genetically had a heterozygous mutation of both CYP2C9 and CYP2C19,⁴ normally responsible for biotransformation of phenytoin in the human liver microsomal P-450 system.⁵ He developed gynaecomastia after increasing the dose of phenytoin.

The patient was an 18 year old man with a diagnosis of left parietofrontal lobe epilepsy since the age of 2 years, until which time his developmental milestones were normal. He had complex partial seizures occurring at least once every day despite various anticonvulsant drugs of usually sufficient dose including clonazepam, phenytoin, and carbamazepine, and zonisamide since the age of 9 years, when he had an epilepsy surgery for a focal high intensity abnormality on T2 weighted MRI in the left parieto-occipital area. His seizures were not controlled. At the age of 18 years, the patient had chronic implantation of subdural electrodes for evaluating the intractable seizures, and based on the results of the invasive evaluation, he had focal resection in the left parietal and mesial parietofrontal areas. After surgery his seizures decreased in frequency to once every week, and became less severe, accompanied by loss of awareness in only a third. Before and after the surgery he was taking phenytoin (175 mg/day), carbamazepine (900 mg/day), and zonisamide (400 mg/day) giving blood concentrations of 14.3 mg/l, 7.9 mg/l, and 13.2 mg/l, respectively. Two months after surgery, partly because of sleep deprivation, the patient had a cluster of complex partial seizures, some resulting in secondary generalisation, occurring seven times in 90 minutes. After a total of 375 mg phenytoin was intravenously loaded, his seizures were well controlled. Subsequently the medication was maintained at phenytoin (190 mg/day), carbamazepine (1100 mg/day), and zonisamide (400 mg/day), and the steady state, basal blood concentrations of these anticonvulsant drugs were 16.6 mg/l, 5.2 mg/l, and 9.7 mg/l respectively.

About a month later, the patient noticed bilateral enlargement of his breasts associated with some tenderness restricted to the centre of the breast. The size was about 3 cm in diameter. No galactorrhea was seen. Blood concentrations of luteinising hormone, follicle stimulating hormone, prolactin, and oestradiol were all normal. His liver function was also within normal limits except for slight increases in γ -GTP. The patient had had moderate gingival hypertrophy and mild hypertrichosis. He was taking no medication other than the anticonvulsant drugs.

On rare occasions gynaecomastia has been reported in patients taking phenytoin, and in some of them it disappeared after stopping phenytoin.⁷ The mechanism as to how gynaecomastia is caused by this drug is uncertain. It was pointed out that some drugs interfere with testosterone synthesis as well as action by blocking the cytosol receptor of androgen in target tissues. It has been shown that liver enzyme inducing antiepileptic drugs such as carbamazepine and phenytoin are associated with increased concentrations of serum sex hormone binding globulin and decreased amounts of free androgen available in the tissue.⁶ However, as for most drugs causing gynaecomastia, its mechanism is not well defined.

The anticonvulsant drug zonisamide has been clinically available in Japan for patients with seizures since 1989, and it is reported that three patients (age ranging from 3 years to 32 years) taking zonisamide (60 to 600

mg/day) developed gynaecomastia from 10 days to 1 year after taking zonisamide, and in all of them it disappeared after stopping zonisamide.³ Therefore, in the present patient, it is possible that both phenytoin and zonisamide played important parts in the development of gynaecomastia. However, the patient had been on zonisamide for the past 8 years, and its dosage was not increased before gynaecomastia developed. On the other hand, after phenytoin was loaded when he had frequent seizures, its maintenance dosage increased. Therefore, phenytoin is most likely a causative agent. Adolescent gynaecomastia usually occurs bilaterally, although asymmetric, in many boys as a physiological type, often during puberty with a mean onset age of 14 years, and it is correlated with transiently raised oestradiol of unknown origin before completion of puberty.¹ However, there was no increase in oestradiol in the present patient.

The patient had a heterozygous point mutation in the defective allele of CYP2C9 and CYP2C19,⁴ and in such patients V_{max} values in the pharmacokinetics of phenytoin were 40% lower than those in patients with a normal type CYP2C subfamily (see subject No 43 in fig 1 of Odani *et al*) and thus our patient's maintenance dose of phenytoin (175 mg/day) was relatively small to achieve an appropriate blood concentration (14.3 mg/l). After having increased the maintenance dose of phenytoin by 15 mg/day, the blood concentration was kept <20 mg/l, and clinically he did not show toxic symptoms such as cerebellar ataxia and gaze evoked nystagmus. The presence of a heterozygous CYP2C subfamily mutation might have played some additional part either in developing this rare side effect or in facilitating physiological gynaecomastia of the adolescent type.

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CORRESPONDENCE

Neuropsychological prediction of dementia in Parkinson's disease

Mahieux *et al*¹ report on an interesting study of predictors of dementia in Parkinson's disease. We have certain reservations about the results because of the methodological limitations of the study.

The diagnosis of dementia was made by retrospective case note review or retrospective completion of questionnaires including some by non-specialists which raises questions about the validity of diagnosis. The researchers making the diagnosis of dementia were not blind to neuropsychological test score, which raises the possibility of observer bias. The study was uncontrolled so that the estimate of the incidence of dementia cannot be adequately interpreted because it is not known what the incidence in the general population would be using this method of case identification.

The findings of predictors of dementia are a little puzzling. Although four variables are reported as predictors, this seems to be misleading because for all but one of these the 95% confidence interval for the relative risk includes the figure one, indicating that the relative risk is not significant at the 5% level using a hypothesis test.² The p values for two of these variables were indeed greater than 0.05, but although the p value is given for the WAIS picture completion subtest as 0.03 (table 3, not table 2 as stated), the 95% confidence interval for the relative risk includes one. If these two statistical tests give different answers, which is correct?

For only one predictor variable did the 95% confidence interval of the relative risk lie outside one. This variable, age at onset of Parkinson's disease, was entered into the multivariate model, but it seems that age at inception to the study was not entered into the model. It is well known that dementia in Parkinson's disease is associated with age.^{3,4} If age onset is correlated with age at entry to the study as has been found by others^{3,5} then age at onset of Parkinson's disease is confounded. Many studies have reported that dementia in Parkinson's disease is associated with older age at onset, but those studies which have controlled for the effect of age have not found such an association.^{5,6}

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The authors reply:

We appreciate the interest of Hughes *et al* in our study on the neuropsychological prediction of dementia in Parkinson's disease.¹

The validity of the diagnosis of dementia was discussed in the paper. Hughes *et al* conjecture that the knowledge of initial neuropsychological tests scores would raise an observer bias. But the final diagnosis (dementia or not) was made by independent raters in 22 cases out of 86, and in every case we used a special case report form which did not even refer to the initial neuropsychological examination.

We agree that the incidence of dementia in our population cannot be interpreted as that of an inpopulation epidemiological study. We mentioned it as a mere additional descriptive characteristic.

We agree that the significance of the completion subtest was borderline in the multivariate analysis, as the confidence interval of the relative risk includes one, according to the calculation done by BMDP software. The level of significance is < 0.05, as mentioned in the table, again according to the test performed by the BMDP package. This minor discrepancy is not unusual and should not affect the interpretation of our results in such an exploratory clinical epidemiological study.

With regard to age and age at onset, these two variables correlate strongly. The two have been reported as predictive factors for dementia in Parkinson's disease.²⁻⁵ Some authors consider that age at onset of Parkinson's disease is a potentially more important variable.⁵⁻⁷ Moreover, the inclusion of age instead of age at onset in the multivariate analysis modifies the results only slightly. The WAIS-R completion subtest and age remain significant and independent predictors of dementia with respective risk ratios of 5.344 for age > 68 years (95% CI 1.7-17.1; *p* < 0.01) and 10.929 for a completion score < 10 (95% CI 2.5-48.3).

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G FÉNELON
A FLAHAULT

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Repeated syncope and extended paediatric hydrosyringomyelia/Chiari I malformation

I have read with interest the letter recently published on *Repeated syncope and extended paediatric hydrosyringomyelia/Chiari I malformation*.¹ The case reported is quite unusual, as syncope seems to be a very rare manifestation of this condition, even when associated with a Chiari I malformation, at least in adults. From a series of 100 adult patients with syringomyelia diagnosed over the past 10 years at this institute, two thirds of whom had an associated Chiari type I anomaly, only one patient had syncope, which was triggered by sneezing. Another three patients had drop attacks without loss of consciousness, one with a Chiari type I anomaly, and two with an associated ventricular dilatation (figure).

In the paper mentioned by the authors on cardiovascular reflexes in syringomyelia,² all patients with autonomic involvement, even those without syringobulbia, had an abnormal neurological examination, and sweating abnormalities and Horner's syndrome were often encountered. The fact that neurological examination was normal in the patient described by Woelfle *et al*,¹ as well as the absence of Horner syndrome and sweating abnormalities, make autonomic dysfunction an unlikely explanation for the episodes described, although it may be a contributing factor. As syncope was associated with occipital headaches, transient brainstem compression may play a significant part. As the authors suggest, the precise mechanism of these episodes and of drop attacks is difficult to determine, and they may be multifactorial.

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MRI of a 50 year old woman with syringomyelia, Noonan's syndrome, and frequent drop attacks. There is a cervical syrinx and moderate dilatation of the fourth ventricle. There is no Chiari anomaly.

- 1 Woelfle J, Haverkamp F, Kreft B. Repeated syncope and extended paediatric hydrosyringomyelia/Chiari I malformation: relation or coincidence? *J Neurol Neurosurg Psychiatry* 1998;64:278-9.
- 2 Nogues MA, Newman PK, Male W, *et al.* Cardiovascular reflexes in syringomyelia. *Brain* 1982;105:835-49.

The authors reply:

As Nogues mentions, the association of hydrosyringomyelia and syncope is a very rare event. To our knowledge, our patient is the first child reported demonstrating such a clinical picture.¹ In his opinion, the normal neurological examination in our patient makes autonomic dysfunction as the underlying mechanism of the repeated syncope unlikely. Considering the association of syncope with occipital headache, he suggests that transient brainstem compression may be a causal factor in the mechanism leading to syncope. However, the association of headache was not a consistent finding in all of the five noted syncopal events in our patient. Furthermore, hydrosyringomyelia usually remains asymptomatic in childhood,² indicating a time dependent degree of damage to the spinal cord. Thus, in our opinion a normal neurological status in children does not necessarily exclude temporary dysfunction of the sympathetic system, assuming that temporary, preclinical damage to the spinal cord in childhood may well progress to permanent autonomic dysfunction in adulthood. In addition, even in adults with some symptoms of autonomic dysfunction, the lesion of autonomic outflow paths in the spinal cord may be incomplete, with absence of Horner's syndrome and preservation of some autonomic reflexes.³ In our patient, autonomic dysfunction was supposed to be the most likely mechanism due to the pattern of affected syringomyelic areas in combination with the finding of impaired cardiovascular reflexes in adults with hydrosyringomyelia, in whom longstanding pressure changes may have led to permanent, irreversible destruction of autonomic structures in the medulla.⁴

Of course, we are well aware that all the theoretical models outlined in our case report, even the causal relation between syncope and hydrosyringomyelia/Chiari I malformation, remain speculative and neither his nor our theory can be proved. We agree with Nogues, that probably syncope and drop attacks in these patients are of multifactorial origin with various possible contributing factors including neurological, cardiovascular, and neuropsychological influences.

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