Refractory immune thrombocytopenic purpura in a child with vitamin D deficiency

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SUMMARY

Immune thrombocytopenic purpura is an isolated thrombocytopenia consisting of premature platelet destruction mediated by self-reacting antibodies and an impaired platelet production. In children, most of the cases resolve spontaneously within six months. Several studies have shown a high incidence of vitamin D deficiency in auto-immune disorders, including immune thrombocytopenic purpura. We report the clinical history of an eight-year-old boy who presented with refractory immune thrombocytopenic purpura and major vitamin D deficiency. Supplementation in vitamin D was followed by a rapid normalisation of thrombocytosis. After six months of evolution, the child developed a relapse of immune thrombocytopenic purpura concomitant with a decrease of his serum level of vitamin D. Treatment with vitamin D associated with dapsone resulted in a prolonged remission. After thirteen months, dapsone treatment was stopped and the platelet count remained normal. This article reviews the approach of refractory immune thrombocytopenic purpura in children and discusses the potential interest of vitamin D in this disease.

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterised by a low platelet count (below 100 x10^9/L) and the absence of obvious initiating and/or underlying cause of thrombocytopenia. It is caused by destruction of antibody-sensitised platelets in the reticuloendothelial system and impaired production of platelets in the bone marrow.[1] ITP is classified based on patient age (childhood versus adult), presence of favouring factor (primary versus secondary) and duration of illness (newly diagnosed from diagnosis till three months, persistent from three to twelve months, and chronic if lasting for more than twelve months).[2] In childhood ITP, acute thrombocytopenia is typically preceded by a banal infection or an immunisation with a live virus vaccine. In at least two thirds of cases, it resolves within six months.[3] Therefore, the treatment strategy in paediatrics aims to reduce the risk of bleeding in the expectation of spontaneous resolution.[3,4] When necessary, first-line treatments comprise intravenous immunoglobulin (IVIG), corticosteroids and intravenous anti-D IG that is not available anymore for this indication in Belgium.[3,5] Second and third-line therapies include immunosuppressive drugs (corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab, etc.), dapsone or, more recently, TPO receptor agonists.[3,6,7] Splenectomy remains an effective option in rare severe cases.[5]

Here, we report the clinical history of an eight-year-old boy with acute ITP refractory to therapy. An extensive work-up looking for an underlying disorder was performed. The only abnormality identified was a severe vitamin D deficiency. Interestingly, platelet count increased after supplementation of vitamin D combined with dapsone.

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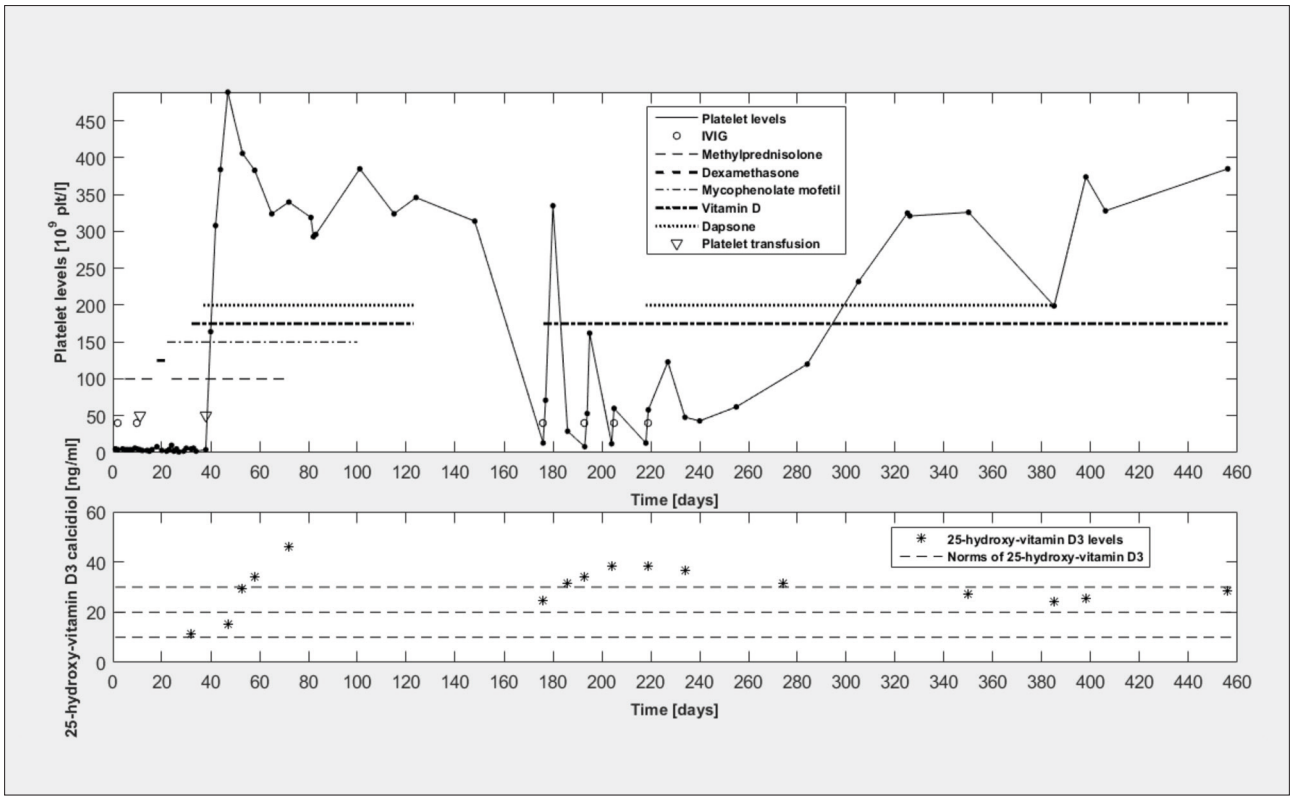

FIGURE 1. Treatment and evolution of platelet count and vitamin D serum level overtime.

CASE REPORT

An eight-year-old boy presented with bruising and diffuse petechial rash. He had no relevant medical history. His family came from Morocco and the parents were consanguineous at the second degree. One week prior to admission, he had an upper respiratory tract infection treated with paracetamol. The clinical examination confirmed the presence of petechiae with no mucosal bleeding or hepatosplenomegaly. The initial biology showed a severe thrombocytopenia ($5x10^9$/L) with normal haemoglobin and white blood cell levels. The coagulation screening test and the immune assessment (lymphocyte phenotyping and levels of IG A, M, and G) were normal. Serologic testing for EBV, CMV, HCV, HIV and antinuclear antibody (ANA) were negative but antiplatelet antibodies were detected.

The child was treated with IVIG (1 g/kg/day x 2). A bone marrow examination, performed on day 5, confirmed an increased number of megakaryocytes. Corticosteroids were administrated without significant effect (*Figure 1*): methylprednisolone (2 mg/kg/day x 2 followed by 4 mg/kg/day x 5), pulses of dexamethasone (40 mg/m²/day x 5). Mycophenolate mofetil (600 mg/m² 2 x a day from day 23) and dapsone (1 mg/kg/day from day 38) were added. The child received also platelet transfusions on day 15 and 39 for macroscopic haematuria.

In the meantime, multiple investigations were performed to identify favouring factor or underlying platelet disorder. Since the parents were consanguineous, a wide genetic screening was done and was normal. The karyotype and a chromosomal breakage analysis were normal. An indium-labelled platelet scintigraphy confirmed a decreased platelet survival with destruction almost exclusively in the spleen. An urea-breath test failed to detect *Helicobacter Pylori* infection. A nutritional assessment showed normal levels of ferritin, vitamin B12 and folic acid. Only the dosage of vitamin D revealed a severe deficiency with a serum level of 25-hydroxy-vitamin D3 calcidiol of 11.2 ng/ml (deficient <10, insufficient <20, optimal >30). Supplementation of vitamin D (25000 UI 2 x a week) was initiated on day 33.

Unexpectedly, platelet counts improved from day 40 (*Figure 1*). Thrombocytosis remained normal despite the progressive tapering of corticosteroids, mycophenolate mofetil, vitamin D and dapsone. However, on day 175, the child relapsed with a platelet count of $13x10^9$/L. Surprisingly, the vitamin D level was also decreased (24,7 ng/ml). A new course of IVIG (1 g/kg) was administrated and the oral vitamin D supplementation was resumed. Three additional courses of IVIG were perfused on day 193, 205 and 219. Dapsone therapy was recommenced on day 220 in combination with vitamin D supplementation (25000 UI/week). The platelet

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Refractory ITP requires extensive workup to identify favouring factor or underlying platelet disorder.**

2 **This observation and other publications suggest that vitamin D deficiency could play a role in ITP. We propose to investigate the vitamin D status and, if necessary, to supplement patients with chronic or refractory ITP.**

count normalised progressively. Dapsone was discontinued on day 385 and oral vitamin D supplements were continued to maintain vitamin D level above 30 ng/ml. Nineteen months after diagnosis, the child remains in remission.

DISCUSSION

This report illustrates a severe and refractory ITP in childhood. In these cases, a thorough approach is required to identify and potentially treat factors predisposing to immune thrombocytopenia or underlying platelet disorders.[3,4,8] Initially, anamnesis, physical examination and blood smear exclude other causes of thrombocytopenia. When clinically suspected or in case of atypical evolution, inherited thrombocytopenia should be investigated by genetic analysis.[3,4] An immune assessment including lymphocyte count and phenotyping is recommended to detect disorders such as autoimmune lymphoproliferative syndrome, common variable immunodeficiency, systemic lupus erythematosus (SLE) and other connective tissue disorders (CTD).[8] In this regard, the detection of ANA should be interpreted with caution. It is often found positive in adults and children with ITP but is not sufficient to establish a diagnosis of SLE or CTD. In children, however, it may be a predictor of chronicity.[4,9] Bone marrow examination is recommended only in atypical cases of newly diagnosed ITP (e.g. protracted fever, bone or joint pain, unexplained anaemia or neutropenia, minimal response to first-line therapy) and ITP persistent more than three to six months.[3,4] The detection of *Helicobacter Pylori* infection, preferably with the urea breath test is only recommended in children from high prevalence areas although it has been demonstrated in about 20% of children with chronic ITP.[4,10] While it was measured in our patient, antiplatelet antibody assay is useless since platelet glycoprotein-specific IgG are elevated in both immune and non-immune thrombocytopenia.[4]

Several treatments have been proposed in children with refractory ITP. Pulsed high-dose dexamethasone, combined with IVIG is efficient in 25% of cases.[11] Rituximab may also be considered.[5] Splenectomy should be delayed at least twelve months unless in very severe disease unresponsive to other measures.[5] Use of azathioprine, danazol, interferon, mycophenolate mofetil, cyclosporine, anti CD-52 antibodies and dapsone has also been reported.[4] A retrospective study showed that dapsone improved platelet count in 66% of patients with chronic and refractory ITP.[6,12] In our patient, dapsone combined with vitamin D supplementation was associated with a rapid normalisation of platelet count.

The role of vitamin D in our case was intriguing. In Belgium, lack of vitamin D is quite common with levels below 10 and 20 ng/ml in respectively 5% and 58% of children.[13] However the prevalence of vitamin D deficiency varies worldwide. It depends on age, sun exposure, diet and eventual program of vitamin D fortification.[14] While the prevalence in the general population was not known, some studies performed in Iran and Croatia reported a vitamin D deficiency in between 74% to 85% patients with ITP.[15,16] In addition, Fattizzo *et al*. have shown lower vitamin D levels in patients with ITP compared to controls. They also found that patients with very low levels of vitamin D had reduced platelet counts compared with other ITP patients.[17] This led us to assess the vitamin D status in our patient and to administrate supplementation. Whether this treatment improved thrombocytosis cannot be concluded at this point. However, several publications are consistent with our observation. Bockow *et al*. reported a remission in two adults with refractory ITP treated with hydroxychloroquine and vitamin D.[18] Other epidemiological studies have highlighted an increased prevalence of vitamin D deficiency in patients with autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus, SLE and inflammatory bowel diseases.[19,20] Low levels of vitamin D also seem to facilitate progression of existing autoimmune diseases.[21] Besides its role in calcium and bone homeostasis, vitamin D has multiple effects on immunity. *In vitro*, it facilitates the induction of T regulatory cells and inhibits B cell proliferation and IG secretion. It modulates the production of auto-antibodies by B cells from patients with autoimmune diseases.[21]

Altogether, these data suggest that vitamin D deficiency

could play a role in immune thrombocytopenia. Currently, we propose to measure the serum level of vitamin D in patients with chronic or atypical ITP. If necessary, we recommend supplementation in combination with existing ITP therapy. Larger studies are required to better determine the effect of vitamin D in ITP therapy and prophylaxis.

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