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**SHORT COMMUNICATION**

# Vogt-Koyanagi-Harada associated with diabetes mellitus and celiac disease in a 3-year-old girl

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PURPOSE. *To present a case of Vogt-Koyanagi-Harada (VKH) associated with type I diabetes mellitus and celiac disease in a 3 year old female.*
METHODS. *We studied a three-year old female who presented with clinical manifestation of VKH and type I Diabetes mellitus and ciliac disease.*
RESULTS. *Patient was found to have hyperglycemia with type I diabetes mellitus. Duodenal mucosal biopsy specimen confirmed the diagnosis of celiac disease. Patient's ocular inflammation was treated by topical and systemic corticosteroid and immune-suppressive therapy. Her diabetes mellitus was controlled by insulin and her celiac disease was controlled by gluten-free diet.*
CONCLUSIONS. *The association of VKH with two autoimmune diseases (celiac disease and type I diabetes mellitus) is rare. This case is, to our knowledge, the youngest patient reported with VKH. (Eur J Ophthalmol 2006; 16: 173-7)*

KEY WORDS. *Vogt-Koyanagi-Harada, IDDM, Celiac Disease*

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## INTRODUCTION

Vogt-Koyanagi-Harada (VKH) is a potentially blinding disease and represents an autoimmune insult against components of melanin-bearing cells. The disease is characterized by an acute onset with chronic progressive bilateral panuveitis associated with exudative retinal detachment. VKH may be associated with signs of meningeal irritation with or without auditory disturbances and skin changes (1). Associations with other autoimmune disorders have been reported (2-4). VKH may occur in children but the condition is rare (5, 6). In Saudi Arabia, VKH has been found to be a common cause of uveitis (7). The disease is uncommon in the United States and European countries. Clinical manifestations of VKH disease are well outlined but the exact etiology and therapy for this condition remain to be elucidated. Evidence suggests involvement of a T-lymphocyte-mediated autoimmune process directed against as yet unidentified antigen or a group of antigens associated with the melanocytes. Although the exact target antigen has not been identified, several candidates had been proposed. These include tyrosinase or tyrosinase-related proteins and unidentified 75 kDa protein obtained from cultured human melanoma cells (G-361), and the S-100 protein (8-10). The mechanism that triggers this autoimmune attack against


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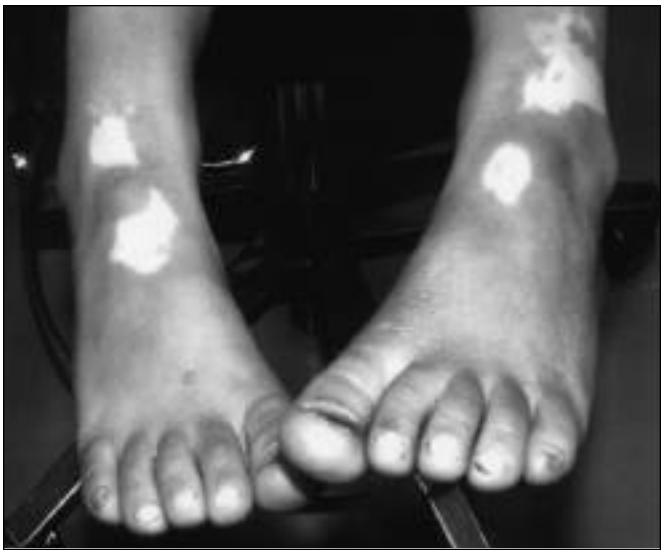

**Fig. 1 -** *Patches of vitiligo over feet.*

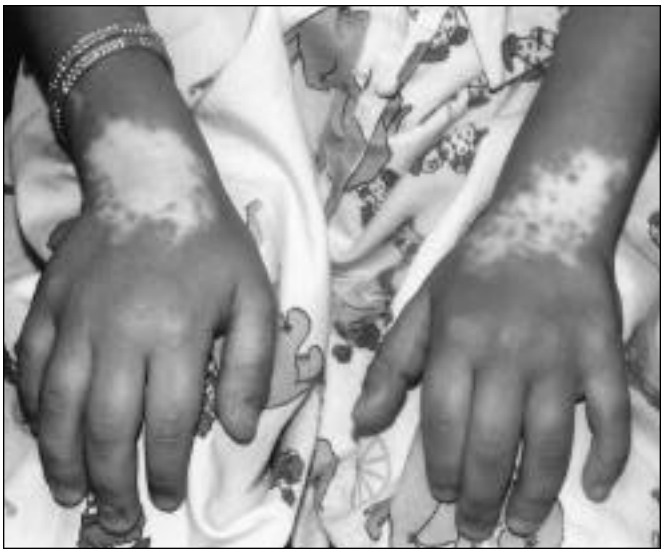

**Fig. 2 -** *Patches of vitiligo over arms.*

**Fig. 3 -** *Abdominal distention secondary to celiac disease.*

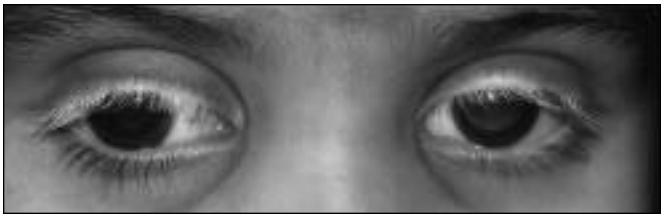

**Fig. 4 -** *Poliosis of both eyes.*

melanocytes is unknown but sensitization to melanocytic antigens by means of cutaneous injury or viral infections has been proposed as possible factors in some cases (11). Disturbed expression of Fas/FasL on CD4(+) and CD8(+) T cells were found in patients with VKH (12, 13). VKH disease is common among communities with heavy pigments such as Hispanics (Mestizos), Asians, Native Americans, Middle Easterners, and Asian Indians, but not black subjects of sub-Saharan African descent (1, 7, 14-16). Genetically determined susceptibility to the triggering event for VKH disease has been suggested. Increased risk among those with certain HLA genotypes showing strong association with the DRBI*0405 and DRBI*0410 and VKH disease were previously reported (17-19). VKH has been reported in association with diabetes mellitus (3, 20).

To our knowledge, the association of VKH disease with type I diabetes mellitus and celiac disease has not been previously reported. The purpose of this article is to report

a case of VKH disease in a 3-year-old girl with type I diabetes mellitus and celiac disease.

## Case report

A 3-year-old Saudi girl presented with history of decrease in vision associated with recurrent episodes of abdominal pain. The patient had recurrent episodes of redness and progressive rapid loss of vision followed by vitiligo (Figs. 1, 2), headache, and poliosis of the eyelashes. The patient also developed alopecia. The patient was evaluated by a pediatrician who found evidence of type I diabetes mellitus and celiac disease proven by antibodies to endomysium and tissue transglutaminase histopathologic studies of duodenal biopsy specimen (Fig. 3). There was no history of trauma and no history of arthritis. Family history was significant by the fact that parents were first cousins and her elder sister had congenital hypothyroidism.

On eye examination, the patient was found to have a visual acuity of light perception and projection in both eyes. Tension by applanation was 20 mm Hg in the right eye and 25 mm Hg in the left eye. Biomicroscopy of the right eye revealed poliosis of eyelashes (Fig. 4). There was mild conjunctival hyperemia and the cornea showed large mutton fat keratic precipitates over the lower quadrants of the endothelium. The anterior chamber was shallow with peripheral anterior synechiae. 4+ cells and 3+ flare were noted. There was also posterior synechiae and a cataractous lens. Biomicroscopy of the left eye revealed poliosis of eyelashes. There was mild conjunctival hyperemia. The cornea showed large diffuse mutton fat keratic precipitates. The anterior chamber showed shallow depth with 4+ cells and 2+ flare. There was evidence of peripheral anterior synechiae. Posterior synechiae was noted with an opaque cataract. Diagnostic ultrasonography showed bilateral exudative retinal detachment.

The patient was treated for her type I diabetes mellitus and celiac disease. She was started on insulin and gluten free diet. She was also started on intravenous methylprednisolone pulse therapy and her blood sugar was controlled by insulin sliding scale. In addition, she was given cyclosporine 5 mg/kg orally per day with good control of her bowel symptoms. Topical 1% prednisolone acetate eyedrops were given every hour, and topical dexamethasone 0.5% ophthalmic ointment to both eyes at bedtime. She was given Betagan 0.5% eyedrops to both eyes every 12 hours and dorzolamide 2% eyedrops to both eyes twice daily. Following therapy, the patient had improvement of her anterior uveitis and resolution of her exudative detachment over the next 3 weeks. Poliosis and vitiligo increased over her face, arms, and trunk. The patient underwent uneventful bilateral lens aspiration. The postoperative inflammation was controlled with intensive local and systemic steroid. Visual outcome, however, was poor due to severe retinal pigment atrophy and degeneration (Fig. 5).

## DISCUSSION

VKH disease is a chronic systemic disorder leading to bilateral granulomatous inflammation of the eyes associated with auditory disturbances, meningitis, vitiligo, poliosis, and alopecia. The disease is rare in children and may represent an autoimmune insult to the beta islets of the pancreas and to the intestinal mucosa. VKH is an immune-mediated disorder leading to damage of melanin bearing cells. The exact mechanisms that trigger the autoimmune process are unknown. Immunization with melanocytes, specific proteins, and tyrosinase-related proteins can induce an experimental form of the immune disease in Lewis rats that resembles human form of VKH disease (9). In this patient, the diagnosis of sympathetic ophthalmia was ruled out by the absent history of penetrating injury or ocular surgery to the eye prior to the onset of her uveitis. Until specific features of laboratory abnormalities of VKH disease are identified allowing more precise definition of the disease, we shall utilize criteria for diagnosis of VKH disease as previously outlined (1). The exact etiology of this disorder is not known.

Immunogenetic factors play a role in the pathogenesis of VKH disease. The higher frequency of HLA-DR4 among Japanese patients with VKH as well as the strong association between HLA DRB*0405 and HLA DRB1*0410 and VKH may indicate a genetic susceptibility to this disorder (17, 18). VKH may represent an autoimmune process directed against certain antigen or group of antigens in melanin-bearing cells. The clinical course of VKH disease is variable. Some patients have limited episodes of inflammatory activity while others have recurrent smoldering episodes of severe intraocular inflammation leading to destruction of the posterior segment ocular structures with rapid deterioration in vision. Systemic high dose corticosteroids may inhibit the inflammatory changes within the eye but spontaneous attachment of non-rhegmatoge-

nous exudative retinal detachment is apparent in most patients with VKH.

The course of VKH is usually more aggressive in children than in adults (5). In a study of 13 patients with VKH in children, the authors found that the final visual acuity was worse in children than in adults. The ocular complications are more frequent and more severe in children than in adults.

Despite therapy, final visual outcome in children with VKH is poor. Ocular complications contributing to loss of vision in children with VKH disease include glaucoma, cataract, significant retinal pigment epithelial proliferation, retinochoroiditic fibrosis, and subretinal neovascularization.

Glaucoma is a common complication of VKH and may occur in 46% of children and 14% of adults (5). The increase in intraocular pressure may be secondary to the immune-mediated damage to the melanin-bearing cells in the trabecular meshwork.

The majority of children with VKH disease develop ocular findings preceding the onset of systemic findings (5, 6). In our patient, the ocular findings preceded the vitiligo, poliosis, diabetes mellitus, and celiac disease. Indeed, our patient developed uveitis before the discovery of other autoimmune disorders. Early aggressive therapy with immunosuppressive agents should be considered in the management of patients with VKH disease.

The association of VKH with type I diabetes mellitus and celiac disease is intriguing. Celiac disease is a small bowel enteropathy due to an immune-mediated hypersensitivity to gluten. Celiac disease has been associated with type I diabetes mellitus and other autoimmune disorders (21-27). Both type I diabetes mellitus and celiac disease appear to be mediated by an autoimmune process. Immunologic screening should always be considered at the time of diagnosis of celiac disease for possible associated other autoimmune disorders.

The association of VKH with multiple autoimmune disorders has been a known phenomenon (28). The association of childhood celiac disease and diabetes mellitus varies in different populations. In western countries, it is estimated that 1.5 to 4.5% of patients with celiac disease have type I diabetes mellitus. The majority of cases present as diabetes and subsequently develop celiac disease. The diagnosis of celiac disease in a child with type I diabetes mellitus and VKH disease whose parents are first cousins and whose sister has hypothyroidism suggests genetically determined etiology. Unfortunately, HLA typing was not carried out on this patient. Diagnosis of celiac disease and type I diabetes mellitus is more common in patients who are the product of consanguineous marriages.

To our knowledge, this is the first case of a 3-year-old child with VKH disease associated with celiac disease and type I diabetes mellitus. The treatment of this condition can pose a dilemma. The use of high-dose steroids may aggravate type I diabetes mellitus, which requires higher doses of insulin.

Systemic suppression with cyclosporine may prevent the acute exacerbation of this inflammatory disease. Management of this patient with three disorders was a challenge. Future therapy should be focused on strategies that can make the individual tolerant to the auto antigen in order to abrogate the autoimmune process. The trigger that initiated these disorders is unknown. Future search for the trigger of the disease is highly desirable to elucidate the pathogenesis and design new approaches for its treatment.

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## REFERENCES

1. Read RW, Holland GN, Rao NA, et al. Perspective: Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease: Report of an International Committee On Nomenclature. Am J Ophthalmol 2001; 131: 647-52.
2. Federman DG, Kravetz JD, Ruser CB, et al. Vogt-Koyanagi-Harada syndrome and ulcerative colitis. South Med J 2004; 97:169-71.
3. Pezzi PP, Paroli MP, Priori R, et al. Vogt-Koyanagi-Harada syndrome and keratoconjunctivitis sicca. Am J Ophthalmol 2004; 137: 769-70.
4. Paroli MP, Pinca M, Speranza S, Marino M, Pivetti-Pezzi P. Paracentral corneal melting in a patient with Vogt-Koyana-

gi-Harada's syndrome, psoriasis, and Hashimoto's thyroiditis. Ocul Immunol Inflamm 2003; 11: 309-13.
5. Tabbara KF, Chavis PS, Freeman WR. Vogt-Koyanagi-Harada syndrome in children compared to adults. Acta Ophthalmol Scand 1998; 76: 723-6.
6. Rathinam SR, Vijayalakshmi P, Namperumalsamy P, Nozik RA, Cunningham ET Jr. Vogt-Koyanagi-Harada syndrome in children. Ocul Immunol Inflamm 1998; 6: 155-61.
7. Islam SM, Tabbara KF. Causes of uveitis at The Eye Center in Saudi Arabia: a retrospective review. Ophthalmic Epidemiol 2002; 9: 239-49.
8. Yamaki K, Gocho K, Hayakawa K, Kondo I, Sakuragi S. Tyrosinase family proteins are antigens specific to Vogt-Koyanagi-Harada disease. J Immunol 2000; 165: 7323-9.
9. Yamaki K, Kondo I, Nakamura H, Miyano M, Konno S, Sakuragi S. Ocular and extraocular inflammation induced by immunization of tyrosinase related protein 1 and 2 in Lewis rats. Exp Eye Res 2000; 71: 3619.
10. Kobayashi H, Kokubo T, Takahashi M, et al. Tyrosinase epitope recognized by an HLA-DR-restricted T-cell line from a Vogt-Koyanagi-Harada disease patient. Immunogenetics 1998; 47: 398-403.
11. Rathinam SR, Namperumalsamy P, Nozik RA, Cunningham ET Jr. Vogt-Koyanagi-Harada syndrome after cutaneous injury. Ophthalmology 1999; 106: 635-8.
12. Yang P, Ji L, Zhou H, et al. A. Disturbed expression of Fas/FasL on CD4(+) and CD8(+)T cells in Behçet's disease, Vogt- Koyanagi-Harada syndrome, and idiopathic anterior uveitis. Ocul Immunol Inflamm 2001; 9: 185-91.
13. Yang P, Chen L, Zhou H, et al. Resistance of lymphocytes to Fas-mediated apoptosis in Behçet's disease and Vogt-Koyanagi-Harada syndrome. Ocul Immunol Inflamm 2002;10: 47-52.
14. Weisz JM, Holland GN, Roer LN, et al. Association between Vogt-Koyanagi-Harada syndrome and HLA-DR1 and DR4 in Hispanic patients in living in southern California. Ophthalmology 1995; 102: 1012-5.
15. Arellanes-Garcia L, Bautista N, Mora P, Ortega-Larrocea G, Burguet A, Gorodezky C. HLA-DR is strongly associated with Vogt-Koyanagi-Harada disease in Mexican Mestizo patients. Ocul Immunol Inflamm 1998; 6: 93-100.
16. Goldberg AC, Yamamoto JH, Chiarella JM, et al. HLA-DRB1 *0405 is predominant allele in Brazilian patients with Vogt-Koyanagi-Harada disease. Hum Immunol 1998; 59: 183-8.
17. Shindo Y, Ohno S, Yamamoto T, Nakamura S, Inoko H. Complete association of the HLA-DRB1 *04 and DQB1 *04 alleles with Vogt-Koyanagi-Harada's disease. Hum Immunol 1994; 39: 169-76.
18. Shindo Y, Inoko H, Yamamoto T, Ohno S. HLA-DRB1 typing of Vogt-Koyanagi-Harada's disease by PCR-RFLP association with DRB1 *0405 and DRB1 *0410. Br J Ophthalmol 1994; 78: 223-6.
19. Nomura S, Matsuzaki T, Ozaki Y, et al. Clinical significance of HLA-DRB1 *0410 in Japanese patients with idiopathic thrombocytopenic purpura. Blood 1998; 91: 3616-22.
20. Yawata N, Nakamura S, Kijima M, et al. High incidence of glucose intolerance in Vogt-Koyanagi-Harada disease. Br J Ophthalmol 1999; 83: 39-42.
21. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ. Celiac disease associated with type 1 diabetes mellitus. Endocrinol Metab Clin North Am 2004; 33: 197-214.
22. Sabbatella L, Di Tola M, Picarelli A. The high frequency of coeliac disease and other autoimmune diseases in subjects affected by Type I (insulin-dependent) diabetes mellitus and in their first-degree relatives. Diabetologia 2002; 45: 748.
23. Winnock F, Van Autreve J, Gorus FK, Belgian Diabetes Registry. Beta-cell thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type diabetes. Clin Exp Immunol 2001; 126: 236-41.
24. Gillett PM, Gillett HR, Israel DM, et al. High prevalence of celiac disease in patients with type 1 diabetes detected by antibodies t endomysium and tissue trans glutaminase. Can J Gastroenterol 2001; 15: 297-301.
25. Collin P, Hakanen M, Salmi J, Maki M, Kaukinen K. Autoimmune hypopituitarism in patients with coeliac disease: symptoms confusingly similar. Scand J Gastroenterol 2001; 36: 558-60.
26. Galli-Tsinopoulou A, Nousia-Arvanitakis S, Dracoulacos D, Xefteri M, Karamouzis M. Autoantibodies predicting diabetes mellitus type I in celiac disease. Horm Res 1999; 52: 119-24.
27. Maruyama Y, Hayashi H, Takahashi K, Iino K, Kora Y. A case of insulin dependent diabetes mellitus following systemic treatment for Vogt-Koyanagi-Harada syndrome. Ophthalmic Surg Lasers 2000; 31: 487-90.
28. Egashira K, Yamamoto T, Tsuji S, Ohnishi A, Murai Y. A case of myasthenia gravis complicated with chronic rheumatoid arthritis with Vogt-Koyanagi-Harada disease. Rinsho Shinkeigaku 1987; 27: 859-61.