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Review Article

Immune Thrombocytopenic Purpura in Review

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Abstract

Background: Immune thrombocytopenic purpura (ITP) characterized by high risk of bleeding, this bleeding is due to 2 main factors the first is the damage of the platelets which is mediated by antibodies and also disordered platelet synthesis, all the previous characteristics identify Immune thrombocytopenic purpura (ITP) as autoimmune disease.

Aim: In this review, we will look into the prevalence, pathophysiology, diagnosis and management of immune thrombocytopenic purpura.

Conclusion: ITP is a serious disease that cause sever bleeding that can be life threatening in some cases, the causes of this disease are idiopathic mostly but it is classifies as autoimmune disease, the diagnosis of ITP is mainly by excluding other causes that can give the same symptoms. Treatment is classified into three steps if one fails, we move to the next one starting from corticosteroids, then splenectomy and finally the new group of medications whose mechanism, and data are not sufficient so more studies should be conducted.

Keywords: *Immune Thrombocytopenic Purpura; Management of Immune Thrombocytopenic Purpura; Immune Thrombocytopenic Purpura Diagnosis; ITP Prevalence*

Introduction

Immune thrombocytopenic purpura (ITP) characterized by high risk of bleeding, this bleeding is due to 2 main factors the first is the damage of the platelets which is mediated by antibodies and also disordered platelet synthesis, all the previous characteristics identify Immune thrombocytopenic purpura (ITP) as autoimmune disease [1]. The general symptoms that the patients shows are mainly the usual symptoms of thrombocytopenia, such as purpura, petechiae, mucosal bleeding such as epistaxis, if the case became sever the patient could have fatal intracranial hemorrhage [2].

The causes of ITP are unknown in most cases, idiopathic in about 80% of cases, but mostly considered as autoimmune disease [3], the rest 20% of the patients have the disease as secondary to other diseases [2] infections are the most diseases that followed by ITP, studies show that children contribute to about 50% of the cases detected per year [3,4], ITP has also been linked to many other diseases such

as hepatitis C, Helicobacter pylori, varicella-zoster virus and human immunodeficiency virus HIV, also to less extent chronic lymphocytic leukemia (CLL) with an incidence of 1 - 5% [3].

The diagnosis of ITP is based mainly on the exclusion criteria based on many factors such as the physical examination, the family history of the patient, complete blood count (CBC), and smearing [5]. The adult disease differs in the clinical presentation from the childhood disease, childhood ITP is generally acute and self-limited while the adult ones is persistent with recurrent relapses, as it is very serious, it usually requires medical treatment. The symptoms and the clinical presentation of the disease differs between patients; about 21% of the patients show no symptoms and usually diagnosed by accident after having a blood test, but most cases complain mucocutaneous bleeding and bleeding from many sites in the body, the least percentage come with life-threatening hemorrhage, mostly intracranial hemorrhage [6]. There is a relation between the count of the platelets and the symptoms shown by the patients as Normal platelet counts varies from 150×10^9/L to 450×10^9/L, while signs of bleeding reveal when the level drop to less than 50×10^9/L [1].

The main goal of the treatment is to restore the number of platelets and keep it hemostatic, mostly 20 - 30 x 10^9L this is in case where the disease is symptomatic, American Society of Hematology (ASH) had agreed a guidelines at 1996 for treating ITP, the treatment should be started once the diagnosed patients show a platelets count less than 30 x 10^9L, but the 2011 guidelines suggest that the treatment decision should be taken based on many factors such as the severity of the disease, the probability of bleeding and the patient preferences [7]. The children mostly resolve by themselves, but adult's treatment is based on the cause of the disease so the most treatment guidelines are suitable for primary ITP patients [8], while secondary ITP treatment is based on the cause itself, but in severe cases of secondary ITP, some of the primary ITP guidelines are used to ensure the stability of the patient, this is concurrently with the treatment [9].

In this review, we will look into the prevalence, pathophysiology, diagnosis and management of immune thrombocytopenic purpura.

Participants and Methods

Study design: Review article.

Study duration: Data were collected between 1 June and 30 October 2020.

Data collection: Medline and PubMed public database searches have been carried out for papers written all over the world on immune thrombocytopenic purpura. The keyword search headings included "immune thrombocytopenic purpura, management of immune thrombocytopenic purpura, immune thrombocytopenic purpura diagnosis, ITP prevalence" and a combination of these were used. For additional supporting data, the sources list of each research was searched.

Criteria of inclusion: The papers have been chosen on the basis of the project importance, including one of the following topics: immune thrombocytopenic purpura.

Criteria for exclusion: All other publications that did not have their main purpose in any of these areas or multiple studies and reviews were excluded.

Statistical analysis

No predictive analytics technology has been used. In order to evaluate the initial results and the methods of conducting the surgical procedure, the group members reviewed the data. The validity and minimization of error were double revised for each member's results.

Prevalence

Although the knowledge about the incidence of ITP is essential to study both its public health and medical impact, the studies about this are still very few [10] and most of the data published are taken from other papers or secondary resources [11-13] this difficulty of

studying ITP is mainly because of the difference in mechanisms of pathogenesis [14]. Also, because there are no clear laboratory parameters for its diagnosis [15]. That's why the diagnosis of ITP is based on (the exclusion criteria) where the other causes are excluded then we suggest ITP [15,16]. Focusing on the incidence of this disease is an important step as the research is focusing toward finding treatment for ITP [15,16].

Between 1959 and 2003, eight studies were conducted about acute ITP in children [17]. These studies used different methodologies that can be classifies into 3 main categories (1) prospective cohort [18-20], (2) retrospective chart review [17,18] and (3) active surveillance [21,22]. The least age shown in these studies was between the age of birth and one year, while the highest age was between 14 to 18 years old. Comparison of the results from the different studies was hard cause different criteria to identify patients, some of them diagnosed ITP based on the number of platelets only, while other included the presence of bleeding as an indication of the disease.

The presence of chronic ITP in children was mentioned in only one study in the Northern Health Region of the UK [23]. The chronic ITP was defined as presence of platelets count less than 150,000/lL for more than six months. This study was conducted between June 1984 and May 1994, the number of children who fit the inclusion criteria were Twenty-six, to study the percentage of the cases comparing to the total population which was 564,000 and 586,000 children less than 15 years old, the percentage was 0.46 per 105 children/year.

The existence of ITP in adults was mentioned in three studies; also each study used different designs, one used retrospective chart review [24] and the other used prospective registration [25] while the third used retrospective secondary analysis [26]. The definition of adult was different between the studies as two of the three studies identifies adult as those who aged more than 15 years old, while one study defined it as those aged more than 17 years old. The first study was conducted in Denmark, it required age more than 15 and having platelets count less than 100,000/lL in the absence of other cause. 221 patients fit the inclusion criteria with an incidence of 2.6 per 105 adults/year [25]. The second study required having platelets count less than 50,000/lL, accompanied with confirmation using bone marrow biopsy, 245 adults were found to fit the inclusion criteria with an incidence of 1.6 per 105 adults/year [26]. The third study the patient should be part of the GPRD and has one of the following Oxford Medical codes D313.12 (idiopathic thrombocytopenic purpura), D313012 (ITP-idiopathic thrombocytopenic purpura), D313000 (idiopathic thrombocytopenic purpura) or 2871C (thrombocytopenia idiopathic), 840 adults fit these criteria with an incidence of 3.9 per 105 adult/person-years [26].

Pathophysiology

The pathogenesis is not very clear, but it is thought to be an autoimmune disease, that occurs due to the production of immunoglobulin G IgG autoantibodies, which target the destruction of the platelet membrane glycoproteins IIb-IIIa [27], so the platelets become attacked by phagocytosis by the liver cells represented as Kupffer cells and the kidney cells represented as macrophages. this theory is highly suggested because it was found that autoantibodies was found in 40 - 60% of the patients [28]. Also what makes this theory more real is the infection of normal people after receiving plasma from with immune thrombocytopenic purpura, that was rich in IgG [29] other mechanisms can also cause ITP such as deficiency in the production of thrombopoietin; this hormone stimulates the production of the platelets so any deficiency will cause defect in the production of the platelets, infections such as exposure to viruses, helicobacter pylori infection especially for children triggers ITP, finally the pregnancy is supposed to have a role in causing ITP [30,31].

Diagnosis

Clinical signs: The first step toward diagnosis is the clinical presentation of the patient, also the clinical signs could help determine the severity of the disease, it could be done by examining the mucous membrane and the skin of the patient and finding out if bleeding could happen when minimal pressure or trauma is applied. The main special difference about bleeding because of ITP and other forms of bleeding is that the Mucocutaneous bleeding in ITP happens due to primary hemostasis defect, while secondary hemostasis defect that could be accompanied with much deeper bleeding of the organs is common in coagulation disorders. The common clinical picture is

manifested with purpura, petechiae and ecchymosis that happen mostly in the upper and lower extremities. The mucosal membrane of some tissues is also suspected to Petechiae, such as nasal septum, hard Palate, or gum that can lead to gum and nose bleeding. Females may also complain Menorrhagia. When the platelets count become less than < 10,000 u/L, spontaneous hematomas that might spread through the whole body could occur [32]. Some severe symptoms could happen but in rare cases such as intracerebral hemorrhage, and overt gastrointestinal bleeding.

Differential diagnosis: It help in determining the different causes of the disease and also knowing the classification of the disease we have in this case as it could be one of the following hemolytic uremic syndromes, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura. Paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, lymphoproliferative disorders, or might be an induced drug (secondary to other diseases or medications) infection (HIV, Hepatitis C) and drug-induced thrombocytopenia (alcohol, heparin, sulfonamides).

Investigations: The normal hemoglobin and leucocytes counts with isolated thrombocytopenia, is very evident for ITP, unless hemorrhage is present. since the diagnosis of ITP is based on the exclusion criteria, ruling out other suspected diseases that can cause isolated thrombocytopenia is a must.to achieve this many diagnosis should be made such as peripheral blood smear, HIV and Hepatitis C testing and coagulation studies [33]. Enlarged platelets could be seen using peripheral blood smear. If the diagnosis is uncertain, the patient is not responding to the treatment or the smear of the blood reveals the presence of abnormalities other than thrombocytopenia, then Bone marrow aspiration could be made [33].

Measuring platelets-associated antibodies: The direct test to measure the platelets bound to antibodies [34] has a sensitivity that estimated to ranges between 49% and 66%, while the specificity varies from 78 to 92 percent and the estimated positive predictive value of 80 to 83 percent [35,36]. While detection of the antibodies that remain unbound to the plasma is not important and not useful, and also a negative test cannot be used to ignore the diagnosis [35,37]. 55 to 67 percent of laboratory agrees that detection of antibody bound to plasma proteins is important, while the agreement about the importance of plasma antibody is much lower than this [38]. These different tests help in differentiating between primary and secondary immune thrombocytopenic purpura, and also differing children who have a self-limited disease from children who will develop chronic condition [39].

Management

First-line treatments

Corticosteroids such as prednisone and Dexamethasone are considered the first line treatment for adults, they act by decreasing the destruction of the platelets mediated by immunity, this mechanism is mainly due to decreasing the activation of x dendritic cells and B-cells [40] high percentage of patients that might reach 80% show good respond to the steroids, but most of them relapse when steroids are stopped, Prednisone has been considered the master of all the steroids, with a dose of mg/kg/d for 2 - 4 weeks, but recent studies proved that high doses of dexamethasone can be more effective than Prednisone. A study conducted in Hong Kong, where 125 patients were treated with short course of dexamethasone, the number of platelets changed from less than 20 x 10^9/L to more than 50 × 10^9/L in 50% of the patients, and the results kept being the same for six months [41].

A study of 100 patients showed that the rate of response to high doses of dexamethasone is high 42.7%, compared to prednisone that was only [42]. Also, another study of 26 patients showed similar results where both of them mastered the initial results with 100% in percentage. However, long-term remission with pulsed dexamethasone was slightly more common at 77 percent vs. 22 percent with daily prednisone [43].

Corticosteroids are safe with pregnancy [7], corticosteroids and mostly high doses of dexamethasone are very effective in treating ITP as initial treatment. The side effects of corticosteroids are mostly weight gain, hypertension, and diabetes that can cause problems with certain patients, but generally corticosteroids are safe group and considered the first line for treating ITP [44].

If corticosteroids are contraindicated or the patient is resistant to this treatment, Rh_o(D) immune globulin (anti-RhD) or intravenous immunoglobulin (IVIG) could be used as they improve the efficacy the treatment [45]. If the platelets count should be raised quickly in case of severe bleeding IVIG can be used. The usual dose is 1 g/kg/day infusion for 1 - 2 days; this dosage can be changed based on the preference of the physician [46]. Review of 28 papers indicated that 83% of the cases showed a peak platelet count > 50,000/mm^3, while 64% of cases obtained a peak platelet count > 100,000/mm^3 after treatment with IVIG [47] another study of 19 patients diagnosed with chronic ITP, indicated that when treated using IVIG, the response rate increased to 75%, also the bleeding stop if the treatment is applied within 12 hours of the bleeding, the last thing is that in 53% of patients, the number of platelets increased in the first hour [48]. Although this treatment is very effective, its usage is not very common due to high cost and serious side effects such as pulmonary and renal insufficiency and also anaphylaxis [49]. If the patient is RhD positive, Anti-RhD in combination with corticosteroids can be used as treatment, the efficacy reached 50 - 70% in one case, while in other studies it was 37%, but the side effects such as, headache nausea, fever, and severe hemolysis are also detected so this treatment should be administrated with caution [44,46].

Second-line treatments

If the primary therapy failed, and complete remission that happens in 70 - 90% of the cases was not achieved, we move to the second line treatment which is removal of the spleen, splenectomy, cause this could help decrease the retention of the platelets by the spleen [50]. ASH 2011 guidelines still consider splenectomy as the second choice if treatment with corticosteroids, IVIG, and anti-RhD failed [45]. Theoretically this strategy can improve and save the platelets as they are destroyed by the spleen. 65 - 70% response was indicated in some studies, mainly this response is defined as cessation of significant bleeding, with long term response up to 60 - 70% [51,52]. A study of 175 patient indicated that 88% of the patients reported good response after the treatment while 20% relapsed. This study showed that young patients and those who use corticosteroids showed better response after splenectomy [53]. Open or laparoscopically splenectomy may be performed by any of them. There are comparable response rates between the two. Laparoscopic surgery is longer concerning operational time, however, tends to have shorter hospital stays, less postoperative discomfort, and a shorter postoperative recovery, so it is normally suggested [54].

Chronic and persistent ITP can also be treated using modern option such as The monoclonal antibody against the CD20 antigen (anti-CD20), rituximab with a standard dose 375 mg/m^2/week intravenously (IV) for four weeks [9] many studies were conducted to compare the efficacy of rituximab to splenectomy, one of them conducted in 105 patients showed that splenectomy was more effective compared to rituximab, in number the efficacy was 82.8% against 39.5% [55]. Another study showed that there was no difference between the two treatments, this study was conducted for a 143 patients [56].

Third-line treatments

Chronic refractory ITP is the term used to describe the condition when the initial therapy and splenectomy fails in the treatment. Treatment decision is taken only if the patient has the risk of severe hemorrhage; sometimes the treatment includes using prednisone again, although it is not preferable due to the severe side effects [4]. Many new treatments such as azathioprine, cyclophosphamide, cyclosporin A, danazol, dapsone, mycophenolate mofetil, vinblastine, vincristine and the thrombopoietin receptor agonist (TPO-RA) drugs eltrombopag and romiplostim are introduced into the market as treatment for Chronic refractory ITP [45] side effects of these medications are tolerable, but this is not very significant as most of the studies are conducted in small groups so more studies should be made.

Azathioprine

It was confirmed that azathioprine dosed at 150 mg/day was successful in chronic refractory ITP. A retrospective analysis covering a six-month cycle reported a response rate of 71.4 percent, with 38 percent of patients responding completely. There was a 64 percent response in a prospective study of 53 patients, with 40 percent sustaining a response after one year. A study in France recorded a 40 percent response rate, 29 percent of those after discontinuing azathioprine with a persistent response. Another 96-patient retrospective analysis found that 54 percent of patients. While only 2 percent had a sustained response, patients responded to azathioprine. There have been reports of leukopenia and transaminase rises, as well as alopecia, gastrointestinal symptoms and an increased risk of malignancy, particularly lymphoma. However, for many of these studies, the sample sizes were limited, so more studies are required to solidify the evidence of azathioprine's efficacy and safety [57-59].

Conclusion

ITP is a serious disease that cause sever bleeding that can be life threatening in some cases, the causes of this disease are idiopathic mostly but it is classifies as autoimmune disease, the diagnosis of ITP is mainly by excluding other causes that can give the same symptoms. Treatment is classified into three steps if one fails, we move to the next one starting from corticosteroids, then splenectomy and finally the new group of medications whose mechanism, and data are not sufficient so more studies should be conducted.

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