Hypothyroidism in children with cystinosis

J. R. BURKE, M. M. EL-BISHTI, M. N. MAISEY, AND C. CHANTLER

From the Evelina Children's Department, and Department of Nuclear Medicine, Guy's Hospital, London

Summary  Eight children with cystinosis (3 with renal transplants, 2 on maintenance haemodialysis, 2 with chronic renal failure, and one with normal renal function) were studied for evidence of hypothyroidism, and compared with a control group of children with chronic renal failure due to other causes. Abnormal thyroid function was present in all the cystinotic patients: thyroxine (T4) low in 1, free thyroxine index (FTI) low in 2, thyroid-stimulating hormone (TSH) raised in 6; all had a supranormal TSH response to thyrotrophin-releasing hormone (TRH) stimulation, indicating impaired thyroid reserve compared with patients in the control group who had a depressed or normal TSH response. Increased growth velocity with thyroid supplementation occurred in only 2 patients, and the onset of puberty may have contributed to this improvement. Hypothyroidism is a common finding in cystinosis, and it is suggested that thyroxine treatment be started when the TSH concentration becomes raised.

Cystinosis usually presents in the first 12–18 months of life with failure to thrive, polyuria, and polydipsia. Investigations show a generalised amino-aciduria, glycosuria, metabolic acidosis, hypokalaemia, and hypophosphataemia. The diagnosis is confirmed by the demonstration of cystine crystals in the bone marrow and by slit lamp examination of the eyes. Cystine deposits are found in most organs at post-mortem examination (Jackson and Clarke, 1953) but the two organs that usually show malfunction are the kidney, with progression to end-stage renal failure by 10–12 years, and the eye with photophobia and chorioretinitis.

In our experience cystinotic patients appear more growth retarded than any other group with renal failure. 38% of the children accepted at Guy's Hospital between 1972 and 1976 for haemodialysis or transplants were <3rd height centile and nearly half of these were cystinotic (Fig. 1). The reason for the severe growth retardation is unknown. Growth failure begins before the renal function is impaired and the growth hormone (GH) release is normal (Lucky et al., 1977). Hypothyroidism has been reported in cystinosis (Harris, 1962; Chan et al., 1970; Lucky et al., 1977), but the effect of thyroid supplementation on growth is not known. This study was performed to define whether hypothyroidism is an isolated or a common finding in cystinosis, and to investigate the effect of thyroid supplementation on the growth of those with functional thyroid impairment.

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children from the dialysis and 3 from the transplant programme, in whom renal failure was caused by conditions other than cystinosis, were studied for comparison.

As cystinosis is inherited as an autosomal recessive condition, the thyroid function of parents with cystinotic children was also studied for evidence of heterozygote dysfunction.

Methods

Bone age was estimated by the TW2 method (Tanner et al., 1975). Radioimmunoassay was used for the measurement of thyroxine (T4; Radiochemical Centre), triiodothyronine (T3; Radiochemical Centre), and thyroid-stimulating hormone (TSH; Abbott). T3 resin uptake was determined (Radiochemical Centre) and the free thyroxine index (FTI) calculated. Detection of thyroid antibodies was by immunofluorescence.

Perchlorate discharge test was performed by giving 20 μCi I131 orally and measuring the thyroid radioactivity with a scintillation detector at 30, 60, 90, and 120 min. Potassium perchlorate, 1 g orally, was then given and measurements continued at 30-min intervals for a further 2 hours.

TSH estimations were performed on venous blood taken before the IV administration of 200 μg of thyrotrophin-releasing hormone (TRH) and at 20 and 60 min after injection.

Results

None of the patients was clinically hypothyroid or had a palpable goitre. In the cystinotic group, T4 was reduced in only one patient; FTI was reduced in 2 patients but T3 level was normal in both; basal TSH was raised in 6 of the 8 patients (Table 1). In the control group, FTI was reduced in one patient but the T3 level was normal, and basal TSH was normal in all 6 patients (Table 2).

After stimulation with TRH there was a pronounced difference in the TSH response between the cystinotic patients and the control group (Fig. 2). All the cystinotic patients had an exaggerated response of TSH to TRH stimulation in contrast to those in the control group in whom an impaired TSH response was shown.

Perchlorate discharge test was abnormal in 2 cystinotic patients. Antithyroid antibodies were not detected in any patient.

Seven of the patients were given thyroxine in a daily dose of 50 μg for 4 weeks and then the dose was increased to 100 μg daily. On this dosage the TSH levels were all in the normal range. Growth in the 12 months before taking thyroxine and after starting it was compared and expressed as the SD from the mean growth velocity of normal children with a chronological age corresponding to the bone age of the patients (Tanner et al., 1966).

One child died during the study; of the remaining

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### Table 1 Eight children with cystinosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Bone age</th>
<th>T4 (70–190 nmol/l)</th>
<th>T3 (1–2–3–0 nmol/l)</th>
<th>T3 RU (92–117 %)</th>
<th>FTI (70–180)</th>
<th>TSH (0–5 mU/l)</th>
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<tbody>
<tr>
<td>1</td>
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<td>16-3</td>
<td>132-8</td>
<td>11-4</td>
<td>86</td>
<td>2-14</td>
<td>129*</td>
<td>67*</td>
<td>&gt;40*</td>
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<tr>
<td>2</td>
<td>HD</td>
<td>14</td>
<td>134-9</td>
<td>10-3</td>
<td>110</td>
<td>2-77</td>
<td>112</td>
<td>98</td>
<td>&gt;40*</td>
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<tr>
<td>3</td>
<td>T</td>
<td>13-8</td>
<td>114</td>
<td>7-4</td>
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<td>111</td>
<td>124</td>
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<tr>
<td>4</td>
<td>T</td>
<td>10-7</td>
<td>115</td>
<td>8-5</td>
<td>141</td>
<td>2-13</td>
<td>108</td>
<td>129</td>
<td>4-3</td>
</tr>
<tr>
<td>5</td>
<td>T</td>
<td>9-7</td>
<td>112-6</td>
<td>7-3</td>
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<td>1-7</td>
<td>98</td>
<td>101</td>
<td>8-8</td>
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<td>6</td>
<td>CRF</td>
<td>5-9</td>
<td>88-2</td>
<td>3-0</td>
<td>60*</td>
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<tr>
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<td>CRF</td>
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<td>7-4</td>
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<td>2-72</td>
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<td>112</td>
<td>8-1*</td>
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<td>8</td>
<td>N</td>
<td>2-1</td>
<td>82</td>
<td>2-2</td>
<td>113</td>
<td>3-49</td>
<td>116</td>
<td>97</td>
<td>4-5</td>
</tr>
</tbody>
</table>

HD = haemodialysis; T = transplant; CRF = chronic renal failure; N = normal renal function; R3 RU = T3 resin uptake.

* Abnormal results, normal ranges are shown.

Conversion SI to traditional units—T4: 1 nmol/l ≥ 0-07 μg/100 ml, T3 1 nmol/l ≥ 0-65 ng/ml.

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### Table 2 Children with renal disease other than secondary to cystinosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Bone age</th>
<th>T4 (70–190 nmol/l)</th>
<th>T3 (1–2–3–0 nmol/l)</th>
<th>T3 RU (92–117 %)</th>
<th>FTI (70–180)</th>
<th>TSH (0–5 mU/l)</th>
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<td>94</td>
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<td>118</td>
<td>80</td>
<td>4-2</td>
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<td>63*</td>
<td>2-77</td>
<td>103</td>
<td>61*</td>
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<tr>
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<td>T</td>
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<td>83</td>
<td>2-37</td>
<td>107</td>
<td>78</td>
<td>2-7</td>
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</table>
Hypothyroidism in children with cystinosis

was therefore recorded in the parents of these cystinotic children.

Discussion

Thyroid function may be abnormal in children and adults with renal failure of varying aetiology. In the study of Wassner et al. (1977), 22 children had low-normal mean values of T4, T3, and FTI, and a normal level of TSH. Two children were hypothyroid—one secondary to cystinosis and the other after radiotherapy. Both had subnormal T4, T3, and raised TSH. Adults with chronic renal failure and on haemodialysis may have subnormal T4, T3, FTI, and a depressed TSH response to TRH stimulation (Ramirez et al., 1973; Dandona et al., 1977). After transplantation in adults, thyroid function usually returns to normal except for diminished T3 concentrations which may be related to prednisolone administration (Ramirez et al., 1977).

In the present study thyroid function was abnormal in all 8 cystinotic patients. Both T4 and FTI were depressed in one patient and another had a low FTI. Baseline TSH was raised in 6 and all had a supranormal TSH response to TRH administration, indicating impaired thyroid reserve and possibly incipient thyroid failure.

In the control group one child with a normal functioning transplant for 18 months had a reduced level of T4 and FTI. Baseline TSH levels were normal but 5 children (2 on haemodialysis and the 3 transplants) had a depressed TSH response to TRH administration and the 6th had a normal response.

The cause of the thyroid failure in cystinotic

6 children, 2 showed an improvement in growth but entered puberty during the study, growth deteriorated in 2, and was static in the remaining 2 children treated with thyroxine (Table 3).

Of the 14 parents studied, mild abnormal thyroid function was present in 2. The mother of Case 6 had a high baseline TSH and a supranormal response of TSH to TRH, a similar result to that seen in the cystinotic children. The father of Case 4 had a normal baseline TSH but a depressed TSH response to TRH. No definite evidence of heterozygote dysfunction

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**Table 3  Effect of thyroxine on growth velocity**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Before treatment</th>
<th>After treatment</th>
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<tbody>
<tr>
<td></td>
<td>12 months before</td>
<td>12 months after</td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>Bone age at start of thyroxine</td>
</tr>
<tr>
<td>1†</td>
<td>130.8</td>
<td>132.8</td>
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<tr>
<td>2‡</td>
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<tr>
<td>7§</td>
<td>107</td>
<td>111</td>
</tr>
</tbody>
</table>

*Ratio of growth velocity standard deviation to bone age; †entered puberty since starting treatment; ‡received high dose corticosteroids for rejection episodes; § had transplants after beginning treatment.
patients is believed to be due to deposition of cystine crystals in the thyroid gland. Necropsy of Case 4 showed a partially atrophied thyroid and histologically some of the follicles were atrophic with cystine crystals present. Similar pathological findings have been identified before (Jackson and Clarke, 1953; Chan et al., 1970). Perchlorate discharge test was abnormal in 2 patients suggesting an organification defect. An autoimmune aetiology such as Hashimoto’s disease is unlikely as thyroid antibodies were negative. No abnormality of pituitary function to account for thyroid failure has been reported in cystinotic patients. GH and adrenocortical stimulation were normal in the patients studied by Lucky et al. (1977) and 2 patients in this study had normal GH stimulation. The defect in thyroid function in cystinotic patients appears different from that present in the children with chronic renal failure described by Czernichow et al. (1976). The abnormality in their children appeared to be at the hypothalamic-pituitary level with no increase in TSH after TRH administration—a similar finding to our controls. Our findings would therefore support a primary thyroid failure as the cause of impaired thyroid function in cystinosis.

Chan et al. (1970) reported a 10-year-old boy with chronic renal failure and clinical signs of hypothyroidism who showed an increase in height velocity after starting thyroid extract. Malekzadeh et al. (1977) described biochemical hypothyroidism in 4 patients with transplants but they did not state whether there was increased growth after beginning thyroxine. In our study thyroid supplementation was given to 7 patients in a dosage sufficient to bring the baseline TSH into the normal range. Subsequent growth rate increased in only 2 patients who were on haemodialysis and in whom a pubertal growth spurt probably contributed, as both patients were pubertal before starting thyroxine. Two patients with chronic renal failure had transplants after starting thyroxine and so required high corticosteroid dosage for 6 months of the study. One of the main side effects of corticosteroids is growth inhibition and Falliers et al. (1963) showed that a dose as little as 6 mg/m² prednisolone per day is sufficient to suppress growth. One transplant patient (Case 3) was treated for 3 rejection episodes during the 12 months on thyroxine and daily prednisolone dosage averaged 15 mg/m² per day. Another transplant patient (Case 4) died from pancreatitis 6 months after starting thyroxine and his average daily prednisolone dosage during that period was 18 mg/m² per day. The growth inhibition of corticosteroids is less when it is given on alternate days (Hoda et al., 1975). However, Case 5 who had a normal functioning transplant for 14 months before the start of the study, and was receiving prednisolone 20 mg/m² on alternate days throughout, did not show an increase in growth velocity. Because Case 6 had mild abnormal thyroid function and normal renal function, he was not given thyroxine. It seems unlikely that impaired thyroid reserve causes the growth retardation notable in this group of patients and further studies of factors responsible for growth will be necessary to identify the cause.

Thyroid dysfunction is a consistent complication of cystinosis even being present in a 2-year-old child with normal renal function, but true hypothyroidism seems relatively uncommon. However in time the thyroid function will probably gradually deteriorate to clinical hypothyroidism. Careful monitoring of thyroid function is therefore mandatory to avoid an easily treatable complication. A raised level of TSH is a reliable indicator of abnormal function, but impaired function cannot be excluded without a TRH stimulation test. It is suggested that treatment with thyroxine be begun when the TSH rises above normal in a dose sufficient to suppress the TSH to normal levels.

We thank Dr C. Brook for performing bone age estimations, Mrs G. Mashiter for thyroid function tests, and Dr D. Turner for histology. Dr J. Burke was supported by a Commonwealth Medical Fellowship awarded by the British Council.

References


Correspondence to Dr C. Chantler, Evelina Department of Paediatrics, Guy’s Hospital, St Thomas Street, London SE1 9RT.
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