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EC DIABETES AND METABOLIC RESEARCH
Case Report

Late-Onset Type 1 Diabetes Mellitus Associated with Vogt-Koyanagi-Harada Syndrome

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Abstract

Introduction: Vogt-Koyanagi-Harada syndrome (VKH) is a very rare autoimmune disorder characterized by the association of uveitis with hypoacusis, meningeal syndrome and cutaneous signs. The association of this syndrome with diabetes mellitus, especially type 1, is only exceptionally reported in the literature. It poses both diagnostic and therapeutic problems. We report one case.

Case Report: A 42-year-old patient with no notable pathological history was explored for an acute decrease in visual acuity. Ophthalmologic examination revealed bilateral granulomatous uveitis associated with images of retinal vasculitis. The investigations concluded that there is VKH disease with ocular, neurological and cutaneous involvement. Systemic corticosteroid therapy was started. One-week check-up found high blood glucose levels repeatedly defining diabetes with ketoacidosis. The very short interval did not plead for the hypothesis of steroid-induced diabetes. The subsequent investigations concluded that there is associated type 1 diabetes mellitus and Hashimoto's thyroiditis.

Conclusion: During VKH syndrome, diabetes is often steroid-induced but it is important to remember, although extremely rare, the possible association with type 1 diabetes that can be revealed by systemic corticosteroids. Our observation is characterized by the association, in addition, with Hashimoto's thyroiditis. This triple association was reported only twice before.

Keywords: *Type 1 Diabetes Mellitus; Vogt-Koyanagi-Harada Syndrome; Hypothyroidism; Hashimoto's Thyroiditis; Autoimmunity*

Abbreviations

Anti-GAD: Anti-Glutamic Acid Decarboxylase Antibodies; Anti-IA2: Anti- Tyrosine Phosphatase-Related Islet Antigen 2 Antibodies; Anti-TPO: Anti-Thyroperoxidase Antibodies; fT4: Free Tetra-Iodothyronine; MRI: Magnetic Resonance Imaging; TSH: Thyroid Stimulating Hormone

Introduction

The Vogt-Koyanagi-Harada (VKH) syndrome, or better yet, disease, is a rare systemic condition characterized by diffuse granulomatous inflammation [1]. It affects preferentially young adults with a maximum incidence between 30 and 50 years, women and subjects with dark skin [2-4]. The exact cause of this disease is not yet well understood [2,3]; it appears to be multifactorial, involving both cellular and humoral immune dysfunction, a most often viral triggering infection, and a particular genetically predisposed susceptibility [3]. The HLA-DRB1 * 0405 allele is most frequently associated with the development of this disease [3,4].

The specific clinical presentation classically associates bilateral uveitis, typically total (panuveitis) and granulomatous, hypoacusis, lymphocytic meningitis and cutaneous signs such as vitiligo, alopecia or poliosis [2-4]. This derives from the pathogenesis of the disease where the dys-immune reaction mainly affects the tissues containing melanin (eyes, ears and skin) [3,4].

The disease can have variable clinical presentations (phenotypes) ranging from incomplete forms (probable VKH) to complete form or "definite VKH" and from acute to chronic forms. The diagnosis is currently based on the new diagnostic and classification criteria established in 2000 by the "International Committee on Vogt-Koyanagi-Harada Disease Nomenclature" [5].

The association of VKH disease with other autoimmune/dys-immune disorders is rarely reported; that with type 1 diabetes remains exceptional and only a few sporadic cases are found in the medical literature [6-8]. This association is particularly challenging for the cli-

nician, both diagnostically and therapeutically, especially in late-onset forms (type 2 diabetes mellitus or steroid-induced diabetes?) and difficulty in equilibrating diabetes with corticosteroid therapy prescribed for VKH [8,9].

We report an original case of VKH disease associated to late-onset type 1 diabetes mellitus and Hashimoto's thyroiditis in Tunisian adult.

Case Report

A 42-year-old Tunisian patient with no notable pathological history was explored for an acute bilateral decrease in visual acuity. Ophthalmologic examination revealed a bilateral total uveitis associated with images of retinal vasculitis. The somatic examination found an acrofacial vitiligo (Figure 1 and 2) and a poliosis of the eyebrows and scalp with multifocal involvement (Figure 3).

The etiological investigations of this bilateral granulomatous panuveitis were negative, eliminating in particular atypical bacterial or parasitic infection, systemic granulomatosis, granulomatous vasculitis, tuberculosis, as well as cancer or hematological malignancy.

Lumbar puncture showed aseptic lymphocytic meningitis (leukocytes = 15/ml with 80% lymphocytes, red blood cells = 1/ml, proteinorachie = 1.2g/l, glycorrhachia = 3.8 mmol/l for a blood glucose at 6.9 mmol/l, and negative direct examination and culture). Cerebral MRI and angio-MR were without significant abnormalities.

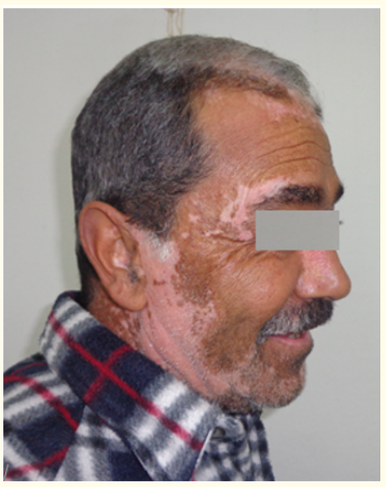

Figure 1: *Facial vitiligo.*

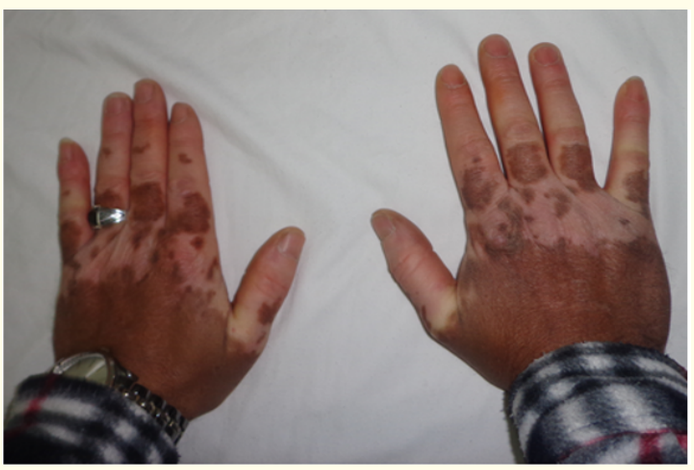

Figure 2: *Acral vitiligo.*

Figure 3: *Scalp poliosis.*

In front of the combination of bilateral panuveitis with poliosis, vitiligo, aseptic lymphocytic meningitis, and the negativity of other investigations, the diagnosis of VKH disease was retained. The patient was treated with methylprednisolone pulses at a dose of 1 g/day for three consecutive days, then with oral prednisone at a dose of 1 mg/kg/day.

The evolution was favorable on the ocular level. Systematic biological check-up after one week noted repeatedly high glycemic values that biologically defined diabetes: fasting glucose level at 10.5 mmol/l and postprandial glucose level at 18.9 mmol/l with ketoacidosis on the second day of surveillance.

The very short interval did not plead for the hypothesis of steroid-induced diabetes. In addition, the normal corpulence and the presence of vitiligo were suggesting type 1 diabetes. Anti-GAD autoantibodies were positive at 324 IU/l and anti-IA2 autoantibodies also positive at 22 IU. Thus, the diagnosis of type 1 diabetes was retained. Glycated hemoglobin A1c (HbA1) was at 7.1%. The patient was treated with analogues insulins according to the basal-bolus protocol balancing his basal plasma glucose levels and his postprandial blood glucose excursions.

Thyroid tests showed a TSH level at 28.3 µIU/ml, an fT4 level at 6.3 pmol/l, positive anti-TPO antibodies at 126 IU/ml (N < 8 IU/l) and positive anti-thyroglobulin antibodies at 68 IU/ml (N < 18 IU/l) consistent with the diagnosis of Hashimoto's thyroiditis. Oral thyroxin was prescribed in progressive doses until the normalization of TSH at 2.4 µIU/ml.

HLA typing was not performed for our patient.

Discussion

In patients with VKH, diabetes is classically either type 2 or secondary induced by systemic corticosteroids used as a basic treatment for this condition [12,13]. The distribution of diabetes in these cases is similar to that of type 2 diabetes in the normal adult population. The prevalence of type 1 diabetes in VKH is much rarer.

The review of the literature finds only nine cases of association of type 1 diabetes and VKH disease reported as sporadic cases (Table 1) [6-11]. As for the triple association (VKH, type 1 diabetes, and Hashimoto's thyroiditis), only two cases have already been published [6,9]. Our observation is, to our knowledge, the third reporting this exceptional autoimmune association.

Origin of patients [Ref]	Age/sex	Author associations	HLA typing	Number
Japon [6]	62/F	Palmoplantar Pustulosis and Hashimoto's thyroiditis	DR4 DR7 DRB1*0403, 0701 DQB1*0302, 0202 DQA1*0301, 0201	1
Japon [7]	30/F	Grave's disease	DRB1*0405 DQB1*0401	1
Japon [8]	29/M	-	DR9 DQB1*0303	1
Japon [6]	-/F	Nephrotic syndrome	-	1
Japon [6]	40/M	-	-	1
Japon [6]	75/F	-	DRB1*0405	1
Saudi Arabia [9]	45/M	Hashimoto thyroïdites	-	1
Saudi Arabia [10]	03/F	Coeliac disease	-	1
Australia [11]	11/M	Psoriasis and minor Thalassemia	DRB1*0405	1
Tunisia [our case]	42/M	Hashimoto thyroiditis	-	1
Total case				10

Table 1: *Association of VKH and Diabetes Mellitus type 1: Cases in the World Literature.*

F: Female; M: Male; VKH: Vogt-Koyanagi-Harada.

This association (VKH and Hashimoto thyroiditis) seems to be explained by a common dysimmunitary disorder, and once again it signs the autoimmune nature of VKH disease; in fact, recent data converge on the dysimmunitary theory that is increasingly being used as the source of VKH [2,3]. The main mechanism evoked is that of T-cell mediated autoimmunity directed against melanocytes [3]. This hypothesis is comforted by the association with other autoimmune/dysimmunitary pathologies such as Graves' disease [7], celiac disease [10], psoriasis [11], and palmar-plantar pustulosis [6], as well as multiple associations in the same patient as illustrated by the observations of Suzuki H (VKH, type 1 diabetes, and Graves' disease) [7], Nishi M (VKH, type 1 diabetes, and Hashimoto's thyroiditis) [6], Jaggarao N (VKH, type 1 diabetes, and Hashimoto thyroiditis) [9] and our case.

Our observation is also characterized by the late onset of type 1 diabetes. Indeed, de novo type 1 diabetes remains exceptional after the age of 30 [14]. It is a classic childhood and adolescent disease in which 85% of cases are diagnosed before the age of 20 and the incidence declines sharply after the age of 14 [15]. These late forms constitute only 2 to 5% of all cases of diabetes mellitus diagnosed after the age of 30 [16,17], but represent a real diagnostic challenge for the clinician because the clinic is not specific and the determination of specific autoantibodies is often difficult to perform and interpret at this age. Some authors even advocate the use of genetic susceptibility analysis to adjust the diagnosis in doubtful cases [16].

Systemic corticosteroids, which is the gold standard for the treatment of VKH disease, often prescribed in high doses (1 - 2 mg/kg/day) and sometimes initiated by intravenous pulses [1-4,13], is perhaps the condition revealing the type 1 diabetes remaining until then unknown. The time limit between the beginning of corticosteroid therapy and the diagnosis of diabetes is highly variable, ranging from a few weeks to several years [6,8,11].

For the dose of corticosteroid therapy in cases of VKH disease associated with diabetes (whatever the type), no particular recommendations has been found in the literature. Corticosteroid treatment of VKH is the same without dose reduction, and usually diabetes will be controlled by insulin therapy [6-11].

In addition, special monitoring of every patient with VKH treated with corticosteroid therapy is crucial because this condition can lead sometimes to severe metabolic complications such as hyperosmolar coma [7].

Conclusion

During the course of VKH syndrome, diabetes is often type 2 or steroid-induced but it is important to remember, although extremely rare, the possible association with type 1 diabetes that can be revealed by systemic corticosteroids. This association deserves to be known because of its clinical and therapeutic considerations. Our observation is to our knowledge, the third reporting the association of VKH disease with type 1 diabetes and Hashimoto's thyroiditis.

Conflicts of Interest

No conflicts of interest.

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