does not interfere with fetal growth as measured by birthweight.

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References

D. Vidyasagar*

Research Foundation, Children’s Hospital of Winnipeg and Department of Paediatrics, University of Manitoba, Canada.

*Address: The Children’s Hospital, Winnipeg 3, Manitoba, Canada.

Growth Retardation and Thyroxine-binding Globulin Deficiency

The combination of growth retardation and thyroxine-binding globulin (TBG) deficiency* had not been reported until recently when Nikolai (1969) presented a 11-year-old Caucasian boy with delayed bone age and zero TBG levels.

The present paper reports a second case of TBG deficiency associated with delayed bone age and growth retardation. The case differs in that the TBG levels were low but not zero.

Methods

Thyroid function studies. (See Table for normal values.) Blood for thyroid function studies was collected iodine-free and the serum separated.

Thyroid hormone levels. Total thyroxine iodine (total T₄ iodine) was determined by the method of Murphy and Pattee (1964). Values obtained are similar to those found using the older protein bound iodine (PBI) estimation, but the former test gives more reliable results in the presence of extraneous iodide contamination.

Free binding sites. Binding sites on serum thyroxine-binding proteins, not occupied by thyroid hormone, were estimated by the tri-iodothyronine resin uptake method of Woldring, Bakker, and Doorenbos (1961), and expressed as a percentage of a normal control serum (T₃ uptake % N).

Free thyroxine index. The free thyroxine index (FTI) is roughly proportional to the freely circulating thyroid hormone.

\[ \text{FTI} = \frac{(\text{Total } T₄ \text{ iodine}) \times (T₃ \text{ uptake } \% N)}{100} \]

A normal FTI suggests euthyroidism and a low FTI hypothyroidism. It gives a more reliable estimate of the patient’s thyroid status than when either the total T₄ or the T₃ uptake is considered singly.

Thyroid binding proteins. Thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA) were measured by a modified technique of Elzinga, Carr, and Beierwaltes (1961). Individual specimens of sera were enriched with ¹²⁵I labelled thyroxine (T₄) in chemical concentrations ranging from 30–500 μg/100 ml. The serum proteins were separated on paper (Schleicher and Schuell 2043A) by reverse flow electrophoresis and the T₄ binding fractions located by radioautography. The radioactivity in each fraction was counted, from which the T₄ binding capacities of TBG and TBPA were calculated.

Case Report

The patient was a 9-year-old boy who had been referred by his school medical officer for investigation of short stature and loss of visual acuity in his right eye. On examination he was an alert boy 114 cm tall (5 cm less than the 3rd centile) and 21·8 kg in weight (1 kg greater than the 3rd centile). There was no clinical evidence of thyroid dysfunction. His pulse rate was 84/minute and blood pressure 100/70 mm Hg. Fundal examination and visual fields were normal. Lenses partially corrected a loss of visual acuity in his right eye from 6/18 to 6/9.

Radiological examination of his wrists showed a bone age of between 6 and 6½ years (Greulich and Pyle). A skull x-ray was normal.

The following were found to be within normal limits; the serum levels of albumin, globulin, uric acid, cholesterol, calcium, magnesium, phosphorus, aspartate transaminase, alkaline phosphatase, and creatinine; blood urea nitrogen and the urinary hydroxyproline excretion; trypptic activity in stools and xylose tolerance test.

Endocrine function studies included a normal 24-hour urinary excretion of 11-hydroxycorticotosteroids and
17-ketosteroids. A peak growth hormone level of 7.4 ng./ml was obtained following insulin-induced hypoglycaemia and considered a normal response.

The total T4 iodine was low at 3 μg/100 ml serum (N: 4.3–7.2), the T3 resin uptake % N elevated at 135 (N: 85–114), and the free T4 index was normal at 4.1 (N: 3.5–7.0). Also the three-hour thyroidal uptake of 125I was normal at 21.2% (N: 8–25%). For a laboratory diagnosis of hypothyroidism the low T4 iodine was not supported by low levels of T3 uptake, free T4 index, or 125I uptake. The apparent discrepancy between these results prompted investigation of T4 binding in the serum. The two parameters considered were the thyroxine binding pre-albumin (TBPA) which was normal at 182 μg T4 bound/100 ml serum (N: 160–210) and the TBG which was strikingly depressed at 5 μg/100 ml serum (N: 12–25).

Results of thyroid function studies in his immediate family are shown in the Table. It can be seen that both parents and sister have normal TBPA and TBG levels. There were no other relatives available for testing in this country.

A buccal smear was negative for Barr bodies and consistent with a normal male karyotype.

Discussion

A 9-year-old boy is described with growth retardation and deficient but not zero levels of TBG. Despite extensive investigation no cause has been found for his growth retardation, and this must be labelled the unsatisfactory term ‘constitutional’.

He is euthyroid clinically, has a normal free thyroxine index and indirect parameters of thyroid function such as serum cholesterol, alkaline phosphatase, creatine phosphokinase, and urinary hydroxyproline excretion are within the normal range.

Recognized acquired causes of TBG deficiency could not be shown. Low levels are found in nephrosis, acromegaly, after treatment with drugs including corticosteroids, androgens, salicylates, diphenylhydantoin, and in major non-thyroidal disease (Lancet, 1969). It is therefore presumed that he has a genetic deficiency of TBG.

Though several families of individuals with TBG deficiency have been studied in detail since Gordon et al. (1952) first described the nature of the circulating thyroid hormone-plasma protein complex, the complexities of genetic control of TBG synthesis have not yet been completely unravelled.

The evidence for at least two modes of inheritance has been recently reviewed by Roberts, Nikolai, and Lohrenz (1970). There is abundant evidence for the TBG deficiency state being X chromosome linked in some families (Nikolai and Seal, 1966; Marshall, Levy, and Steinberg, 1966). Affected males have zero TBG levels and heterozygous females levels exactly half normal. This fits well into the Lyon hypothesis, and additional support for the X-linked nature of the trait has come from the study of a child with (XO) Turner’s syndrome (Refetoff and Selenkow, 1968), and another child with XXY/XY/XO mosaicism (Moloshok et al., 1969), both with TBG deficiency.

However, another less well-defined mode of inheritance appears likely in males with low but not zero levels of TBG (Roberts et al., 1970; Kraemer and Wiswell, 1968). Study of these families suggests the possibility of an autosomal method of transmission.

No firm conclusion as to the mode of inheritance can be made in our patient, but he could represent a spontaneous mutation, or in view of the low but not zero levels of TBG, may fall into the autosomal transmission group. Further members of the family will need to be studied to clarify this further.

It is also hoped that study of affected individuals with this disease will enable the exact nature of the TBG deficiency to be delineated. It is postulated that the protein may be either completely absent or may be quantitatively normal, yet abnormal in its physiochemical properties, with resultant diminished affinity for thyroxine. Marshall and Pensky (1969) using immunological techniques have found normal TBG levels in two X-linked TBG ‘deficient’ patients, and thus favour the theory of a protein with altered molecular structure.

However, other workers (Roberts et al., 1970) using stepwise increasing concentrations of radioactive T4 in their electrophoretic studies have

<table>
<thead>
<tr>
<th>Relation to Patient</th>
<th>T4 Iodine (μg/100 ml) (N4.3–7.2)</th>
<th>T3 Resin Uptake % N (N85–114)</th>
<th>Free T4 Index (N3.5–7.0)</th>
<th>TBG Capacity (μg T4/100 ml) (N12–25)</th>
<th>TBPA Capacity (μg T4/100 ml) (N160–210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>5.6</td>
<td>92</td>
<td>5.2</td>
<td>19</td>
<td>188</td>
</tr>
<tr>
<td>Mother</td>
<td>4.9</td>
<td>94</td>
<td>4.6</td>
<td>23</td>
<td>187</td>
</tr>
<tr>
<td>Patient</td>
<td>3.0</td>
<td>135</td>
<td>4.1</td>
<td>5</td>
<td>182</td>
</tr>
<tr>
<td>Sister</td>
<td>5.3</td>
<td>93</td>
<td>4.9</td>
<td>23</td>
<td>188</td>
</tr>
</tbody>
</table>
failed to confirm the idea of reduced affinity for $T_4$ in TBG deficiency. This is the second reported case of TBG deficiency and growth retardation. The patient reported by Nikolai (1969) had been erroneously diagnosed as having isolated TSH deficiency and had failed to respond to several years of thyroid therapy. The true nature of his condition was subsequently revealed during a study of a family with X-linked TBG deficiency. As in our patient, no cause was found for his growth retardation.

Our patient differs, however, in having low but measurable levels of TBG and, as discussed above, probably represents a different mode of inheritance.

**Summary**

A 9-year-old boy was found to have constitutional growth retardation and thyroxine-binding globulin deficiency. He is the second child reported with this combination of defects and differs from the original patient in having low but not zero thyroxine-binding globulin levels.

He also illustrates the importance of assessing other parameters of thyroid function, such as the $T_3$ resin uptake, in children with low total thyroxine iodine (or protein bound iodine) levels, before embarking on thyroid replacement therapy.

**References**


J. L. Penfold,* G. M. Kneebone, M. Wellby,* and R. K. Oldfield

Department of Child Health, University of Adelaide: Queen Elizabeth Hospital, Woodville, and Biochemistry Department, Adelaide Children's Hospital, North Adelaide, South Australia.

*Correspondence to Dr. J. L. Penfold, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada.

**Growth Hormone Response to Oral Glucose Load in Untreated Diabetic Children**

There have been contradictory reports of the plasma growth hormone levels to be found in children with untreated juvenile diabetes. Parker et al. (1968) and Drash et al. (1968) found normal fasting growth hormone levels after an oral glucose load. In contrast, Johansen and Hansen (1969) reported persistently high growth hormone levels fasting and throughout the day in untreated juvenile diabetics. In addition, Parker et al. (1968) found normal growth hormone responses during the arginine infusion test, while Drash et al. (1968) reported raised levels during this provocative test.

**Patients and Methods**

Twelve newly diagnosed diabetic children were investigated, before treatment with insulin was started. Five were girls and 7 were boys. Their ages ranged from 1 year 9 months to 14 years and none of the patients was overweight. All were fasted overnight (12–15 hours).

Control data were obtained from 9 non-obese, metabolically and endocrinologically normal children, with no family history of diabetes or coronary disease: 3 were girls and 6 were boys. Their ages were similar to the diabetic children, ranging from 2 years 7 months to 15 years 2 months. They were all on a normal diet. All were fasted overnight (12–15 hours) before blood collection.

They had been referred to the Endocrine Clinic because their parents were concerned about the child being much smaller than its sibs. All these children were on the 3rd to 10th centile for height and weight, while their sibs were on the 50th centile or above. Parent's permission was obtained from all cases before investigation. In the youngest child of the group, to avoid repeated venepunctures, an indwelling catheter was used.
Growth retardation and thyroxine-binding globulin deficiency.

J L Penfold, G M Kneebone, M Wellby and R K Oldfield

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