

Four patients with hypothyroid Graves' disease

A.J. Starrenburg-Razenberg^{1*}, M. Castro Cabezas¹, I.M. Gan², T.L. Njo³, A.P. Rietveld¹, J.W.F. Elte¹

Departments of ¹Internal Medicine and Endocrinology, ²Ophthalmology, ³Clinical Laboratory, Sint Franciscus Gasthuis, Rotterdam, the Netherlands, *corresponding author: tel.: +31 (0)10-461 61 61, fax: +31 (0)10-461 26 92, e-mail: arazenberg@hotmail.com

ABSTRACT

In autoimmune hypothyroidism (Hashimoto's disease), TPO (thyroid peroxidase) antibodies may be detected, while in autoimmune hyperthyroidism (Graves' disease) thyroid-stimulating hormone (TSH) receptor antibodies (TSH-R-ABs) are frequently present. Less well known is the fact that autoimmune hypothyroidism can present with TSH-R-ABs and ophthalmic Graves' disease (OGD). This condition is also known as hypothyroid Graves' disease. In this report we describe four patients with this uncommon phenomenon.

These four cases demonstrate that differences between Hashimoto and Graves' disease are less clear than expected. Hypothetically the thyroid cell might be 'attacked' by blocking and stimulating antibodies. Dependent on the relative concentrations, hypothyroidism or hyperthyroidism may occur. So the differences between Hashimoto's disease and Graves' disease, at least in these cases, may be gradual and small.

KEYWORDS

Hypothyroidism, Graves disease

INTRODUCTION

Functional disorders of the thyroid gland often result from autoimmune processes that either cause overproduction of thyroid hormones (Graves' disease) or glandular destruction and hormone deficiency (Hashimoto's disease). In Hashimoto's disease thyroid peroxidase antibodies (TPO-ABs) may be detected, while in Graves' disease thyroid-stimulating hormone (TSH) receptor antibodies (TSH-R-ABs) and TPO-ABs are frequently present.^{1,2} Less well known is the fact that autoimmune hypothyroidism can present with ophthalmic Graves' disease (OGD). This

condition is also known as hypothyroid Graves' disease and was already reported by Wyse *et al.* in 1968.³ In this report we describe four patients with this rather rare disorder.

CASE REPORTS

Case 1. A 60-year-old woman was referred to us by her ophthalmologist because of fatigue and her OGD, expressing in an unilateral lid retraction. Ten years before she was seen because of hypertension and Graves' disease including OGD for which she had been successfully treated with suppression and suppletion therapy. Ophthalmic treatment only consisted of topical lubricants for discomfort. At presentation laboratory tests showed elevated TSH (144 mU/l), low FT₄ (5.2 pmol/l), strongly positive TPO-ABs (185 IE/ml) and weakly positive TSH-R-ABs (1.0 IE/l). She received 75 µg of levothyroxine (L-T₄) daily. With that dosage she stayed euthyroid.

Case 2. A 44-year-old man was referred to our department by the ophthalmologist because of fatigue and weight gain. Few years earlier he underwent surgery on fibrotic extraocular muscles treating troublesome diplopia due to clinical OGD. However, he presented with new ophthalmic findings: mild periorbital oedema, unilateral lid retraction and exophthalmos of the right eye (*figure 1*). His medical history only revealed tonsillectomy. Furthermore he smoked ten cigarettes per day, which had previously been 25 cigarettes daily. Laboratory results were compatible with hypothyroidism (FT₄ 11 pmol/l, TSH 58.2 mU/l). Further investigations showed elevated TSH-R-ABs (56 E/l) and strongly positive TPO-ABs (399 IU/l). He started L-T₄ suppletion, 150 µg daily and remained under supervision of his general practitioner.

Figure 1. Ophthalmic Graves' disease of case 2



Case 3. A 69-year-old woman was referred by her ophthalmologist because of severe congestive Graves' ophthalmopathy and signs of optic nerve involvement. Her history revealed hypothyroidism for which she was under supervision by her general practitioner and received 100 µg of L-T₄ daily. At presentation she was euthyroid. Laboratory results showed normal TSH (3.8 mU/l), normal FT₄ (19 pmol/l), positive TSH-R-ABs 8.5 IE/l and TPO-ABs 89 IU/ml. She was treated with high-dose intravenous steroids and followed by an oral taper regimen. Eventually orbital decompression surgery was performed.

Case 4. A 44-year-old woman presented to the ophthalmologist with exophthalmos and subjective pressure sensations behind her eyes. The diagnosis of OGD was made and she was referred to our internal department for further clinical assessment. For years she was known with hypothyroidism for which she received 75 µg of L-T₄ daily. She smoked six cigarettes per day. Laboratory results showed TSH 0.023 mU/l, FT₄ 18 pmol/l, positive TSH-R-ABs 15.4 IE/l and positive TPO-ABs 354 U/ml. For her OGD she received methylprednisolone 1000 mg intravenously once daily for three days, followed by prednisolone 40 mg daily. The clinical features improved, but she developed herpes zoster at her left nates, which was treated with valaciclovir.

The laboratory results of all four patients are shown in table 1.

Table 1. Laboratory results from the four patients

	FT ₄ (pmol/l)	TSH (mU/l)	TSH-R-AB (IE/l)	TPO (IE/ml)
Reference values	10-24	0.16-4.6	<1	<26
Patient 1	5.2	144	1	185
Patient 2	11	58.2	56	399
Patient 3	19	3.8	8.5	89
Patient 4	18	0.023	15.4	354

METHODS

Serum levels of free T₄ and human TSH were measured using the Immulite 2000 free T₄ and Immulite 2000 third-generation TSH assay (Siemens Medical Solutions Diagnostica B.V., Breda, the Netherlands). Thyroid peroxidase antibodies were measured with the Immunocap 250 (Phadia B.V., Woerden, the Netherlands).

In cases 1, 3 and 4 TSH receptor antibodies in serum were measured with a highly sensitive radioreceptor assay using the human recombinant TSH receptor (DYNOTest TRAK human from B.R.A.H.M.S. Diagnostica, Berlin, Germany). In case 2 the same test was used but with animal (pig) TSH receptor.

DISCUSSION

Our four cases had OGD, hypothyroidism and positive TSH-R-ABs, leading to the diagnosis of hypothyroid Graves' disease. This phenomenon might be more common than is generally recognised. As mentioned in the introduction, this phenomenon was already reported by Wyse *et al.* in 1968.³ Christy *et al.* described three cases with nonthyrotoxic Graves' disease and concomitant hypothyroidism in 1977. They refer to Werner, who reported ten euthyroid patients with classical OGD in 1955. After this description, the concept of hyperthyroidism being an essential component of Graves' disease has been modified.⁴ McDermott *et al.* also described two cases and a review of 21 cases in 1968 in which primary autoimmune or idiopathic hypothyroidism was followed by the development of thyrotoxicosis.⁵ They were intrigued by the phenomenon of hypothyroidism progressing to hyperthyroidism. One of their explanations was that Graves' and Hashimoto's disease might occur in one patient, but at different times pointing to the possibility of spontaneous transition. Another explanation could be that blocking antibodies change into stimulating antibodies which may then be responsible for the change from hypothyroidism to hyperthyroidism.⁵

Another example of hypothyroid Graves' disease was reported by Elte *et al.* in 1983. The article is about patients with pretibial myxoedema. Usually patients with pretibial myxoedema have eye signs of Graves' disease and are euthyroid or hyperthyroid. However, from the 17 patients, one appeared to be hypothyroid.⁶

The pathogenesis is unknown, but hypotheses centre on the TSH receptor and its antibodies. The initial hypothyroid phase would be due to autoimmune damage to the thyroid gland rather than resulting from inhibitory antibodies. Thyroxine treatment has been

postulated to be the trigger for this change by causing decreased immunological surveillance.⁷ There have been descriptions and reviews about hypothyroidism preceding hyperthyroidism.⁸⁻¹¹

Our hypothesis is that the thyroid cell might be 'attacked' by blocking and stimulating antibodies. Dependent on the relative concentrations, hypothyroidism or hyperthyroidism may occur. So the difference between Hashimoto's disease and Graves' disease may be gradual and small.

During the last 50 years several case reports have been published in literature about hypothyroid Graves' disease. However, in medical textbooks this phenomenon is hardly ever mentioned. Hypothyroid Graves' disease thus is not very well known, which might have led to an underestimation considering the reports published and our own experience, as described in this article.

REFERENCES

1. Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Jameson JL, editor. *Harrison's Endocrinology*. 16th ed. McGraw Hill; 2006. p.71-111.
2. Davies TF, Larsen PR. Adrenocortical diseases. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, editors. *Williams Textbook of Endocrinology*, 10th ed. Elsevier; 2003. p.378-401.
3. Wyse EP, McConehey WM, Woolner LB, Scholz DA, Kearns TP. Ophthalmopathy without hyperthyroidism in patients with histologic Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 1968;28(11):1623-9.
4. Christy JH, Morse SM. Hypothyroid Graves' disease. *Am J Med*. 1977;62:291-6.
5. McDermott MT, Kidd GS, Dodson LE, Hofeldt FD. Case report: Hyperthyroidism following hypothyroidism. *Am J Med Sci*. 1986;291(3):194-8.
6. Elte JWF, Hensen EJ. Pretibial myoedema. Report of 17 cases and review of the literature. *Neth J Med*. 1983;26(8):220-7.
7. Kang BH. Hyperthyroidism following hypothyroidism - a case report. *Med J Malaysia*. 1991;46(3):287-9.
8. Irvine WJ, Lamberg BA, Cullen DR, Gordin R. Primary hypothyroidism preceding throtoxicosis: a report of 2 cases and a review of the literature. *J Clin Immunol*. 1979;2:349-52.
9. Skare S, Frey HMM, Konow-Thorsen R. Primary hypothyroidism followed by hyperthyroidism. Five case reports. *Acta Endocrinol*. 1984;105:179-83.
10. Cho BY, Shong YK, Lee HK, Koh CS, Min HK. Graves' hyperthyroidism following primary hypothyroidism: sequential changes in various activities of thyrotropin receptor antibodies. *Acta Endocrinol*. 1989;120:447-50.
11. Yamasaki H, Takeda K, Nakauchi Y, Suehiro T, Hashimoto K. Hypothyroidism preceding hyperthyroidism in a patient with continuously positive thyroid stimulating antibody. *Intern Med*. 1995;34(4):247-50.