Childhood Immune Thrombocytopenia—Who Will Spontaneously Recover?

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Although the majority of children with immune thrombocytopenia (ITP) have a short duration of the disease, the very rare but significant complications of the disease often cause fear and anxiety among families of children with ITP. Added to the reduced quality of life (QoL) of those children are restrictions imposed on daily activities to avoid trauma. Treatment decisions in chronic ITP and especially regarding splenectomy are hampered by the inability to predict when recovery will take place. Identification of predictors of recovery would be beneficial for improving treatment decisions and QoL of both children and families. This literature review focuses on clinical parameters and emerging genetic biomarkers for prediction of duration of childhood ITP. Higher recovery rates were found among infants with newly diagnosed ITP. In contrast onset of the disease at adolescence was associated with worse recovery rates. Six clinical features were found to be associated with short duration of disease; the most prominent ones were abrupt onset of bleeding symptoms (<2 weeks) and age at onset ≤ 10 years. Two genetic biomarkers have been suggested as predictors of chronic disease: overexpression of vanin-1 (*VNN-1*), an oxidative stress sensor, and the Q63R missense variant of the gene encoding the cannabinoid receptor type 2. To be clinically useful each of those predictors requires further validation in larger studies. Genetic biomarkers will potentially offer direct and early prognosis estimation.
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Childhood immune thrombocytopenia (ITP) is usually a self-limited disorder lasting for a few weeks or months, but in approximately 25%–30% of the children, the condition becomes chronic.[1–4] In chronic ITP spontaneous recovery occurs within 5 years of diagnosis in about 50% of children[5] and in few children even many years later.[6] Confronted with a child with newly diagnosed ITP the physician cannot determine if the child has a self-limited disease or will have long-term chronic disorder. Similarly while treating a child with chronic ITP the physician does not know if and when will the child recover.

Although childhood ITP is considered to be a benign disease it may rarely result in significant morbidity and mortality.[7,8] Therefore, families of children with ITP often live with fear and anxiety. Furthermore, restrictions imposed on daily activities to avoid trauma contribute significantly to children's already a reduced quality of life (QoL). Negative impact of the disease on QoL of the child and his family has been documented.[9,10] Identification of predictors of early recovery would be beneficial for reducing stress and improving QoL for both children and families.

Management of children with chronic ITP remains controversial. Splenectomy induces complete and sustained remission in more than 75% of children with chronic ITP.[11] However, the high rate of spontaneous remissions, possible failure to achieve durable remission and the life-long risk of overwhelming septicemia following splenectomy suggest that this procedure should not be undertaken lightly. Additionally, new drug therapies have emerged, including rituximab[12] and most recently thrombopoiesis-stimulating agents that may influence therapeutic directions.[13] Defining predictors of recovery from chronic childhood ITP will eventually improve treatment decisions.

This literature review focuses on clinical parameters and on emerging genetic biomarkers for prediction of duration of childhood ITP.

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PREDICTORS OF DISEASE DURATION IN NEWLY DIAGNOSED ITP

Although traditionally chronic ITP was defined as lasting for more than 6 months, based on high rates of recovery of children with ITP occurring between 7–12 months from diagnosis[2,14] the International Working Group suggested that chronic ITP should be defined as thrombocytopenia (platelet count $<100 \times 10^9$/L) lasting longer than 12 months.[15] Nevertheless, all studies cited herein used the traditional more than 6 months definition of chronic ITP. Young age at diagnosis and initial therapy with intravenous immunoglobulin (IVIG) have been suggested to predict short duration of ITP. Predictive scores for early recovery have also been developed. Recently, two genetic biomarkers were identified to be associated with long duration of the disease in children.

AGE AT DIAGNOSIS

Short duration of the disease was reported in the majority (70%–75%) of children with ITP; however, infants and adolescent seem to have different chances of recovery. The Intercontinental Cooperative ITP Study Group registry I (ICIS I, 1997–2000) followed children with newly diagnosed ITP worldwide in order to study the natural history of ITP. Of 2,540 children, 203 were infants (7.6%). The recovery rate was 77%, which is significantly higher compared to 68.6% in older children ($P < .0001$).[7] Donato et al studied childhood ITP in Argentina and also suggested a high recovery rate of 89.8% among 275 infants with ITP.[14]

In contrast, onset of the disease in adolescence was found to be associated with recovery rates of only 32%–53%, which is a significantly worse prognosis compared to younger children.[7,14,16] Of 2,540 children in ICIS I, 311 were age 10–16 years and their recovery rate was only 53% compared to 72% observed in children between 1 and 10 years of age.[7] Donato et al found a 49% recovery rate among 210 children aged 9–18 years at diagnosis compared to 71.3% for children 1–8 years of age at diagnosis.[14] Lowe and Buchanan retrospectively reviewed children diagnosed with ITP between 10–18 years of age and found only a 32% recovery rate.[16]

TYPE OF INITIAL THERAPY

Does initial ITP therapy affect disease duration? This subject was studied in a retrospective manner using the ICIS I data.[17] Matched-pairs analysis of the ICIS I data identified 449 children not recovering after 6 months, who were then compared to matched children with adequate platelet counts. Children initially treated with IVIG were more likely to have a normal platelet count 6 months after diagnosis than children receiving no therapy or corticosteroids.[17] Our retrospective study of 472 children with newly diagnosed ITP from two pediatric hematology centers in Israel suggested no difference in prognosis between children who were initially treated with IVIG, corticosteroids, or observation only (unpublished data). The association between initial therapy and resolution of ITP in children should be further studied.

CLINICAL PREDICTION SCORE

A prospective study designed to identify predictors for short duration of disease in children with newly diagnosed childhood ITP was performed by the Nordic group.[18] Between the years 1998–2000, 409 newly diagnosed children with ITP were recruited from 98 pediatric centers in the Nordic countries. Six clinical features significantly associated with short duration of the disease (<3 months) were identified: abrupt onset of the disease (<2 weeks duration of bleeding symptoms), age at onset of ≤10 years, preceding infection, platelet count $<5 \times 10^9$/L at diagnosis, wet purpura, and male gender. A scoring system was designed whereby each parameter was awarded a numerical values based on the odds ratio for brief disease. Abrupt onset of the disease and age at onset ≤10 years had the highest odds ratio. A high Nordic score (10–14 points) predicted brief and uneventful course of the disease, while a low score (0–4 points) predicted prolonged course (see Table 1). Indeed, the majority of children with a high score (78%) had a brief course of the disease, while only 22% of the children with a low score had a short course of the disease. Danto et al applying the Nordic score to children older than 12 months at the time of diagnosis

Table 1. Nordic Prediction Score for Brief Course of ITP

Clinical Feature	Prediction Weight
Abrupt onset	5
Age at diagnosis <10 years	3
Postinfection	2
Platelet count $<5 \times 10^9$/L	2
Wet purpura	1
Male gender	1

Abrupt onset: symptoms for <14 days; postinfection: infection or vaccination <1 month prior to onset; wet purpura: purpura with oozing, mucosal bleeding; High score = 10–14; Intermediate score = 5–9; Low score = 0–4; Adapted from Edslev et al.[18]