Misdiagnosis of Thyroid Disorders in Down Syndrome: Time to Re-Examine the Myth?

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Abstract

There is a reported association between thyroid disorders and Down syndrome, but is this association based on valid and reliable research evidence? We evaluated thyroid function test results of 110 healthy adults with Down syndrome to determine biochemical thyroid status. Approximately two thirds were biochemically euthyroid when assessed by standard reference ranges for the general population. We believe that there is a need for revalidation of “normal” thyroid function tests parameters when applied to the Down syndrome population and that persons with Down syndrome are possibly being misdiagnosed and inappropriately treated for a nonexistent medical disorder.

In numerous publications over the last 40 years, researchers have apparently confirmed a definitive association between Down syndrome and thyroid disorder (for a review, see Prasher, 1999). The vast majority of studies, however, have been prevalence studies based on thyroid function tests. There have been virtually no incidence studies, no studies in which researchers investigated the natural course of thyroid disorders in people with Down syndrome, and no critical reviews of the validity of definitions of thyroid disorders. The latter is particularly important to the use of thyroid function test reference ranges developed for the general population and used to diagnosis disease in the Down syndrome population.

The role and clinical accuracy of thyroid function tests in the general population has recently been questioned (Reilly, 2000). Controversy remains regarding whether a diagnosis of hypothyroidism should be made on biochemical and/or clinical grounds (Skinner et al., 1997; Weetman, 1997). For individuals with Down syndrome, a diagnosis of hypothyroidism is often made on a single thyroid function test result, with little regard for other causes of the abnormal results and with little reference to the clinical state. False-positive results can lead to life-long mistreatment, which is then never questioned.

Our purpose in this study was to question the accepted assumption that there is a strong association between Down syndrome and thyroid disorders and one that is accurately diagnosed by standard thyroid function test. Are the standard general population laboratory free thyroxine (fT4) and thyroid stimulating hormone (TSH) reference ranges really applicable to the Down syndrome population?

Method

We assessed 250 adults with Down syndrome to determine physical and psychiatric health status. Appropriate caregivers and the individuals themselves were interviewed for evidence of ill-health or decline in adaptive behavior, medical records were reviewed, standard physical and mental state examinations undertaken, and inves-
tigators (including hematological, B12, and folate levels, biochemical, glucose level, and, where appropriate, EEG and magnetic resonance imaging) were done. Psychiatric disorders and severity of mental retardation (intellectual disability) were diagnosed according to International Classification of Mental and Behavioral Disorders Diagnostic Criteria for Research (10th ed.)—DCR-10 criteria (World Health Organization, 1993). All prescribed medication was reviewed.

Thyroid screening for plasma fT4 and TSH were undertaken. Plasma fT4 was measured by Amerlex-MAB assay (Lifescreen, Watford), with an interassay coefficient of variation of 13.9% to 6.2% over the concentration range of 6.1 to 50.2 pmol/L. Thyroid stimulating hormone was measured by an Amersham coated tube (Lifescreen, Watford), with an interassay coefficient of variation of 6.0% to 11.6% over the concentration range of 0.38 to 30 mU/L. Thyroid hormone tests were all undertaken within the same clinical chemistry department and within a few hours of receipt of morning samples.

To determine the thyroid parameters for healthy adults with Down syndrome, we excluded a number of individuals from the total sample. These included subjects on thyroxine replacement, those found to have hypothyroidism, individuals with a concurrent significant physical or psychiatric illness (e.g., dementia, depression, systemic infection), marked decline in adaptive behavior, persons on medication known to affect thyroid status, and persons who were positive for either thyroperoxidase (TPO) or thyroglobulin (Tg) antibodies. The former antibodies have been reported to be associated with latent hypothyroidism. The remaining subjects were deemed to be healthy and clinically well. This allowed for thyroid function status to be assessed in a sample of healthy adults with Down syndrome.

Of the 250 adults with Down syndrome who participated, thyroid function test results were available for 199 (80%) of the sample. A minority of subjects would not cooperate with having a venipuncture or a sample of blood was not obtained after two attempts. Of the 199 subjects, 89 individuals were excluded from further data analysis. The reasons for exclusion were presence of dementia of Alzheimer type (n = 28), depression (n = 10), on thyroxine replacement therapy (n = 25), on medication that could alter thyroid status (n = 3), untreated hypothyroidism (n = 10), and positive thyroid antibodies (n = 13). The remaining 110 adults with Down syndrome were found to be healthy and had available thyroid function tests.

The mean age of the final study sample (N = 110) was 41.7 years (standard deviation [SD] = 11.46, range = 17 to 71); there were 67 males (61%) and 43 females (39%). Ninety percent had cytogenetically proven trisomy 21; 3%, a translocation form of Down syndrome; 2%, mosaicism; and 5%, clinical Down syndrome but no available cytogenetic information. The majority of the individuals had moderate intellectual disability (63%); 20%, mild; and 17%, severe. Over three quarters of the sample lived in the community; 40 (36%), in community group homes; and 41%, in their own family home. Twenty-five individuals (23%) were residents in a long-stay hospital setting.

The normal fT4 range for the general population for the clinical chemistry department was 9.0 to 20.0 pmol/l. The equivalent figure for TSH was 0.4 to 5.5 mU/l. Only 79 (72%) healthy Down syndrome persons were found to be biochemically euthyroid (normal fT4, normal TSH). Subclinical hypothyroidism (normal fT4, raised TSH) was found in 14 (13%) and low fT4 and normal TSH in 17 (15%) of individuals. These findings demonstrate a high rate (28%) of thyroid dysfunction in healthy adults with Down syndrome as compared to the general population.

Calculations from the empirical cumulative distribution show that the median fT4 of 11.0 pmol/l (lower quartile 9.5, upper quartile 12.1) for adults with Down syndrome is significantly below that for the general population. These findings suggest that the plasma fT4 reference range of 7.5 to 15.4 pmol/l for the Down syndrome population (2.5% to 97.5% range) is shifted towards the lower level than that seen for the general population (reference range 9.0 to 20.0 pmol/l). In contrast, the median TSH for adults with Down syndrome was found to be 2.84 mmol/l (lower quartile 2.0, upper quartile 4.2). The reference range

Results

Of the 250 adults with Down syndrome who participated, thyroid function test results were available for 199 (80%) of the sample. A minority...
(2.5% to 97.5% percentile range) was 0.7 to 7.9 mU/L for the Down syndrome sample, shifted higher as compared to the general population reference range (0.4 to 5.5 mU/L).

Discussion

Although higher rates of thyroid disorders in the Down syndrome population have been reported for many years, no researchers to date have specifically investigated thyroid status of healthy adults with Down syndrome or questioned the applicability of criteria standardized for the general population. The diagnosis of abnormality of thyroid status in people with Down syndrome has to date been solely dependent on the definition of normality for the general population (Dayan, Saravanan, & Bayly, 2002). Any given individual with Down syndrome is not diagnosed as having thyroid disorders by reference to a “normal” thyroid distribution for the Down syndrome population but by comparison to findings for the general population. A change in the general population references range for fT4 and TSH would lead to a significant clinical impact on the diagnosis and treatment of thyroid disorders in the Down syndrome population. It is essential that clinicians have access to accurate laboratory tests that are applicable to their specific patient, particularly one who already belongs to a vulnerable population.

The present study confirms the high rate of thyroid disorders in adults with Down syndrome when compared to reference ranges for the general population. However, it is the first study in which the focus is on healthy adult Down syndrome individuals. The study sample was representative of the total population of adults with Down syndrome because it included both males and females, from a wide age and severity of intellectual disability distribution, living in both the community and hospital settings. Over one quarter of persons with Down syndrome who were healthy and well and who had no clinical symptomatology of a thyroid disorder or any other significant medical illness were still found to have abnormal plasma thyroid hormone levels. Are these individuals showing evidence of a subclinical thyroid disorder that would soon express itself as an overt disease? As part of the inclusion criteria for this study, those individuals who were thyroxine antibody positive were excluded to ensure no person with latent thyroid disorders was included.

A tendency towards lower fT4 and a higher TSH in the Down syndrome population remains an area for considerable debate in the community of clinicians and academics, more so now because in a recent paper, van Trotsenburg, Vulsma, van Santen, Cheung, and de Vijlder (2003) reported findings similar to those in the present study on adults with Down syndrome: a decreased fT4 concentration (left-shift normal distribution) and mildly elevated TSH concentrations in children with Down syndrome. Such findings suggest that for the Down syndrome population, so-called “subclinical hypothyroidism” is present at birth and persists throughout life. Van Trotsenburg et al. suggested that these findings support the existence of a Down syndrome-specific thyroid disorder that may be explained by the thyroid gland of these individuals being relatively insensitive to TSH due to abnormalities in TSH receptor signalling or because their gland is relatively insensitive to TSH due to low level thyroid damage (e.g., autoimmune thyroid disease). If the thyroid hormone receptors in the pituitary gland were insensitive in adults with Down syndrome, the result would be a raised fT4 with normal or slightly raised TSH (as seen in thyroid hormone receptor defects). If the thyroid hormone was oversensitive to thyroid hormone, separately from the pituitary, the thyroid function test would be normal but the patient would be symptomatic.

We propose an alternative explanation that these individuals with Down syndrome are clinically and biochemically healthy but are detected as having a thyroid disorder by “abnormal” blood results due to an inappropriate comparison with normal reference ranges for the general population. We suggest that the majority of these persons would have “normal” thyroid function test results if compared to an appropriate Down syndrome reference group. For example, in this study, if the fT4 reference range 7.5 to 15.4 pmol/L and TSH reference range 0.7 to 7.9 mU/L are used, then the abnormality rate for the study sample falls to acceptable levels. Adults with Down syndrome are susceptible to premature ageing, and it is possible that the thyroid biochemical findings (e.g., higher TSH) reflect this. Use of present standard thyroid function test laboratory-reference ranges do not allow researchers or physicians to take an age-effect into account.

Of the two explanations put forward to explain the high rates of thyroid dysfunction in the Down syndrome population, there are only two
approaches that can be tested to determine which explanation is correct. First, one could identify the failing part of the hypothalamo-pituitary-thyroid axis in a selected number of persons with Down syndrome. Second, researchers could conduct a large randomized controlled trial to study the effects of thyroid hormone (thyroxine ± triiodothyronine) versus placebo administration, with outcome determined on a number of cognitive, motor, and adaptive measures. If the trial result is positive, this would support the possibility of a thyroid (regulation) disorder. However, Tirosh, Taub, Scher, Jaffe, and Hochberg (1989) conducted such a study with 7 persons who had Down syndrome and failed to document any cognitive, social, response time, or physical change attributable to the 8- to 14-week drug treatment period. Such limited research would further support the hypothesis we propose. Clinicians and academics must at least question the assumption of a “proven” link between Down syndrome and thyroid dysfunction.

It is paramount to establish normative thyroid function test data for the Down syndrome population, especially when determining the presence of an illness that has lifelong implications for a given individual. Is the overreliance on the biochemical status of the general population to diagnosis disease in the Down syndrome population fundamentally flawed? This study highlights this as a possibility and suggests that many people with Down syndrome are inappropriately diagnosed as suffering from hypothyroidism, resulting in subsequent mistreatment. False negative and false positive results should be considered in interpreting thyroid function test results, which should not be assumed to be completely reliable. Laboratories are recommended to keep all samples from persons with Down syndrome for at least one week for repeat or further testing (e.g., use of different assay to confirm results; testing for thyroid receptor antibodies). Better communication between clinicians and the laboratory is necessary. The scientific community must establish beyond reasonable doubt whether it is appropriate to continue to use normative thyroid reference ranges based on the general population or whether these ranges should be modified when detecting thyroid disorders in the Down syndrome population. There is, of course, already a precedent set; if the heights of children with Down syndrome are compared with the normal reference growth charts for children from the general population, then virtually all children with Down syndrome would be below the lower second percentile and, by definition, be pathologically abnormal. However, when the height of a given child with Down syndrome is plotted on a growth chart specific for children with Down syndrome, their height is usually seen to be “normal” and of no real clinical concern.

The collection of postmortem series of thyroid tissue from adults with Down syndrome to determine whether they are more frequently infiltrated with lymphocytes (autoimmune disease) or show other forms of damage to the thyroid gland along with good clinical and biochemical data could be one way to resolve this debate.

References


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