Short reports

Thyroid-stimulating immunoglobulins in neonatal Graves's disease

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SUMMARY Two patients with neonatal Graves's disease are reported. One of them had a delayed onset because of suppression of the fetal thyroid gland by antithyroid drug taken by the mother during pregnancy. Thyroid-stimulating immunoglobulins (TSAb), measured by a receptor assay, were present in both babies when they were thyrotoxic, and also in their mothers. TSAb were undetectable in both babies 1 year after birth. This strongly supports a pathogenetic role of TSAb in this condition through transplacental transfer of maternal TSAb.

There is strong evidence to suggest that Graves's disease is related to the presence of thyroid-stimulating immunoglobulins (TSAb).¹ Neonatal Graves's disease is a rare but interesting disease in which the transfer of maternal immunoglobulins (Igs) across the placenta to the fetus is implicated in the pathogenesis.²⁻³ In all previous studies, mouse bioassay techniques were used to detect such Igs. Employing a radioreceptor assay, we have demonstrated TSAb in 2 babies with neonatal Graves's disease and their mothers. As far as we are aware, this is the first study of TSAb activity as measured by receptor assay in patients with this disease.

Case reports

Case 1. The mother of the first baby had been treated for Graves's disease during her second pregnancy in 1975 but the baby born was normal. She relapsed again during the third pregnancy in 1976 and was treated until the 35th week of gestation. Two days later, a baby girl was delivered prematurely, birth-weight 2970 g.

On day 8, the baby was found to have rather prominent eyes. On day 17, tachycardia was noted and thyroid function tests were requested (Table 1). By 5 weeks of age, she was clinically thyrotoxic with irritability, failure to gain weight, tachycardia, and bilateral eye signs although thyroid gland was not palpable. Treatment with Lugol's iodine, propranolol, and chloral hydrate was started. A good response

Table 1 *Thyroid function and TSAb indices in Case 1*

Age	Thyopac-4 (µg/100 ml)	Thyopac-3 (%)	Free thyroxine index	TSAb index (%)	Maternal TSAb index (%)
Day 17	18	71	23.9	—	—
7 weeks	8.3	97	8.5	55.6	58.0
1 year	8.8	98	9.1	87.4	77.5
Normal adult range	4.5-12	88-116	4.3-11.7		83.3-126

Conversion: traditional to SI units—T4: 1 µg/100 ml = 12.87 nmol/l.

was noted and the eye signs regressed. The baby remained asymptomatic after the antithyroid drugs were stopped at 13 weeks. Both the mother and the baby defaulted from follow-up until the baby was 1-year old although the mother sought treatment from private practitioners.

Case 2. The mother had received radioactive iodine therapy for thyrotoxicosis 1 year before delivery of the baby. In the 35th week of pregnancy, she relapsed again but no treatment was given.

A girl was delivered during the 43rd week of pregnancy, birthweight 2300 g. On day 2, she began to manifest hyperthyroid features with irritability, sweating, and tachycardia. Thyroid function tests on day 4 confirmed hyperthyroidism (Table 2). There was a good response to carbimazole and potassium iodide which were stopped after 6 weeks and the baby remained euthyroid thereafter.

Methods

Serum thyroxine was measured by Thyopac-4 kit (Amersham), thyroid hormone binding capacity by Thyopac-3 kit (Amersham), and free thyroxine index calculated from these values.

TSAb activity was measured by a receptor assay⁴

Table 2 *Thyroid function and TSAb indices in Case 2*

Age	Thyopac-4 (µg/100 ml)	Thyopac-3 (%)	Free thyroxine index	TSAb index (%)	Maternal TSAb index (%)
Day 4	26	70.4	36.9	—	—
Day 25	4.4	122.3	3.6	62.6	61.8
1 year	10.1	110.6	9.1	91.0	—

which depends on the ability of patient's Igs to inhibit the binding of (125 I) bovine thyrotrophin (bTSH) to crude human thyroid membranes obtained after homogenisation and centrifugation at $10\,000 \times g$. Immunoglobulins were precipitated from sera by saturated 3.75 mol/l ammonium sulphate. Highly purified bTSH was iodinated by the lactoperoxidase method.

After 200 μ l of Igs or unlabelled bTSH and 50 μ l of crude thyroid membranes were incubated at 37°C for 10 min, 50 μ l of (125 I) bTSH was added, and incubation continued for 60 min. After addition of 1 ml cold buffer, the incubation mixture was centrifuged at $25\,000 \times g$ for 30 min at 4°C, and the bound count expressed as a percentage of total radioactivity added. Pooled normal Igs were used as control in each assay. Nonspecific binding determined as (125 I) bTSH bound in presence of 0.1 unit bTSH per ml and 20 mg/ml of pooled normal Igs was subtracted from the binding in each sample. The TSAb activity was expressed as a TSAb index⁵ defined as:

$[(^{125}\text{I}) \text{ bound in presence of patient's Igs}/(^{125}\text{I}) \text{ bound in presence of pooled normal Igs}] \times 100\%$.

Previous studies⁶ in our laboratory have established the TSAb index in normal controls to be above 83%, thus any TSAb index below 83% was regarded as TSAb-positive, and that above 83% as TSAb-negative. The intra-assay and interassay coefficients of variation were 5% and 12% respectively. In particular, we have found the TSAb indices in 10 normal women 6 weeks' postpartum to range from 99.7 to 119.6% (mean 109.9%) and in 9 euthyroid 1-year-old babies to range from 84.2 to 128.4% (mean 98.6%).

Results

The thyroid function tests and TSAb indices of Case 1 and the maternal TSAb indices are shown in Table 1. The earliest thyroid function tests at day 17 showed hyperthyroidism but these had returned to normal at 7 weeks of age with treatment. The TSAb index of the baby at 7 weeks was positive at 55.6% and the corresponding TSAb index in the mother then was positive too at 58%. The TSAb index in the baby became negative (87.4%) at 1 year of age whereas the mother's TSAb index then was still positive (77.5%). The rise in the maternal TSAb index between 7 weeks postpartum and 1 year is presumably related to treatment given by other doctors during that year, and we have evidence that the TSAb index returns towards normality after a period of treatment with antithyroid drugs.⁶

Table 2 shows the thyroid function tests and TSAb indices of Case 2. Hyperthyroidism was documented as early as day 4. On day 25 when the

baby was still receiving antithyroid drugs, the TSAb index was positive at 62.6% and the corresponding TSAb index in the mother was also positive at 61.8%. At 1 year of age, the TSAb index in the baby was negative at 91%.

Discussion

Two patients with neonatal Graves's disease are reported. In Case 1, the clinical manifestations were delayed probably due to the late withdrawal of antithyroid drug in the pregnant mother so that the thyroid gland was suppressed *in utero* and during the baby's first few weeks of life. In Case 2, thyrotoxicosis was evident almost from birth, probably because no antithyroid drug had been given to the mother during pregnancy.

In both cases, TSAb were positive in the babies who still required drugs for the thyrotoxicosis. TSAb were also positive in their mothers at the same time. This is in keeping with the hypothesis that maternal TSAb cross the placenta and are responsible for the manifestations of neonatal Graves's disease. It is interesting to note that TSAb could still be detected in Case 1 as late as 7 weeks of life. TSAb were not detectable at 1 year of age in either baby when each was euthyroid without any treatment.

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