Screening for Hypothyroidism in Down Syndrome Using the Capillary Thyroid Stimulating Hormone Method

Sheena McGowan, BSc[1], Jeremy Jones, BSc, MSc[2], Donald McMillan, PhD[3], Kirsty McLaughlin, BSc[4], Sarah Smith, MSc, CSci, FIBMS[4], Kath Leyland, FRCPCH[5], Patricia Charleton, FRCPCH[6], and Malcolm Donaldson, MD[1], on behalf of the Scottish Down Syndrome Screening Group*

Objectives To analyze data from the Scottish capillary thyroid stimulating hormone (TSH) screening program for hypothyroidism in Down syndrome to identify a threshold for capillary TSH elevation below which low venous free thyroxine (fT4) (<9 pmol/L) and/or frank venous TSH elevation (>10 mU/L) range is unlikely.

Study design Review of proformas prospectively submitted on all children with Down syndrome referred via the screening program between 2003 and 2013.

Results Ninety-nine patients with Down syndrome (50 females, 49 males) were identified, 76 school-age (≥5 years) and 23 preschool (<5 years), mean (range) age at referral 9.4 (0.9-18.1) years. Pearson correlation between capillary TSH and venous TSH was 0.814; between capillary TSH and venous fT4 −0.522 ($P = .01$). Receiver operator curve analysis showed that capillary TSH values of 4 and 6 mU/L were 95.9% and 73.5% sensitive, 5.8% and 80.8% specific, respectively, in predicting venous TSH >10 mU/L. Fifty-three children had capillary TSH values of 4-5.9 mU/L of whom only one, a boy of 15.8 years, had subnormal venous fT4 (<9 pmol/L), and venous TSH >10 mU/L was found in 13 (4 preschool).

Conclusions Venous fT4 is normal in almost all patients with Down syndrome with capillary TSH 4-6 mU/L. We propose an algorithm incorporating rescreening by finger prick after 6 months, rather than venepuncture, in school-aged children with borderline capillary TSH elevation. Further data are needed before this approach can be recommended for preschool children. *(J Pediatr 2015;166:1013-7)*.

Subjects with Down syndrome are at increased risk of primary thyroid dysfunction,[1] particularly autoimmune thyroiditis.[2] The prevalence of hypothyroidism in Down syndrome increases with age and is estimated as no less than 5.7% in children and adolescents in Scotland[3] and 11.9% among adults.[4] Clinical detection is difficult because symptoms of cold intolerance, constipation, dry skin and hair, and tiredness are nonspecific and occur commonly in euthyroid subjects with Down syndrome. The increased risk of hypothyroidism in Down syndrome and the difficulty of clinical diagnosis provide a need for screening. The American Academy of Pediatrics guidelines recommends thyroid stimulating hormone (TSH) measurement at 6 months and 1 year of age and then annually,[5] and in the United Kingdom the Down Syndrome Medical Interest Group advocates screening from 1 year of age with at least 2 yearly venous thyroid function tests thereafter.[6]

Venepuncture will identify TSH elevation and decrease in venous free thyroxine (fT4) as well as detecting thyroid autoantibodies. However, venepuncture has disadvantages including hospital or clinic attendance requiring the child to be taken out of school; distress to the child and parent; and sometimes the need for restraint with which staff may feel uncomfortable. These considerations led in the West of Scotland during the 1990s to the development of an alternative method—capillary TSH screening.[7] After obtaining parental consent, the school nurse takes a capillary blood sample from a finger prick using an autolet and spots the sample onto one of the filter strips employed for newborn blood spot screening. There is no need for the parent to be present or for the child to be taken out of school during this procedure. The sample is then sent to the Newborn Screening Laboratory and "piggy-backed" onto the existing TSH service for analysis. A value of ≥4 mU/L triggers referral to a clinician. In 2011, McGowan et al reported the outcome in 1329 Scottish children tested between 1997 and 2009.[3] Thyroid dysfunction was confirmed in 98 subjects aged 0.9-17.9 years, 13 of whom were preschool children. Symptoms were reported in one-third of patients and 60 were treated with levothyroxine (L-T4) either at referral or subsequently. Using the capillary method in the Republic of Ireland,

fT4	Free thyroxine
L-T4	Levothyroxine
TPO	Thyroperoxidase
TSH	Thyroid stimulating hormone

From the [1]Section of Child Health, Royal Hospital for Sick Children, University of Glasgow School of Medicine, Yorkhill; [2]National Health Service Greater Glasgow and Clyde, Royal Hospital for Sick Children, Yorkhill; [3]Academic Unit of Surgery, Glasgow University School of Medicine, Royal Infirmary; [4]National Health Service Greater Glasgow and Clyde, West of Scotland Genetic Services, Newborn Screening Laboratory, Southern General Hospital; [5]National Health Service Greater Glasgow and Clyde, Southbank Development Center, Glasgow, United Kingdom; and [6]National Health Service Grampian, Royal Aberdeen Children's Hospital, Aberdeen, United Kingdom

*List of members of the Scottish Down Syndrome Thyroid Screening Group is available at www.jpeds.com (**Appendix**).

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.12.035

Murphy et al recorded a 4.6% prevalence of thyroid dysfunction in 305 children, with parents reporting minimal distress with finger prick testing.[8]

The optimal management of children with Down syndrome with mild capillary TSH elevation (eg, 4-5.9 mU/L of whole blood) remains problematic. Such children are likely to have normal venous fT4, and normal or mildly elevated venous TSH, and may not, therefore, require immediate treatment. The present study seeks to establish a threshold value for capillary TSH below which low venous fT4 (<9 pmol/L) and significant venous TSH elevation (>10 mU/L) are unlikely, rendering repeat capillary screening more appropriate than automatic recall to hospital or clinic for venepuncture.

Methods

Since 1997, details have been kept on patients with Down syndrome tested by the Newborn Screening Laboratory in Scotland. These include date and age at each capillary screening test, capillary TSH values, and, in cases which have been referred, venous thyroid function tests and clinical outcome in terms of whether or not treatment with L-T4 was required.

At initial screening in Scotland, parents are asked to give written consent for screening throughout childhood, until their child leaves school. Data from screened children are kept on a password-protected computer in the Section of Child Health at the Royal Hospital for Sick Children, Yorkhill, Glasgow. The study was registered with the department of Clinical Effectiveness at the Royal Hospital for Sick Children, National Health Service Greater Glasgow and Clyde.

The current study explored the relationship between capillary TSH and both venous TSH and fT4 in all patients referred since 2003 with capillary TSH ≥4 mU/L. Individuals were divided into 2 age ranges: preschool (<5 years) and school-age (≥5 years). Values for capillary TSH were divided into the following ranges: 4-5.9, 6.0-10.9, 11.0-20, and >20 mU/L of whole blood. In the context of TSH elevation, hypothyroidism was defined as compensated or decompensated according to whether venous fT4 was within or below the reference range.

Information was collated from the submitted proformas in terms of symptoms, height, and weight at the time of initial referral. Children were grouped according whether they had symptoms (such as fatigue, weight gain, constipation, dry hair, and dry skin); no symptoms reported; equivocal symptoms; and those in whom data were not available. Height and weight were expressed according to Down-specific data from the United Kingdom and Republic of Ireland[9] as SDS using the Excel add-in LMS growth program of Professor TJ Cole (http://www.healthforallchildren.com/?product_cat=software).

Since 2002, the laboratory has used the Perkin Elmer AutoDELFIA neonatal hTSH assay (PerkinElmer Life and Analytical Sciences, Wallac Oy, Finland) for Down as well as newborn thyroid screening. The assay has a sensitivity of 2 mU/L, and the capillary TSH cut-off for referral is set at ≥4 mU/L of whole blood. Venous thyroid function tests were carried out locally as required, with a reference range at the Royal Hospital for Sick Children of 0.55-5.8 mU/L for TSH and 9-23 pmol/L for fT4. Thyroperoxidase (TPO) antibodies were measured when TSH elevation was found, with the reference range for our laboratory being <50 IU/mL.

Data Analyses

Height and weight SDS were expressed as median and IQR values for all patients, and also in subgroups according to symptoms and to biochemical severity as reflected by venous TSH levels. Growth data were tested for normality using the Anderson-Darling test and analyzed using a combination of 1-way ANOVA for normally distributed data and Kruskal-Wallis followed by Mann-Whitney test for nonparametric data. The relationship between capillary and venous TSH, and between capillary TSH and venous fT4 was examined by using Pearson correlation and also by tabulating the data according to preschool and school-age status. The sensitivity and specificity of capillary TSH in predicting a subnormal venous fT4 (<9 pmol/L) and significant venous TSH elevation, defined as >10 mU/L, was examined by receiver operator curve analysis. A P value of <.05 was considered statistically significant. Analyses were carried out using Minitab, (Minitab Inc, State College, Pennsylvania) v 15 and SPSS v 21.0 (SPSS Inc, Chicago, Illinois).

Results

Between October 2003 and June 2013, 99 patients with Down syndrome were referred by the screening laboratory with capillary TSH ≥4 mU/L. Sex incidence was equal (50 females, 49 males), median (range) age at referral 9.4 (0.9-18.1) years. Of the 99 children, 23 were preschool (<5 years) and 76 were of school age (≥5 years). Twenty children had symptoms that could have been thyroid-related; 43 had no symptoms, 6 had possible symptoms, and data were unavailable in 30. Of 70 children in whom both height and weight data were available the median (IQR) SDS values were −0.066 (−1.007 to 0.678) for height and 0.288 (−0.609 to 0.85) for weight. For children with symptoms (n = 16) compared with those without (n = 36) median (IQR) height SDS was −0.616 (−1.075 to 0.95) vs −0.021 (−0.75 to 0.67); weight SDS 0.288 (−0.66 to 0.58) vs 0.174 (−0.57 to 0.89). These differences were not significant (P = .53 and .68). When growth was examined in relation to venous TSH values of <10, 10-20, and >20 mU/L no differences were found for median height SDS (−0.04, −0.179 and 0.279 [P = .49]) or median weight SDS (0.084, 0.499 and 0.285 [P = .86]).

Correlation between Capillary TSH and Venous fT4 and TSH

Pearson correlation between capillary and venous TSH was, as expected, high at +0.814 (P = .01). However, correlation between capillary TSH and venous fT4 was low, albeit significant, at −0.522 (P = .01).