Hypothyroidism and sex chromosomes

C SARRI, G B CÔTÉ, CH MENGRELI, I LAMBADARIDIS, AND S PANTELAKIS
From the Institute of Child Health and Paediatric Unit, Aghia Sophia Children’s Hospital, Athens, Greece.

SUMMARY The observation of Campbell and Price in 1979 that their Unit had diagnosed four subjects with both Klinefelter’s syndrome and congenital hypothyroidism raised the suspicion of an association between the two conditions. This, and the published reports of an XX male, five XXY males, and one mosaic XY/XXY with congenital or acquired forms of hypothyroidism, together with the higher incidence in women and the absence of sex difference among inherited congenital cases, suggested a possible sex chromosome effect in the aetiology of sporadic hypothyroidism.

Various hypotheses can be tested either by examining the frequency of hypothyroidism in sex chromatin positive males or by establishing a higher frequency of sex chromatin positive males among hypothyroid cases than in normal males. We examined 57 boys with hypothyroidism for the presence of sex chromatin and found all to be negative. From this relatively small sample we can only exclude the possibility of a very large (100 fold) difference in frequency between the two populations and therefore more data are needed.

The observation by Campbell and Price1 that their Unit had diagnosed four subjects with both Klinefelter’s syndrome and congenital hypothyroidism raised the suspicion of an association between the two conditions. Their report was criticised2 but the suspicion remained.3

An obvious way to resolve the question is to follow the earlier suggestion of Herbeuval et al4 and perform an X chromatin test in all males found to have congenital hypothyroidism. This we did at the Athens Institute of Child Health where a national neonatal screening programme for congenital hypothyroidism has been in operation for the whole of Greece since 1979.5-7

Material and methods

The methods used here for the neonatal screening of hypothyroidism include the determination of thyroid stimulating hormone (TSH) and serum thyroxine (T4) and have been described elsewhere.5 6 Hypothyroidism was confirmed in a total of 205 cases (54 boys and 151 girls) over a period of six and a half years out of a screened population of 687 938 newborns, giving an overall incidence of 1 in 3355 (1/6370 boys and 1/2278 girls). Six boys born in remote regions were kept informed by telephone

Received for publication 2 August 1986.
Revised version accepted for publication 11 May 1987.
male karyotype 46, X.inv(Y)(p11q11). His phenotype included the same pericentric inversion.

Discussion

The article by Campbell and Price1 deserves closer scrutiny. It is worth noting that their case 1 did not have classical XXY Klinefelter’s syndrome but was an XX male with a small extra satellite chromosome, and had already been included as such in a study on 46,XX males by the same Unit.8

This extra marker chromosome was not an altered Y but most likely the result of a translocation between two acrocentric chromosomes. The two Xs were not heteromorphic and there was no direct evidence for either an X,Y translocation or mosaicism with a Y bearing line to account for the patient’s maleness. XX males resemble males with Klinefelter’s syndrome but they seem to escape the latter’s mild mental retardation; the aetiology of their syndrome is clearly different from that of Klinefelter’s and most likely heterogeneous.9 It thus seems more appropriate to speak of a possible association between hypothyroidism and X chromatin positivity rather than Klinefelter’s syndrome.

Cases 2 and 3 had also been previously published.10 11 It should be borne in mind that the latter was a referral to Edinburgh from Zimbabwe so that comments on the occurrence of either disease in the British Isles should take this into account.

Finally, case 4 was a mosaic XY/XXY who may not even have had the congenital form of hypothyroidism, as recognised by the authors.1-3 However, the association of positive X chromatin with acquired hypothyroidism in males would also be interesting and has been reported elsewhere.12 13

A priori, one can entertain at least three simple hypotheses to predict the number of cases who will be X chromatin positive in our sample of males with congenital hypothyroidism. The first one (null hypothesis) is that of a chance event: males with congenital hypothyroidism would have the same probability of having positive X chromatin as any other male. The incidence of X chromatin positive newborn males in Greece is 1 in 673 (0-15%),14 in agreement with similar findings in the rest of the world.15

The second hypothesis is that the presence of both diseases in a person “reflects more than chance concurrence” as suggested by Campbell and Price.1 The two conditions would be associated by some mechanism and X chromatin positive male embryos would be more liable to develop congenital hypothyroidism than by chance alone, with a probability similar to that found in the Edinburgh MRC Cytogenetics Registry. If we exclude the proband, we have one case of hypothyroidism among 140 X chromatin positive males (3 in 419), or 1 in 94 220 male newborns. In Greece, such a population contains 15 cases of congenital hypothyroidism. If the two conditions are associated, we would therefore expect one case of positive X chromatin in every 15 Greek boys with congenital hypothyroidism. The third hypothesis is based on the fact that girls are three times more likely than boys to develop congenital hypothyroidism,16-19 contrary to Campbell and Price’s claim that “there is no sex difference”.1 Like all girls, X chromatin positive males would then have an increased liability to develop congenital hypothyroidism, with an incidence of 1 in every 2278, or 1 in 5 539 094 male newborns. Such a population contains 241 cases of congenital hypothyroidism. The third hypothesis thus predicts an incidence of one case of positive X chromatin in every 241 Greek boys with congenital hypothyroidism.

The first, second, and third hypotheses respectively predict 0-08, 3-80, and 0-24 positive X chromatin cases among the 57 boys tested. Our negative results (0-00/57) at present give more support to the first and third hypotheses although a much larger sample would be required to accept or reject unambiguously any of the three hypotheses.

However, the published cases with sex chromosome abnormalities, the well documented propensity for women to be affected more often than men with both congenital and acquired forms of hypothyroidism, and the fact that acquired forms have also been described in two XXY men12 13 indicate that the sex chromosomes could have a role in the aetiology of hypothyroidism, even if only as part of a more complex system. This view is reinforced by the fact that a 1:1 sex ratio was found in our cases of hypothyroidism where the thyroid gland was found in the normal position20; these are due to the direct action of autosomal recessive alleles, the inheritance of which has nothing to do with the patient’s sex chromosomes.

More data are required to estimate the exact risk of males with abnormal sex chromosomes developing hypothyroidism, but the possibility that they may be at higher risk than normal males should be borne in mind in investigating the causes and mechanisms of thyroid diseases.

References

Hypothyroidism and sex chromosomes


Correspondence and requests for reprints to Dr G B Côté, Genetics Division, Institute of Child Health, GR-115 27 Athens, Greece.
Hypothyroidism and sex chromosomes.

C Sarri, G B Côté, C Mengreli, I Lambadaridis and S Pantelakis

doi: 10.1136/jmg.25.4.247

Updated information and services can be found at:
http://jmg.bmj.com/content/25/4/247

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/