CASE REPORTS

Ophthalmic Graves' disease in monozygotic twins

J. R. THORNHAM M.B., B.S. J. E. NUTT Ph.D.
F. CLARK F.R.C.P.

Summary
A pair of identical female twins with ophthalmic Graves' disease is described. Monozygosity was confirmed by analysis of blood groups and red cell isoenzymes. Thyroid status was assessed by standard tests (serum thyroid (Thyopac-4), protein-bound iodine, Thyopac-3 and thyroid uptake of ^131I). In addition, serum triiodothyronine and the response in thyroid stimulating hormone to thyrotrophin releasing hormone was measured. Circulating autoantibodies to thyroid tissue were detected in both sisters by complement fixation and immunofluorescence methods but long acting thyroid stimulator was not found.

There have been several reports of various forms of thyroid disease occurring in uniovular or monozygotic twins including Hashimoto's disease (Irvine et al., 1961), myxoedema (Hennen and Dodinval, 1965), toxic diffuse goitre (Hassan et al., 1966) and thyrotoxicosis and Hashimoto's disease (Jayson et al., 1967). A pair of monozygotic twins is described who both suffer from ophthalmic Graves' disease, and corneal dystrophy.

Case report
The twins J.O. and D.S. were born in 1931 (Fig. 1). J.O. was first seen in 1971 complaining of swelling of 4 months' duration around the right eye and particularly of the lids. There was associated vertical double vision and aching and excessive watering of the eye. Apart from moderate anxiety she felt well and had no symptoms referable to her thyroid. There was no relevant past history. Her youngest child had Still's disease. She was in sinus rhythm (pulse 88/min), blood pressure 140/85 mmHg, had a warm moist skin and some tremor of the outstretched fingers. The isthmus of the thyroid gland was just palpable. There was a puffy oedematous swelling of the right eyelid and a measurable exophthalmos of 6 mm (right 18 mm, left 12 mm, base 110 mm by Hertel measurement). In addition she had weakness of elevation of the right eye affecting both the superior rectus and inferior oblique muscles, together with injection of the bulbar conjunctival vessels and a fine bilateral superficial punctate keratitis. Slit lamp examination revealed a fine dust-like stromal dystrophy of the cornea (cornea farinata). Her thyroid function tests (Tables 1 and 2) indicated that she had Graves' disease and suggested that she was borderline hyperthyroid. Following her initial visit her anxiety responded to diazepam and she has remained euthyroid clinically. The PBI has varied between 4-3 and 9-4 µg/100 ml and Thyopac-3 between 96% and 117% (derived free thyroxine index 4-4–9-7). Her eye has improved without active therapy.

D.S. presented two years after her sister in 1973 with a 2-month history of puffiness around the right eye, which was watering excessively, and some diplopia on looking to the left. She admitted to minor depressive symptoms but gave no history of thyroid disorder and was clinically euthyroid (pulse 80/min, blood pressure 140/90 mmHg) but had a palpable thyroid gland. There was a puffy oedematous swelling affecting her right upper lid principally together with an obvious exophthalmos of 10 mm (right 22 mm, left 12 mm, base 102 mm by Hertel measurement). She also had weakness of elevation of the right eye, affecting both the superior rectus and inferior oblique muscles and both eyes showed the stromal dystrophy seen in her twin sister. Thyroid function tests (Tables 1 and 2) confirmed that she was euthyroid. The failure of triiodothyronine to suppress the normal 6-hour thyroid uptake was compatible with a diagnosis of thyroid autonomy. She has remained euthyroid clinically since (PBI varying between 6-2 and 7-1 µg/100 ml, Thyopac-3 between 114% and 121% and a derived free thyroxine index between 5-4 and 5-9). The condition of her eye has not altered significantly.

Seventeen blood group and red cell isoenzyme systems and A.B.H. secretor status were examined.

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Case reports

**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>Serum PBI (µg/100 ml)</th>
<th>Serum thyroxine (Thyopac-4) (µg/100 ml)</th>
<th>Serum triiodothyronine (ng/ml)</th>
<th>Thypac-3 (% of control)</th>
<th>Free thyroxine index (PBI/Thyopac-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.O.</td>
<td>8·6</td>
<td>—</td>
<td>1·69</td>
<td>102</td>
<td>8·4</td>
</tr>
<tr>
<td>D.S.</td>
<td>7·2</td>
<td>9·4</td>
<td>1·72</td>
<td>109</td>
<td>6·6</td>
</tr>
<tr>
<td>Normal</td>
<td>2·5-8·2</td>
<td>3·7-14·0</td>
<td>0·79-1·73</td>
<td>91-122</td>
<td>3·7-8·6</td>
</tr>
</tbody>
</table>

**Table 2.** Thyroid 6-hr ¹³¹I uptake (%)

<table>
<thead>
<tr>
<th></th>
<th>Original</th>
<th>After T₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.O.</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>D.S.</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Normal</td>
<td>11-40·2</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

**Table 3.** Thyroid antibodies

<table>
<thead>
<tr>
<th>Tanned red cell test (titre)</th>
<th>Complement fixation test (titre)</th>
<th>Immuno-fluorescent test for cytoplasmic antibody</th>
<th>Long Acting Thyroid Stimulator (LATS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.O. Negative</td>
<td>1/28</td>
<td>Positive</td>
<td>Undetectable</td>
</tr>
<tr>
<td>D.S. Negative</td>
<td>1/44</td>
<td>Positive</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

**Table 4.** TRH test. TSH response (µu/ml) to 200 µg TRH i.v.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>20</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.O.</td>
<td>0·8</td>
<td>1·2</td>
<td>1·3</td>
</tr>
<tr>
<td>D.S.</td>
<td>&lt;0·5</td>
<td>8·0</td>
<td>5·1</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;0·5-4·0</td>
<td>6·5-20·5</td>
<td>4·0-15·6</td>
</tr>
</tbody>
</table>

in each twin and, for both, the results were as follows:

A₁, CCDee, NsNs, P₄₁⁺⁺, kk, G6PD B, Fy(a+b⁻), Jk(a+b⁺), Le(a⁻b⁺), Se, ADA₁, 6PGD A, LDH normal, AK₁, AP BA, PGM 1-1, MDH normal.

On the basis of these Mendelian characters the probability of monozygosity was 0·9836. Dermatoglyphic characters showed the considerable similarity expected with monozygosity (for J.O. and D.S.
the total ridge count was 97 and 87 respectively; \textit{atd} angle 78 and 80); when these were included in the calculations, the probability that the twins were monozygous rose to 0.9978.

Discussion

Ophthalmic Graves’ disease is a term used to describe the condition in which the eye signs of Graves’ disease occur in the absence of hyperthyroidism past or present (Rundle and Wilson, 1945; Hall et al., 1970). However, there is no fundamental difference between the exophthalmos of thyrotoxicosis and that associated with normal thyroid function apart from the greater tendency to asymmetry in ophthalmic Graves’ disease (Havard, 1972). The latter can be recognized by the typical clinical findings and in the majority of cases the diagnosis confirmed by failure of suppression of $^{131}$I uptake by triiodothyronine (Table 2) or by the presence of thyroid autoantibodies (Table 3) or some other thyroid abnormality. The two patients presented fulfilled these diagnostic criteria and also that more recently proposed by Ormston et al. (1973) who examined the effect of thyrotrophin-releasing hormone (TRH) on serum thyroid-stimulating hormone (TSH) response in patients with ophthalmic Graves’ disease. J.O. who had an elevated level of triiodothyronine (T$_3$) in serum also showed an impaired TSH response to TRH and is probably an example of the condition of ‘sub-clinical T$_3$ thyrotoxicosis’. D.S. had a serum T$_3$ at the upper and a TSH response to TRH at the lower limit of normal (Table 4). Both show failure of suppression of 6-hr thyroid uptake of $^{131}$I by T$_3$ although in the case of D.S. the original uptake lay within the normal range. Ormston et al. (1973) have suggested that the TRH test can replace the T$_3$ suppression test in routine clinical practice as it is safer, shorter and more convenient. In addition, the type of response to TRH may indicate the nature of the unilateral exophthalmos in any particular instance and also give an indication of the prognosis of the eye signs.

The monozygous nature of the twin relationship is not in doubt with the results of blood group, isoenzyme and dermatoglyphic studies as well as their similar facial appearance. It is also of interest that in both patients the exophthalmos affected the right eye and that they also had an identical form of corneal dystrophy.

A hereditary tendency in Graves’ disease is well recognized (Skillern, 1973, Leading Article, 1973) but the nature of the genetic abnormality remains uncertain. It is probably inherited on a multifactorial or polygenic basis (Hall, Dingle and Roberts, 1972). A similar mode of inheritance is likely in Hashimoto’s disease.

The present cases of ophthalmic Graves’ disease occurring in monozygous twins re-emphasize the role of hereditary factors in autoimmune thyroid disease.

Acknowledgments

We wish to thank Professor R. Hall, Dr D. F. Roberts, Mr J. M. L. Howat, Dr D. C. Evered and Dr T. Bird for their assistance and advice.

Addendum

Both patients were shown to have thyroid-stimulating antibodies (T$\text{S}$Ab) activity in their serum as determined by radioreceptor assay (Hall, Smith and Mukhtar, 1975), values for the PS Ab index being 35 and 46 for D.S. and 49 and 68 for J.O. The significance of this finding in relation to ophthalmic Graves’ disease is obscure at present.

References


Leading Article (1973) British Medical Journal, 2, 5.


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