The Vogt–Koyanagi–Harada syndrome: association with autoimmune polyglandular syndrome type 1

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Summary

We describe a young woman with primary adrenal insufficiency, hypoparathyroidism (autoimmune polyglandular syndrome type 1), Graves disease, vitiligo, and alopecia universalis. Five years after the diagnosis, she presented with recurrent ophthalmological and neurological disorders as features of Vogt–Koyanagi–Harada syndrome. A marked therapeutic response was noted on systemic high-dose corticosteroid treatment. To the best of our knowledge, such a spectre of autoimmune diseases has not been reported previously.

Keywords: Vogt–Koyanagi–Harada syndrome, autoimmune polyglandular syndrome type 1

The Vogt–Koyanagi–Harada syndrome is a rare, but well documented clinical entity with probably cell-mediated autoimmune pathogenesis, marked by ocular, dermatological and neurological disorders of variable severity. The American Uveitis Society¹ established diagnostic criteria (box 1) in 1980.

Primary adrenal insufficiency, chronic mucocutaneous candidiasis and hypoparathyroidism define the autoimmune polyglandular syndrome type 1. Primary gonadal failure, vitiligo, alopecia, pernicious anemia, insulin-dependent diabetes, hypothyroidism, keratopathy, periodic malabsorption, chronic hepatitis and hypoplasia of dental enamel, nails, and tympanic membranes can be included.²

Case report

In 1988, a 20-year-old woman was admitted with a history of increasing fatigue, nausea and gradual, but complete, loss of body hair since

the age of 18 years. After menarche at the age of 15 years, she menstruated four or five times yearly and had no pregnancy. There was a five-year history of vitiligo. No history of endocrine disease among the patient's relatives was elicited. Examination revealed a warm pale skin, alopecia universalis, numerous patches of vitiligo and no sign of mucocutaneous candidiasis. Dental caries was extended. When supine, the pulse was 120 beats/min and blood pressure was 90/60 mmHg.

Investigations suggested adrenal insufficiency (box 2), which was confirmed by low plasma cortisol after intravenous administration of adrenocorticotropin, low plasma aldosterone and high plasma renin activity levels. A high free thyroxine and low thyroid-stimulating hormone after intravenous thyrotropin-releasing hormone stimulation (0.2 mg) revealed thyrotoxicosis. Scintiscan and ultrasound examination confirmed a small goitre. Hormone measurements are shown in the table. Shortly after introduction of hydrocortisone and methimazole therapy, serum calcium levels decreased to normal. Three months later, normal plasma thyroxine and cortisol were maintained on therapy and fludrocortisone was added. Menstrual cycles became regular, the ionized calcium level was 0.96 mmol/l (1.12–1.23), phosphate 1.89 mmol/l and parathyroid hormone 6.3 pmol/l. There were no signs of malabsorption. She had normal biochemical indices of renal, hepatic and haematological function. Hepatitis B surface antigen was not detected. Therapy with calcitriol was introduced.

Thyroid microsomal and thyroglobulin antibodies (1/10) were detected by indirect immunofluorescence, as were adrenal antibodies (1/

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Vogt–Koyanagi–Harada syndrome: diagnostic criteria

- no previous eye trauma
- posterior uveitis
- one or more of: bilateral iridocyclitis, papillitis, meningoencephalitis, pleocytosis of the CSF, deafness, alopecia, poliosis and vitiligo

Investigations of the patient's serum

Parameter	Values (normal range)
potassium (mmol/l)	5.2 (3.5–5.1)
sodium (mmol/l)	134 (136–146)
bicarbonate (mmol/l)	17 (24–32)
blood urea (mmol/l)	12 (3.3–8.3)
calcium (mmol/l)	3.15 (2.12–2.62)
phosphate (mmol/l)	1.5 (0.8–1.6)
albumin (g/l)	41 (34–55)
alkaline phosphatase (U/l)	60 (8–80)

Table Baseline hormone measurements and function tests (rapid adrenocorticotropin test and thyrotropin-releasing hormone test)

Parameter	Time (min)			Normal range
	0	30	60	
Cortisol (nmol/l)	110	142	192	166–710
Thyroid-stimulating hormone (mU/l)	0.4	0.5	0.4	0–9
Parathyroid hormone (pmol/l)	15			10–55
Thyroxine (nmol/l)	314			55–160
Follicle-stimulating hormone (mU/l)	7.2			4.5–20
Luteinising hormone (mU/l)	6.7			5–20
Oestradiol (nmol/l)	350			0.64–9.6
Progesterone (pmol/l)	0.2			74–440
Testosterone (nmol/l)	1.3			1.7–3.5
Aldosterone (nmol/l)				
supine	<0.03			0.03–0.42
upright	0.1			0.19–0.94
Plasma renin activity (nmol/l/h)				
supine	3.36			0.15–2.16
upright	6.1			1.16–4.39

20) against human adrenal tissue. Parathyroid antibodies were not determined. Smooth muscle, mitochondrial, antinuclear and parietal cell antibodies were negative. Cutaneous hypersensitivity was assessed by *Candida albicans* antigen and PPD, but no response was seen. Computed tomography (CT) showed the absence of calcification in the adrenals. Methimazole was excluded after 15 months of treatment.

In 1993 the patient was admitted with a history of cramping abdominal pain. She presented with a headache and a sudden painless bilateral visual acuity loss, with photophobia, oscilloscopia and a blind spot in the right eye. At that time she experienced two brief seizures. Intravenous hydrocortisone (150 mg) was introduced for three days due to impending adrenal crisis of uncertain cause with dramatic improvement. When peroral therapy with 40 mg hydrocortisone was started all symptoms and signs reappeared. Visual disturbance was unchanged. She developed dizziness, right hypoacusia, light dysphagia and nasal 'twang'.

Ophthalmological examination revealed a visual acuity of 6/50 bilaterally. Posterior uveitis and right optic disc swelling were seen. Echography showed a mild, diffuse low-reflective, chorioidal thickening and overlying exudative retinal detachment. Neurological examination revealed right palatal paresis. The superficial abdominal reflexes were lost. Audiometric evaluation revealed sensorineural impairment of the right ear. Pattern reversal visual evoked potentials showed bilaterally prolonged P100 latency. Brainstem auditory evoked potentials showed that wave V was absent on the right side. Examination of cerebrospinal fluid (CSF) revealed pleocytosis, predominantly lymphocytes. CSF albumin, IgG, IgA, IgM, and complement components were normal. Oligoclonal bands are not found by isoelectric focusing. The percentage of CD8(T suppressor cells) was lower in CSF (16%) than in peripheral blood (20%). The ratio of CD4 (T helper cells) to CD8 cells was higher in CSF (3.4) than in peripheral blood (2.4). CT showed no structural brain abnormalities. Repeated electroencephalograms

(EEGs) showed bilateral paroxysms of sharp and slow waves and left fronto-temporal spike discharges. Carbamazepine was initiated. Her HLA typing profile was A3A9, B18, DR4DR5, DRw52 DRW53, DQw3.

Topical and high-dose systemic corticosteroid (hydrocortisone 200 mg) treatment resulted in neurological, ophthalmological and otological recovery. Six weeks after presentation, her visual acuity was 6/6 (left eye) and 6/8 (right eye). Evoked potentials and EEG were normal. She took her replacement therapy regularly, with gradual tapering of hydrocortisone to 50 mg/day.

Seven months after the first attack of Vogt-Koyanagi-Harada syndrome she had a recurrence of thyrotoxicosis and had to be placed on methimazole. Thyroid microsomal and thyroglobulin antibodies were positive (1/80 and 1/40, respectively). Two weeks after, she presented with second attack of uveitis and right hemiparesis. During the following three months she remained on high-dose systemic corticosteroids. Neurological recovery was complete. Ophthalmological improvement was partially achieved. Skin and hair lesions persisted.

Discussion

Autoimmune polyglandular syndrome type 1 usually develops in children, but it can also be sporadic in young adults, as in this case. It is only rarely associated with Graves' disease,³ such that some reports find no association.^{2,4} This syndrome is sometimes accompanied by other autoimmune disorders, but the association with Vogt-Koyanagi-Harada syndrome has never been reported. Vogt-Koyanagi-Harada syndrome has only been reported in association with diabetes mellitus and hypothyroidism.⁵

At presentation, the patient had severe hypercalcaemia due to corticosteroid deficiency and thyroid hormone oversecretion.² Hyperparathyroidism was excluded by the suppressed serum parathyroid hormone levels. Probably, she had hypoparathyroidism at that time, but hypercalcaemia delayed the diagnosis

until corticosteroid replacement therapy unmasked it.² The occurrence of extensive caries, dry rough skin, and alopecia, which are commonly associated with hypoparathyroidism in autoimmune polyglandular syndrome type 1,² supported this opinion. Nevertheless, hypercalcaemia is not a common presentation of autoimmune polyglandular syndrome type 1, and for that reason, this case was particularly interesting.

Adrenal antibodies are positive even seven years after the onset of Addison's disease, which is not an unusual finding in this syndrome.³ Low plasma aldosterone levels also suggest an autoimmune origin.^{3,6} Persistence of thyroid antibodies may reflect a continuing autoimmune process. Existence of steroid cell antibodies in Addison's disease strongly correlates with concurrent ovarian failure.⁶ The importance of parathyroid antibody detection in autoimmune polyglandular syndrome is less clear⁴ since there is no significant prevalence even in idiopathic hypoparathyroidism. Melanocyte antibodies can only be detected in patients with vitiligo and autoimmune polyglandular syndrome type 1.⁷ It would be interesting to examine the serum of our patient for these antibodies, especially as she does not have hyperpigmented skin but does have Vogt-Koyanagi-Harada syndrome. It might be that melanocyte antibodies are responsible for the highly variable presentation of hyperpigmentation reported in autoimmune polyglandular syndrome type 1.⁴ Since vitiligo occurred before uveitis was diagnosed, it was difficult to confirm the additional effects of Vogt-Koyanagi-Harada syndrome on the course of the lesion.⁵ The response to *Candida albicans* skin test is often absent in autoimmune polyglandular syndrome type 1, as in this case.

Ophthalmological, dermatological and neurological findings were compatible with a diagnosis of Vogt-Koyanagi-Harada syndrome, which was confirmed by complementary investigations. A unifying mechanism for its diverse clinical manifestations affecting central nervous system, eye, integument and auditory system has not been found, although an autoimmune process was suggested.^{8,9} The percentage of helper T-cells was higher in CSF than in peripheral blood suggesting their important role in Vogt-Koyanagi-Harada syndrome.⁸

Autoimmune polyglandular syndrome type 1

- can be associated with Vogt-Koyanagi-Harada syndrome
- most common in children but also occurs sporadically in young adults
- rarely includes Graves' disease
- hypercalcaemia uncommon
- alopecia often accompanies hypoparathyroidism
- adrenal antibodies are positive years after onset of Addison's disease which is characterised by a highly variable pattern of hyperpigmentation
- melanocyte antibodies only detected in patients with vitiligo
- response to *C albicans* skin test often absent
- link with HLA not confirmed

Box 3

Vogt-Koyanagi-Harada syndrome

- can be associated with diabetes mellitus and hypothyroidism
- early systemic pulse and high-dose corticosteroid therapy is the recommended treatment

Box 4

The link with HLA in autoimmune polyglandular syndrome type 1 has not been confirmed except in a small subset of patients with increased HLA-A antigens.¹⁰ The presence of HLA DR4 and HLA DRw52 DRw53 haplotype may indicate susceptibility to Vogt-Koyanagi-Harada syndrome, but may not represent specific tissue involvement or determine the prognosis.⁹ Vitiligo was also strongly associated with HLA DR4.

The onset of Vogt-Koyanagi-Harada syndrome was masked by high doses of corticosteroids. On dose reduction the full picture was seen and recognised as a cause of the adrenocortical crisis. Although patients with Vogt-Koyanagi-Harada syndrome have limited therapeutic options, this finding supports the choice of early, pulse and high-dose systemic therapy in its treatment. It is of therapeutic and clinical interest to detect such associations of autoimmune diseases.

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