Case report

Panhypopituitarism in a child with common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) represents a group of heterogeneous, still undifferentiated, syndromes that are all characterized by defective antibody formation. It is often associated with autoimmune disease.

Methods: An African-American girl was diagnosed with CVID at age 3 years. She was seen during an adrenal crisis precipitated by pneumonia at the age of 8 years and 10 months. The diagnosis of panhypopituitarism was established soon after.

Results: Panhypopituitarism in this patient was believed to be the result of the autoimmune process known as lymphocytic hypophysitis. This hypothesis was suggested by the results of magnetic resonance imaging.

Conclusions: Awareness of the possibility of this process in children or adults with CVID may lead to earlier diagnosis of panhypopituitarism. These patients also have failure to thrive, and earlier diagnosis may avoid a life-threatening event.

INTRODUCTION

Common variable immune deficiency (CVID) designates a group of currently undifferentiated syndromes all characterized by defective antibody formation. The diagnosis is based on the exclusion of other known causes of humoral defects.1 The Pan-American Group and the European Society for Immunodeficiencies have also delineated specific criteria. These include absence of isohemagglutinins and/or poor vaccine responses in persons older than 2 years of age.2 Patients are considered more likely to have CVID if they are deficient in immunoglobulin A (IgA) and have low IgG (>2 standard deviations below the age-appropriate norm) than if they have only low IgG.3 In half of patients, the IgM level also is reduced. Although most patients have a normal number of B cells, some patients have reduced or even absent B cells. The T cell function can also be affected to varying degrees.3-5 Approximately 20% of CVID patients are affected by autoimmune diseases.4,6 The most common of these are antibody-mediated hemolytic anemia, immune thrombocytopenia, and pernicious anemia. Autoimmune endocrine diseases have also been reported frequently with CVID. These include Hashimoto’s disease, Addison’s disease, and insulin-dependent type I diabetes. We report the case of a girl with CVID who was seen at the age of 8 and 10/12 years with panhypopituitarism that manifested as an adrenal crisis precipitated by pneumonia. The panhypopituitarism in this case is believed to be secondary to autoimmune lymphocytic hypophysitis, as supported by results of magnetic resonance imaging (MRI).

CASE REPORT

The patient is a girl who has been followed at our immune deficiency clinic with a diagnosis of CVID since April 1996. Her pediatrician referred her at the age of 5 and 11/12 years because of recurrent otitis media, recurrent sinusitis, an episode of pneumonia, and low Ig levels. She was born full term with a birth weight of 2.81 kg after an uneventful pregnancy. She received all of her childhood immunizations without adverse effects. The family history was negative for immune deficiencies. The child had never received any anticonvulsants and had never received steroids. A younger sibling was healthy.

The physical examination at the initial visit revealed a child in no acute distress with normal activity, height of 102 cm, slightly below the third percentile, and a weight of 15.6 kg corresponding to the third percentile. She was afebrile, heart rate was 101 beats/minute, and blood pressure was 100 mm Hg/62 mm Hg. Sclera were bilaterally clear. The left tympanic membrane was perforated but there was no discharge, and small tonsils were documented as well as mobile, nonenlarged anterior cervical lymph nodes. There were no skin lesions noted. Examination of the heart revealed a regular rate and rhythm with no murmur. There was no hepatosplenomegaly, and the neurologic examination was grossly normal.

Laboratory evaluation revealed decreased levels of the three major Ig classes. Her T and B lymphocyte markers were normal on several occasions, but the mitogen proliferation assay to pokeweed, concanaavalin A, and phytohemagglutinin showed decreased levels of these mitogens. Her response to pneumococcal vaccine (Pneumovax) was very poor, with levels of four of four serotypes below protective levels before and after vaccination. The baseline Haemophilus influenzae type B (Hib) titer was low, but the administration of a protein-conjugated Hib booster vaccine produced a good response. The antimumps IgG was not detectable 1:8. The measles, rubella, and varicella titers were all protective. Hu-
man immunodeficiency virus DNA by polymerase chain reaction was negative (Table 1).

The patient was considered to be IgA deficient, with a poor polysaccharide response and possible early CVID. No specific therapy was initiated, but she was followed closely. Over the next 12 months, she was noted to have a persistent cough and a perforated left tympanic membrane that was failing to heal. She was growing slightly below the third percentile for weight and height, with a weight/height ratio at the 15th percentile. A repeat Hib titer had dropped below the level of protection. Another Hib booster vaccine was given with a rise to only borderline protective level. Tests for isohemagglutinins were negative. Her IgG level dropped further, and the level of IgA became undetectable.

At this point, the patient was diagnosed with CVID, and intravenous Ig (IVIG) infusions were started in the summer of 1997. The cough improved significantly, and the patient did not have any infections that required an antibiotic for 1 year.

In December 1998, the patient was diagnosed with sinusitis and treated with a course of oral antibiotics without improvement. The family reported that the child had a poor appetite and was always complaining of feeling cold. There was no linear growth for 6 months and no weight gain. She never complained of headache or changes in vision. The clinic staff noted a significant lability of mood with unexplained episodes of crying in this child. In January 1998 the child was brought to the emergency room for loss of consciousness.

The family reported that she had gastroenteritis in the 2 days preceding the episode. Her blood sugar level was 2.77 mmol/L (50 mg/dL), but she responded rapidly to oral carbohydrates and was discharged from the emergency room with dietary instructions. Over the next few days, the patient apparently improved, only to be found unconscious again 2 weeks later. At that time, her blood pressure was 62 mm Hg/46 mm Hg, and her blood sugar level was 0.99 mmol/L (18 mg/dL). In the emergency room, significant respiratory distress was noted, and a chest x-ray revealed bilateral pneumonia. She was admitted to the intensive care unit, intubated, and started on vasopressors. The persistence of hypoglycemia despite multiple dextrose boluses in addition to the presence of severe hypotension and sepsis raised the possibility of adrenal crisis. The patient was started on stress doses of hydrocortisone. A cortisol level of 17.3 nmol/L (55.2 to 331.0 nmol/L) confirmed the diagnosis of adrenal insufficiency. An abdominal ultrasound did not show adrenal gland hemorrhage. Computed tomography scan of the abdomen, a more sensitive test for hemorrhage, was initially deferred because of the severity of the child’s illness, but later confirmed that no hemorrhage was present. Tuberculosis was considered, but the skin test (purified protein derivative) was negative with a positive Candida control.

Despite steroid treatment for the adrenal insufficiency, the child could not be weaned from the glucose drip without becoming hypoglycemic. Her serum sodium, potassium, and

| Immunoglobulin levels at the initial evaluation: |
| IgG: 419 mg/dL (663–1447) IgA: 7 mg/dL (23–209) IgM: 39 mg/dL (43–214) IgE: 1 kIU/L (1–145) |
| IgG1: 358 mg/dL (292–816) IgG2: 5 mg/dL (83–513) IgG3: 46 mg/dL (8–111) IgG4: 2 mg/dL (1–12) |

| Immunoglobulin levels prior to initiation of IVIG: |
| IgG: 386 mg/dL (633–1535) IgA: < 7 mg/dL (23–209) IgM: 23 mg/dL (48–228) |

| T and B cell markers at the initial evaluation: |
| CD3: +: 8428/mm³ (1072–3890), 86% (55–82) CD4+: 5586/mm³ (562–2692), 57% (27–57%) |
| CD8+: 2842/mm³ (331–1445), 29% (14–34%) NK (CD16+ and/or CD56+ CD33: 392/mm³ (15–300), 4% (1–15%) CD19+ (B4): 980/mm³ (200–1259), 10% (9–29%) |
| Concurrent complete blood count: hemoglobin 12.3 g/dL (11.7–15.9), white blood cell count 17.9 cells/cumm (4.1–1259), differential–35% neutrophils, no bands, 55% lymphocytes, 7% monocytes, 3% eosinophils, and platelet count 449 platelets/mm³ (130–450), normal in size and morphology. |

| Lymphocyte proliferation: by ³H-thymidine incorporation (cpm) |
| (expected response is 20–100 times the control cpm) Control lymphocytes: 182 cpm. Stimulated with phytohemagglutinin at 5 µg/mL: 2155 cpm |
| PWM 40 µg/mL: 195 cpm and concanavalin A 100 µg/mL: 3029 cpm |

| Antibody titers: |
| Response to pneumococcal polysaccharide: (Protective with antibody titers > 2.0 µg/mL, appropriate with fourfold increase) Prevaccine titers to 3 serotypes 3 = 0.4 µg/mL 7F = 0.0 µg/mL 9N = 0.0 µg/mL 14 = 0.0 µg/mL Postvaccine titers to 3 serotypes 3 = 0.6 µg/mL 7F = 0.1 µg/mL 9N = 0.1 µg/mL 14 = 0.2 µg/mL |
| Response to H. influenzae b (Hib) boosters (patient had previously received vaccine): Prebooster: 0.4 µg/mL, postbooster: 3.3 µg/mL (protective >2.0) at the initial evaluation. One year later: Hib: 0.3 µg/mL, post-second booster titer: 2.0 µg/mL |

| Other titers (on initial presentation): Mumps IgG: <1:8 (not protective), Measles IgG: 1.61 (protective >0.69), Rubella IgG: 3.33 (protective >0.99), Varicella IgG: 4.83 (protective > 2.39) (no history of infection elicited, no vaccine administered) |

**HIV DNA by PCR:** negative.

*All standards are age adjusted.
cpm, counts per minute.*
bicarbonate levels remained within normal range, suggestive of adrenal insufficiency secondary to adrenocorticotropic hormone deficiency. An associated growth hormone (GH) deficiency would also explain the persistent hypoglycemia. The diagnosis of panhypopituitarism was substantiated after levels of GH obtained while the patient was still hypoglycemic were undetectable. The thyroid-stimulating hormone level was 0.1 mIU/L (0.2 to 4.7 mIU/L), thyroxine level was 12.9 nmol/L (71 to 165 nmol/L) and prolactin level was undetectable. The bone age was significantly delayed at 71 months, with a chronologic age of 107 months. This suggested that partial pituitary hormonal deficiencies might have been present for some time before overt symptoms occurred.

Recombinant human GH (rhGH) was administered, resulting in rapid improvement of glycemic control. Brain MRI showed an atrophic anterior pituitary gland (Fig. 1). This finding suggested pituitary gland destruction caused by autoimmune lymphocytic hypophysitis.

Two years after adrenal crisis, the patient is still doing remarkably well. She remains on monthly IVIG infusions, with trough IgG levels of 850 to 950 mg/dL. She is also currently on hormonal replacement therapy with levothyroxine, hydrocortisone, and rhGH. She grew 5.7 cm during the first year on this therapy and 4.8 cm during the second year.

DISCUSSION

CVID is an incompletely defined syndrome characterized by defective antibody formation. Patients are usually seen because of recurrent pyogenic sinopulmonary infections in the second or third decade of life. Although the mode of inheritance is not well established and the genetic defect(s) is not clearly identified, it is well recognized that in approximately 25% of CVID cases, there is a family history of IgA deficiency and/or CVID.

At the time of diagnosis, children with CVID, unless affected by another underlying disease or infection, usually are not seen because of failure to thrive or poor growth. Once IVIG infusions and adequate management of any underlying infections are undertaken, these children can grow normally and reach expected adult height. Our patient remained small (growing slightly below the third percentile for height and weight “following her own curve”). In retrospect, this may have been partially the result of hormonal insufficiency. Our patient was not initially considered to have failure to thrive because of the weight gain along the third percentile and because of a possibility of familial short stature (mother and grandmother were both less than 5 feet tall). However, the rapid weight gain after treatment for panhypopituitarism makes it more likely that her poor growth was a consequence of endocrinopathy.

Various endocrinopathies have been reported in association with immune deficiencies. An isolated GH deficiency associated with an X-linked form of hypogammaglobulinemia is well established. Interactions between endocrine and immune systems have been described, primarily involving GH, insulin-like growth factor, and cortisol. One case report shows an association of congenital hypothyroidism with severe immunodeficiency. CVID is, however, often associated with autoimmune diseases, and we therefore considered the possibility of an autoimmune process involving the anterior pituitary gland. There is one previous case report of panhypopituitarism associated with hypogammaglobulinemia that is thought to be secondary to autoimmune disease.

Lymphocytic hypophysitis is an autoimmune process characterized by destruction and lymphocytic infiltration of the pituitary gland, with or without a mass lesion. It leads to various degrees of hypopituitarism that classically involve loss of adrenocorticotropic hormone and GH before the loss of other pituitary hormones. This can be differentiated from adenomas, which tend to first affect thyroid-stimulating hormone and cells that produce follicle-stimulating hormone/luteinizing hormone, and which frequently cause prolactin levels to increase as the result of compression of the pituitary stalk. Some characteristic findings on MRI can help in making the diagnosis of lymphocytic hypophysitis, especially in the early active stages of the disease, when a high signal on T2-weighted images can be noted. These findings are caused by active inflammation, edema, and hyperemia, and therefore are not necessarily specific. In later stages of the autoimmune process, atrophy and even empty sella have been reported. The optic chiasma can also be involved, with visual field defects noted on the physical examination.

Lymphocytic hypophysitis is a rare disorder usually associated with pregnancy and the postpartum state. The first case of lymphocytic hypophysitis was described by Goudie and Pinkerton in 1962 in a young woman who had recently...
given birth. The youngest biopsy-proven case is in a 9-year-old girl. Male patients have been reported, but there is a marked female predominance (84% of reported cases).

The diagnosis of lymphocytic hypophysitis can be made by biopsy when surgery is indicated (ie, with pituitary gland enlargement). The pituitary gland may, however, become atrophic, even progressing to empty sella syndrome. In the absence of a biopsy or autopsy, confirmation of the diagnosis remains a challenge. Detection of pituitary autoantibodies has been attempted since the mid-1970s. Methodologic problems inherent to pituitary immunofluorescence studies have made the test unreliable for diagnostic purposes. The diversity of anterior pituitary antigens used for the experimental assays adds to the technical problems.

CVID patients, although prone to autoimmune diseases, usually do not have detectable autoantibodies, and antibody testing is further complicated by the IVIG these patients receive as treatment.

The MRI of our patient showed an atrophic anterior pituitary gland, supporting autoimmune lymphocytic hypophysitis, and leading to panhypopituitarism. Fortunately, she survived and did not require surgery, thus neither surgical nor autopsy tissue were available for immunofluorescence staining. This case does suggest, however, that patients with CVID are susceptible to autoimmune lymphocytic hypophysitis, and that signs or symptoms suggestive of hypopituitarism should be investigated promptly in these patients to avoid a potentially life-threatening adrenal crisis.

CONCLUSION
We report a case of pediatric panhypopituitarism associated with CVID. MRI findings of atrophy support the contention that this is secondary to late autoimmune lymphocytic hypophysitis. CVID patients should be monitored regularly for evidence of autoimmune disease. Pituitary gland function should be evaluated in patients who have poor growth despite adequate therapy. Knowledge of this possible complication may allow for an early diagnosis and initiation of appropriate hormonal replacement therapy before the occurrence of a life-threatening event such as an adrenal crisis.

REFERENCES

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