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IMMUNE THROMBOCYTOPENIA IN CHILDREN

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Abstract: *Immune thrombocytopenia is a hematological disorder defined by an isolated decrease in platelet numbers. We present a retrospective-descriptive study that enrolls twenty-five children (aged 0-18 years old) admitted to Brasov Children's Hospital from the 1st of January 2020 until the 1st of September 2023 with the diagnosis of idiopathic thrombocytopenic purpura (ITP).*

We could find proof of recent viral infection in seven patients out of twenty-five; three of them also had immunological findings- positive antinuclear, positive direct Coombs test, or antiplatelet antibodies. The medical literature mentions glucocorticoids and IVIG therapy as the first line of treatment for immune thrombocytopenic purpura, while new pharmaceutical agents are still under review.

Key words: *Idiopathic thrombocytopenic purpura, COVID-19, SARS-CoV-2, immune thrombocytopenia*

1. Introduction

Immune thrombocytopenia, which was known before as idiopathic thrombocytopenic purpura, is defined as isolated thrombocytopenia caused by an association of platelet destruction with a lower platelet production rate [1], in the case of primary ITP.

The secondary ITP hypothesis states that there is a high chance of association between a viral infection and the debut of a thrombocytopenic purpura episode [2].

Clinically, patients with ITP may present with acute severe or insidious hemorrhages, with minimal symptoms or even asymptomatic [3].

Immune thrombocytopenia manifests itself in different syndromes, defined by temporal criteria: the acute form (less than 3 months from diagnosis), persistent ITP (3 to 12 months from diagnosis), and the chronic form that persists for more than 12 months [4].

Clinically, immune thrombocytopenia may manifest as dry purpura-isolated cutaneous bleeding, or as wet purpura-mucous bleeding located on oral, nasal, and gastro-intestinal mucosa [5].

The diagnosis is supported by the isolated thrombocytopenia observed on the blood count, and the peripheral blood smear reveals normal leukocyte, platelet, and erythrocyte morphology [6].

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The diagnosis is one of exclusion. There are no clinical elements or laboratory tests that can confirm with certainty the installation of an idiopathic thrombocytopenic purpura [7]. The differential diagnosis can be made with leukemia, myelodysplastic syndrome, aplastic anemia, or pseudo-thrombocytopenia by platelet agglutination secondary to the collection method [8].

2. Material and Methods

Patients enrolled in this retrospective-descriptive study were admitted to Brasov Children's Hospital from the 1st of January 2020 until the 1st of September 2023 for isolated thrombocytopenia associated with purpura, petechiae, or bleeding.

The inclusion criteria for this study were as follows:

- thrombocytopenia (<100.000 platelets/mm3)
- no hematological disorders that stem from medullar suppression (leukemia, medullar aplasia, lymphoma)
- first episode between 1st of January 2020 until 1st of September 2023 (pandemic and post-pandemic eras-no other hospital admissions or thrombocytopenic episodes before the mentioned period).

The search engines we used to complete the literature review (table 1) were PubMed and Google Scholar and the keywords used were ''Idiopathic thrombocytopenic purpura'', ''COVID-19'', ''SARS-CoV-2'', ''immune hrombocytopenia.''

Literature review of treatment guidelines for immune thrombocytopenia Table 1

YEAR	FIRST LINE OF TREATMENT	SECOND LINE OF TREATMENT	THIRD LINE
2021 [11]	Observation, cortisone	Rituximab, splenectomy, thrombopoietin receptor agonists	
2020 [14]	Cortisone, IVIG	Rituximab, splenectomy, Immunosuppressive therapy, oral tyrosine kinase inhibitor (fostamatinib)	Combination therapy
2021[15]	Cortisone, IVIG, anti-D	Rituximab, splenectomy, thrombopoietin receptor agonists	oral tyrosine kinase inhibitor (TKI), immunosuppressive therapy
2019[16]	Cortisone, IVIG	Rituximab, splenectomy, thrombopoietin receptor agonists	
2016[17]	Cortisone, IVIG, anti-D	Splenectomy Rituximab	Thrombopoietin receptor agonists
2017[18]	Cortisone, IVIG, anti-D	Splenectomy Rituximab	Thrombopoietin receptor agonists

3. Results and Discussion

A total of twenty-five patients were included in our study, with ages ranging from 9 months old to 17 years old.

Two patients were under 1 year old, twelve patients in the 1-5 years old age range, four patients in the 6-12 years old range, and seven teenagers included (>12 years old). As to gender distribution, there were eight girls and seventeen boys.

The temporal distribution of the cases was as follows: 1 case in 2020, 6 cases in 2021, 8 cases in 2022, and 10 cases in 2023.

Sixteen children had under 10.000 thrombocytes/mm3 on the complete blood count at admission, three of them had between 10.000 and 19.000 thrombocytes/mm3, and the rest of them-six, had over 20.000 thrombocytes/mm3. It is important to mention that none of the patients exceeded 30.000 thrombocytes/mm3 at admission.

As to clinical presentation, all sixteen patients with <10.000 thrombocytes/mm3 manifested wet purpura (epistaxis, oral hemorrhage, melena), as well as one patient with a platelet count between 10.000 to 20.000 thrombocytes/mm3. The rest of the eight patients presented only with dry purpura-petechiae or bruising.

As to the results we obtained after the serological screening of our patients, it is important to mention one patient had positive IgM Epstein Barr virus antibodies, two of them had high titers of IgM anti-Parvovirus B-19, one patient had positive IgM SARS-CoV-2 virus antibodies, and none of them tested positive for IgM anti-Toxoplasma gondii, hepatitis B or C, HIV (figure 1).

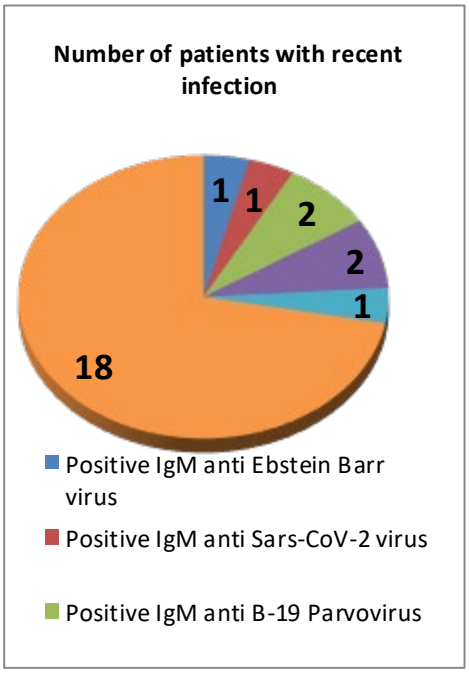

Fig.1. *Recent infection record of studied patients*

Returning to the Covid-19 infection discussion, twelve out of twenty-five patients were evaluated for the IgM or IgG anti-SARS-CoV-2 antibodies and nine of them had positive IgG antibodies, along with the one patient with positive IgM antibodies that we mentioned earlier. We could not prove with certainty that the Covid-19 infection was the sole cause of the thrombocytopenic episode, as none of the patients had clear MIS-C criteria and these patients had positive IgG antibodies to Epstein Barr virus or Cytomegalovirus, therefore making it impossible to track the clear causal agent.

A systematic review from 2020 that comprised twenty-three articles states that the Sars-CoV-2 virus may induce an episode of thrombocytopenic purpura [9], but we could not highlight a direct link between the Covid-19 infection and the hematological disorder.

In addition to these serological discoveries, two patients were recovering after a chickenpox infection and one of them had a recent type A influenza infection (the debut of the infection was <14 days from admission).

As to the immunological findings (figure 2), one patient assessed positive for antinuclear antibodies, all of them had negative anti-DNA antibodies titers, and only one patient had positive anti-platelet antibodies. Another patient had one positive direct Coombs test, with a history of hemolytic anemia and clinical and laboratory criteria for Evans syndrome, secondary to common variable immune deficiency.

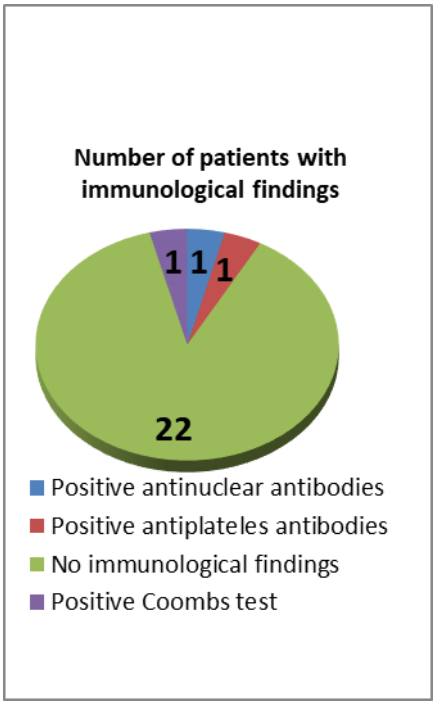

Fig.2. *Immunological findings in studied patients*

The treatment during hospitalization consisted of corticosteroid therapy for all hospitalized patients, along with IVIG (23 out of twenty-five patients received IVIG). As to the doses used for IVIG therapy, sixteen out of twenty-five received a dose of 800mg/kg, five of them received 1 g/kg, and two of them received less than 800 mg/kg.

After hospitalization, all patients received corticosteroid therapy, with a careful decrease of dosage while monitoring the complete blood count and any signs of active bleeding/bruising.

Eighteen out of twenty-five patients experienced only one episode of thrombocytopenic purpura, while one patient experienced six episodes and is still under surveillance, as corticosteroids and IVIG therapy, showed modest results and a second line of therapy was administered- cyclosporine (an immunosuppressant medication).

The patient with common variable immune deficiency who presented with severe thrombocytopenia did not respond well to IVIG and cortisone, and the platelet count did not go over 50 000 /mm3 in over three weeks of the first line of treatment. Therefore, 800 mg/m2/day of mycophenolate mofetil was given to the patient and the number of platelets increased after a week of administration to >100.000 /mm3, returning to normal after approximately 14 days.

Most of the medical literature we consulted mentions corticosteroids and IVIG therapy as the first line of treatment, as well as adding the notion of observation. Observation means that there is the possibility of keeping the patient under surveillance, without administering any pharmaceutical therapy, if the before mentioned patient had more than 30.000 platelets/mm3 on the complete blood count and there are no signs of life-threatening bleeding-an asymptomatic patient or with minimal bleeding [10].

The ITP guidelines of the American Society of Hematology (ASH) from 2019 [11] recommend as the first line of treatment corticosteroids, IVIG, anti-D

(with the important mention that in case of minor bleeding, corticosteroids are preferred), while thrombopoietin receptor agonists (romiplostim, eltrombopag) represent the main medication as second line of treatment.

Interestingly, they also recommend delaying splenectomy for at least 12 months since diagnosis (in a chronic form of immune thrombocytopenia).

Thrombopoietin receptor agonists as the second line of treatment is a long-studied approach. A systematic review from 2021 [12] that gathered nineteen cohort studies and sixteen randomized controlled trials highlighted the fact that adverse effects seldom appeared, and the overall mortality was lower compared to other second or third line of treatment medications.

The International 2019 consensus on the management of primary immune thrombocytopenia [13] discusses thrombopoietin receptor agonists, especially romiplostim and eltrombopag, and their efficacy as second-line treatment in ITP. They stimulate the production of platelets, increasing the platelet count. Interestingly, the therapeutic effect lasts only during administration for approximately two-thirds of patients, with the platelet count decreasing after cessation of therapy. For long-term administration, eltrombopag has been well-studied and is well-tolerated for chronic use.

As adverse effects, bone marrow fibrosis has been reported, but the cessation of therapy was necessary in a few cases. There are some reports of mild elevation of transaminase levels.

The efficacy is proven by high response rates (studies show response rates between 70 and 96%). With such high response rates and few mild adverse effects, thrombopoietin receptor agonists seem to be a facile decision when corticosteroids and/or IVIG fail.

One article from 2020 [14] mentions combination therapy as the third line of therapy, which consists in associating different pharmaceutical agents that are traditionally used as individual medications in idiopathic thrombocytopenic purpura or even new combinations of drugs (cyclosporine, rituximab, mycophenolate mofetil, cyclophosphamide, vincristine, recombinant human TPO, in different associations and different doses).

Conclusions

1. Out of twenty-five patients, only seven had recent proof of viral infections, it being difficult to prove with no doubt that there is a direct causal link between the infection and the thrombocytopenic episode.
2. Only two patients needed association with a second line of therapy (the addition of cyclosporine A, and mycophenolate mofetil), as there were modest results after corticosteroids and IVIG therapy.
3. Corticosteroids and intravenous immunoglobulin remain the first line of therapy in most guidelines, even as new pharmaceutical agents are discovered trials are needed to remove these two options from the most used drugs in immune thrombocytopenia treatment.

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