lesions or both, and mental retardation or seizures or both. Rushton and Shaywitz\(^1\) discuss a family in which the mother and paternal grandfather of a proband with tuberous sclerosis appear to be non-manifesting obligate heterozygotes for the tuberous sclerosis gene. These authors propose segregation of a second unlinked autosomal dominant modifying gene to explain the apparent non-expression of the tuberous sclerosis gene, but they fail to consider that they have insufficient information to conclude that these two relatives do not manifest the gene.

In addition to physical examination and Wood’s lamp examination of the skin, examination of the retina by indirect ophthalmoscopy, CT scan of the brain, ultrasound examination of the kidneys or an excretory urogram or both, and skeletal survey should be diagnostic screening tests that are completed on each subject at risk for carrying the tuberous sclerosis gene. Only when all the clinical and laboratory parameters of gene expression have been investigated can a subject be judged to be a non-manifesting heterozygote by pedigree analysis.

Would Rushton and Shaywitz\(^2\) invoke this second gene hypothesis even if their patients were fully evaluated, since we so readily accept ‘non-penetration’ of other variably expressed autosomal dominant genes?

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Reference


This letter was shown to Drs Rushton and Shaywitz who reply as follows:

SIR,

When our investigation on the inheritance of tuberous sclerosis was begun, we were aware of recent studies which had shown the value of neuroradiological techniques for the detection of intracranial calcifications in persons who were otherwise asymptomatic.\(^1\)\(^2\) The obligate heterozygotes in the pedigree which we presented were older adults who did not wish to have more children. We decided that it was ethically unjustifiable to subject these normal persons to the expense and radiation exposure required for computerised axial tomography of the brain.

The most important test of our hypothesis of a second modifying gene in this disorder will be to examine the future progeny of the young sister of our index case. When she approaches reproductive age, she will be offered full diagnostic evaluation for tuberous sclerosis, including CAT scan. This information can then be used for genetic counselling purposes.

Tuberous sclerosis is certainly an autosomal dominant disorder with variable penetrance. The fact that we usually attribute this phenomenon to ‘variable penetrance’ implies our lack of knowledge regarding modulation of expression of human dominant gene action. Pedigree analyses in the future will hopefully provide further understanding of this intriguing syndrome.

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References


Congenital hypothyroidism and Klinefelter’s syndrome

SIR,

The paper by Campbell and Price (JMG, December 1979) overlooks the recognised association of autoimmune thyroiditis with abnormal chromosomal states such as Down’s syndrome\(^1\) and Turner’s syndrome.\(^2\)

The case histories in the paper do not preclude an acquired autoimmune thyroiditis as a cause of the hypothyroidism with onset in infancy or early childhood. Hashimoto’s disease may be present in young patients with lower antibody titres, and therefore low titres do not exclude the diagnosis.\(^3\)

Case 4 with presentation at the age of 7 years and a bone age of 2.5 years is not congenital hypothyroidism. Consequently, there must be considerable doubt about the validity of the authors’ concept of the association between congenital hypothyroidism and Klinefelter’s syndrome.

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References


This letter was shown to Drs Campbell and Price who reply as follows:

SIR,

We are, of course, aware of the reported associations between autoimmunity and chromosomal abnormalities. In the case of Turner's and Klinefelter's syndromes the evidence is conflicting: our own series of females with sex chromosome aneuploidy showed no significant increase of autoantibodies, and studies of patients with Klinefelter's syndrome have shown incidences of autoimmunity higher than, lower than, and the same as appropriate control groups. As Professor Harris notes, in juvenile Hashimoto's disease circulating thyroid autoantibodies may be present only in low titre, or may even be absent altogether. Without histological evidence, we cannot exclude an autoimmune basis for the hypothyroidism in our patients, but most children with thyroiditis have an enlarged thyroid gland. This was not the case in any of our patients.

Although case 4 presented at the age of 7 years, it is not possible to date the onset of the condition precisely. As we noted, it may have been later in childhood but the presence of epiphyseal dysgenesis in the femoral head indicates that thyroid deficiency was present before the age of 9 to 12 months.

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References

Klinefelter's syndrome.

F Harris

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