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Case Report

Autoimmune Polyglandular Syndrome Type IIIB Associated with Immune Thrombocytopenia, Leukopenia, Beta Thalessemia Trait, and Language Impairment

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Abstract

Autoimmune Polyglandular Syndrome (APS) is characterized by presence of immune dysfunction of two or more endocrine glands and other non-endocrine organs. Only few cases of APS III associated with different immunological or genetic disorders have been reported. We present a 17-year old boy presented with easy fatigability, recurrent abdominal pain, pallor and language impairment; evaluated to have Autoimmune Thyroiditis, Megaloblastic Anemia due to vitamin B12 deficiency and Type 1 Diabetes Mellitus; with final diagnosis as APS IIIB with Immune Thrombocytopenia, leucopenia and Beta Thalessemia trait. The child requires lifelong monitoring of glandular functions and hormone replacement therapy for established glandular failure or failures. APS IIIB is as yet known to occur in middle aged women. It should be suspected in younger ages and diagnosed early to prevent the complications associated with the chronic endocrine deficiencies.

Keywords: Autoimmune polyglandular syndrome, language impairment, thalassemia

Introduction

Autoimmune Polyglandular Syndrome (APS) is a condition characterized by presence of immune dysfunction of two or more endocrine glands and other non-endocrine organs. Neufeld and Blizzard classified it in two major types, APS I and II. APS type III (APS III) was subsequently described for autoimmune thyroiditis occurring with other organ-specific autoimmune diseases. It has 3 subcategories: (1) APS IIIA - Autoimmune thyroiditis with immune-mediated diabetes (IMD) mellitus (also known as polyglandular autoimmune syndrome type 3 variant) (2)APS IIIB - Autoimmune thyroiditis with Megaloblastic Anemia and (3)APS IIIC - Autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease.[1]

The exact prevalence of APS III is unknown.[2] APS III is typically observed in middle-aged women. It is often observed in individuals in the same family, suggesting that its inheritance could be an autosomal dominant trait with incomplete penetrance.[3] Autoimmunity, environmental factors, and genetic factors are considered as etiology of APS. APS III, as well as APS II, are associated with HLA class II genes with apparently distinctive HLA alleles for each. The underlying non-HLA genes of APS III have not been defined genetically yet.

We are reporting a case of APS III B in a 17-year-old male child who presented with easy fatigability, recurrent abdominal pain, pallor since one month and language impairment. After evaluation, he was diagnosed with Autoimmune Thyroiditis, megaloblastic Anemia due to vitamin B12 deficiency and type 1 diabetes mellitus. Clinical examination and further laboratory findings revealed APS III with Immune Thrombocytopenia, leucopenia and Beta Thalessemia trait. To the best of authors' knowledge, no case of APS IIIB associated with Beta Thalessemia trait, Immune Thrombocytopenia, leucopenia and language impairment has been reported in children. Coexistence of Beta Thalessemia

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trait may be the result of association of both conditions with human leucocyte antigen.

Case Report

A 17-year-old male child, a product of of nonconsanguineous marriage. He presented with easy fatigability, decreased oral intake, and abdominal pain of 1 month duration. The patient was also suffering from chronic language impairment though comprehension, reading, and writing were normal. One year back, he was hospitalized at the peripheral institution for pallor and easy fatigability and improved with blood transfusion and short duration steroid therapy for anemia with thrombocytopenia. His mother was on levothyroxine for hypothyroidism.

Physical examination showed no apparent abnormal findings except pallor and icterus. No skin lesions were present. Liver span was 15 cm, and spleen was not palpable. Respiratory rate was 36/min, and SPO_2 was 98% at room air. Blood pressure was 106/60 mmHg with tachycardia (Heart rate 110/min, regular) and hemic murmur which disappeared after blood transfusion.

Complete blood count showed severe anemia (Hb4.1 g/dl), leukopenia (total lymphocyte count 3.88 × 10^3/μL) with 50% lymphocytes, thrombocytopenia (platelet count of 45 × 10^3/μL), and mean corpuscular volume 88.1fl. Peripheral blood smear suggested dimorphic anemia with teardrop cells, pencil cells and ovalocytes, and reduced platelet counts. Corrected reticulocyte count was 1.5%. Lactate dehydrogenase was raised (1460 IU/L). S. Ferritin (80.36 ng/ml), total iron-binding capacity (285 μg/dl), and S. Iron (165 μg/dl) were normal. B12 levels (60.89 pg/ml) and folic acid levels were low (10.66 ng/ml). Bone marrow examination revealed hypercellular marrow with increased megakaryopoiesis, myelopoiesis with evidence of ineffective erythropoiesis. Bone marrow biopsy suggested megaloblastic marrow. A primary diagnosis of megaloblastic anemia due to Vitamin B12 deficiency was established.

High-performance liquid chromatography study revealed hemoglobin A (HbA) 93.9%, HbF 2.7%, and HbA2 3.4% and was suggestive of β thalassemia trait. Fasting blood sugar was 176 mg/dl, postprandial blood sugar was 250 mg/dl with low C-peptide levels suggestive of Type 1 diabetes mellitus. HbA_1c (5.6%) was in the upper limit of normal. Anti-parietal cell antibodies were positive, and anti-islet cell antibodies were negative. Free thyroxine (T4) was 8.69 pg/ml, and thyroid-stimulating hormone was raised (25.7 μIU/ml). Anti-thyroid peroxidase antibodies were strongly positive (810 IU/ml). An ultrasound suggested thyroiditis. To differentiate between APS II and III, S. cortisol and cosyntropin stimulation test were normal. Liver function tests including serum glutamic oxaloacetic transaminase (68 U/L), serum glutamic pyruvic transaminase (65 U/L) and S. bilirubin (total 2.9 mg/dl, direct 1.9 mg/dl) were raised. viral hepatitis markers tested negative. His renal function tests, electrolytes, G6PD, antinuclear antibodies, HIV, tissue transglutaminase IgA, parathyroid hormone and stool for occult blood and blood culture were normal. Duodenal biopsy revealed chronic nonspecific duodenitis with no evidence of celiac disease. Audiometry suggested normal hearing.

Discussion

The exact prevalence of APS III is unknown.[1] Neufeld and Blizzard's classification distinguishes two broad categories as follows: APS type I and APS type II.[2] APS 1 (juvenile) is characterized by multiple hormonal deficiencies with mucocutaneous candidiasis and ectodermal dystrophy and usually manifests in early adolescence or in infancy with hypoparathyroidism, Addison's disease, type 1A diabetes, hypogonadism, and thyroid disease. APS II usually manifests in the 3rd or 4th decade of life. Associated endocrine diseases include autoimmune thyroid disease (Graves disease or autoimmune thyroiditis), Type 1A diabetes, and Addison's disease. Hypoparathyroidism is of rare occurrence, and there is no mucocutaneous candidiasis.

In some situations, autoimmune thyroiditis occurs with other organ-specific autoimmune diseases and is not classifiable under APS 1 or II. APS III was subsequently described to encompass this entity. APS III is classified into the following three subcategories as follows: (1) APS IIIA-autoimmune thyroiditis with immune-mediated diabetes mellitus (also known as polyglandular autoimmune syndrome type 3 variant), (2) APS IIIB-autoimmune thyroiditis with megaloblastic anemia, and (3) APS IIIC-autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease. Our patient qualifies for APS IIIB.

A rare case of APS III in monozygotic twins, in which one of the twins also had autoimmune leukopenia, was reported.[3] A case of APS III with autoimmune leukopenia also was reported.[4] Leukopenia was documented 4 times in repeated reports in a period of hospital stay of 14 days in our patient. A case of APS III complicated with autoimmune hepatitis was reported in Japan.[5] Our patient also had abnormal liver function tests. Another report from Japan described a 61-year-old woman with slowly progressive type 1 diabetes mellitus associated with chronic thyroiditis, pernicious anemia, and idiopathic thrombocytopenic purpura.[6] In the present case, thrombocytopenia was repeatedly documented during a hospital stay. Growth hormone deficiency was reported once in an 8-year-old child who had type 1 diabetes mellitus, suggesting that it may also be a component of APS III.[7] However, development in our case is normal with normal stature, but the child had language impairment.

History, clinical examination, and laboratory findings were nonsuggestive of common variable immunodeficiency in our case. Autoimmunity, environmental factors, and genetic factors are considered as etiology of APS. APS III, as well as APS II, are associated with the human leukocyte antigen gene complex (HLA) class II genes with apparently distinctive HLA

alleles for each. The underlying nonHLA genes of APS III have not been defined yet. Coexistence of beta thalassemia trait may be the result of the association of both conditions with human leukocyte antigen.

APS III is often observed in individuals in the same family, suggesting that its inheritance could be an autosomal dominant trait with incomplete penetrance.[8] Autoimmune thyroiditis is the characteristic of all subcategories of APS III. Easy fatigability is a frequent symptom in patients with autoimmune thyroiditis. Megaloblastic anemia also presents with fatigue, weakness, lightheadedness, and palpitations secondary to anemia. Vague gastrointestinal symptoms may also be present. An elevated serum thyrotropin is sufficient to confirm the diagnosis of hypothyroidism.

Conclusion

Clustering of findings such as immune thrombocytopenia, leukopenia, beta thalassemia trait, and language impairment at this age is absolutely rare. It should be suspected and diagnosed early to halt the progression of complications associated with the chronic hormonal deficiencies. APS III patients require lifelong monitoring of endocrine functions and hormone replacement therapy for established endocrine failure or failures. Periodic screening for other hormonal deficiencies should be performed in patients already diagnosed with APS III.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his consent for his images and other clinical information to be reported in the journal. The patient understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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