Immune Thrombocytopenic Purpura: an Auto immune Disease Associated with Low Platelets Count in Children

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الملخص:

نبذة والاهداف :مرض نقص الصفائح الدموية المناعي الفرفري [او نقص الصفائح الدموية الفرفري مجهول السبب] هو مرض مناعي ذاتي يتميز بنقص في عدد الصفائح الدموية في وجود وظيفة طبيعية للنخاع العظمي .يحدث المرض بسبب تكون اجسام مضادة ذاتية ضد بعض التركيبات في سطح الصفائح الدموية مما يؤدي الى تدمير الصفائح الدموية. يحدث المرض قي حالتين: حالة حادة عند الاطفال واخرى مزمنة عند البالغين. الصورة الحادة تحدث بعد الاصابة بالأمراض الفيروسية وتتحسن ذاتيا خلال شهور قليلة. يعتمد تشخيص المرض على اكتشاف نقص في عدد الصفائح الدموية عند اجراء تحليل شامل لخلايا الدم مع استبعاد اية اسباب اخرى لنقص الصفائح الدموية .هذه الدراسة تهدف الى قياس عدد الصفائح الدموية عند الاطفال من مركزين طبيين في طرابلس, ليبيا , ودراسة

العلاقة بين احتمال الاصابة بهذا المرض والامراض الفيروسية عند الاطفال. المواد وطريقة البحث: تم اجراء الدراسة من يونيو الى اكتوبرعام2018 .العدد الكلي لـ 700 عينة دم تم جمعها وتحليلها بجهاز تحليل مكونات الدم طبقا لأبحاث الدم القياسية. النتائج: من ال700 عينة وجدنا 77 عينة 11 في المائةلديهم نقص الصفائح الدموية المناعي الفرفري. كل العينات ال77 التي اظهرت نقصا مؤقتا في عدد صفائح الدم لديها وظيفة طبيعية لنخاع العظام وجميعها ادخلت الى المستشفى نتيجة للإصابة بأنواع مختلفة من الامراض الفيروسية وجميعها لم يثبت استعمال اي منها لاي ادوية قد يصاحبها نقص في عدد الصفائح الدموية. جميع الحالات ال77 تم تعافيها ذاتيا خلال شهور قليلة. بالإضافة الى ان معدل الاصابة بمرض نقص الصفائح الدموية المناعي الفرفري كان اعلى بشكل مميز عند الاطفال بعمر 5.1 سنوات. الخلاصة: بعض الامراض الفيروسية يصاحبها مرض نقص الصفائح الدموية المناعي الفرفري بسبب تكون اجسام مضادة غير طبيعية تهاجم الصفائح الدموية وفي اغلب الحالات يرجع عدد الصفائح الدموية الى مستواها الطبيعي خلال شهور قليلة.

الكلمات المفتاحية: مرض نقص الصفائح الدموية المناعي, الصفائح الدموية, مرض المناعة الذاتي, الاطفال.

ABSTRACT

Background and objectives Immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura (ITP) is an auto immune disease which characterized by low platelet count in the presence of a normal bone marrow function. This disease caused by development of of auto- antibodies against several platelets surface structures which leads to platelets destruction. The

disease occurs in two conditions: an acute form in children and chronic illness in adults. The acute form often follows viral infections and self limited within few months. The valuable diagnosis of this disease is done by identifying a low platelet count on a complete blood count test to exclusion the other possible causes of thrombocytopenia. This study aimed at measuring Platelets count of Paediatric patients from two different medical centers in Tripoli, Libya, and investigating the relationship between ITP incidence and viral infection in children. **Materials and Methods:** This study was carried in the period from June to October 2018. A total of 700 whole blood samples from two different medical centers were collected and investigated for absolute platelet count using a complete blood analyzer according to the standard Haematological procedures. **Results:** out of 700 samples, 77 cases (11%) of ITP were detected. All those 77 ITP cases had normal bone marrow function results, and they attended to these medical centers as a result of different viral infections(p=0.03) and they never used any medications that may associated with low platelets count. 100% of cases were self-limited within few months. ITP incidence was significantly higher in patients aged 1-5 years (p=0.02). **Conclusion:** Some viral infections may lead to Immune thrombocytopenic purpura because of developing anti-platelets auto antibodies, and most of cases return to normal platelets counts.

Keywords*:* immune thrombocytopenic purpura, Platelets, autoimmune disease, Paediatrics

1-Introduction:

Immune thrombocytopenic purpura (ITP) or idiopathic thrombocytopenic purpura is an auto immune disorder and characterized mainly by low platelet count with normal bone marrow function with absence of other causes of low platelets (Rodeghiero F, et al, 2009; 113: 2386 -2393) (George JN. 2003; 2:381-388) .The disease has two clinical features: it appears as an acute form in paediatrics or a chronic condition in adults. The clinical acute condition mainly occurs after viral infections and return normal after few months. The pathogenic cause of the chronic idiopathic thrombocytopenia being unknown and it continues longer than six months. The major complications of ITP in very low platelets counts are characteristic red or purple bruise-like rash and bleeding especially inside brain (Cines DB, et al, 2005*;* 56:425–442). The pathophysiology of immune thrombocytopenic purpura (ITP) based on formation of auto- antibodies against several platelets surface structures. Immune thrombocytopenic purpura (ITP) can be easily diagnosed by detecting thrombocytopenia on a complete blood count (a general analysis of blood components).

Hospitalization or treatment with medications e.g. corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Platelet transfusions, or immunosuppressive drugs is only recommend in significant bleeding conditions (Lambert Michele P, et al, 2017*;*129 :2829–2835).

The anti-platelets auto antibodies are of the immunoglobulin G (IgG) type, and attack platelet membrane glycoprotein IIb-IIIa or Ib-IX (Coopamah M, et al, 2003*;* 17*:* 69- 80) (Schwartz RS, et al, 2007*;* 357: 2299-2301). The

complexes of platelets and their auto- IgG are opsonised and engulfed by macrophages in the spleen and the liver. Abnormal T cell activity has a role in the production of auto-antibody in ITP (Semple J, et al, 1991*;* 78**:** 2619–2625) (Stasi R, 2008*;* 112:1147–1150) (Yu J, et al, 2008; 112 :1325-1328) and these abnormal T cells can be targeted by B cell depleting medications, such as rituximab (Godeau B, et al, 2008; 11 :999–1004).

Immune thrombocytopenic purpura (ITP) is disease in which the main haemostasis process is affected due to low platelet counts. The incidence rate of ITP in paediatrics is known to be 1.6- 5.3 per 100,000 person-years (Zeller B, et al, 2005; 94:178-184) (Frederiksen H, et al, 1999; 94: 909-913) (Bolton PH, et al, 1997; 350: 620- 623) (Neylon AJ, et al, 2003; 122: 966-974) (Abrahamson PE, et al, 2009; 83: 83-89). Unlike the chronic ITP, ITP in children generally recovered with or without therapy within 6-12 months after diagnosis. (Kim TO, et al, 2017; 155: 86-91) (Kuhne T, 2017; 37: 36-44). It is well-known that ITP pathogenesis follows infection, viruses such as Epstein-Barr virus, hepatitis C virus and human immunodeficiency virus have been associated with ITP (Nagamine T, et al, 1996; 24: 135-140) (Rand ML , et al, 1998;19:253-259) (Yan M, et al, 2020; 13: 781-786)(Franchini M, et al, 2017; 10: 99-106). Upper respiratory infections develop ITP by 1-4 weeks in 50-60% of paediatric patients. The pathology of ITP is known to be related to infection, but there are no enough studies on its association with viral disease in children. The purpose of our study is to determine the relationship between viral infections and ITP incidence in patient children.

2-Methods:

2.1. Patients and setting:

The study was carried out in the period from June to October 2018, by collecting whole blood samples from paediatric patients attending in Tripoli Medical Center and Aljala- Paediatric Hospital, Tripoli-Libya. Written informed consent was obtained from patients' parents in the study. The Ethical clearance for the study was obtained by the Ethical Committee of department of medical laboratories, university of Tripoli, Libya.

2.2. Sample techniques:

Samples were collected randomly in different days by assembling 700 whole blood samples from Aljala- Paediatric Hospital and Tripoli-Medical Center, Tripoli-Libya. Samples were tested in Haematology laboratory according to the standard Haematological procedures. Whole blood was analyzed automatically for platelets count using complete blood analyzer [mindray, BC 2800] after the sample number, date of analysis, patient's name, and patient's age have been introduced. Important data such as age, gender, platelets count, clinical state of the patients, types of medications, and cause of hospital-attending were collected and documented in specific form.

3. *Statistical analysis:*

Statistics (number, percentage) were used to describe patient baseline characteristics. Results were presented as absolute platelet counts and p-

values. Data was analyzed using SPSS version 18. The relationship between viral infections and ITP incidence rate was analyzed using the chi-square test, and *p*-values <0.05 were considered statistically significant.

4. Results:

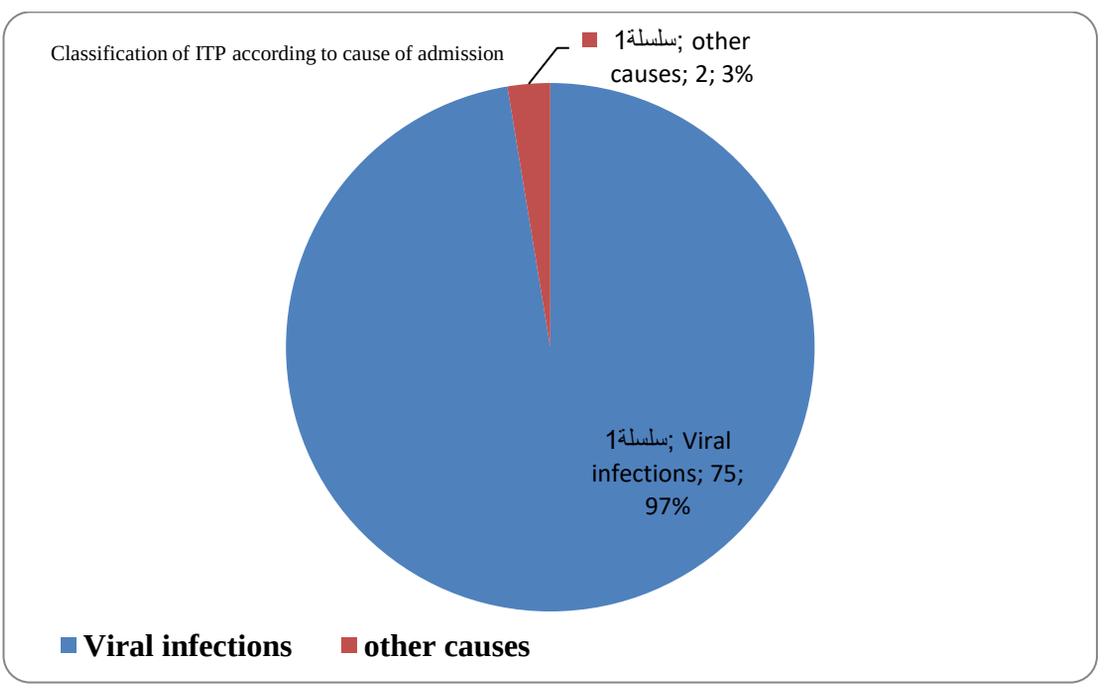
Seven hundreds blood samples were collected [383 males (48%), 362 females (52%)].Age between 1-15 years. 77 of total (11 %) showed temporary thrombocytopenia with normal bone marrow function (ITP). Table 1 represents the demographic information of the ITP-patients.

Table 1. Demographic characteristics of patients with ITP

Positive-cases **(low platelets count)**	**Number (%)** **Total =77**
Age	
1-5 years	**39(51%)**
6-10 years	**27(35%)**
11-15 years	**11(14%)**
Gender	
Male	**36(47%)**
Female	**41(53%)**
Male to female ratio	**0,9**

Upon correlation with the cause of the hosital adminstration, 97% of cases (75 cases) had ITP as a result of different types of viral infections ($p=0.03$) , whereas in 3% of cases could not be identifeied (lack of informations). In figure 1, the clear relationship betwenn viral infections and temporary low platelets count is displayed.

Figure 1. Classification of cases depending on the reason of hospitalization



To accurate assessment the relationship between viral infections and ITP incidence, we compared the incidence of ITP among different age groups and correlated it with

viral infections. The ITP incidence was signifiantly higher in pediatric aged 1-5 years (p=0.02) compared with other aged groups.

Table 2. Causality of ITP incidence with viral infections (*P*- value)

ITP incidence	1-5 Year	6-10 Year	11-15 Year
Viral infections	0.02	0.114	0.411

5.Discussion:

Immune thrombocytopenic purpura (ITP) is a disease caused by an immune imbalance. The impaired functions of T cells activate B cells to produce abnormal antibodies against platelets. The anti-platelets antibodies attach to the glycoprotein membranes in the platelets surface, the macrophages in the spleen and liver destroy the platelets that carry the auto antibodies. This immune disorder leads to gradual decrease in the platelets count. The Immune thrombocytopenic purpura (ITP) occurs as acute clinical disease in children or as chronic more complicated disease in adults (Rodeghiero F, 2009; 113: 2386 -2393) (Cines DB, et al, 2005*;* 56 :425–442) (Lambert MP, et al, 2017*;*129 :2829–2835).

Most of immune thrombocytopenic purpura (ITP) cases in children will end up in full recovery within six months, even without therapy. Some chronic cases usually remit during follow-up observation, and few cases will end up

with only mild thrombocytopenia (Watts RG, et al, 2004*;* 43:691–702) (Treutiger I, et al, 2007*;* 92:704-707).

Recent researchers have found a relationship between ITP and numbers of immune relate genes. Some genes such as FCGR3a-V158 allele and KIRDS2/DL2 increase the susceptibility to ITP, others such as KIR2DS5 shown to be protective (Nourse JP, 2012*;* 23: 45–50) (Seymour LA, et al, 2014*;* 83*:*154-160).

In paediatrics, there is no significant difference was noted in the rate of infection between males and females, comparing to 1:1, 2 to 1, 7 in adults (Cines DB, et al, 2005; 106 :2244–2251).

Recently, autoimmune diseases were reported to be the most common cause of acute ITP in paediatric patients. Autoantibodies on platelet surface are known to be generated by viral antigens (Kuhne T, 2017; 37: 36-44) (Nugent DJ. 2002; 16: 27-29). Viruses, including Cytomegalovirus, Hepatitis C virus, Epstein-Barr virus, varicella virus, herpes virus, Human immunodeficiency virus, and Influenza virus, are associated with the development of ITP (Nagamine T, et al, 1996; 24: 135-140) (Yan M, et al, 2020; 13: 781-786)

(Morse EE, et al, 1966; 117:573-579) (Hsiao CC. 2000; 36:445-448) (Murray JC, et al, 1994;16:314-319).

Furthermore, there have been cases demonstrating a correlation between coronavirus and Zika virus infections and ITP (Magdi M, et al, 2019; 6:001155) (Zea-vera AF, et al, 2017; 26: 890-892).

This study aimed at investigating the platelets count of paediatric patients from two different hospitals and found a significant correlation between temporary low platelets counts and the transient immune disparity state that follows several viral diseases (P=0.03). Also, ITP showed the highest prevalence among patient children who aged between 1-5 years (P=0.02) which confirmed results of previous study that investigated the relation between different viral infections and ITP incidence in larger paediatric cohort (Jae Hee Lim, et al, 2021; 10: 1356).

6. Conclusion:

Immune thrombocytopenic purpura (ITP) can be easily diagnosed by detecting thrombocytopenia on a complete blood count with totally health bone marrow. Our study has found that most temporary thrombocytopenic cases in children developed after different kinds of viral infections. Further studies to determine which viral diseases have impact on the platelets count

are needed. The developing of serological tests for the detection of anti-platelets antibodies is also recommended.

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