Child abuse and the clinical course of drug misuse

Charnaud & Griffiths (2000) in response to the finding of increased psychiatric symptoms in female drug users by Marsden *et al* (2000) postulate that this finding may be a sequela of earlier child abuse. It is interesting to note the high incidence of childhood sexual abuse found in their study population based in Cornwall. In a Dublin sample, the level of sexual abuse for both males and females was considerably lower (21%). However, the effects of abuse appeared to have a significant influence in subsequent clinical progression of substance misuse. Those patients with a history of sexual abuse in the past had a significantly younger mean age of first opiate use (16.7 years *v.* 19.1 years for those without a history of sexual abuse) (Browne *et al*, 1998). The duration of drug misuse was also considerably longer (mean 10.8 *v.* 8.4 years).

We would support the suggestion of Charnaud & Griffiths (2000) that the evaluation of previous history of sexual abuse can predict the best plan of treatment for these patients. We would suggest that the long-term clinical progression of sexually abused drug misusers is that of more rapid progression to intravenous drug misuse with all the prognostic features that this implies.

Charnaud, B. & Griffiths, V. (2000) Drug dependence and child abuse (letter). *British Journal of Psychiatry*, **177**, 84.

Marsden, J., Gossop, M., Stewart, D., *et al* (2000) Psychiatric symptoms among clients seeking treatment for drug dependence. Intake data from the National Treatment Outcome Research Study. *British Journal of Psychiatry*, **176**, 285–289.

Browne, R., Keating, S. & O'Connor, J. (1998) Sexual abuse in childhood and subsequent illicit drug abuse in adolescence and early adulthood. *Irish Journal of Psychological Medicine*, **15**, 123–126.

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Apolipoprotein E, Alzheimer's disease and Down's syndrome

We read with interest the article by Deb *et al* (2000) apparently demonstrating findings contrary to our own (Prasher *et al*, 1997). Overall, we agree with the findings by Deb *et al*, although clarification on several important points is required.

The principle reason why we did not find a statistically significant association (at the 5% significance level) between apolipoprotein E (ApoE) ε4 and Alzheimer's disease in adults with Down's syndrome was because at that time there was a much smaller sample size of adults with Down's syndrome and dementia available for meta-analysis (102 subjects previously included compared to 158 in Deb *et al*'s report). The three additional reports included in Deb *et al*'s meta-analysis are of significantly larger samples. However, even with this greater number of subjects available for meta-analysis the power remains at 76%. Given the proportions of ε4 in the groups with and without dementia in the Deb *et al* paper, for a power of 90%, a minimum of 224 adults with Down's syndrome and dementia are required to demonstrate statistical significance at the 5% level. Furthermore, the ε4 allele frequency in the different studies varies from 5.9% to 33.4% in subjects with dementia (Deb *et al*, 2000) and therefore future studies are still required if an association between ApoE ε4 genotype and Alzheimer's disease in adults with Down's syndrome is to be established.

Deb *et al* are incorrect to exclude the study by Wisniewski *et al* (1995) because "they diagnosed Alzheimer's disease on the basis of neuropathological findings alone". Wisniewski *et al* (1995) made a diagnosis of dementia (not Alzheimer's disease) by a clinical assessment alone "as judged by the physician following the patient". However, the inclusion of this study in the present meta-analysis makes little difference to the findings by Deb *et al* (2000) as only one person with an ε4 allele was present.

The increase in risk of developing dementia in adults with Down's syndrome (odds ratio 2.02) appears to be less than that in populations with no learning disability where it can be increased by as much as 30 times for people with two copies of the ε4 allele (Swartz *et al*, 1999). From the allele frequency given by Deb *et al* (2000) the diagnostic accuracy of ApoE ε4 for adults with Down's syndrome and dementia is of some clinical value. The sensitivity is 18% (95% CI 13.5–22%) and specificity 90% (95% CI 88–92%). The absence of an ε4 allele strongly suggests the absence of Alzheimer's disease. ApoE genotyping in the Down's syndrome population may possibly be used to screen for dementia.

We conclude, as previously (Prasher *et al*, 1997), that the presence of an ε4 allele is neither sufficient nor necessary to cause Alzheimer's disease but ApoE ε4 genotype does have a role to play in the presentation of Alzheimer's disease in adults with Down's syndrome. The effect is, however, 'overwhelmed' by the excessive amyloidosis due to the triplication of the amyloid precursor gene.

Deb, S., Braganza, J., Norton, N., *et al* (2000) *APOE* ε4 influences the manifestation of Alzheimer's disease in adults with Down's syndrome. *British Journal of Psychiatry*, **177**, 468–472.

Prasher, V. P., Chowdhury, T. A., Rowe, B. R., *et al* (1997) ApoE genotype and Alzheimer's disease in adults with Down's syndrome: meta-analysis. *American Journal on Mental Retardation*, **102**, 103–110.

Swartz, R. H., Black, S. E., St George-Hyslop, P. (1999) Apolipoprotein E and Alzheimer's disease: a genetic molecular and neuroimaging review. *Canadian Journal of Neurological Sciences*, **26**, 77–88.

Wisniewski, T., Morelli, L., Wegiel, J., *et al* (1995) The influence of Apolipoprotein E isotypes on Alzheimer's disease pathology in 40 cases of Down's syndrome. *Annals of Neurology*, **37**, 136–138.

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Authors' reply: We thank Drs Prasher & Haque for their interest in our paper and are pleased that they agree with our conclusions. It is quite obvious that the difference in findings in the meta-analysis between our study and Prasher *et al*'s study was due to the inclusion of data in our study that were not available at the time of Prasher *et al*'s study. According to our calculation, our meta-analysis has 92% power (95% CI 88–96%) at the 5% level. However, traditional power calculation is not applicable in this case because instead of simply adding allele frequencies among all studies, we have used the computerised version of the Woolf (1995) method of meta-analysis that takes account of each study individually. Also, because of the varied nature of studies included in the meta-analysis we did not feel it appropriate to calculate specificity and sensitivity in the traditional way.

It was not stated in Prasher *et al*'s (1997) paper which 31 patients (15 with and 16 without dementia) out of 40 patients with Down's syndrome, presented in Wisniewski *et al*'s (1995) study, were included in their meta-analysis. The age of death of patients reported in Wisniewski *et al*'s study ranged widely between 15 and 69 years. They mentioned at the bottom of their table that "The presence of dementia is defined as a deterioration of competence, as judged by the physician following the patient". No detail

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about diagnosis was mentioned in the text and no patient over age 30 had an ε4 allele. For these reasons we chose not to include this study in our meta-analysis. However, as Prasher & Haque point out inclusion of this study would have made little difference to our findings.

Whereas Prasher & Haque rightly suggest that further research is needed to clarify the role of ApoE ε4 in Alzheimer's disease in people with Down's syndrome, we were surprised to see that they have recommended ApoE genotyping as a possible screening test for dementia in this population. This will be totally inappropriate at this stage considering the uncertain relationship between Alzheimer's neuropathology and ApoE genotype in people with Down's syndrome, as we mentioned in the last paragraph of the Discussion in our paper.

We agree with Prasher & Haque that the presence of ε4 allele is neither necessary nor sufficient for the development of Alzheimer's disease.

Woolf, B. (1995) On estimating the relation between blood group and disease. *Analysis of Human Genetics*, **19**, 251–253.

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Chronic fatigue syndrome and depression

I found MacHale *et al*'s (2000) discussion of their results confusing. According to the abstract and methods, they screened their patients with chronic fatigue syndrome (CFS) to exclude those with depression. Then they examined this group further using a standardised psychiatric interview (Schedule for Affective Disorders and Schizophrenia), in order to "exclude subjects with current psychiatric illness, with a particular emphasis on depression". The data from the Hamilton Rating Scale for Depression are difficult to interpret given the number of illness-rated items, but the scores did not indicate a significant degree of depression either. So, having excluded "subjects with depression or anxiety", why did the authors claim in their discussion that "the main limitation of the present study is that our CFS subjects had high levels of depression"?

If this is correct, why was their depression not picked up by the three measures? Why were these patients not excluded from the research as stated by the authors or, funds permitting, used as a comparison group (Costa *et al*, 1995; Fischler *et al*, 1998)? How depressed were the 10 patients on antidepressants and, if these were not effective, could their suboptimal treatment have contributed to their ongoing fatigue?

I was also baffled by the authors' suggestion that the thalamic hyperperfusion may reflect "increased attention to motor and cognitive tasks". What were the patients doing? The abstract states that the scans were conducted at rest. If the subjects had just completed a battery of cognitive tests, why did the authors not check to see whether the data available supported their hypothesis (Fischler *et al*, 1998)?

If this paper was subjected to peer review, why did no one query the selective discussion of the findings and the misrepresentation of the literature on CFS and psychopathology?

Costa, D. C., Tannock, C. & Brostoff, J. (1995) Brainstem perfusion is impaired in chronic fatigue syndrome. *Quarterly Journal of Medicine*, **88**, 767–773.

Fischler, B., Flamen, P., Everaert, H., *et al* (1998) Physiopathological significance of ^{99m}TcHMPAO SPECT scan anomalies in chronic fatigue syndrome: a replication study. *Journal of Chronic Fatigue Syndrome*, **4**, 15–30.

MacHale, S. M., Lawrie, S. M., Cavanagh, J. T., *et al* (2000) Cerebral perfusion in chronic fatigue syndrome and depression. *British Journal of Psychiatry*, **176**, 550–556.

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Authors' reply: As explained in the method section, the potential participants were screened by excluding those scoring above case threshold in the Hospital Anxiety and Depression (HAD) scale, a self-rating scale that does not require a detailed interview. The remaining participants were then interviewed using the Schedule for Affective Disorders and Schizophrenia to further exclude any current mental illness.

First, in the discussion we say: "The main limitation of the present study is that our CFS subjects had high levels of depression: almost half were on psychotropic medication and five had a previous history of depression". "Had high levels of depression" is defined by what follows after the colon. There is, therefore, no contradiction. Participants were not currently depressed, but some were receiving antidepressant medication and some had previously been depressed.

Second, regarding that point made relating to our comment that "thalamic overactivity in CFS (and depression) may, therefore, reflect increased attention to motor and cognitive tasks . . .". The perceived contradiction is that participants were at rest during uptake of the tracer, i.e. not currently engaged in motor or cognitive tasks. It is clearly speculative that increased thalamic activity at rest will also mean increased thalamic activity during tasks. What was implied, however, was that increased baseline or resting activity of the thalamus may be an underlying brain marker that is related to patients being more attentive to motor and cognitive activity, as they occur.

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