



Case Series

Immune Thrombocytopenia in Children with Neurofibromatosis Type 1

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Abstract

Introduction: Neurofibromatosis type 1 (NF1) is the most common neurocutaneous syndrome. Primary immune thrombocytopenia (ITP) is a haematological autoimmune disorder that is the most common cause of thrombocytopenia in children. Autoimmune diseases have been reported in association with NF1, either by coincidence or predisposition. The aim of the study was to present our experience with children with NF1 and ITP who were treated in an NF1 clinic and haematology unit of a tertiary paediatric referral hospital. **Methods:** The clinical database of the NF1 multidisciplinary clinic of Schneider Children's Medical Centre of Israel was reviewed for all patients age 0-18 years diagnosed and followed with NF1 and ITP during 2017-2022. We present the children and discuss our knowledge regarding the link between NF1 and ITP, the natural history of ITP in individuals with NF1, and possible causes of this association. **Results:** During the study, 290 children with NF1 and younger than 18 years were referred to our NF1 clinic 1% (3/290) of the patients were also diagnosed with ITP. Two of our three patients developed chronic ITP and required frequent therapy; one of the two had intracranial bleeding. **Conclusion:** Our study suggests that the incidence of ITP is increased in NF1 with the possibility of persistent ITP and more severe bleeding complications. The relation between NF1 and autoimmune phenomena still needs to be elucidated.

Keywords: Neurofibromatosis type 1; Immune Thrombocytopenia; Autoimmune Disorder; Intracranial Bleeding

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; ITP: Immune Thrombocytopenia; NF1: Neuro Fibromatosis type 1

Highlights

- Autoimmune diseases have been reported in association with NF1, either by coincidence or predisposition.
- We present our experience with children with NF1 and ITP who were treated in an NF1 clinic and haematology unit of a tertiary paediatric referral hospital.

- Three out of 290 children with NF1 were diagnosed with Primary immune thrombocytopenia (ITP)-1%.
- Two of our three patients developed chronic ITP and required frequent therapy; one of the two had intracranial bleeding.
- Our study suggests that the incidence of ITP is increased in NF1 with the possibility of persistent ITP and more severe bleeding complications

Introduction

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous syndrome; the estimated incidence is 1 in 2500-3000 [1]. Nearly half the patients have familial mutations, and

the remainder de novo mutations. NF1 is caused by a mutation in the NF1 gene, which codes for the protein neurofibromin, a negative regulator of the Ras/MAPK pathway. Neurofibromin, a tumour suppressor protein, catalyzes Ras GTPase activity, thereby inactivating the Ras transduction pathway and resulting in downstream overexpression of mTOR, MAPK, and c-kit [1]. In individuals who do not have a parent with NF1, the diagnostic criteria for NF1 are the presence of two or more of the following: six or more café-au-lait macule, freckling in the axillary or inguinal regions, two or more neurofibromas, optic pathway glioma, two or more iris Lisch nodules or choroidal abnormalities, an osseous lesion, and the pathogenic NF1 variant. In individuals whose parents were diagnosed with NF1, only one of the above criteria is needed [2] NF1 is associated with marked clinical variability, including neurodevelopmental delay, skeletal growth, vascular abnormalities, gastrointestinal manifestations, precocious puberty, and tumors of the central or peripheral nervous system [3]. In adults with NF1, autoimmune diseases are frequently reported in association with NF1, either by coincidence or predisposition [4]. Primary immune thrombocytopenia (ITP), the most common cause of thrombocytopenia in children, is a haematological autoimmune disorder characterized mainly by mucocutaneous bleeding and low

platelet count of less than 100,000/ μ L. The incidence of paediatric ITP is 4.2 per 100,000 per year [5]. The peak incidence is age 2 to 5 years. Twenty-five percent of the children with ITP do not recover within 12 months of diagnosis and their condition is then defined as chronic. The aim of the study was to present our experience with children with NF1 and ITP who were treated in an NF1 clinic and haematology unit of a tertiary paediatric referral hospital. We discuss our knowledge regarding the link between NF1 and ITP, the natural history of ITP in children with NF1 and the possible causes of this association

Methods

The clinical database of the NF1 multidisciplinary clinic of Schneider Children's Medical Center of Israel was reviewed for all patients age 0-18 years diagnosed and followed with NF1 and ITP during 2017-2022. The local ethics committee approved the study.

Results

During the study, 290 children with NF1 and younger than 18 years were referred to our NF1 clinic. 1% (3/290) of the patients were also diagnosed with ITP (Table 1) and here are the data

No	Age(y)	F/M	Familial NFI	Chronic ITP	Peteciae	Hematomas	Major Bleeding	Resolved
1	8.5	F	+	-	+	+	-	+
2	4.5	F	-	+	+	+	-	-
3	12.5	M	-	+	+	+	+	+

Table 1: Children with neurofibromatosis type 1 and Immune thrombocytopenia.

Patient 1

An 8.5-year-old girl presented with new-onset symptoms of petechiae and hematomas. Her complete blood count was normal, other than a platelet count of 2000/ μ L. A peripheral blood smear suggested ITP. Intravenous immunoglobulin treatment was initiated. At age 3 years, she had been diagnosed clinically with NF1, based on multiple café ale spots and inguinal freckling, in the absence of a family history of NF1. Her birth history revealed normal at-term delivery and birth weight. She had mild gross motor delay, and started walking only at age 19 months. Due to fine motor delay, she required occupational therapy. Language development and intelligence were normal, yet learning disabilities and attention deficit hyperactivity disorder (ADHD) were diagnosed in childhood. Following therapy with intravenous immunoglobulin

for ITP, her platelet count increased to 140,000/ μ L and then normalized. The acute ITP resolved with no recurrence during the subsequent 5 years.

Patient 2

A girl was diagnosed with ITP at age 4.5 years , following admission due to petechiae and purpura over her legs and arms. Her birth history and childhood milestones were normal. She had been diagnosed with familial NF1 at the age of one year. At diagnosis of ITP, her platelet count was 5000/ μ L. Bone marrow examination showed normal cellularity, no increased blasts, and an increased number of megakaryocytes, which was consistent with the diagnosis of ITP. Treatment with intravenous immunoglobulin was initiated, but the response was minimal. Over the years, she

was treated for refractory ITP with intravenous immunoglobulin, corticosteroid and thrombopoietin agonists (eltrombopag and romiplostim), rituximab, and combinations of the above, without remission. Currently, she is 7.5 years old, has chronic ITP and is treated with intravenous immunoglobulin every other week. She is a good student. Other than skin manifestations, she did not have major bleeding, over the years.

Patient 3

A 12-year-old male with multiple café au lait spots, and an unremarkable medical history apart from learning disabilities and ADHD, was diagnosed with new onset ITP. Therapy with multiple therapeutic agents, including intravenous immunoglobulin, corticosteroids and various thrombopoietin agonists, showed minimal response. At the time of diagnosis of ITP, he was also diagnosed with Hashimoto's thyroiditis requiring replacement therapy. Three years after the diagnosis of ITP he presented to our hospital with several hours of severe headache, dizziness, the inability to walk and worsening hemiparesis, with no report of trauma, fever or other illness. Initial examination showed confusion, facial asymmetry and left hemiparesis. His platelet count was 1000/ μL , blood pressure 108/87 and heart rate 117 beats per minute. A brain computerized tomography and later magnetic resonance imaging (Figure 1) revealed a right thalamic haemorrhage. He was treated in the intensive care unit with a high dose of corticosteroids, intravenous immunoglobulin, platelet transfusion and recombinant factor VII. Due to lack of improvement in platelet count and worsening clinical condition, he underwent emergent splenectomy within hours of admission. His platelet count rose to above 150,000/ μL within hours after surgery, and was above 1,000,000/ μL at discharge. His neurological status improved and after rehabilitation, he has had no sequelae. Despite the clinical diagnosis of NF1 based on multiple café ale spots and inguinal freckling, no pathogenic NF1 variant was found.

However, on the T2-weighted image (2) The signal is dark, representing deoxyhemoglobin as well as significant surrounding vasogenic edema.

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Discussion

In children, ITP is typically acute and short-lived. Complete remission has been reported in 69% of children within 6 months [6,7]. Among children with chronic ITP (defined as ongoing or active disease at 12-months follow-up), 28% were reported to achieve remission within 24 months [7]. Severe bleeding is very uncommon; the rate of intracranial haemorrhage was reported as 0.6-1% [8]. ITP is an immune-regulated disorder mediated by antiplatelet autoantibodies and antigen-specific T cells that lead to peripheral platelet destruction in the spleen and impaired platelet production in the bone marrow [9]. Since NF1 is not considered to have an autoimmune mechanism, the occurrence of ITP and NF1 could be coincidental. However, the appearance of autoimmune phenomena has been described in patients with NF1. Accordingly, Nanda et al. [10] reported a list of the most frequent autoimmune diseases that were found to be associated with NF1, mainly in adults. Possible mechanisms were suggested for the predisposition to autoimmunity in NF1 [4]. One is through unregulated RAS activity in T cells, which can result in lymphocytic proliferation, and regulation of T-cell activity [11]. The other is by autoimmunity that involves free DNA released from proliferating cells. This has been detected in association with both NF1 and systemic autoimmune diseases, triggering an antigenic response. In two of the three patients described in this report, ITP became chronic, and required frequent therapy. In one of these patients, the ITP was complicated by a severe adverse event, with intracranial bleeding. Given the small sample size of patients described here, the significant proportion of chronic ITP observed in NF1 patients compared to the general population prompts the question of whether this truly represents a higher incidence or is merely a result of better detection in NF1 patients. A search for NF1 and ITP in the literature revealed a case report of an adolescent with NF1 and chronic ITP that was complicated by intracranial bleeding [12] and an abnormal uterine bleeding in an adolescent girl having co-existent type-1 neurofibromatosis and ITP [13]. The pathophysiology driving the development from

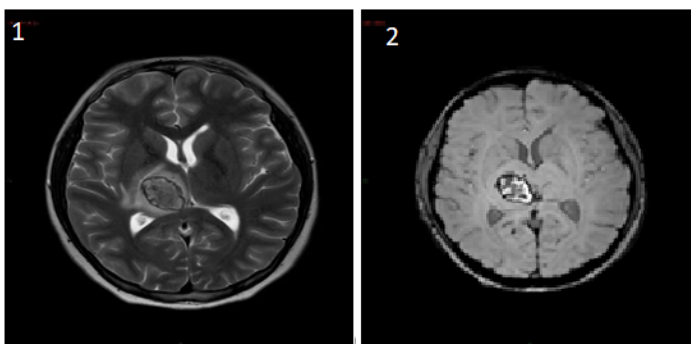


Figure 1: Acute Rt.Thalamic Intracerebral Hemorrhage: (1) T1-weighted axial MRI (2) T2-weighted axial MRI. (1) On the T1-weighted image, the abnormality in the Rt thalamus, indicating acute hemorrhage is not well seen, as the signal is isointense.

acute ITP to chronicity remains undefined. However, factors that have been reported to be associated with a chronic course in ITP include an impaired bone marrow microenvironment, female gender, older age at presentation, gradual initiation of disease, frequent bleeding, immunological markers and higher platelets at baseline [14]. The pathogenic role of T-cells in ITP has also been investigated, including a potential focus on new therapies [15]. Intracranial haemorrhage is a rare complication of ITP in children, with 53% of the reported incidents occurring during the chronic phase. The main risk factor for intracranial haemorrhage is a platelet count less than 10,000/ μ L [16]. as was seen in our patient. The only definitive treatment that has been described in extreme instances is splenectomy, as performed in that patient.

Conclusion

Our study suggest that the incidence of ITP is increased in NF1 with the possibility of persistent ITP and more severe bleeding complications. The limitation of this report is the small number of patients. Thus, further investigation should focus on the incidence of ITP in patients with NF1, the remission rate, the complication of intracranial haemorrhage and the relation between NF1 and autoimmune phenomena.

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