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Common variable immunodeficiency with hypoglycemia, Kikuchi lymphadenitis, and hemiparesis in two siblings

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Common variable immunodeficiency is a heterogeneous group of disorders with arthritis and/or arthralgia as its most commonly associated autoimmune manifestation. We report 2 cases of common variable immunodeficiency in siblings who also had other unusual signs and symptoms. A 10-year-old boy suffered from bradycardia, hypothermia, hypoglycemia, and chronic eczema. His 13-year-old sister suffered from Kikuchi lymphadenitis, hypoperfusion and atrophy of the left cerebral hemisphere, and hemiparesis. They both showed classical laboratory findings of common variable immunodeficiency and the boy's associated symptoms responded to intravenous immunoglobulin therapy. The findings from these cases suggest that a defect in the neuro-endocrine-immune axis may be one of the genetic bases of common variable immunodeficiency.

Key words: Common variable immunodeficiency, hypogammaglobulinemia, hypoglycemia, Kikuchi lymphadenitis, neuro-endocrine-immune axis

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders characterized by a generalized failure of antibody synthesis that results in hypogammaglobulinemia, antibody deficiency, and recurrent bacterial infections [1]. The onset of the disease, often manifesting as repeated episodes of infection, usually occurs either between 1 and 5 years, or between 16 and 20 years of age [1]. Various immunologic defects, including an intrinsic B-cell defect, excessive T-suppressor activity, and defective T/B-cell interaction, have been postulated to be responsible for the failure of B-cell differentiation in CVID [2]. In addition, patients exhibit increased susceptibility to a protean array of autoimmune, gastrointestinal, neoplastic, and inflammatory disorders [1, 3]. Common variable immunodeficiency can be associated with some syndromes [2,4], but the abnormalities are often confined to the immune system. The combination of hypoglycemia, Kikuchi lymphadenitis, and hemiparesis with CVID in 2 siblings in this report suggests that a defect in the neuro-endocrine-immune axis might be one of the genetic bases of CVID.

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Case Report

Case 1

A 10-year-old boy suffered from painful swelling of both ankle joints for several years. He was a full-term baby of an uncomplicated pregnancy and delivery from a non-consanguineous couple. He received regular immunizations with no adverse effect. There was no history of otitis, sinusitis, bronchitis, or pneumonia. Physical examination found swelling over bilateral ankle joints with limitation in range of motion. Several erythematous nodules were noted on the dorsal aspect of both feet. There was no lymphadenopathy. Tonsillar tissues were visible.

History taking revealed an episode of cold sweating and drowsiness at the age of 8 months. Since the age of 18 months, episodes of cold sweating, consciousness disturbance, pallor, and flaccidity were noted in the early mornings before breakfast although these symptoms would resolve once the patient was fed. These episodes were often accompanied by bradycardia (40-50 beats/min) and hypothermia (oral temperature as low as 35.5°C).

The patient was admitted to National Taiwan University Hospital at the age of 6 years. He had hypoglycemia, with a pre-radial blood glucose level of 23 mg/dL (normal range, 70-115 mg/dL), and mild metabolic acidosis (pH 7.26, HCO_3^- 15.1 mEq/L, base excess –10 mEq/L). Insulin-like growth factor-1 (107

ng/mL) and thyroid functions were normal. Further evaluation revealed appropriate response of cortisol, insulin, C-peptide, and growth hormone (GH) to hypoglycemia. After 16 h of fasting in the hospital, he had a normal elevation of blood ketone bodies (>2 mM). Insulin level at that time was low (0.2 μU/mL), even though lactic acid and serum amino acid analysis were normal. Blood glucose responded normally to glucagon.

At the age of 9 years, the patient was admitted due to carbuncles on the scalp. Mild mental retardation, unstable gait, and bilateral ankle clonus were also noted at that time. His intelligence quotient was 85 as evaluated by the Wechsler Intelligence Scale for Children-revised. His body height and weight were normal but bone age was delayed (4-4.5 years old). He still suffered from frequent hypoglycemic attacks. In addition, asthmatic attacks and severe atopic dermatitis also occurred.

Results of laboratory investigations at the age of 10 years were as follows: albumin 4.6 g/dL, globulin 2.7 g/dL, aspartate aminotransferase 18 U/L, and alanine aminotransferase 13 U/L. Antinuclear antibody and rheumatoid factor were negative. There was no destruction of bilateral ankle joint on radiography. The immunological findings are summarized in Table 1.

He received regular intravenous γ-globulin replacement therapy of 400 mg/kg every 4 weeks. After 1 year, there were no longer any episodes of hypoglycemia. His eczema, arthritis, and mental retardation had also improved.

Case 2

The 13-year-old elder sister of the patient in Case 1 had recurrent vertigo since early childhood and premenstrual migraine with aura since puberty. One year prior to this examination, she experienced a high-grade fever with painful left neck lymphadenitis and episodes of transient right-sided hemiparesis. Biopsy of the neck lymph nodes showed focal, well-circumscribed paracortical necrotizing lesions with proliferation of large atypical lymphoid cells, abundant karyorrhectic debris, scattered fibrin deposits, and collections of large mononuclear cells. These findings were compatible with histiocytic necrotizing lymphadenitis or Kikuchi disease.

Bone marrow biopsy revealed hypocellular marrow with no malignant cells. Virologic studies were negative including toxoplasma, parvovirus, and Epstein-Barr virus. Electroencephalography showed spikes over the left hemisphere and brain magnetic resonance image

Table 1. Laboratory data of the 2 siblings with CVID

	Younger brother	Elder sister	Reference range
Onset age	8-month-old	12-year-old	
Initial presentation	Cold sweating	Vertigo	
	Consciousness disturbance	Migraine	
	Hypothermia	Lymphadenitis	
Hemoglobin (gm/dL)	12.5	14.0	
WBC (/mm^3) (Seg/Lym)	4610 (59/31)	6880 (83/10)	
C3 (mg/dL)	114	108	81.61-118.41
C4 (mg/dL)	19.8	27.4	27.45 ± 10.72
ESR (mm)(1 h/2 h)	9/24	6/11	
Immunoglobulin levels			
IgG (mg/dL)	639	690	1348 ± 298
IgA (mg/dL)	25.2	11.1	184 ± 78
IgM (mg/dL)	34.9	23.7	187 ± 63
IgE (mg/dL)	350	ND	<150
Lymphocyte phenotype			
T cell ($CD3^+$)	62	89	66-76
B cell ($CD19^+$)	27	1	12-22
NK cell ($CD16^+56^+$)	4	5	
$CD3^+CD4^+$	30	29	33-41
$CD3^+CD8^+$	23	31	27-35
Mitogen response (SI)			
Con A (40 μg/mL)	31.0	16.0	>3
PHA (4 μg/mL)	127.9	74.8	>3
PWM (4 μg/mL)	124.6	123.3	>3
Anti-CD3/antiCD-28 (2 μg/mL each)	4.8	105.4	>3

Abbreviations: CVID = common variable immunodeficiency; WBC = white blood cells; ESR = erythrocyte sedimentation rate; NK cell = natural killer cell; SI = stimulation index; Con A = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen; ND = not done

revealed an absence of flow at the left posterior communicating artery. Single photon emission computed tomography also showed hypoperfusion of the radiopharmaceuticals over the left frontal, temporal, and cerebellar areas. Her condition responded partially to prednisolone and anticonvulsant therapy. Under the impression of familiar hypogammaglobulinemia, immunologic functions were analyzed. The results are summarized in Table 1.

Under the impression of familial hypogammaglobulinemia, she received intravenous immunoglobulin supplementation of 400 mg/kg per month, similar to the regimen of her brother. In contrast to the rapid response of her brother, however, she still suffered from low immunoglobulins, recurrent lymphadenitis, right-sided hemiparesis, and brain atrophy after 1 year of treatment.

Discussion

The patient in Case 1 presented with a unique combination of hypogammaglobulinemia with hypoglycemia, arthritis, chronic eczema, and asthma. The diagnosis of CVID depends on the exclusion of the other more common immunodeficiency syndromes. Because this patient had sustained low immunoglobulin (Ig) M levels, hyper-IgM syndrome was unlikely. Normal tonsillar tissues and the number of B-lymphocytes excluded the possibility of a severe form of X-linked agammaglobulinemia. Although this patient had an extremely high level of serum IgE concentration and an eczematous skin rash, he had no typical facial dysmorphism and no defective phagocytosis function. Therefore, hyper-IgE syndrome was unlikely. Common variable immunodeficiency was then diagnosed despite the lack of recurrent infection history.

Arthritis and/or arthralgia were the most common (8%-33%) autoimmune manifestations in CVID [3], probably induced by circulating immune complexes deposited in the synovial tissue [5]. Molecular mimicry and cross-reactivity against endogenous and microbial peptide, and the failure to clear immune complexes due to chronic infection, may play a role in the development of an autoimmune disease in CVID patients [6]. In addition to arthritis, the boy described in this report also had severe chronic eczema and asthma, which may be related to his abnormal immune status. His sister had Kikuchi disease, cerebral vascular abnormality, and hemiparesis in addition to CVID. Kikuchi disease is a disease of unknown etiology. It may be related to viral infection but has also been associated with autoimmune diseases such as systemic lupus erythematosus. The cause of cerebral vascular abnormality in this patient was not clear. Either vasculitis or vasospasm could explain the cerebral hypoperfusion and hemiparesis. However, irreversible atrophy of the left side of her brain had also occurred. Since both Kikuchi disease and cerebral vascular abnormality were rare, it is likely that these conditions are also related to her immune defects.

Since the boy and his sister both showed similar humoral immunodeficiency, an autosomal recessive disorder is suggested. To date, no evidence has been provided regarding the relation between B-lymphocyte abnormality in CVID affecting and immunoglobulin genes or and rearrangement or isotype switching [1]. It has been hypothesized that the B-lymphocytes from most patients with CVID are not intrinsically abnormal and that their dysfunction may be a result of the lack of appropriate external stimuli, causing a differentiation arrest at an immature B-lymphocyte level [7].

There is only one previous case report describing the combination of Swiss agammaglobulinemia, hypoglycemia, and eosinophilia [8]. The cause of hypoglycemia was not clear but the patient had severe bacterial infection. Recently, considerable evidence has been reported to suggest that hormones, such as growth hormone, insulin-like growth factors (IGFs), prolactin, catecholamine, and endogenous opioids, can affect lymphocyte survival, proliferation and/or secretion of cytokines or immunoglobulins. This relationship has been referred to as the neuro-endocrine-immune axis [9]. Data from various hormone-deficient mice and recombinant or pure hormone preparations confirmed the effects of hormones on lymphocyte responses, although there is still no compelling evidence in humans that such hormones specifically act on certain lineages during the development of the lymphohemopoietic system. Growth hormone and IGF-1 are considered to be general anabolic hormones with effects on target cells in multiple tissues including bone marrow and thymus, which enable them to modulate the development and function of the immune system [10]. Receptors for GH and IGFs are widely expressed on leukocytes and it is possible that GH, IGFs, and other hormones may act on the lymphohemopoietic system and affect lymphopoiesis [10]. Although the combination of immune deficiency and hypoglycemia is rare, it is possible that anabolic hormones other than GH and IGF-1 may be involved in both glucose level control and differentiation of B-lymphocytes.

It is interesting to note that the hypoglycemic attack in the boy of this report was associated with hypothermia and bradycardia. The presence of these 2 symptoms suggested an abnormal body response to hypoglycemia. Thus, this patient may have had a defect

in the autonomic nervous system, which was the underlying cause of hypoglycemia. Although there was no conclusive evidence for this etiology, it seems plausible since abnormal autonomic tone could affect brain vascularity, which could explain the condition in the sister.

In conclusion, we have reported the cause of 2 siblings with CVID who had associated conditions encompassing the autoimmune, endocrine, and/or autonomic nervous systems. These cases suggest that CVID involves the neuro-endocrine-immune axis. Although these cases only further expand the etiologic complexity reported for CVID, they also suggest that certain genetic defects may exert broad effects on the neuro-endocrine-immune axis in this disease.

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