck the platelet count, if it is drug induced the platelet should return to the normal.

In the present study, 8 cases of ITP out of 256 cases all in the age group of 1-12 years, 6 males and 2 females. All the patient presented with mild-to-moderate thrombocytopenia (between 50 thousand to 90 thousand cells per cu. mm). One case presented with platelet count of 16 thousand cells per cu. mm. He presented with petechiae over the lips and lower leg.



11 Year Old Boy Presented With Petechiae over Lips and Lower Limb in a Case of ITP

This patient showed improvement on treatment with steroid and platelet concentrate. Bone marrow examination was done in this patient after platelet stabilization shows increased number of megakaryocyte. Similar clinical findings and response to treatment was noted by Watts RG et al.¹⁰

In all these cases antibody against platelet can be detected. Most of these are against platelet membrane glycoprotein IIb-IIIa and are of IgG type. The coating of platelet with IgG render them susceptible to opsonisation and phagocytosis by splenic macrophages as well as Kupffer cells in the liver. These IgG antibodies damage megakaryocyte, the precursors of platelets. Recently it is found that impaired production of glycoprotein hormone thrombopoietin, which is a stimulant for platelet production may be contributory factor in the reduction of circulating platelets.^{11,12}

Next common cause of decreased platelet count seen in liver disease. In our study 6 cases of chronic liver disease were seen. Four cases of which patients was chronic alcoholic presented with ascites, pedal oedema and liver shrinkage and splenomegaly. There were features of portal hypertension with prominent veins over the abdomen and two cases of which presented with haematemesis.

One case Hepatitis C positive confirmed by ELISA technique with hyperbilirubinaemia and mildly elevated liver enzymes. One case of HIV positive which was initially tested by Tridot spot method and later confirmed by western blot method with past history of repeated unprotected sexual exposure. Patient presented with fever, with loss of weight, diarrhoea and thrombocytopenia (mild).

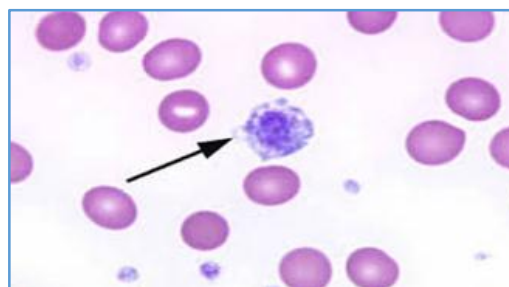
Chronic immune thrombocytopenic purpura (CITP) is a diagnosis of exclusion occurs de novo or secondary to other underlying condition. Chronic infection with HIV and Hepatitis C Virus are well recognized cause of CITP.

Hepatitis C viral infection can be associated with chronic thrombocytopenia even in the absence of overt liver disease. HCV associated thrombocytopenia may be considered complex and multifactorial in origin. Since different mechanisms have been implicated in its pathophysiology with respect to autoimmune thrombocytopenia in chronic HCV infection. Detection of specific antibodies against platelet glycoprotein have been reported.¹³ Similar study by Rajan et al suggests that thrombocytopenia has been described with Hepatitis infection even in absence of chronic liver disease.¹⁴

Chronic Immune Thrombocytopenia (CITP) is a diagnosis of exclusion occurs de novo or secondary to underlying condition. Chronic infection with HIV virus, hepatitis C virus are well recognised cause of CITP. Between 6-8 percent of HIV patients may develop thrombocytopenia. HCV related thrombocytopenia is typically less severe than primary CITP. Screening for HCV infection should be considered in patients with ITP with risk factor for infections or in patients with unexplained mild elevation of liver enzymes.¹⁵

Thrombocytopenia is a common finding in advanced liver disease. It is predominantly a result of portal hypertension and platelet sequestration in enlarged spleen. Liver is the site of Thrombopoietin (TPO) a hormone that leads to proliferation and differentiation of megakaryocytes and platelet function.¹⁶

Megaloblastic anaemia is encountered in 3 cases. All presented with anaemia with macro-ovalocytes and thrombocytopenia. Hypersegmented neutrophils are seen in 2 cases. Patient was put on haematinics, but did not improve in haemoglobin and there was no increase in reticulocyte count (count 2%). One patient was pure vegetarian. Bone marrow examination was done after initial coagulation profile, showed megaloblasts and hypersegmented neutrophils in the marrow. Patient was given parenteral dose of vitamin B₁₂ injection once weekly for 8 weeks. There was improvement in peripheral smear findings and clinically. In other 2 cases, serum folate levels were estimated, it was low. Patient was asked to take more green leafy vegetables, pulses and cereals in the diet and tablet folic acid 5 mg with elemental iron was supplemented for 2 months, showed clinical improvement and there was correction of peripheral smear findings. The thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis as well as thrombosthenia.¹⁷



One Patient of Megaloblastic Anaemia showing Macro-ovalocyte and Giant Platelet

Hypersplenism accounted for 3 cases. In 2 cases, patient had cirrhosis with portal hypertension. Clinically, spleen and liver was enlarged with ascites. In both cases, platelet counts were decreased from mild-to-moderate. In one case, a 20-year-old man from malarial endemic area shows bicytopenia (leucopenia+ thrombocytopenia), patient showed schizonts and gametocytes of plasmodium falciparum. OptiMAL Rapid Malaria Dipstick Test also confirmed the species. U/S showed moderate splenomegaly. Antimalarial treatment was started with sodium artesunate. The platelet and leukocyte counts started rising from 4th day of treatment. Similar studies were encountered in study by Ravinder Pal Singh et al.¹⁸

Thrombocytopenia due to Heparin administration was seen in 3 cases. 2 cases with hemiparesis (CVA), one case was suspected of pulmonary embolism. Unfractionated heparin was given 1-2 weeks caused decreased platelet counts. Later, it was switched over to oral warfarin. Unlike other drug-induced thrombocytopenia, HIT is unique for its association with thrombosis rather than haemorrhage. The mechanism it causes thrombocytopenia is platelet activation with release of platelet factor 4(PF4) from platelet alpha granules causing a complex with IgG antibodies forming heparin P4-IgG complexes resulting in destruction of platelet.¹⁹

In 2 cases of AML, there was mild-to-moderate thrombocytopenia without any bleeding manifestations like petechia or purpura; mechanism probably due to hyperfunction of spleen and liver which phagocytes the blood cells.

Familial platelet disorder with predisposition to acute myeloid leukaemia characterised by qualitative and quantitative defects have propensity to develop acute myeloid leukaemia.²⁰

Mild thrombocytopenia was seen in 2 cases of blood transfusion where 6-8 units of blood were given for patients with road traffic accident. This was due to dilutional thrombocytopenia. DIC is more common in massively transfused patients than their elective surgical counterparts and it can be reduced with the use of blood component therapy.²¹

CONCLUSION: To conclude thrombocytopenia is a relatively common finding in CBC results. It is more in months from June – October in rainy season as chances of mosquitoes breeding and incidence of viral infections are high. Smear study is mandatory in all cases of thrombocytopenia to differentiate true thrombocytopenia from spurious thrombocytopenia. Proper history, detailed clinical examination, appropriate lab investigations arrives at cause of thrombocytopenia. Thrombocytopenia can rarely be fatal, counts less than 10000/cu. mm leads to intracranial bleeding. An important approach to the successful treatment of thrombocytopenia is the understanding the underlying pathophysiological process in the development of disease. Prompt investigation and identification may be crucial and sometime as lifesaving as in TTP, HIT, acute leukaemia or even severe ITP.

Notable progress has been made in the recent years in developing new treatment option for thrombocytopenia like ITP. Early diagnosis, treatment, vector control, community awareness are essential to decrease the incidence of thrombocytopenia.

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