LETTERS TO THE EDITOR

Psychological aspects of von Recklinghausen neurofibromatosis (NF1)

In the December 1995 issue of your journal, Mouridsen and Sorensen reviewed the psychological aspects of NF1.¹ They provided an excellent insight into many issues, such as the frequency of poor self-image and psychiatric disturbance. However, there have been a number of recent publications,²⁻⁹ which were not included in the review, and which provide a number of areas of consensus concerning the cognitive phenotype of patients with NF1.

(1) Mutations in the NF1 gene are associated with a lowering of IQ in, at least, a subset of patients. The mean full scale IQ score (for a clinic derived population) is in the range of 90-94. Hoffman *et al*² also reported a significant pairwise difference between each child with NF1 and an unaffected sib on full scale IQ, verbal IQ, and Judgement of Line Orientation (a test of visuospatial function).

(2) There does not appear to be an association between the left shift in IQ and any clinical variable (such as clinical severity of disease, macrocephaly, or family history of NF1).^{2,3}

(3) There is a slight increase in the incidence of mental retardation in NF1 (4-8%) compared to the general population.^{3,5}

(4) At least 40% (and probably more) patients with NF1 have learning disabilities. In our study of 40 children (aged 8 to 16 years),³ 65% had impaired performance (that is, more than 2 SD below the mean) on at least one test of academic achievement.

(5) There does not appear to be a specific profile of learning disabilities in patients with NF1. There is no consistent discrepancy between verbal and performance IQ. The Judgment of Line Orientation (a test of visuospatial function) is consistently abnormal in all studies to date and thus, at some level, is a robust indicator of NF1 related neuropsychological deficits. However, language based learning problems (for example, reading and spelling) are more common than non-verbal learning deficits. Poor attentional and organisational skills affect performance in many areas, although increased distractibility is not usually associated with hyperactivity.²⁻⁵

There have also been a number of recent studies concerning the significance of areas of hyperintense T2 signal on MRI (UBO or unidentified bright objects) in relation to cognitive deficits in patients with NF1.^{2,6-9} In our study,⁸ children with areas of increased signal intensity on MRI (UBO+) had significantly lower IQ scores than children without these lesions. However, the association between "UBOs" and learning disabilities remains controversial. Moore⁷ found no statistical difference in overall IQ scores between the UBO+ and UBO- groups. However, when the results were analysed according to the site of increased T2 lesions, there was a significant association between deficits in IQ, memory, motor function, and attention span and T2 signal lesions

in the thalamus and hypothalamus. Hoffman *et al*² and Denckla *et al*⁶ found that the number and volume of T2 signal lesions were highly correlated with pairwise deficits in IQ scores (compared to unaffected sibs). In addition they found an association between impaired visuospatial function (as shown in the Judgment of Line Orientation) and the volume of T2 signal lesions in the basal ganglia.

Although there appears to be some association between T2 signal lesions on MRI and cognitive deficits in children with NF1, the exact nature of this association and its relationship to the number, volume, and location of lesions remains to be elucidated. The available evidence suggests that these T2 signal lesions represent areas of dysplastic gliosis and aberrant myelination in the developing brain.¹⁰ If the relationship between MRI lesions and cognitive deficits in NF1 is validated then this association may provide important insight into the pathogenesis of cognitive deficits in patients with NF1.

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The male excess in Down's syndrome

Mutton *et al*¹ confirmed earlier reports of a male excess in cases of Down's syndrome (DS). The cause of this excess is not established, but it seems not to be sex selective spontaneous abortion: in their data, these cases numbered 63 males and 51 females.

I should like to suggest a cause of this excess. It is that in cases of DS, the timing of insemination in relation to ovulation is not optimal. It is widely believed (at least among non-geneticists) that the timing of fruitful coitus within the human menstrual cycle is associated with offspring sex ratio, male zygotes being preferentially formed when the fruitful insemination is either early or late. In a meta-analysis on this point, Gray² estimated that fruitful inseminations around ovulation

have a relative risk of only 90% of yielding males as contrasted with early or late inseminations. A similar phenomenon has been reported in other species, such as white tailed deer,³ Barbary macaque,⁴ golden hamster,⁵ and Norway rat.⁶

If the present hypothesis were true, one might expect an excess of DS in cases of rhythm failure. The evidence on this point is equivocal,⁷ but suspicion is raised by the reportedly high maternal age specific rates in children born to Catholic women.^{8,9}

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Predictive genetic testing in children

The paper by Michie *et al* (*J Med Genet* 1996;33:313-18) describes a situation which is going to arise with increasing frequency as more dominantly inherited disorders become reliably detectable by molecular methods. The discussion focuses on the views of the parents and of the professionals but there is no word from the children. At the ages of 4 and 2 years they are too young to give their opinion, but perhaps a proxy should have done this for them.

For a few disorders (for example, retinoblastoma) surveillance starts in infancy but usually predictive testing for risk of malignant disease is done with a view to prevention of disease by regular surveillance into adulthood. We need to know what testing procedure is most likely to lead to a responsible attitude to the irksome and unpleasant screening regimens. Parents have their children's best interests at heart but may find it difficult to remember that charming 5 year olds may develop into rebellious teenagers or into 20 year olds who know they are invincible. The poor compliance of diabetics at this stage of life is well known.

Instinct tells me that compliance is likely to be higher when the child has been actively involved in the decision on the timing of the test. Discussion of the need for a test is fine from an early age, but let parent and child together await the result. A teenager may well