School based screening for hypothyroidism in Down’s syndrome by dried blood spot TSH measurement

S E Noble, K Leyland, C A Findlay, C E Clark, J Redfern, J M Mackenzie, R W A Girdwood, M D C Donaldson

Abstract

Objective—To determine the feasibility of annual hypothyroid screening of children with Down’s syndrome by measuring thyroid stimulating hormone (TSH) on dried blood spots at school, and to describe the outcome in positive children.

Design—Establishment of a register of school children with Down’s syndrome, and procedures for obtaining permission from parents, annual capillary blood samples, TSH measurement, and clinical assessment of children with TSH values > 10 mU/litre.


Results—200 of 214 school children with Down’s syndrome were screened. Four of the unscreened children were receiving thyroxine treatment, and only 5 remained unscreened by default. 15 of the 200 children had capillary TSH > 10 mU/litre, and all but 1 had evidence of Hashimoto’s thyroiditis. Seven of the 15 children started thyroxine treatment immediately, 6 with a pronounced rise in venous TSH and subnormal free thyroxine (T4), and one with mildly raised TSH and normal T4 but symptoms suggesting hypothyroidism. Eight children with mildly raised venous TSH and normal T4 were left untreated; 1 year after testing positive, T4 remained > 9 pmol/litre in all cases, but 4 children were started on thyroxine because of a rise in TSH. TSH fell in 3 of the 4 remaining children and there was a marginal rise in 1; all remain untreated. The prevalence of thyroid disease in this population is ≥ 8.9%.

Conclusion—Dried blood spot TSH measurement is effective for detecting hypothyroidism in Down’s syndrome and capillary sampling is easily performed at school. The existing programme could be extended to the whole of Scotland within a few years.

Keywords: Down’s syndrome; thyroid stimulating hormone; hypothyroidism; screening

It is well recognised that thyroid dysfunction occurs more frequently in Down’s syndrome than in the general population.1–3 Primary hypothyroidism, the most common problem, can be described as decompensated or compensated according to whether the plasma thyroxine (T4) or free T4 (fT4) is low or maintained within the normal range. Although an increased prevalence of congenital hypothyroidism in Down’s syndrome is recognised,1–5 a mild and transient rise in thyroid stimulating hormone (TSH) in infancy is more usual,3–6 and acquired hypothyroidism as a result of Hashimoto’s thyroiditis is the most common disorder.1–3–7–9 Some studies have reported relative hypothyroxinaemia in individuals with Down’s syndrome compared with controls.7–9–10 The prevalence of hypothyroidism is also increased in Down’s syndrome.1–11–12

Prevalence figures for hypothyroidism in Down’s syndrome will vary not only according to the age of the population tested, but also according to the type and extent of thyroid dysfunction measured: thyroid autoantibody status, TSH concentration, and T4 or fT4 concentrations. A community study in Bedford found raised TSH concentrations in seven of 101 individuals (7%) aged 5–21 years.7 In Birmingham, a survey of 160 adults with Down’s syndrome showed prevalences for decompensated and compensated hypothyroidism of 8.1% and 11.9%, respectively.7

Clearly, it is desirable to detect hypothyroidism as early as possible in any individual, and especially in children who already have growth impairment and learning disability. However, clinical diagnosis is difficult in Down’s syndrome. The hypothyroid features can be masked by the phenotypic appearance,7–11 and symptoms such as weight gain, poor growth, and dulling of affect might be attributed to the syndrome itself. Conversely, symptoms such as weight gain and cold intolerance might be attributed to hypothyroidism in individuals with Down’s syndrome who have only marginally raised TSH values and low normal T4 concentrations. This might account for the particularly high prevalence figure for hypothyroidism in a recent study from Finland.14

Given these difficulties and the increased prevalence of hypothyroidism in Down’s syndrome, regular screening has been recommended.3–5 However, screening by venous sampling can be difficult technically, is often traumatic for the child, and becomes ethically questionable in older subjects in whom considerable restraint may be required. For these reasons, venepuncture is not usually...
feasible at the school or surgery, whereas hospital based screening is difficult to organise.

In contrast, capillary TSH sampling, using the dried blood method used for neonatal screening, is technically simple, can be performed in the community, and is easily accommodated by the national or regional screening laboratory. The purpose of our study was to examine the feasibility of capillary TSH screening in school children with Down’s syndrome aged 4–19 years and to describe the outcome in those children who were referred after a positive test. The relative insensitivity of the dried blood spot TSH assay (lower limit of detection approximately 10 mU/litre) was seen as a potential advantage because the mild TSH rise (5–9 mU/l) that occurs frequently in Down’s syndrome, would not be detected, thus avoiding unnecessary intervention, whereas evolving hypothyroidism would be missed if screening was being carried out on a regular basis.

Subjects and methods
A register was created for children and adolescents with Down’s syndrome aged 4–19 years who were attending schools within Glasgow and Lanarkshire Health Boards. The information was supplied by school doctors and nurses from the two health boards. For the academic years August 1996 to June 1997 (year 1) and August 1997 to June 1998 (year 2) school nurses were asked to verify inclusion of new school entrants, and to record the details of school leavers. Information from the preschool child health surveillance programme was used to cross check new entrants. After ethical approval had been obtained, the school nurses distributed letters to the parents explaining that annual screening for an underactive thyroid was being proposed using a finger prick test, and enclosing a consent form. Four options were offered: consent to annual screening; refusal; opportunity for further discussion with the school doctor or nurse; and non-participation if the child had recently been screened elsewhere or was already on thyroxine treatment.

For children for whom consent had been given, school nurses obtained capillary blood using autolets, filling two circles on neonatal screening cards. The cards were sent to the National Screening Laboratory in Glasgow, where TSH was measured using a monoclonal antibody coated tube immunoradiometric assay (sensitivity 1 mU/litre). For year 1 the laboratory reported results of < 10 mU/litre as negative, requested a repeat sample if the value was 10–14 mU/litre, and referred the case to a paediatric endocrinologist (MDCD) for clinical assessment if either the initial value was > 15 mU/litre or the repeat value was > 10 mU/litre. Because all repeat samples in year 1 confirmed the raised TSH values, all cases testing > 10 mU/litre in year 2 were referred directly to the paediatric endocrinologist. Clinical assessment of referred cases included examination for symptoms such as fatigue, cold intolerance, dry skin and hair, and constipation, together with signs such as myxoedema, bradycardia, cool peripheries, and slow tendon reflexes. The presence or absence of goitre was also noted. Height was measured using a Holtain stadiometer and expressed as centile position using growth charts specific for Down’s syndrome (Castlemead publications), derived from the data of Cronk et al. Venous blood was taken for plasma TSH and fT4 measurement using an Abbot axsym analyser. Thyroid autoantibodies were measured as microsomal and thyroglobulin antibodies by murex haemaglutination during year 1. By year 2 the laboratory had changed to measuring thyroid peroxidase (TPO) antibodies with a chemiluminescence method using an immulite analyser (Euro DPC Ltd, Gwynedd, UK).

Results
In year 1, 204 children and adolescents with Down’s syndrome aged 4–19 years were identified as attending schools in Glasgow and Lanarkshire Health Boards (fig 1). Twenty six children were receiving education in mainstream schools; the rest in special schools. Four children were already receiving thyroxine. One had begun treatment in the neonatal period for probable congenital hypothyroidism and three children, one of whom also has diabetes mellitus, had developed hypothyroidism (compensated in two) aged 8, 10, and 11 years. In addition to these four children, six had been tested by venepuncture either by their paediatrician or family doctor. A further 14 (6.9%) were
TSH screening carried out at school during the academic years 1996–7 (year 1) and 1997–8 (year 2) Table 1 Clinical and biochemical data on 15 children and adolescents with Down’s syndrome who were found to have raised TSH values on capillary screening for hypothyroidism in Down’s syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Year</th>
<th>Sex</th>
<th>Down’s height centile</th>
<th>Capillary TSH</th>
<th>Venous blood</th>
<th>Thyroid autoantibodies</th>
<th>Clinical features</th>
<th>Treated</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mic</td>
<td>Tg</td>
<td>TP</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>1</td>
<td>F</td>
<td>5</td>
<td>119</td>
<td>113</td>
<td>5.2</td>
<td>&gt; 1/6400</td>
<td>1/400</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>1</td>
<td>F</td>
<td>&lt; 5</td>
<td>86</td>
<td>114</td>
<td>7</td>
<td>&gt; 1/6400</td>
<td>1/100</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>1</td>
<td>M</td>
<td>50</td>
<td>51</td>
<td>108</td>
<td>7.7</td>
<td>&gt; 1/6400</td>
<td>Neg</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>1</td>
<td>M</td>
<td>75</td>
<td>29</td>
<td>36.9</td>
<td>8.9</td>
<td>&gt; 1/6400</td>
<td>1/1600</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>1</td>
<td>M</td>
<td>&gt; 95</td>
<td>19</td>
<td>11.6 (13.8)</td>
<td>9.4 (10)</td>
<td>1/400</td>
<td>Neg</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>1</td>
<td>F</td>
<td>50–75</td>
<td>17</td>
<td>7.8 (0.04)</td>
<td>11.8 (28.9)</td>
<td>1/6400</td>
<td>Neg</td>
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<tr>
<td>7</td>
<td>14</td>
<td>1</td>
<td>M</td>
<td>75–90</td>
<td>13</td>
<td>12.7 (19.1)</td>
<td>11.3 (10.5)</td>
<td>1/6400</td>
<td>Neg</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>1</td>
<td>M</td>
<td>&gt; 95</td>
<td>11</td>
<td>10.8 (15.7)</td>
<td>12 (12)</td>
<td>1/6400</td>
<td>1/1600</td>
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<tr>
<td>9</td>
<td>17</td>
<td>1</td>
<td>F</td>
<td>25–50</td>
<td>13</td>
<td>10 (7.9)</td>
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<tr>
<td>10</td>
<td>16</td>
<td>1</td>
<td>M</td>
<td>5</td>
<td>16</td>
<td>8.7 (4.7)</td>
<td>19.7 (12.4)</td>
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<tr>
<td>11</td>
<td>14</td>
<td>2</td>
<td>F</td>
<td>50–75</td>
<td>14</td>
<td>14.8</td>
<td>13.1</td>
<td>&gt; 1000</td>
<td>Cold intolerance, lethargy</td>
</tr>
<tr>
<td>12</td>
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<td>12</td>
<td>40.8</td>
<td>8</td>
<td>1/1600</td>
<td>Neg</td>
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<tr>
<td>13</td>
<td>13</td>
<td>2</td>
<td>M</td>
<td>&gt; 95</td>
<td>12</td>
<td>40.8</td>
<td>8</td>
<td>1/1600</td>
<td>Neg</td>
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<tr>
<td>14</td>
<td>12</td>
<td>2</td>
<td>M</td>
<td>25–50</td>
<td>14</td>
<td>7.3 (4.3)</td>
<td>10.3 (10)</td>
<td>&lt; 50</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>9</td>
<td>2</td>
<td>F</td>
<td>10–25</td>
<td>18</td>
<td>9.5 (12.5)</td>
<td>18 (15.5)</td>
<td>825</td>
<td>Juvenile arthritis, no thyroid symptoms</td>
</tr>
</tbody>
</table>

Venous TSH and free T4 values 1 year after screening are given in parenthesis for the eight children who were not initially treated with thyroxine.

Normal values: capillary TSH, < 10 mU/litre; venous TSH, < 5 mU/litre; fT4, 9–27 pmol/litre; Mic and Tg titres, < 1/100; TPO, < 50 IU/ml.

*Thyroxine started after retesting one year later.

‡See text for details.

Venous TSH, thyroid stimulating hormone; fT4, free thyroxine; Mic, microsomal; Tg, thyroglobulin; TPO, thyroid peroxidase; Neg, < 1/100.

Discussion

We have found dried blood spot TSH screening by capillary testing in school aged children with Down’s syndrome to be feasible in most cases. The procedure has been well tolerated by most of the children screened and although some refused capillary testing we believe that the number of refusals would have been far higher had venous sampling been attempted.

Capillary sampling can be carried out in the school setting with minimal inconvenience and disruption to the child and their parents. In contrast, we found venepuncture in hospital very difficult to perform in several of the cases referred with TSH rises, and intend to monitor
their future progress by capillary rather than venous sampling. Capillary TSH sampling could also be extended to the screening and monitoring of other at risk groups including Turner’s syndrome.  

The uptake of screening in the two health boards has been excellent, particularly in Lanarkshire, where no patients were unscreened by default or error. In Glasgow, difficulties were encountered with the return of consent forms during year 1, and the request was refused in two cases, but by year 2 this problem had been largely resolved, and over the two year screening period only five (2.3%) of the 214 school children remained untested by either capillary TSH screening or venepuncture elsewhere.

Capillary TSH screening yielded 15 positive tests over a two year period and all but one child was thyroid autoantibody positive. Symptoms and signs of hypothyroidism were few, even in those children with subnormal fT4 and very high TSH concentrations, and none of the 15 children had been taken to the doctor with hypothyroid symptoms. Height status represented by centile on Down’s syndrome growth chart was subnormal in only one girl (patient 2) with decompensated hypothyroidism. Otherwise, Down’s specific based height centile was non-contributory, with 10 of the 15 children on or above the 50th centile.

Six cases with pronounced rises in TSH clearly required immediate treatment with thyroxine, and this was also instituted in a seventh patient with a mildly raised TSH concentration but symptoms suggestive of hypothyroidism. The decision regarding management of the eight children with mildly raised TSH values and no symptoms was more difficult but we elected to keep them under observation. One year after capillary testing, four of the children were started on thyroid treatment after a rise in TSH to between 13.8 and 20.4 mU/litre, with one girl having a transient phase of biochemical hyperthyroidism beforehand. From our initial experience, we suspect that almost all cases with venous TSH > 10 mU/litre on initial testing will go on to require thyroxine treatment at some stage. However, our data are too few for definite conclusions to be drawn at present. Consequently, in asymptomatic children with TSH values between 10 and 15 mU/litre we will, with parental agreement, continue a policy of surveillance.

Concerning the optimal frequency of screening it is of note that one girl showed a capillary TSH of 55 mU/litre in year 2, having tested (40.8 mU/litre) three months after a borderline negative in the previous year. A second boy TSH of 55 mU/litre in year 2, having tested and 15 mU/litre we will, with parental agreement, continue a policy of surveillance.

The decision to start screening at school entry was taken for logistic reasons and because we assumed that the prevalence of decompensated hypothyroidism from Hashimoto’s thyroiditis would be low in this age group, with cases of congenital hypothyroidism having been identified by the neonatal screening programme. However, one child identified by screening was only 5 years old, and we have recently seen two preschool boys with positive TPO antibodies and high TSH values, one of whom had clinically severe hypothyroidism. We suggest that capillary TSH testing at 18 months and 3 years is desirable in preschool children, but that a programme for comprehensive screening of school aged children should take priority.

There is a particular need for a screening procedure for school leavers, because the likelihood of developing hypothyroidism becomes greater with age. In Glasgow, a thyroid register exists so that the family practitioners of adult patients receiving thyroxine are automatically notified to carry out thyroid function tests on an annual basis and provided with a sample container and stamped addressed envelope for sampling and postage. Introduction of a similar system for adults with Down’s syndrome should be considered.

We wish to thank all the school nurses in Lanarkshire and Glasgow Health Boards for their patience and support, also M McIntyre, M Telford, A Brown, and H Smith for their clerical assistance.

Cost of chickenpox

The incidence of chickenpox is said to be approximately equal to the number of births. Over 95% of cases are in children under 15 with the highest incidence in the 5–9 year age range. Details of the financial cost of the disease have been reported from Canada.

In two papers (Barbara Law and colleagues. *Pediatrics* 1999;104:1–6 and 7–14) costs are calculated from studies of 179 otherwise healthy 1–9 year olds with uncomplicated chickenpox treated at home, 160 otherwise healthy children with complicated (treated in hospital) chickenpox, and 40 children with leukaemia admitted to hospital with chickenpox. For uncomplicated cases the total cost to society per case was estimated at around CDN$370 for younger children and CDN$240 for children aged 5–9. Medical costs were about 10% of the total. The total national cost was estimated at CDN$110 million annually.

For children admitted to hospital the total cost to society per case was around CDN$8000 for otherwise healthy children and for children with leukaemia the medical cost of an admission with chickenpox was over CDN$7000. This brought the estimated total national cost of chickenpox to CDN$122 million, with CDN$24 million of that cost being borne by the health ministry. Added to that there were considerable quality of life costs for children and parents. In the USA it has been calculated that vaccination against chickenpox would result in a total saving to society of US$66 per child vaccinated. (CDN$1 approximately US$0.68.)

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