TSH and PRL response to thyrotrophin-releasing hormone in children with chronic renal failure undergoing haemodialysis

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SUMMARY Eight children (aged between 8½ and 15½ years) with chronic renal failure receiving intermittent haemodialysis, and 2 children with renal transplants were studied. The response of TSH and prolactin (PRL), and basal T4 and T3 values was measured. Basal TSH was normal, and rose only slightly after TRH stimulation. Plasma T4 and T3 were below normal levels in 6 children. Mean basal PRL was raised and could not be stimulated by TRH. This study demonstrates the involvement of the hypothalamus and pituitary in chronic renal disease. The cause of the abnormal secretion of TSH and PRL in chronic renal failure is discussed in the light of clinical importance.

Patients and methods

Eight children with chronic renal failure (CRF) undergoing haemodialysis for 1 to 86 months, and 2 children who had had successful renal transplants 25 and 44 months earlier were investigated. Clinical details are shown in Table 1. Haemodialysis was generally performed for 6 hours 3-times a week.

No child showed galactorrhoea or gynaecomastia and no thyroid disease had been diagnosed. The aims of the study were explained to the patients and their parents and their informed consent was obtained. 22 (12 girls and 10 boys) healthy children, aged between 8 and 15 years, in hospital because of their short stature served as a control group. Five of these children have achieved almost complete sexual maturation, the rest were prepubertal. They were in

Table 1  Clinical data of 8 children with chronic renal failure and 2 children with renal transplants

| Case | Sex | Age (years) | Pubertal status* | Bone age† (years) | Height (cm) | Diagnosis | Haemodialysis treatment (months) | Other treatment
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>15-6</td>
<td>Stage 3</td>
<td>15</td>
<td>144</td>
<td>Chronic pyelonephritis</td>
<td>48</td>
<td>—</td>
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<tr>
<td>2</td>
<td>M</td>
<td>8-5</td>
<td>Stage 1</td>
<td>5</td>
<td>122</td>
<td>Haemolytic uremic syndrome</td>
<td>10</td>
<td>—</td>
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<tr>
<td>3</td>
<td>M</td>
<td>9-0</td>
<td>Stage 1</td>
<td>7</td>
<td>124</td>
<td>Haemolytic uremic syndrome</td>
<td>1</td>
<td>α-Methyldopa, reserpine, dipydralazine</td>
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<tr>
<td>4</td>
<td>M</td>
<td>12-6</td>
<td>Stage 1</td>
<td>12</td>
<td>132</td>
<td>Oxalosis</td>
<td>12</td>
<td>Frusenide</td>
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<tr>
<td>5</td>
<td>F</td>
<td>15-2</td>
<td>Stage 3</td>
<td>15</td>
<td>147</td>
<td>Renal hypoplasia</td>
<td>86</td>
<td>—</td>
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<tr>
<td>6</td>
<td>F</td>
<td>12-8</td>
<td>Stage 1</td>
<td>11½</td>
<td>147</td>
<td>Polycystic kidney</td>
<td>22</td>
<td>—</td>
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<tr>
<td>7</td>
<td>F</td>
<td>15-1</td>
<td>Stage 2</td>
<td>13½</td>
<td>150</td>
<td>Chronic pyelonephritis</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>11-0</td>
<td>Stage 1</td>
<td>8</td>
<td>120</td>
<td>Glomerulonephritis</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>15-5</td>
<td>Stage 1</td>
<td>10</td>
<td>138</td>
<td>Megacystis-negareter-syndrome</td>
<td></td>
<td>Renal transplant</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>14-2</td>
<td>Stage 1</td>
<td>7</td>
<td>134</td>
<td>Glomerulonephritis</td>
<td></td>
<td>Renal transplant</td>
</tr>
</tbody>
</table>

*Pubertal status rated according to Tanner and Whitehouse (1976), †bone age estimated according to Greulich and Pyle (1959).
good health and endocrine studies showed no abnormality.

Synthetic TRH (Relefact TRH, Hoechst AG, Frankfurt) was administered intravenously at a dose of 200 μg dissolved in 2 ml saline. All children were fasted overnight and remained in bed before and during the test. The test was performed at least 18 hours after haemodialysis. Blood samples were withdrawn through an indwelling cannula in an arm vein at 0, 15, 30, 45, 60, 90, and 120 minutes after TRH injection. Heparinised blood was immediately centrifuged at 4°C, and the plasma stored at −20°C until assayed for TSH, PRL, T4, and T3. Plasma TSH was determined by a double antibody radioimmunoassay (Utiger, 1965) (Amersham Buckler, Düsseldorf, Germany) (normal value, 0–7 μU/ml); plasma PRL by the double antibody method of Reuter et al. (1976) (Union Carbide, Slearos, Belgium) (normal 6–10 ng/ml); plasma T4 by a competitive protein-binding radioassay (Res-O-Mat T4, Byck-Mallinchrodt Co, Dietzenbach, Germany) (normal 4·5–11·4 μg/100 ml), and T3 by radioimmunoassay (T3 RIA-KIT, Serono, Freiburg, Germany) (normal 0·6–1·7 ng/ml).

Statistical evaluations were by the Wilcoxon, Mann and Whitney U test for unpaired groups.

Results

Mean plasma concentration and SDs for basal TSH, PRL, T4, and T3 in controls and in children with CRF are shown in Table 2 which also shows the peak levels after TRH stimulation. The range of values and the results in the children with transplants are shown in Figs 1 and 2. No significant difference in basal levels of TSH, T4, or T3 was found. However, 6 of the 8 children with CRF had T3 or T4 levels below the normal range; PRL basal levels were significantly higher in the children with CRF failure. Basal levels were within the normal range in the children with transplants. After TRH stimulation, TSH rose in both groups with a peak response >8·0 μU/ml. In 5 cases TSH values had not fallen to basal levels 90 minutes after TRH injection. PRL levels after TRH stimulation rose in the control children, but were not significantly different from basal levels in children with CRF. Case 3, who was receiving medication for acute hypertension (Table 1) and who had been on dialysis for only one month, had a normal basal PRL level (4·8 ng/ml) with only a slight rise after TRH. Sex, puberty, or duration of haemodialysis had no influence on the raised basal

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>TSH (μU/ml)</th>
<th>PRL (ng/ml)</th>
<th>T4 (μg/100ml)</th>
<th>T3 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Peak</td>
<td>Basal</td>
<td>Peak</td>
</tr>
<tr>
<td>Controls (n = 22)</td>
<td>3·8 [2·3]</td>
<td>12·0 [4·2]</td>
<td>5·5* [2·9]</td>
<td>30·6 [11·1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8·27 [2·23]</td>
<td>1·17 [0·23]</td>
</tr>
<tr>
<td>Chronic renal failure (n = 8)</td>
<td>4·5 [1·8]</td>
<td>9·8 [5·2]</td>
<td>17·8* [9·9]</td>
<td>21·4 [8·1]</td>
</tr>
</tbody>
</table>

* = U test 2α <0·05.

Conversion: traditional units to SI—T4: 1 μg/100 ml = 12·87 nmol/l, T3: 1 ng/ml = 1·536 nmol/l.
TSH and PRL response to thyrotrophin-releasing hormone

Fig. 2  Concentration of serum PRL after IV TRH. Range is shown as mean values ± SD in 8 children with chronic renal failure and 2 children with successful renal transplants, compared with 22 healthy children.

level of plasma PRL, or on the failure to increase PRL concentration after TRH injection in children with CRF.

Discussion

Studies of thyroid function in patients with CRF have produced conflicting results; both hyperthyroidism (Schmidt et al., 1971) and hypothyroidism with low T3 and T4 levels have been reported (Ramirez et al., 1972; Czernichow et al., 1976; Kölendorf et al., 1978). Raised plasma-free thyroxine was reported by Bailey et al. (1967) in dialysed patients, and after successful renal transplants these parameters returned to normal. Heparin administration during haemodialysis raises levels of free T4, but not total T4 (Schatz et al., 1969).

The thyroxine-binding capacity of TBG in chronic renal failure is normal (Joasso et al., 1974; Kölendorf et al., 1978), whereas the binding capacity of thyroxine-binding prealbumin is low (Jaffiol et al., 1970). Joasso et al. (1974) suggested that the change in serum T4 was due to some unidentified substance, which displaces T4 from TBG in serum of patients with renal failure. TSH, T4, and T3 are not dialysable (Bindeballe et al., 1973; Silverberg et al., 1973). Impairment of the peripheral conversion of T4 to T3 was also suggested (Lim et al., 1977). Normal 131I uptake after stimulation of thyroid with TSH in dialysed patients has been reported (Silverberg et al., 1973).

Except in cystinosis, primary thyroid disease is unlikely to be responsible for the low levels of thyroid hormones (Burke et al., 1978). TSH production might be expected to be stimulated by low levels of thyroid hormones, and raised basal value of serum TSH in dialysed patients has been reported (Waldhäußl et al., 1971); others have found normal (Czernichow et al., 1976) or low values (Silverberg et al., 1973). Basal TSH was normal in our patients.

Despite low serum thyroid hormones and normal basal TSH level, exogenous TRH could not stimulate pituitary TSH release, suggesting a defect in pituitary secretion of TSH (Ramirez et al., 1972; Silverberg et al., 1973). The negative feedback mechanism seems, however, to be intact, for high dosages of T3 lowered TSH (Czernichow et al., 1976). The cause of the pituitary abnormalities in these patients is unknown; severe malnutrition or uraemic toxins may be involved (D’Angelo, 1951; Feldman and Singer, 1975).

A trial of thyroid hormone replacement in dialysed uraemic patients with low serum T4 levels and clinical symptoms of hypothyroidism gave inconsistent results (Silverberg et al., 1973). Chan et al. (1970) reported a 10-year-old boy with CRF and clinical signs of hypothyroidism who showed an increase in height velocity after starting thyroid extract. Increased growth velocity with thyroid supplementation occurred in only 2 out of 7 patients treated by Burke et al. (1978). An improvement in growth and better pubertal development may be achieved with thyroid hormone replacement.

An abnormal response of PRL to TRH, with raised basal PRL which could not be stimulated after TRH injection has been reported in uraemic patients (Czernichow et al., 1976; Archer, 1977; Sciarra et al., 1977). Despite the increased PRL, no galactorrhoea or gynaecomastia was observed. The high prolactin may be responsible for the hypergonadism or amenorrhoea in several patients (Thorner, 1977). Whether the hyperprolactinaemia in the uraemic child affects gonadal maturation, and therefore delay in puberty, needs further clarification. The cause and clinical importance of the raised PRL are still poorly understood. High PRL levels are found in primary hypothyroidism (personal observation) often combined with the triad galactorrhoea,
precocious puberty, and hypothyroidism (van Wyk and Grumbach, 1960). None of our patients exhibited clinical signs of hypothyroidism. The abnormal TSH response to TRH would even suggest a secondary hypothyroidism. In our patient receiving medication for acute hypertension PRL secretion was normal. This is despite the fact that several drugs—such as reserpine and α-methyldopa—have been found to increase serum PRL levels (Archer, 1977; Thorner, 1977).

The source of high PRL values in uremic patients is still unknown. A loss of renal degradation cannot be the only cause, several other peptide hormones are not raised. Cowden et al. (1978) demonstrated a progressive rise in PRL concentrations as renal function deteriorates, and a return to normal after successful renal transplants. PRL is supposed to have a fundamental osmoregulatory role in many species of fish and amphibians (Lam, 1972). Its possible role as an osmoregulator in man remains controversial. The role of the hypothalamus and pituitary in the abnormal secretion of PRL is obscure. Since increased PRL secretion is due to a decrease in hypothalamic prolactin-inhibiting factor or an increase in prolactin-releasing factor (L’Hermite et al., 1974), a dysfunction of the hypothalamus may result in decreased prolactin-inhibiting factor or increased prolactin-releasing factor biosynthesis or secretion.

This study has demonstrated the involvement of the hypothalamus and pituitary in children with CRF. Levels of T3 and T4 tend to be low and this is due to inadequate TSH production. PRL is high, but the pituitary reserve is limited so it does not rise further after TRH stimulation. The renal cause of the hypothalamic–pituitary dysfunction remains poorly understood.

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References


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