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Management of chronic immune thrombocytopenia in children and adolescents: lessons from an Austrian national cross-sectional study of 81 patients

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ABSTRACT

Chronic immune thrombocytopenia (cITP) is often associated with an underlying predisposition towards autoimmunity, recognition of which is relevant to guide treatment. International recommendations on diagnostic steps and therapeutic measures of cITP in childhood exist. However, due to the low prevalence (1–2/100,000) and a variation of availability of immunological and hematological tests and treatments across pediatric units, we postulated that these guidelines are not uniformly adhered to and that immune dysregulation syndromes remained undiscovered. To delineate the current management of children and adolescents with cITP in Austria, we performed a nationwide cross-sectional study. Between 2011 and 2014, 81 children with cITP were seen at seven centers (median age 8.75 years; range 1–17; female:male ratio 47:34) at 641 visits during 180 patient years after diagnosis of cITP (>12 months ITP duration). Additional diagnoses were noted, most frequently immune or autoimmune disorders, hematologic diseases, or infections (in 37.3%, including Evans syndrome, autoimmune lymphoproliferative syndrome, systemic lupus erythematosus, and Fanconi anemia), or other symptoms like bi- or pancytopenia (n=9), lymphoproliferation or granulomatous inflammation (n = 3). Both decision to treat as well as choice of treatment varied: smaller centers tended to observe more frequently, larger centers applied a pattern of treatment modalities that appeared to depend less on bleeding tendency than on center policy. More than 50% of therapeutic interventions occurred in bleedings scores ≤ 2 (of 5), suggesting a strong psychosocial intention to treat. Platelet increment upon 479 therapeutic interventions of eight types was evaluated, with multiple treatment approaches being pursued sequentially in refractory patients. These data confirm the hypothesis of heterogeneous diagnostic and therapeutic management of cITP in Austrian children and corroborate the need for (1) a precise panel of parameters to exclude underlying disorders and (2) for biomarkers to predict treatment response.

1. Introduction

In contrast to usually parainfectious and self-limited *newly diagnosed* immune thrombocytopenia, *chronic* immune thrombocytopenia (cITP) poses diagnostic and therapeutic challenges and may be accompanied by reduced quality of life [1,2]. Few predictors of a prolonged clinical course and even fewer prognostic parameters for treatment response exist [3]. Therapeutic options

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include careful observation, pharmacologic immune-modulation, splenectomy, B-cell depletion, and novel drugs such as thrombopoietin receptor agonists and proteasome inhibitors, many of which are not yet licensed for use in children [4–13].

Autoimmune cytopenias occur as "primary" conditions, presumably isolated autoimmune diseases, and as "secondary" phenomena based on an underlying predisposition towards autoimmunity. While not all cytopenias in primary immunodeficiencies (PID) are of autoimmune origin, any chronic autoimmune cytopenia should raise suspicion of an underlying PID or autoimmunity syndrome like, for example, systemic lupus erythemtosus (SLE). This is especially true in case of early-onset autoimmunity or if cytopenia is associated with at least one additional manifestation of autoimmunity. Classical PIDs highly linked to cytopenia are autoimmune lymphoproliferative syndrome (ALPS), common variable immunodeficiency, and hemophagocytic lymphohistiocytosis [14]. Moreover, also rarer conditions such as combined immunodeficiency, CTLA-4 haploinsufficiency, activated PI3-kinase delta syndrome, immune dysregulation polyendocrinopathy X-linked syndrome, gain-of-function mutations in STAT-1 and -3, or LRBA deficiency may present first with autoimmune cytopenia [14–19].

International consensus reports help guiding the management of a rare disease like cITP [10,11]. Nevertheless, multiple factors can be identified that may hamper compliance with these recommendations: first, the majority of patients with newly diagnosed ITP will undergo spontaneous remission. Only few parameters (higher initial platelet counts, insidious onset, older age, female gender, presence of antinuclear antibodies, lack of a timely context to an infection or vaccination) are linked to an increased risk of a chronic course of childhood ITP [3]. Second, even if clinical bleeding signs are minimal (eg, score 1–2 by grading of hemorrhage 0–5) [20], there may be an intention to treat to allow participation in peer and family activities.

Furthermore, availability of immunological and hematological tests to exclude PID and access to alternative treatment options affect the depth of diagnosis and up-to-date management of cITP.

We performed a cross-sectional nationwide retrospective study to analyze the status quo of the management of cITP in Austrian children and adolescents to estimate the proportion of potentially undiagnosed PID or other chronic autoimmune or hematological conditions, to evaluate the experience with novel treatment modalities, and to establish a network of centers to improve future care.

2. Patients and methods

Between 2011 and 2014, data from Austrian pediatric units were retrieved by retrospective chart review in accordance with an institutional research ethics approval (N0. 25-563 ex 12/13, Medical University Graz). Laboratory data were available from 75 of the total cohort of 81 patients aged 1–17 years, and a detailed clinical status was documented from a cumulative number of 641 clinical visits (mean 9 per patient, range 2–21; Table 1). To obtain a quick overview of the most relevant data, we designed a 1-page "cITP patient-record form". Grading of hemorrhage was performed according to Buchanan and Adix [20] with score 1 = minor (≤ 100 petechiae and/or ≤ 5 small bruises [≤ 3 cm in diameter]), score 2 = mild (> 100 petechiae and/or > 5 bruises), score 3 = moderate (any mucosal bleeding not requiring immediate medical attention or intervention), score 4 = severe (mucosal or suspected internal bleeding that requires immediate action), score 5 = life-threatening or fatal bleeding. Response evaluation was done by detecting the platelet increment, classified as "*none*", when the maximum platelet count on days 1–28 after an intervention was < 20 g/L, "*moderate*" when > 20 but ≤ 50 g/L, "*good*" when > 50 but ≤ 150 g/L, and "*excellent*" when > 150 g/L.

3. Results

3.1. Patient characteristics and diagnostic tests

Eighty-one patients (47 females, 34 males; ratio 1.38:1) aged 1–17 years (median 8.75) were reported by seven pediatric centers in Austria, including all Medical Universities. By city and federal state, patients were distributed as follows: Vienna: 32, Graz/Styria: 26, Leoben/Styria: 8, Innsbruck/Tyrol: 6, city of Salzburg: 5, Linz/Upper Austria: 3, Klagenfurt/Carinthia: 1 (Table 1). At study entry, ITP duration was 3.25 years (range 1.5–7). The mean platelet count at initial presentation ("newly diagnosed" ITP) was 28 g/L (n = 75; median 12; range 1–117); the mean platelet count during the latest 6 months before data evaluation was 67 g/L (median 46; range 2–267). To analyze the prevalence of *secondary* cITP, we noted all relevant diagnostic tests performed at any time point during diagnostic work-up for the differential diagnosis of cITP (Table 1). Bone marrow evaluation was undertaken in 40 of 75 patients (53%), antinucleic or antiphospholipid antibodies (ANA and APLA) and immunoglobulin concentrations were analyzed in a vast majority (91% and 85%, respectively; Table 1). ANA and/or APLA were detected positive (titer $> 1{:}80$) in 20% of patients; immunoglobulin concentrations were pathologic in 24% (both 12% increased and 12% decreased). A more in-depth immunological analysis was done in a minority (antibodies against vaccine antigens in 18 patients [26%], autoantibodies against other tissues in 13 [19%], flow cytometric analyses of T-, B-, and NK-lymphocytes in 45 [60% of 75 patients; or 68% of 66 patients, where these techniques were available], and of class-switched $IgD^{-}CD27^{+}$ and non–class-switched $IgD^{+}CD27^{+}$ B memory cells and of T-cell receptor alpha/beta-positive $CD4^{-}CD8^{-}$ double-negative T cells in 29 patients [39% of 75 patients; or 44% of a subcohort of 66 patients where available]; Table 1).

3.2. Other diagnoses and symptoms

Figure 1A shows additional or other diagnoses in 75 patients treated as cITP in the upper three bars (n = 17 of 75; 37.3%; Evans syndrome: n = 5, autoimmune neutropenia: 2, autoimmune hemolytic anemia: 1, autoimmune thyroid disease: 4, ALPS: 1, mannan-binding lectin deficiency: 3, SL: 2, Fanconi anemia: 3, myelodysplastic syndrome/refractory cytopenia of childhood [MDS/RCC]: 2, acute or chronic active infection: cytomegalovirus: 2, Epstein-Barr virus: 1, hepatitis C virus: 1, influenza A: 1). Of note, 18 of these 28 diagnoses belong to the spectrum of autoimmune diseases or immunodeficiencies, and five to bone marrow failure syndromes. One of the three patients with Fanconi anemia had concomitant immune-mediated thrombocytopenia, as published [21]. Two other patients with the working diagnosis of cITP had in fact MDS/RCC. Thus, in four of 81 patients, the diagnosis was revised after a standardized bone marrow failure work-up including diepoxybutane testing. Nine patients had bi- or pancytopenia, two had lymphoproliferation and splenomegaly, one had a granulomatous inflammation of the lung (Fig. 1A, blue bars).

3.3. Reported treatment decisions and indications

To compare the practiced management of cITP, we analyzed the decision to carefully observe or treat a patient correlated to the hemorrhage grading [20]. The grading was taken from the patients charts directly or, if possible, recapitulated from clinical descriptions. Remarkably, 240 ($>50\%$) decisions to treat were made in