INVITED COMMENTARY

Immune Thrombocytopenia- Will it Stay or go Away?

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Immune thrombocytopenia (ITP) is one of the most common acquired bleeding disorders affecting children resulting from platelet destruction and its impaired production. It can be a primary disorder or secondary to some underlying conditions. It is a heterogenous condition with variable clinical manifestations affecting a wide range of age groups right from children to adults and remains a diagnosis of exclusion. Bleeding manifestations are unpredictable; patients with severe thrombocytopenia may have only minor skin bleeds whereas major bleeds like gastrointestinal, hematuria, menorrhagia and rarely intracranial bleeds are also seen in patients of ITP [1].

Though its pathogenesis is incompletely understood, it is mostly attributed to autoreactive antibodies causing excessive immune-mediated clearance of platelets and due to impaired megakaryopoiesis. In recent years, the important role of underlying immune dysregulation has been elucidated. Data from numerous studies point towards immunological imbalance involving all compo-nents of immunity resulting in decreased survival of plate-lets and inhibition of platelet production. Macrophages of the reticuloendothelial system phagocytose the antibody-bound platelets and present it to the T lymphocytes leading to enhancement of the immune response. The FcyR receptors on the macrophages may also be imbalanced towards increased clearance of platelets. In addition, antibody bound platelets may fix complement leading to immune lysis of platelets. The high Th1 to Th2 ratio is responsible for low platelet count in ITP. They also have a lower T-regulatory cell count leading to decreased suppression of the immune response hence associated with more severe disease. More recently, Th17 and Th22 subsets of T cells are also found to be increased which are proinflammatory and found to be upregulated in many autoimmune disorders including ITP. Genetic studies have identified unique differentially expressed genes which are similar to other autoimmune diseases [2].

Childhood ITP and adult ITP are two distinct manifestations considering that childhood ITP is largely benign and has a high rate of spontaneous remission. Approximately 60 to 70% of children will go into spontaneous remission within 12 months of onset and 30 to 40% will enter the chronic ITP group [3]. The patients who fail to respond to all conventional modalities of treatment fall into the refractory group which is estimated to be less than 5%. At this juncture, the diagnosis of ITP must be revisited, and alternative causes of thrombo-cytopenia particularly autoimmune conditions like systemic lupus erythematosus, autoimmune hepatitis, thyroiditis, etc should be ruled out. Genetic disorders of immune regulation have also been identified; common ones being CTLA4, STAT 3, LRBA, FAS and CASP10 genetic defects. ITP can be the presenting feature or a late manifestation in autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency (CVID), IgG/IgA deficiency, CTLA haploinsufficiency and IPEX [4].

It is well known that ITP causes significant decline in health-related quality of life (HRQoL) and more so in patients with chronic and refractory ITP. They also experience fatigue which further affects their HRQoL. Patients and their families need to continuously adapt their daily activities to the bleeding risks. Patients who progress to chronic ITP have constant uncertainty about the response and side effects of second and third line of treatments [5].

In this scenario, if we had predictors about the time of resolution of ITP at diagnosis, it would definitely help in decreasing the fear and anxiety of the patients and their families. Several studies have identified predictors of chronic ITP. A prospective study from the Nordic countries identified six predictors of early resolution of ITP namely, abrupt onset of disease (less than 2 weeks), age less than 10 years, history of preceding infection, platelet count less than 5000/mm^3, presence of wet purpura and male gender. These clinical features were given a score and higher scores predicted low-risk patients [6]. Ahmed et al published a retrospective study with 188 patients of ITP and found that higher age, lower total leukocyte counts (TLC) and absolute lymphocyte count

(ALC) were associated with a significant risk of developing a persistent ITP beyond 6 months [7]. Another retrospective study involving 601 patients of ITP found that higher age, high platelet counts and a lower ALC at presentation predicted a significant risk of developing chronic ITP [8].

In this current issue of *Indian Pediatrics*, Singaravadivelu et al have published an ambispective study to identify predictors of persistent and chronic ITP in 64 children; 37 children were recruited prospectively [9]. These children had normal clinical profile, blood counts and smear examination except for thrombocytopenia. Clinical and hematological parameters were studied at presentation and at 3 and 12 months for outcomes. The phase of the disease (newly diagnosed, persistent and chronic) and the criteria for outcomes were defined as per Guidelines by International Working Group Definition for ITP in Children and Adults, 2009 [10]. Authors found that ALC count at diagnosis was significantly higher in children who responded at 3 and 12 months. The study cohort had a higher incidence of wet bleeds including intracranial bleeds and a higher rate of chronicity in their cohort. Whether this is due to a referral bias to a large tertiary centre or probably a more aggressive nature of the disease in the ethnic population studied, will only be answered by larger multicentric and prospective studies.

Another interesting finding for clinicians is that 50% of the cohort were not offered any immunomodulatory treatment and the overall response at 3 and 12 months was greater in this group; this reflects the fact that less aggressive disease may not require treatment and is likely to go into spontaneous remission. This is one of the few studies in children with ITP from India for predictors of chronicity and a simple parameter like absolute lymphocyte count at diagnosis will surely be of great value to the clinician. We hope that this study encourages more researchers to study this common hematological condition with complex yet incompletely understood pathophysiology but with huge implications for the patients and their families.

Funding: *None*; Competing interests: *None stated.*

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