Thyroid Function in Males with Fragile X Syndrome

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Short report

Background

Much has been written about thyroid function in the general population, but little in people with intellectual disabilities (ID), particularly in genetic syndromes. There is growing evidence of elevated prevalence of hypothyroidism in people with ID, but the exact figures seem to be compromised by lack of genotypic data within this heterogeneous population.[1] Loss-of-function mutations in Immunoglobulin Superfamily 1 (IGFS1) variants cause an X-linked syndrome of central hypothyroidism and testicular enlargement (macroorchidism). Some of us participated in the identification of the gene and reported mild ID and autism spectrum features in some of the participants.[2] Fragile X syndrome (FXS) is another X-linked syndrome characterized by ID, autism spectrum features and macroorchidism and arises from a loss-of-function mutation of the Fragile X Mental Retardation-1 (FMR1) gene. Given the similarity with FXS with respect to phenotype and pattern of inheritance, we postulated that FXS might be associated with central hypothyroidism as well. However, limited information is available on thyroid function in FXS. A few decades ago, two small studies in 2 and 12, respectively, young males with FXS reported normal thyroid function.[3,4] Another study suggested subtle thyroid function abnormalities within the hypothalamic-pituitary-thyroid axis in males with FXS.[5] This encouraged us to evaluate thyroid function in a large series of males with FXS.

Methods

With the help of 30 ID physicians, we collected regular blood samples for care purposes of 47 males with molecularly confirmed FXS (mean 51.1 years; range: 17-80 years) and performed thyroid function laboratory tests at the Amsterdam University Medical Center.

Results

Two of the 47 patients (4.3%) were previously diagnosed with primary hypothyroidism of unknown etiology. These two patients were treated with thyroxine and their plasma FT4 and TSH concentrations indicated adequate thyroxine treatment. Three of the 47 males (6.4%) had slightly elevated TSH concentration (4.51 mIU/l, 4.54 mIU/l and 4.92 mIU/l, respectively), in combination with FT4 concentrations within the reference interval (17.3 pmol/l, 14.9 pmol/l and 11.1 pmol/l, respectively). In all three men anti-TPO antibodies were absent (<30 U/ml), implicating a relatively low risk of developing clinical hypothyroidism later in life. One individual had an elevated FT4 concentration (32.7 pmol/l) in combination with a normal TSH concentration (0.66 mU/l). In a second blood sample of this patient, collected eight weeks later, FT4 concentration was within the reference interval. The remainder of the participants showed plasma FT4 and TSH concentrations within the reference intervals.

Conclusions

In the present study, biochemical testing demonstrated no indication for central hypothyroidism in males with FXS, implicating that there is no increased risk of central hypothyroidism. Nevertheless, subclinical hypothyroidism prevalence seems elevated compared to the small studies in the past, but within the ranges of the general population. However, one could argue on the clinical relevance in absence of anti-TPO. Furthermore, this prevalence may be an overestimation due to ascertainment bias, since 13 men with FXS did not participate. The same applies for the cases of hypothyroidism of unknown etiology, that were sufficiently treated and that we classified as clinical hypothyroidism, although we had no pretreatment FT4 concentrations available.

This is to our best knowledge the largest thyroid function study in males with FXS. Our prevalence data on subclinical hypothyroidism do not provide sufficient evidence for routine thyroid function screening as part of the FXS health-monitoring program. Besides, blood sampling can be a burden for people with ID and the therapeutic consequences are doubtful. However, low threshold thyroid function testing is indicated when there are clinical signs or symptoms of hypothyroidism.

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