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Winer's statement. He, obviously, has not been staying abreast of neurosurgical developments in this country. Since the development of the Brown-Roberts-Wells CT stereotactic guidance system, which has been available since 1981, and the modification of the classical Leksell stereotaxic unit, CT-guided stereotaxy is literally available in over 200 neurosurgical centres in the United States. I believe, if Dr Robert Winer took a look around him, it is likely that within the short distance of 100 miles he would find a neurosurgical centre, skilled in the use of this technique.

I might refer Dr Winer to the case records of the Massachusetts General Hospital published in the N Engl J Med on 5 June 1986. In the presentation of a 55-year-old right-handed woman with blurred vision, the pathologic diagnosis of a primary central nervous lymphoma was made with CT stereotactic localisation and biopsy using the Brown-Roberts-Wells frame.


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Syncope and sudden death attributed to carbamazepine

Sir: I read with interest the recent report of Stone and Lange on a young epileptic with sudden death attributed to carbamazepine.1 They cited the various articles illustrating the electrophysiological actions of this antiepileptic on the heart, including two isolated cases of carbamazepine-associated bradyarrhythmias.2,3 Separately, I am reporting a rare patient with complex partial seizures of confusion accompanied by profound sinus bradycardia (down to 10 beats a minute during the attacks).4 Results of cardiac testing on our patient were normal. He was prescribed carbamazepine after he could not tolerate phenytoin; plasma therapeutic levels and complete seizure control were achieved. After one year, medication was discontinued and in subsequent follow up, seizures have not recurred. He tolerated carbamazepine well and at no time disorders of cardiac rhythms were documented on his medical visits. He took no concomitant medications. Should this patient's bradyarrhythmia have resulted from his individual propensity to develop bradyarrhythmias (seizure-induced or otherwise), I expect the complications in question should have operated from the use of the drug; furthermore, antecedent cardiac testing failed to show baseline abnormalities.4 My patient was prescribed carbamazepine because of the well-known optimal therapeutic effects of this agent on complex partial seizures. I confess, however, Drs Stone and Lange's detailed review on the subject left me with guarded concern about prescribing carbamazepine in patients with associated cardiac conduction defects. Nevertheless, I venture to say, based on this single experience that the noxious cardiac effects of carbamazepine may be only significant in the presence of underlying heart disease. If the heart is normal, encountering ictal arrhythmias should not be a contraindication for prescribing carbamazepine in epileptics.

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References


Necrotising haemorrhagic encephalomyelopathy in an adult: ? Leigh's disease

Sir: May I be allowed to ask a question and to make a comment on the case reported by Dr Delgado and colleagues1 entitled "Necrotising haemorrhagic encephalomyelopathy in an adult: ? Leigh's disease"? I would like to ask if this patient's work or interests brought him into contact with any chemicals which might have been responsible for the described changes. My question arises from the growing realisation that such cases, whether in children or in adults, give every indication for being expressions of an acute tissue energy deprivation, and there seem to be many environmental as well as genetic causes for this type of metabolic disturbance. The pattern of the damaged brain regions found in the reported case is very similar, as the authors rightly point out, to that found in Wernicke's encephalopathy, and although the latter is rarely as severe as this, it may occasionally be.2 An alcoholic cause appears to be excluded here, but the possibility of another environmental agent being responsible remains, and it is for this reason that I pose the question.

From experimental studies it is now coming to be realised that there are a number of chemicals that may produce acute tissue energy deprivation states that end up with tissue damage of the same type and the same general distribution within the neuraxis as seen in Wernicke's disease. The list of agents known from experimental studies to act in this way is growing and there appear to be several points along the energy generation pathways that may come under attack. Thus, the glycolytic pathway can be blocked at separate points by 6-chloro-6-deoxy-glucose3 and (indirectly) by 6-aminonicotinamide,4 causing acute vasculonecrotic lesions in cortex, basal ganglia, brain stem centres and in spinal cord grey matter.5,6 However, perhaps more importantly in the present context, there are also compounds that undergo nitroreduction in the tissues and in the presence of divergent oxygen, such as would be encountered in highly oxygenated nervous tissue, enter a redox cycling state that brings with it adverse metabolic consequences,7 which include disturbance to electron transport, over-utilisation of cellular NAD(P) and GSH, and the generation of free radical species. This situation occurs with the drugs metronidazole (5-nitroimidazole) and misconidazole (2-nitroimidazole), and with certain nitrofurans, and has also been described following administration to animals of both nitrobenzene and 1,3 dinitrobenzene, chemicals widely used in industry that have found their way onto the domestic market in different forms. All these last chemicals produce in experimental animals, with slight species differences, acute vasculonecrotic lesions8–11 closely similar to the changes seen in acute thiamine deficiency in man and in animals. In view of the growing interest, both clinical and experimental, in this group of disorders, it would be helpful if an answer to my question could be given by the authors of the article noted above. It may be that the question was asked of the patient and the answer was in the negative, but in the interest of good case recording we should have this information.
Leigh’s disease is rather a nosological mess at the present time with cases being reported from various times of life, and with various bits of evidence incriminating different metabolic pathways in the energy generating system. Provided that we keep our eyes firmly fixed on the fact that acute energy deprivation seems to be at its root, and this may come about from various causes, both environmental and genetic, it becomes easier to think constructively about the fundamental nature of the problem.

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The syndrome of irreversible lithium effectuated neurotoxicity

Sir: I read with interest the case report by Tesio et al 1 describing a cerebellar syndrome in lithium poisoning. There is a general lack of awareness about irreversible and untreatable complications of lithium treatment 2 despite evidence to contrary. 3-5 Till recently it has been maintained that the side-effects of lithium are not disabling. 6 I identified 55 cases of persistent sequelae of lithium therapy after a review of published literature though earlier reviews had given a smaller number. 3-5 Some of the cases of persistent sequelae of lithium therapy have been mistaken for neuroleptic malignant syndrome 6 owing to a superficial resemblance. Moreover, some cases of long lasting sequelae of lithium therapy may occur without having acute poisoning, a fact which has not been appreciated in earlier reviews. 3-4 Though most common sequelae are persistent cerebellar symptoms, other clinical manifestations have also been documented. In a typical presentation, acute lithium poisoning precedes the sequelae and the acute phase is generally without cerebellar symptoms. 4 As consciousness returns the neurological sequelae become more apparent. 4 In four cases cerebellar signs were present from the beginning of the acute phase in the cases I reviewed. Atypical presentations may include persistent papilloedema, optic neuritis, isolated downbeat nystagmus, peripheral neuropathy and myopathy. Those with atypical presentations are unlikely to have undergone an acute organic brain syndrome. In such cases symptoms develop insidiously while on long-term lithium therapy and persist after discontinuation for varying periods. Prognosis generally is good and in some cases of chronic lithium neurotoxicity the neurological signs may resolve in less than two months after discontinuation. 7-10 These cases 7-9 cannot be termed long lasting according to criteria laid down by Schou. 4 In general spontaneous recovery may occur in varying degrees over a period of time. Some cases, however, may be unchanged and irreversible. Complete neurological recovery is uncommon but patients may respond to rehabilitative measures with significant functional gains and may return to previous living arrangement. 11

I suggest that these persistent sequelae of lithium be called the syndrome of “Irreversible Lithium Effectuated Neurotoxicity.” Extensive demyelination has been found by biopsy of peripheral nerves so involved. It is likely that toxic demyelination at various sites in the central nervous system especially in the cerebellum may be the mechanism involved in the aetiology of this syndrome.

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Matters arising

References

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Tesio replies:

I agree with Dr Adityanjee’s suggestion that we recognise the persistent sequelae of lithium poisoning as a syndrome to be named the syndrome of irreversible lithium effectuated neurotoxicity.

First, however, I think we should state more definitely the specific features of this syndrome and the minimal criteria for its diagnosis.

The case I and my coworkers described in a previous paper, 1 the review of the literature 2 and Dr Adityanjee’s letter itself suggest that only persistent neurological deficits following acute intoxication could form specific syndrome pathognomic for lithium poisoning. Minimal
Necrotising hemorrhagic encephalopathy in an adult: Leigh's disease?

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