Congenital hypothyroidism with hereditary, raised thyroxine binding globulin

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SUMMARY A boy with congenital hypothyroidism and hereditary raised thyroxine binding globulin is described. This hitherto unreported combination resulted in under treatment of the thyroid deficiency until serum thyroid stimulating hormone measurement became routinely available. Inadequate L-thyroxine replacement treatment between 2 and 7 years of age caused retarded bone maturation, poor growth velocity, and probably added to his educational difficulties.

Abnormalities in serum thyroxine binding globulin may be inherited or acquired, and result in raised or depressed total thyroid hormone concentrations even in euthyroid subjects. If true thyroid dysfunction occurs in the presence of thyroxine binding globulin derangement, diagnosis and management will be unsatisfactory unless the existence of both abnormalities is recognised. We report a patient with congenital hypothyroidism in association with hereditary, raised thyroxine binding globulin, a combination not previously described.

Case history

A boy (birthweight 3180 g) was born at term in 1970. Perinatal and family medical histories were normal. A clinical diagnosis of hypothyroidism was made at 3 months of age when he presented with an umbilical hernia, and this was confirmed by a protein bound iodine value of 3 µg/100 ml (normal range 4·0 to 8·4 µg/100 ml). Treatment with oral L-thyroxine (150 µg daily) was begun at 14 weeks of age. He smiled at 3 months, sat unsupported at 8 months, and walked at 20 months. At 22 months, the family moved to a new area, at which time his height was at the 50th centile, three ossification centres had been reported on a wrist radiograph (now unavailable), and the protein bound iodine concentration was 12 µg/100 ml. Apart from his delay in walking, development was considered normal. In view of the high protein bound iodine concentration, thyroxine treatment was gradually reduced. At 2½ years it was stopped completely for five weeks, whereupon the protein bound iodine fell to 1·7 µg/100 ml. L-thyroxine treatment (50 µg orally daily) was begun again, after which the protein bound iodine rose to 15·2 µg/100 ml. Again his thyroxine treatment was reduced to 25 µg daily and he remained on this dose from age 2·8 years until 7·25 years. Over this period his height fell from the 50th centile to the 3rd centile with a correspondingly slow rate of increase. Radiological bone age was reported as ‘within normal limits’ at chronological age 2 years, and was 6 years (Greulich and Pyle) at a chronological age of 8 years. He entered a normal primary school, but required remedial teaching because of slow progress. Although poor growth caused concern, no alteration was made to the thyroxine dose (25 µg daily) as protein bound iodine

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values were repeatedly normal. Because of continuing poor growth the thyroxine dosage was increased to 75 μg daily at 7-25 years, and at 7-5 years the serum thyroxine concentration (which had just superseded protein bound iodine estimation) was 270 nmol/l (normal range 80 to 140 nmol/l). Serum thyroid stimulating hormone values became routinely available in the laboratory when he was 8 years old and the following results were obtained on a dosage of 75 μg L-thyroxine daily: thyroxine 238 nmol/l; thyroid stimulating hormone 28-9 mIU/l (normal range 2 to 6 mIU/l); and triiodothyronine 4-2 nmol/l (normal range 0-8 to 2-5 nmol/l). Thyroxine binding globulin was then measured and found to be 56-8 mg/100 ml (normal range 8 to 15 mg/100 ml). The presence of a raised thyroxine bound globulin concentration having been established, his thyroxine was gradually increased from 75 μg to 250 μg daily by the age of 8-8 years. Thyroid stimulating hormone values on 100 μg and 150 μg thyroxine daily were 9-4 mIU/l and 11-3 mIU/l respectively. While taking 250 μg daily his thyroid stimulating hormone value remained below 5 mIU/l until 12 years of age. His height increased from the 3rd centile at 7-5 years to the 50th centile at 12 years. Bone age (TW2) was 11-1 years (75th centile) at a chronological age of 10-25 years. At 3 years his IQ (Merrill-Palmer) was 91, but by 8-8 years the full scale IQ (WISC-R) was 64. At 12 years of age these values were unchanged and, with regard to his thyroid function, the free thyroxine was persistently raised at 32-4 to 69 pmol/l (normal range 9 to 23 pmol/l). Thyroxine treatment was reduced to 200 μg orally daily and serum free thyroxine values remained around 27 pmol/l thereafter. It should be noted that from the age of 2 years he was always assessed as clinically euthyroid despite the growth and developmental changes noted above.

The results of thyroid function tests conducted in the first degree relatives are shown in the Table. The parents would not permit testing of the wider family. At a recent assessment when aged 14 years, our patient was clinically and biochemically euthyroid on 175 μg L-thyroxine daily.

### Discussion

This case shows that total thyroid hormone concentrations are unreliable guides to thyroid status where thyroxine binding globulin values are raised. Although described as clinically euthyroid from 2 years onwards, the slow growth velocity, progressively delayed bone maturation (when later assessed accurately), and poor school performance suggested serious under treatment. Indeed, the dose of thyroxine was increased on the basis of growth failure and only later was serum thyroid stimulating hormone measured and found to be unsuppressed at 28-9 mIU/l. Growth velocity and bone maturation advanced rapidly when treatment was increased.

The starting dose of thyroxine (150 μg daily) at 14 weeks would now be considered supraphysiologic, but it is likely that he received at least adequate replacement until 2 years because his growth and early IQ test were within normal limits. Long term developmental retardation is not uncommon, however, if treatment is not started soon after birth. Further cerebral damage ought to have been prevented by quite large doses of thyroxine during the major part of postnatal brain growth—that is up to 2 years of age. It can only be assumed that the later inadequate treatment exaggerated pre-existing cortical damage. Unfortunately he has not shown any evidence of intellectual improvement since the age of 8 years, although a progressive improvement in IQ has been described in adequately treated patients with congenital hypothyroidism, even into adult life. The extended family could not be studied but the thyroxine binding globulin values in the close family members are in keeping with the reported X-linked control, with mother and sister being carriers of the condition. The mother’s thyroxine binding globulin value is considerably higher than that of sister I, although both are presumed carriers (Table).这

| Table Results of thyroid function tests in the patient's immediate family |
|----------------|-----------------|----------------|----------------|----------------|----------------|
| Thyroxine (nmol/l) | Patient* | Mother* | Father | Sister I* | Sister II | Normal range |
| Thyroxine | >292-0 | 212-0 | 109-0 | 177-0 | 115-0 | 80-140 |
| Triiodothyronine (nmol/l) | 5-8 | 4-4 | 2-4 | 4-4 | 3-1 | 0-8-2-5 |
| Free thyroxine (pmol/l) | 32-4 | — | — | — | — | 8-8-23-0 |
| Thyroid stimulating hormone mIU/l | 1-8 | 2-3 | 1-2 | 3-3 | 1-0 | 2-6 |
| Thyroxine binding globulin (mg/l) | 64-2* | 45* | 12-6 | 33-6* | 15-4 | 8-15 |
| Thyroxine/thyroxine binding globulin (nmol/mg) | — | 4-7 | 8-6 | 5-3 | 7-5 | ? |

*Female carriers.

Thyroxine binding globulin values compatible with X linked inheritance.
difference may be explained by variable gene expression or by the mother’s taking of an oestrogen-containing contraceptive pill until two to three months before her serum thyroxine binding globulin was estimated. This may have served to raise her intermediate thyroxine binding globulin values.4

Congenital deficiency of thyroxine binding globulin in association with hypothyroidism has been described5 6 but we cannot find any previous reports of hereditary excess associated with congenital hypothyroidism, a combination which, unfortunately on this occasion, has been associated with serious long term disability.

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Pubertal growth in diabetics

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SUMMARY Mean values for two variables of the pubertal growth spurt, peak height velocity and age at peak velocity, of children attending the diabetic clinic in Bristol are reported. The growth spurt was normal both in timing and intensity in boys, but the peak velocity was reduced and age at peak velocity more variable among girls.

There have been few studies of pubertal growth in diabetic children, and those that have been published show conflicting results.1-3 Despite this reports that pubertal growth is abnormal are still found.4 Stimulated by this observation we carried out a study of growth during puberty of children attending the diabetic clinic at our hospital.

Methods

At the end of 1974 a children’s diabetic clinic was established in Bristol under the care of a paediatric endocrinologist. Although two of the general paediatricians working in Bristol continue to care for diabetics who are specifically referred to them or who present to them on the emergency rota, most children with diabetes in Bristol are seen at the diabetic clinic.

All children attending the clinic had their height measured by trained nursing staff using a Harpenden Stadiometer. Measurements were taken at each visit; rate of attendancy varied from one to six months according to clinical requirements. At the beginning of 1981 the records of all children attending the clinic who could have experienced a pubertal growth spurt within the previous six years were examined. Girls born between the beginning of 1960 and the end of 1971 and boys born between the beginning of 1958 and the end of 1969 were selected for study. The wide limits were used to prevent the omission of children with unusually early or late growth spurts.

A total of 168 records were examined. Yearly growth velocities were calculated using all available measurements of height that had a corresponding measurement within 0-8 and 1-2 years. Velocities were plotted on Tanner and Whitehouse charts against the midpoint of the year in which the velocity

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