ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY (1999) 17: 59-62

CASE REPORT

Effect of IVIG on the Hair Regrowth in a Common Variable Immune Deficiency Patient with Alopecia Universalis

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SUMMARY **Common variable immune deficiency (CVID) is associated with a variety of autoimmune diseases. Alopecia universalis (AU), believed to have an autoimmune basis, has been found in 1.6% of patients with CVID. Intravenous immunoglobulin (IVIG) therapy is used in various immunodeficiency disorders including CVID, and benefit has been shown in the therapy of autoimmune diseases. We report a patient with CVID and AU treated with IVIG who experienced significant hair regrowth. An 8-year-old girl with CVID and AU was treated with IVIG 400 mg/kg every 4 weeks. Since her second dose of IVIG, regrowth of eyelashes, eyebrows, body and scalp hair was observed in this patient. At present, about 1 year treat-ment of IVIG, significant hair regrowth is noted with 5-6 cm of scalp hair. We believe that IVIG may be beneficial in the treatment of AU, at least in patients with CVID.**

Common variable immune deficiency (CVID) is a primary immunodeficiency disease characterized by recurrent bacterial infections, hypogammaglobulinemia, and impaired antibody responses. Most patients have a normal or modestly decreased number of circulating B lymphocytes and intact cell-mediated immunity. However, T cell dysfunction is demonstrable in a significant subset of affected individuals. In addition to a propensity towards frequent and severe infections, such patients have an increased risk of developing autoimmune disease. Alopecia universalis, believed to be a result of autoimmune mechanisms, has been previously reported in patients with CVID. We report the first case of a patient with CVID and alopecia universalis who experienced significant hair regrowth following the institution of intravenous immunoglobulin (IVIG) therapy.

CASE REPORT

An 8-year-old female child was evaluated because of a history of repeated upper respiratory infections, bronchitis, sinusitis and otitis media. There was no history of pneumonia, meningitis, sepsis, oral candidiasis, or urinary tract infection. An eczematous rash involving the flexor surfaces of her arms and cheeks developed, and was treated with topical steroids. Alopecia universalis developed at 4 years of age with complete scalp, eyelash, eyebrow, and body hair loss. This did not improve with conventional therapy consisting of intralesional steroid injections. Monoarthritis of the right knee occurred associated with negative ANA and rheumatoid factor. Her family history was notable for asthma in her maternal aunt and rheumatoid arthritis in her maternal grandmother.

Physical examination revealed complete loss of scalp hair, eyelashes, eyebrows, and body hair.

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An erythematous rash involving the right antecubital fossa and a dry erythematous rash on the left side of her face were present. HEENT examination was normal. There was no significant lymphadenopathy. Her lungs were clear to auscultation and cardiac examination was normal. Hepatosplenomegaly was not present. Mild non-tender swelling of the right knee was found.

Laboratory studies demonstrated Hgb 13 g/dl (normal 11.5-14.8 g/dl), Hct 36.9% (normal 36-46%); WBC 3,600 cell/mm^3 (normal 5,000-14,500) with 54% neutrophils, 36% lymphocytes, 6% eosinophils, 3% monocytes and 1% basophils; and platelets 271,000 (normal 130,000-400,000). Panhypogammaglobulinemia was present with IgG of 405 mg/dl (normal 672-1,584), IgA of 25 mg/dl (normal 29-267), and IgM of 25 mg/dl (normal 48-247). IgE was within normal limits at 5 IU/ml (normal 0-90). Assay of IgG subclasses demonstrated IgG1 of 268 mg/dl (normal 428-943), IgG2 of 51 mg/dl (normal 100-263), IgG3 of 57 mg/dl (normal 31-114), and IgG4 < 7 mg/ml (normal 11-620). Initial antibody titers revealed diphtheria 0.036 AU/ml (normal > 0.010), tetanus 0.810 IU/ml (normal >0.100), and pneumococcal antibody type 3 of 630, type 7 of 420, type 9 of 80, and type 14 of 270 (normal > 200 ng/ml). Following immunization there was a significant antibody response of diphtheria to 0.496 AU/ml and tetanus to 2.770 IU/ml, but a poor antibody response to pneumococcus with type 3 of 460 ng/ml, type 7 of 240 ng/ml, type 9 of 150 ng/ml, and type 14 of 240 ng/ml. Lymphocyte phenotyping demonstrated CD2+ cell = 61% (normal 78-82%), CD3+ cell = 56% (normal

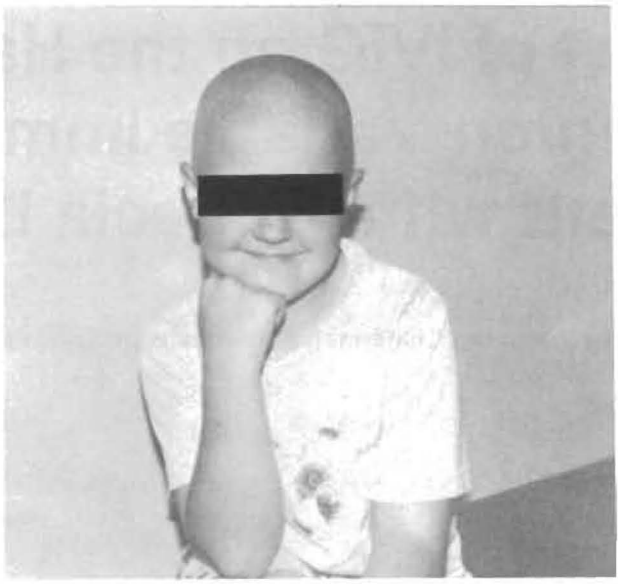

Fig. 1 Effect of IVIG on the hair regrowth in a common variable immune deficiency patient with Alopecia universalis, before IVIG treatment.

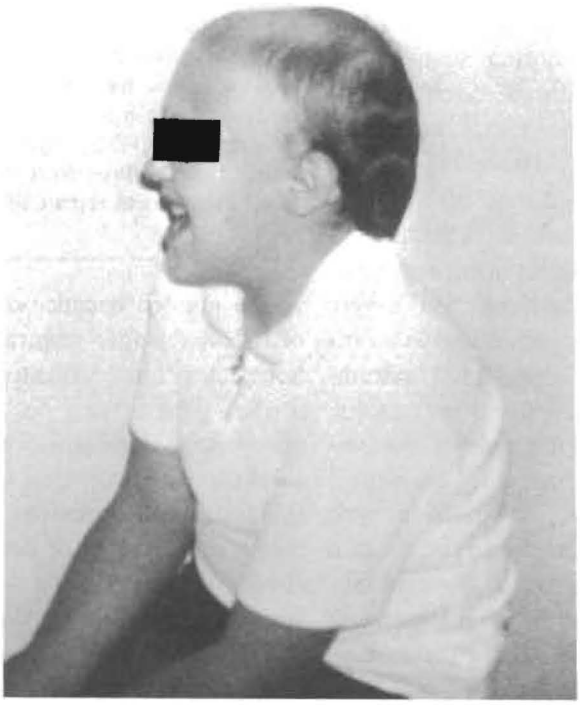

Fig. 2 Effect of IVIG on the hair regrowth in a common variable immune deficiency patient with Alopecia universalis, one year after IVIG treatment.

70-75%), CD4+ cell = 36% (normal 41-47%), CD8+ cell = 21% (normal 23-29%), CD19+ cell = 24% (normal 10-14%), and CD56+ cell = 14% (normal 9-13%). Lymphocyte responses to mitogens were uniformly depressed with phytohemagglutinin 25.0 μg/ml = 20,430 cpm (control 25,909-60,219), concanavalin-A 20.0 μg/ml = 721 cpm (control 18,086-34,698), pokeweed mitogen 0.5 mcg/ml = 5,127 cpm (control 16,125-35,549).

A diagnosis of common variable immunodeficiency (CVID) was made, and the patient was started on intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg every four weeks. This treatment was well tolerated. Her condition improved and she remained free of infection. Hair regrowth was noted since the second dose of IVIG with 2-4 mm of both eyelashes and body hair on the back of her neck, as well as 1-2 mm of scalp hair. At present, after about one year treatment of IVIG, she has rare infections, mostly viral upper respiratory tract infections, which have not required antibiotics. Her health is otherwise very good. Significant hair regrowth is noted with 5 - 6 cm of scalp hair. She continues to receive 18 gm of IVIG every 4 weeks.

DISCUSSION

CVID is a primary immunodeficiency in which B lymphocytes produce no or low levels of serum IgG and IgA, and often IgM as well. This results in recurrent bacterial, viral, and some protozoal infections. The majority of patients have normal numbers of B cells in the peripheral blood, but these B cells may have an intrinsic defect. Other abnormalities demonstrated include a significant decrease in the number of CD4+ T cells, as well as abnormalities of T cell function as shown by depressed lymphocyte proliferation to mitogens and antigens. Cytokine production is often abnormal with reduced IL2, IL4, and interferon secretion, but enhanced IL6 production.

CVID is also associated with a variety of autoimmune diseases in about 20% of cases.[1] These include autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, rheumatoid arthritis, Crohn's disease, ulcerative colitis, anti IgA antibodies, and alopecia. In general, females appear more likely to develop these than males. Alopecia totalis has been found in 1.6% of patients with CVID.[2]

The cause of alopecia universalis is unknown, but there is considerable evidence which suggests an autoimmune etiology. This is derived primarily from skin biopsy results in affected individuals. Notable findings include increased numbers of T cells infiltrating the follicular, perifollicular, and perivascular areas. These T cells are predominantly CD4+ cells.[3] Abnormal expression of MHC I molecules has been noted by proximal hair follicle cells, which are generally MHC I negative. There is also increased MHC II and IL2 receptor expression by follicular and perifollicular cells, and an increased number of MHC II+ Langerhans' cells in the dermal papillae. Adhesion molecules are expressed in increased amount with E-selectin (ELAM-1) by dermal endothelial cells, and ICAM-1 by follicular epithelial and dermal endothelial cells.[4,5] Lastly, a decrease in the degree of vascularization around hair follicles and thickening of the blood vessel walls have been noted.[4]

In an attempt to correlate these pathologic changes with a proposed autoimmune process, Paus *et al.*[6] proposed that in alopecia areata, the anagen hair follicle becomes susceptible to autoimmune attack when there is abnormal expression of MHC I on proximal follicular matrix. Normally, MHC I expression by epithelial cells is suppressed by melanocyte stimulating hormone (MSH). However, MSH can be antagonized by proinflammatory cytokines such as IL1. Gamma interferon (IFN-gamma) and tumor necrosis factor (TNF) can also induce expression of MHC I. In the presence of MHC I, melanogenesis-related proteins derived peptide autoantigen is presented by melanocytes and keratinocytes to CD8+ cells. The presence of CD8+ cells is enhanced by the increased expression of adhesion molecules such as ICAM-1 and E-selectin. Finally, secondary immune responses occur involving CD4+ cells which may in fact be responsible for a majority of the follicular damage that occurs.[6]

Intravenous immunoglobulin therapy has become standard treatment in patients with CVID. It has also been shown to be effective in a variety of autoimmune diseases.[7,8] Spickett *et al.*[9] have reported three patients with CVID and alopecia totalis who received IVIG. In these cases there was no improvement of alopecia noted.[9] Our patient, however, experienced prompt and impressive hair regrowth following the institution of IVIG. The mechanism by which IVIG could be beneficial in the

treatment of AU includes a suppression of the spontaneous release of IL1, TNF and IFN-gamma by peripheral blood mononuclear cells.[10,11] IVIG has also been shown to decrease expression of adhesion molecules including ICAM-1 and E-selectin.[10] Finally, modulation of T cell function might occur via the presence of anti-idiotypic antibodies.[12]

In summary, alopecia universalis possesses characteristics suggestive of an autoimmune basis. Given the increasing role of IVIG in the therapy of autoimmune diseases, it is reasonable to believe such therapy might be beneficial for patients with AU. Indeed, we report a patient with CVID and AU where such benefit was clearly seen. We believe that further studies are warranted in assessing the role of IVIG in the treatment of AU.

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