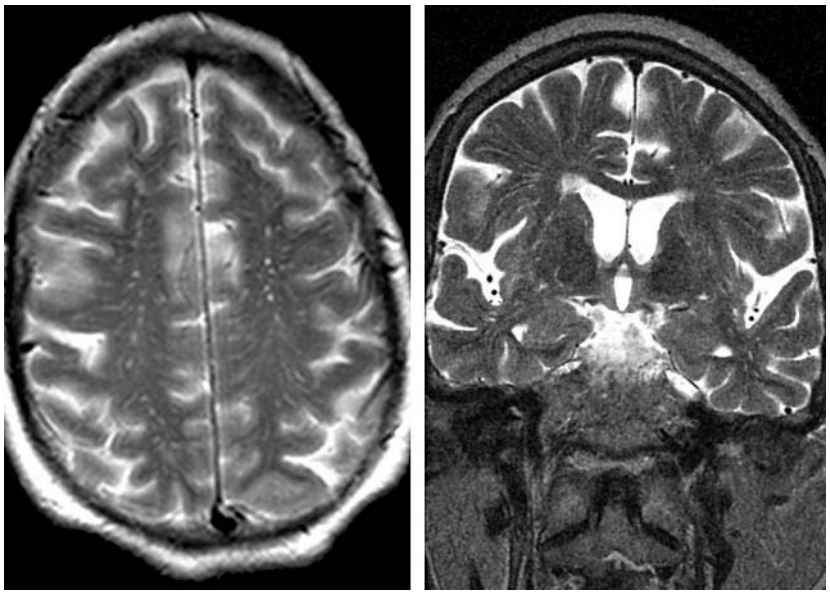

Figure 1 Heavily T2-weighted MRI obtained with high resolution, showing multiple enlarged VRS, visible as well-demarcated CSF like structures, which, dependent on their orientation and plane of imaging, appear as dots (transverse image on the left) or stripes (coronal image on the right).

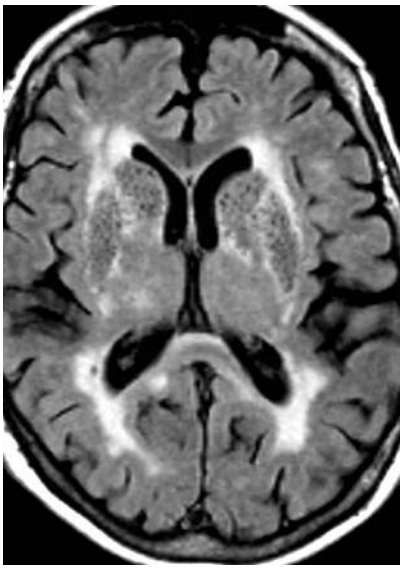

Figure 2 Coexistence of hyperintense white matter lesions (WML), and diffusely widened enlarged hypointense VRS (so-called état criblé) on a CSF-supressed transverse MR image.

white matter lesions (WML), VRS did not seem to have an independent contribution to (decreased) cognitive performance. VRS were also rated separately in the hippocampal region, and although these were significantly correlated with WML, they were not associated with poorer cognitive performance (including episodic memory).

It is tempting to speculate on the pathogenesis of widened VRS and their significance in determining white matter integrity. Clearly, these CSF spaces do not represent viable tissue, and thus present (a mild form of) local atrophy, which may occur independent of cortical atrophy and ventricular widening. In my clinical experience, widened VRS in elderly subjects often coincide with WML on MRI, and this corroborates with the current findings of MacLullich *et al*. Apparently, white matter damage may manifest itself as general atrophy (with ventricular widening), incomplete white matter infarction (with WML on MRI), and by virtue of widened VRS. What is particularly interesting is why some patients may develop extensive WML in the basal ganglia and diffusely widened VRS (so-called état criblé) without significant atrophy (fig 2), while others develop only volume reduction (global atrophy). Perhaps this reflects a different mode of communication of the VRS with the subarachnoid space. This remains a subject of debate.

In summary, the findings by MacLullich *et al* indicate that widened VRS are a common ageing phenomenon that is associated with WML and cognitive function. More work is needed to develop an integrated methods to probe white matter integrity, which should not only address WML, but also the quality of the remaining tissue (e.g. using diffusion tensor MRI), and residual white matter volume by accounting for the degree of widening of the VRS—a measure of focal atrophy.

J Neurol Neurosurg Psychiatry 2004;**75**:1516–1517.
doi: 10.1136/jnnp.2004.044578

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Epilepsy

Longer term outcome of children born to mothers with epilepsy

S D Shorvon

New issues concerning valproate treatment during pregnancy

The teratogenic risk of antiepileptic drugs has been a clinical concern for at least three decades. In an ideal world this risk would be balanced against the benefits of reduced foetal exposure to seizures due to the drug. In the real world, however, statistical data on both sides of this equation are limited. Although it has long been held that maternal seizures during pregnancy can damage the developing foetus, there is actually little hard data to support this view. Convulsive attacks certainly carry some risk—especially in later pregnancy—not least because of the mechanical dangers of convulsions, but the extent of the overall risk is unclear. It also seems inherently unlikely that the short lived anoxia occurring in seizures will have a profound effect on the foetus, although this has often been postulated. The risks of non-convulsive seizures or myoclonus are totally unknown but intuitively are likely to be slight. There is also considerable uncertainty about the extent of the

teratogenic risk of antiepileptic drugs, and the best data concern the rates of major malformations. In recent years, a great deal of attention has focused on the use of the anticonvulsant sodium valproate (and its derivatives such as valproic acid). Valproate was first introduced into practice in 1961 but it was not until the early 1980s that the first reports of teratogenicity were made. It is now recognised that the drug confers an increased risk of neural tube defects (about 1–2% of pregnancies) and also of more minor dysmorphic features, the true incidence of which remains controversial. In an attempt to define teratogenicity rates more accurately, pregnancy registers have been set up in many countries in recent year, and overall malformation rates on valproate monotherapy and polytherapy of between about 3–15% have been reported, with higher rates in polytherapy and at higher doses.

In this issue (pp 1575–83), an important and carefully argued paper[1] is published that adds a new dimension to the problem. The study shows that 41 school aged children exposed to valproate monotherapy in utero have significantly lower verbal IQ (VIQ) scores when compared with 52 children exposed to carbamazepine and 21 to phenytoin monotherapy. In a multivariant analysis, low VIQ was also associated with the occurrence of five or more tonic-clonic seizures during pregnancy and a low maternal IQ. There were higher rates of dysmorphic features—defined as cosmetic variants without disability—in the valproate exposed children, and these were most common in those with low VIQ scores. These longer term developmental effects would not have been identified at birth and thus not in the pregnancy registers. This is a deeply worrying finding and come on the heels of parallel findings from other studies by the same group as well as others.[2–4]

Some caution needs to be exercised in interpreting these results. The study was a retrospective survey, the mothers were not randomised to different monotherapies, there was only a 40% response rate, and there are some inconsistencies (for instance, significant differences in VIQ rates were not found in foetuses exposed to valproate polytherapy and there was only a soft relationship with dose). A biological explanation of the findings would add plausibility, but is outwith the scope of the paper. The authors point out that for methodological reasons the risk is probably overestimated and that the absolute risk will be satisfactorily ascertained only by a prospective community-based study. However, with the publication of these findings such a study may prove difficult to justify and it is now quite possible that exact estimates of the risks of valproate will never be possible to ascertain.

What advice can we therefore give to patients? The authors conclude with a demand that epilepsy services to deliver adequate information and counselling, and who could argue with this? The problem is that available information is not adequate, particularly in patients with idiopathic generalised epilepsy where valproate is the drug of choice for seizure control. We should be grateful for Chadwick and colleagues for identifying what is potentially a major clinical concern and introducing the concept that antiepileptic drug teratogenicity may include long term effects on cognitive development. It is also notable that this effect has been only recently postulated in spite of the fact that valproate has been in use for over 40 years. Further exploration of this vital area is now urgently needed.

J Neurol Neurosurg Psychiatry
2004;**75**:1517–1518.
doi: 10.1136/jnnp.2004.050641

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