

Deficit of Anterior Pituitary Function and Variable Immune Deficiency Syndrome: A Novel Mutation

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Introduction

Common variable immunodeficiency (CVID) is a complex primary immunodeficiency disorder with hypogammaglobulinemia as a major feature. Most of the patients do not have a specific genetic abnormality. Autoimmune disorders occur commonly in patients with CVID. We report a case of a girl with secondary adrenal insufficiency who developed a disseminated varicella zoster infection and zoster meningoencephalitis with vaccine strain. The laboratory evaluation of this patient led to the final diagnosis of CVID with a new variant of TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) mutation and DAVID syndrome (deficit of anterior pituitary function and variable immune deficiency).¹

Case Report

A 7-year-old Caucasian girl with medical history of secondary adrenal insufficiency presented with right-sided jaw pain and swelling for 4 days. Two days prior she developed red blisters on the right side of her upper lip. Fever (T_{\max} 38.5°C) was noted with submandibular lymphadenopathy. She was treated with oral antibiotics for 4 days (amoxicillin then amoxicillin-clavulanic acid) without improvement. The pain, swelling, and blisters progressed and extended to her right cheek and eyelid. Abdominal discomfort and decreased oral intake were also reported without nausea, vomiting, or diarrhea. On the admission day, she had intermittent confusion when engaged in conversations. No sick contact was identified. The patient had received her second varicella vaccine almost 2 years ago.

Past Medical History

She was diagnosed with secondary, autoimmune adrenal insufficiency at the age of 5 years. At the time, she presented with adrenal crisis and severe hypoglycemia after viral upper respiratory infection. She also has elevated thyroid microsomal antibody. However, her thyroid

functions have been normal. She is on hydrocortisone replacement therapy.

Family History

Her 9-year-old sister has alopecia and hypogammaglobulinemia, and her 36-year-old father has psoriasis, alopecia, and hypogammaglobulinemia. Both her father and sister are on immunoglobulin replacement therapy and both of them have elevated thyroid microsomal antibody with normal thyroid functions. Her 21-year-old cousin (a son of the paternal aunt) has alopecia.

Her mother is 32 years old and healthy. Her maternal grandmother has mild diabetes and does not use medication, her maternal grandfather has hypercholesterolemia and hypertension.

The maternal side of the family is of Hungarian heritage. The paternal side of the family is of Polish, French heritage. There is no consanguinity in the family, history of birth defect, mental retardation, multiple spontaneous abortions, or early sudden death.

Physical examination revealed a temperature of 37.9°C, Pulse 120 beats/min, respiratory rate 20 respirations/min, and blood pressure 119/76 mm Hg. Skin examination revealed multiple discrete erythematous papules and vesicles distributed on her cheek, upper and lower right eyelid, right side of upper lip (V2 region), right side of her nasal bridge, and forehead (V1 region). Significant soft tissue swelling of right eyelid, cheek, and upper lip with submandibular lymphadenopathy were noted. There was no corneal involvement. Findings on the rest of the physical examination were unremarkable.

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Hospital Course

In the emergency department, 50 mg of hydrocortisone was administered intravenously (IV). She was started on IV acyclovir and ampicillin-sulbactam for the possibilities of herpes simplex virus (HSV) or varicella zoster virus (VZV) with superinfection with *Streptococcus pyogenes*, as some areas appeared impetiginous.

Initial laboratory evaluation showed white blood cell count of 12200/ μ L (neutrophil 42%, lymphocyte 37%, monocyte 16%, eosinophil 4%, basophil 1%). Her hemoglobin was 12.9 g/dL with hematocrit of 36.1%. Serum electrolytes were as follows: sodium 133 mmol/L, potassium 5.1 mmol/L with moderate hemolysis, chloride 98 mmol/L, HCO_3^- 22 mmol/L, and calcium 9.1 mg/dL. Blood urea nitrogen was 10 mg/dL and creatinine 0.3 mg/dL. Her erythrocyte sedimentation rate was 16 mm/h and C-reactive protein 29.7 mg/L.

Lumbar puncture was performed, and her cerebrospinal fluid (CSF) analysis showed 9 red blood cells/ mm^3 , 227 nucleated cell/ mm^3 (neutrophil 13%, lymphocyte 62%, and monocyte 12%). The CSF glucose was 43mg/dL and protein 72 mg/dL. Her blood sugar was 147 mg/dL. These findings, along with her intermittently confused mental status, were suggestive of viral meningoencephalitis. CSF culture was negative for bacteria. HSV1 and HSV2 polymerase chain reactions (PCR) were negative on blood, CSF, and fluids from vesicles. HSV1 and HSV2 direct fluorescent antibody (DFA) test on fluid from vesicles was also negative. Viral culture from vesicular fluid was negative. However, VZV PCR and VZV DFA were both positive from the skin lesions. CSF and vesicular fluid samples sent to the Centers for Disease Control and Prevention were positive for VZV vaccine stain by DNA PCR studies.

Immunodeficiency evaluation revealed low IgG level of 257 mg/dL (reference 633-1535 mg/dL), IgA of 10 mg/dL (32-258 mg/dL), IgM of 26 mg/dL (48-228 mg/dL), and IgE of <1 mg/dL (1-240 mg/dL). She had normal absolute CD4+ T cell, CD8+ T cell, and B cell counts, slightly decreased in concanavalin A (CON A) but normal pokeweed mitogen proliferation assay. Her diphtheria and tetanus titer were not detected despite being fully vaccinated. She had poor antibody response to pneumococcal antigens (PCV23). Her blood group is AB+, and therefore, isohemagglutinin titers were not detected. Sequencing of tumor necrosis factor receptor superfamily member 13B (TNFRSF13B) encoded for TACI showed homozygous c.81G>A variants that were not previously reported to be associated with CVID. Heterozygous c.1578T>C and c.681C>T were found in autoimmune regulator (AIRE) sequencing. But these variants were also not previously

reported to cause autoimmune polyglandular syndrome type 1 (APS1) or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). She is treated with intravenous immunoglobulin 500 mg/kg every 4 weeks.

Discussion

Several severe infections with vaccine strain of VZV have been reported in immunocompromised pediatric patients in the published literature.²⁻⁶ In these reported cases, as in our case, the patient was inadvertently administered the live attenuated VZV vaccine prior to or without full acknowledgement of an underlying immunocompromising condition (neuroblastoma,^{2,6} adenosine deaminase deficiency,³ cell-mediated immunodeficiency,⁴ acquired immunodeficiency syndrome⁵). All of these patients developed rash, as did our patient. Other manifestations included disseminated disease,³ chronic verrucous lesions,^{2,6} pneumonia,^{4,5} and encephalitis or meningoencephalitis (present case and Kramer et al⁵). Patients in these reports were treated with intravenous acyclovir, but in 2 of the cases acyclovir resistance developed and was confirmed.^{2,6}

The diagnosis of CVID was established in our patient based on the definition of severe reduction in at least 2 serum immunoglobulin isotypes, including IgG, with impaired antibody productions to antigens.⁷⁻⁹ She had significantly low levels of IgG, IgM, IgA, with no antibody response to protein antigens and poor antibody response to polysaccharide antigen (less than 50% of pneumococcal titer were greater than 1.3).¹⁰ T cell abnormalities are frequently seen in CVID. These can be both T cell lymphopenia and abnormal T cell proliferation.^{11,12} In our patient, T cell functional abnormality was shown by the decrease in mitogen response to CON A.

CVID generally presents with recurrent sinopulmonary infections caused by encapsulated or atypical bacteria.¹¹ Viral infections, including herpes zoster infection, are uncommon except for the cases of Good syndrome (CVID with thymoma).^{13,14} The disease presents mainly in young adults but can be observed in children.

Patients with CVID are highly prone to develop autoimmune manifestations, particularly cytopenias, inflammatory bowel diseases, and thyroid diseases.⁹ Prevalence of autoimmune diseases in CVID can be as high as 20%.^{11,12} CVID associated with adrenal insufficiency is rare.¹⁵ Although Addison's disease and immunodeficiency are well described in APS type 1, the immunodeficiency in this syndrome manifests as chronic mucocutaneous candidiasis, which is not seen in our patient. Hypogammaglobulinemia or CVID are not reported as part of the syndrome.¹¹

To our knowledge, DAVID syndrome has been reported in 7 patients, and 2 of these patients are siblings.^{1,16-18} All the patients presented first with CVID and were diagnosed between 3 and 14 years of age, unlike our patient who presented with adrenal crisis without previous history of infections. The sequencing of candidate genes involved in corticotrope differentiation were attempted, including LIF (leukemia inhibitory factor) and IKAROS and EOS (both are zinc finger transcription factors). Although no pathogenic allelic variation identified to date, Quentien et al reported 2 polymorphism concerning IKAROS.¹ Interestingly, none of the DAVID syndrome patients has been sequenced for known genetic mutations of CVID, including TAC1 or APS type 1 (AIRE).

Mutations in TAC1 have been identified in up to 15% of patients with CVID.⁸ Most of these mutations are heterozygous and are also found in the general population. However, all of the homozygous and compound heterozygous mutations are associated with hypogammaglobulinemia.^{7,9,19,20} TAC1 mutation was also found to be associated with autoimmunity.^{20,21} Salzer and colleagues sequenced variants of TAC1 mutation on a large cohort, which included 533 CVID patients and 675 healthy individuals from Europe, North America, and South America. They found that the most frequently mutated allele was C104R (4.6%) followed by A181E (2.3%).²⁰ c.81G>A variant has not been previously reported in patients with CVID or DAVID syndrome, but it also has never been reported in a healthy individual without hypogammaglobulinemia.²⁰⁻²³ We believe that homozygous mutation in this codon of TNFRSF13B is linked to CVID and DAVID syndrome in our patient.

Our patient is currently receiving intravenous immunoglobulin every 4 weeks along with hydrocortisone replacement. Her trough IgG levels ranged from 780 to 960 mg/dL and has had no further infections.

Author Contributions

PP and EMG substantially contributed to conception and drafted the manuscript. PP and DK critically revised the manuscript. All the authors contributed to acquisition, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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