MATTERS ARISING

Acute necrotising encephalopathy of childhood presenting with multifocal, symmetric brain lesions occurring outside Japan

I was interested in the article by Mizuguchi *et al* on acute necrotising encephalopathy of childhood as a new syndrome presenting with multifocal, symmetric brain lesions.[1] The article admirably describes the pathogenesis of this special childhood encephalopathy.

I must point out however, that the authors said that they failed to find any reports of similar cases occurring outside Japan. My instructor and I previously reported three infants with acute encephalopathy with a striking ultrasonographic finding—"bright thalamus"—suggesting panthalamic infarction.[2] Afterwards, five more children with similar problems were treated. Their clinical and neuroimaging manifestations have been reported at the 7th Congress of the International Child Neurology Association in 1994.[3] In the same report 17 children, including 14 Japanese, were reviewed from the English literature.[4–10] Of the three not from Japan; two were from the United Kingdom[9] and one was from the United States.[4] At least eight other cases were presented at a local conference without publication in Taiwan.

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1 Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T, Kamoshita S. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry* 1995;**58**:555–61.
2 Wang HS, Huang SC. Infantile panthalamic infarct with a striking sonographic finding: the "bright thalamus". *Neuroradiology* 1993; **35**:92–6.
3 Wang HS, Huang SC, Hung PC. Acute encephalopathy with panthalamic plus lesions: a major occurrence in oriental children? [abstract 196] *Pediatr Neurol* 1994;**11**: 135–6.
4 Charney EB, Orecchio EJ, Zimmerman RA, Berman PH. Computerized tomography in infantile encephalitis. *Am J Dis Child* 1979; **133**:803–5.
5 Okuno T, Takao T, Ito M, Mikawa H, Nakano Y. Contrast enhanced hypodense areas in a case of acute disseminated encephalitis following influenza A virus. *Computerized Radiology* 1982;**6**:215–7.
6 Aoki N. Acute toxic encephalopathy with symmetrical low density areas in the thalami and the cerebellum. *Childs Nerv Syst* 1985;**1**: 62–5.
7 Ochi J, Okuno T, Uenoyama Y, Narita H, Mikawa H. Symmetrical low density areas in bilateral thalami in an infant with measles encephalitis. *Computerized Radiology* 1986; **10**:137–9.
8 Tateno A, Sakai K, Sakai S. Computed tomography of bilateral thalamic hypodensity in acute encephalopathy. *J Comput Assist Tomogr* 1988;**12**:637–9.
9 Protheroe SM, Mellor DH. Imaging in influenza A encephalitis. *Arch Dis Child* 1991;**66**:702–5.
10 Nagai T, Yagishida A, Tsuchiya Y, *et al*. Symmetric thalamic lesions on CT in influenza A virus infection presenting with or without Reye syndrome. *Brain Dev* 1993;**15**:67–74.

Mizuguchi replies:

I am grateful to Wang for his comments on our paper.[1] Until the submission of our paper, we had been unaware of the occurrence of acute necrotising encephalopathy of childhood (ANE) outside Japan. Now Wang has made it clear that ANE is as prevalent in Taiwan as it is in Japan. Many of the Taiwanese patients described by Wang *et al* have typical features of ANE.[2] The high prevalence of ANE in the far east implies the involvement of genetic or environmental factors pertinent to that region. Wang also reviewed patients with probable ANE reported from the United States and from England. These patients seem to have a mild form of ANE, judging from their clinical course and laboratory findings.

It is our view that the patients having CSF pleocytosis and other evidence of encephalitides, such as the one reported by Okuno *et al*,[3] should be excluded from ANE. Many of these patients show a prolonged course, prominent focal signs, and asymmetric or atypical distribution of brain lesions, features that are incompatible with ANE.

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1 Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T, Kamoshita S. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry* 1995;**58**:555–61.
2 Wang HS, Huang SC. Infantile panthalamic infarct with a striking sonographic finding: the "bright thalamus". *Neuroradiology* 1993; **35**:92–6.
3 Okuno T, Takao T, Ito M, Mikawa H, Nakano Y. Contrast enhanced hypodense areas in a case of acute disseminated encephalitis following influenza A virus. *Computerised Radiology* 1982;**6**:215–7.

Suspected triphenyltin poisoning

In 1990 Wu *et al* reported a patient with suspected acute triphenyltin intoxication.[1] Extensive studies on this class of compounds in animals[2 3] and the comprehensive review by Bock[4] did not produce any firm evidence that these organic aryltin compounds had any serious adverse effects on the nervous system. Indeed, such compounds are currently widely used as agricultural pesticides and although very occasionally toxic effects are reported by field workers, there has never been any suggestion that the nervous system is significantly involved.[5] The reported case of Wu *et al* developed severe ataxia, dysmetria, nystagmus, and blurred vision from which he eventually recovered to a large degree. Even if the compound taken in this suicide attempt had been contaminated in some manner by an alkyltin compound, these are not the signs or symptoms expected.

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1 Wu RM, Chang YC, Chiu HC. Acute triphenyltin intoxication: a case report. *J Neurol Neurosurg Psychiatry* 1990;**53**:356–7.
2 Barnes JM, Stoner HB. The toxicology of tin compounds. *Pharmacol Rev* 1959;**11**: 211–31.
3 Stoner HB. Toxicity of triphenyltin. *Br J Ind Med* 1966;**23**:222–9.
4 Bock R. Triphenyltin compounds and their degradation products. *Residue Reviews* 1981;**79**:1–270.
5 Manzo L, Richelini P, Sabbione E, Pietra R, Bono F, Guardia L. Poisoning by triphenyltin acetate: report of two cases and determination of tin in blood and urine by neutron activation analysis. *Clin Toxicol* 1981;**18**:1343–53.

Wu et al reply:

Cavanagh expresses his concern about the case of acute triphenyltin intoxication reported by us.[1] He claims a lack of evidence for the adverse effects of aryl organotin compounds on the nervous system in animal studies and clinical reports. Finally, he concludes that it certainly was not a case of triphenyltin intoxication.

Firstly, the formulation of the pesticide taken by our patient in a suicide attempt was carefully analysed by gas liquid chromatography coupled with a mass detector. According to the mass spectra obtained, this agent was either triphenyltin acetate or triphenyltin hydroxide. The mass spectra of these two compounds are identical in our analysis. Triphenyltin compounds are widely used as fungicidal and mollusicidal agents in Taiwan agriculture. The patient's girlfriend had hidden the crucial history from both doctor and the patient's family for some reason for the first two months after the incident. As the patient did not recover from his coma, his girlfriend finally told us the truth and provided the pesticide to doctors.

According to the comprehensive review of Bock,[2] when a high dose of triphenyltin acetate was fed to rats (>20 mg/kg), guinea pigs (5–20 ppm), and rabbits (140 mg/kg), they developed muscle weakness, unsteady gait, paralysis in the hind limbs, tremor, and convulsion, and eventually died in coma. Although increased water content of the brain and spinal cord was the only abnormal finding on pathological examination, inhibition of adenosine triphosphatase, protease, and amylase in brain microsomes have been reported in other studies.[3 4] Uncoupling of oxidative phosphorylation in the mitochondria has also been suggested as a contributer to the cellular mechanism of triphenyltin toxicity.[5]

Although triphenyltin compounds have been regarded as less neurotoxic than alkyltin compounds, neurological manifestations in human cases with triphenyltin intoxication have been reported in isolated instances. Headache, vomiting, nausea, and impaired vision were noted in cases poisoned by triphenyltin acetate.[2] Moreover, two cases with triphenyltin acetate poisoning had severe headache, dizziness, vertigo, transient loss of consciousness and, paraesthesia in the legs.[6] Thus it is likely that more severe neurological deficits may develop in our case who had taken a possible lethal dose of triphenyltin compound with the intention of committing suicide. He developed abdominal pain, diarrhoea, and vomiting on the first day of poisoning. Headache, blurred vision, unsteady gait, consciousness disturbance, and polyneuropathy occurred subsequently. Also, systemic problems with abnormal liver function and leukopenia coincided with the neurological manifestations. These clinical features are consistent with the previous studies on animals and clinical reports.

We are grateful to Cavanagh for giving us the opportunity to reiterate the unusual case with acute triphenyltin intoxication in a suicide attempt.

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1 Wu RM, Chang YC, Chiu HC. Acute triphenyltin intoxication: a case report. *J Neurol Neurosurg Psychiatry* 1990;**53**:356–7.
2 Bock R. Triphenyltin compounds and their degradation products. *Residue Reviews*, 1981;**79**:31–270.
3 Stoner HB. Toxicity of triphenyltin. *Br J Ind Med* 1966;**23**:222–9.
4 Ascher KRS, Ishaaya I. Antifeeding and protease- and amylase-inhibiting activity of fentin acetate in *Spodoptera littoralis* larvae. *Pesticide Biochemistry and Physiology* 1973;**3**:326–36.
5 Selwyn MJ. Triorganotin compounds as ionophores and inhibitors of iron translocating ATPase. In: Zuckerman JJ, ed. *Advances in chemistry series.* Vol 157. Washington DC: American Chemical Society 1976:204–26.
6 Manzo L, Richelmi P, Sabbioni E, *et al.* Poisoning by triphenyltin acetate: report of two cases and determination of tin in blood and urine by neutron activation analysis. *Clin Toxicol* 1981;**18**:1343–53.

Cavanagh replies:

Having read Wu's reply to my earlier criticism I still think that this case should not be regarded as anything more than "suspected triphenyltin intoxication". There are too many uncertainties for the conclusions to be anything firmer. One important uncertainty is the remarkably slow though sustained evolution of the signs of change in the nervous system. While ataxia and blurred vision were early events, it was two weeks before he slipped into semicoma in November and he lay in coma virtually until the beginning of February. Signs of peripheral neuropathy developed two months after admission and persisted for several months more. The pattern of the neuropathy suggested an axonal mechanism whereas the electrophysiology gave evidence of myelin loss. Another uncertainty is the dose the subject absorbed, which is unknown, nor do we have any blood concentrations. Although it might seem from the reports that animal studies support the suggestion that triphenyltin can be neurotoxic, when such studies are unaccompanied by thorough morphological work interpretation is always very difficult and experience strongly suggests that these should be taken with the proverbial pinch of salt, especially when they have not been confirmed by others.

Triphenyltin compounds are widely used in the field and are generally considered to be free of serious neurological side effects, unlike trimethyl and triethyl compounds each of which produces its own pattern of affected cell types. On available evidence it is to be doubted whether there will be any future occasion when the claim of Wu and his colleagues will be supported, but should this happen I am content that this discussion and my initial reservations will be quoted.

JP CAVANAGH

NOTICES

Stanley Foundation Research Awards Program
Announcement of available research funds for research on schizophrenia and bipolar disorder

The Theodore and Vada Stanley Foundation, in collaboration with the National Alliance for the Mentally Ill, welcome applications for the 1996 Stanley Foundation Research Awards Program. The purpose of the awards is to support research directly related to the causes or treatment of schizophrenia and bipolar disorder.

The research awards are intended to attract established scientists from other areas of biology and medicine (for example, biochemistry, immunology, virology, and neurology) into research on schizophrenia and bipolar disorder as well as to provide support for innovative research by scientists already in the field whose funding sources are limited. Applicants are invited from all stages of career development.

Awards are for one or two years. They may be up to $75 000 per year for studies involving human subjects and up to $50 000 per year for other studies. Funds may be used for salaries, supplies, and equipment, but it is the policy of the Stanley Foundation not to pay indirect costs for administration of the award. In 1995, 49 applications were funded out of a total of 220 received.

Deadline for receipt of applications is 1 March 1996. The 4 page application consists of a brief outline of the proposed project, a budget, and a list of current and pending sources of funding. Notification of awards is made in June and funding to award recipients begins in August.

The research award applications are reviewed by a professional selection committee.

Requests for applications and questions should be directed to: Research Awards Coordinator, Stanley Foundation Research Awards Program, c/o NAMI, 200 North Glebe Road, Suite 1015, Arlington, VA 22203–3754, USA. Tel (703) 524–7600; fax (703) 524–9094

Sixth Meeting of the European Neurological Society June 8–12 1996 Netherlands Congress Centre, The Hague, The Netherlands.

Administrative Secretariat ENS 1996, c/o AKM Congress Service, PO Box, 4005 Basel, Switzerland, Tel ++41 61 691 51 11, Fax: ++41 691 81 89.

British Neurosurgery Research Group Meeting together with the North American Research Society of Neurological Surgeons Meeting, 1996.

This joint meeting will be held in Newcastle upon Tyne, 23–25 May 1996.

For further information contact: Professor A David Mendelow, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK.

World Federation of Neurosurgical Societies
Awards to young neurosurgeons.

The World Federation of Neurosurgical Societies will give five awards to young neurosurgeons for the best papers submitted for presentation at the XI International Congress of Neurological Surgery to be held in Amsterdam, Netherlands 6–11 July 1997. This will be open to all neurosurgeons born after 31 December 1961. Each award will consist of an honorarium of US $1500, a certificate for the Congress. The papers will be judged by a committee and must contain original, unpublished work on basic research or clinical studies related to neurosurgery.

Young neurosurgeons should submite eight copies of the manuscript (not more than 10 double spaced typewritten pages exclusive of figures and tables) to:
Albert L Rhoton, Jr, MD Chairman, WFNS Young Neurosurgeons' Committee, Department of Neurological Surgery, University of Florida Medical Center, PO Box 100265; 1600 SW Archer Road Gainesville, Florida 32610–0265, USA.

The submission should be accompanied by a supporting letter from the head of the candidate's neurosurgical department. The last date for submission is 1 October 1996.

Announcement from the British Neuropsychiatry Association: 1996 meetings

The 1996 Winter meeting—a joint meeting with The British Neuropsychological Society—will be held on Friday 19 January at the London Zoo. "Disorders of reasoning and perception" is the theme of the morning session and there will be presentation of short scientific papers and single case videos by members of both associations in the afternoon.

The 1996 Summer meeting will be held on 14–16 July at Robinson College, Cambridge. It will include topics on neurodevelopment, language, and the presentation of short scientific papers and single case videos by members. The Association's AGM will be held on 16 July.

For further details of these meetings please contact: Sue Garratt, Administrative Assistant, BNPA, 17 Clocktower Mews, London N1 7BB. Telephone/Fax: 0171 226 5949.

For details of membership of the BNPA, which is open to medical practitioners in psychiatry, neurology, and related clinical neurosciences, please contact: Dr Jonathan Bird, Secretary BNPA, Burden Neurological Hospital, Stoke Lane, Stapleton, Bristol, BS16 1QT. Telephone: 01179 701212 ext 2925/2929 or Sue Garratt at the address given above.

CORRECTIONS

Catarci T, Lenzi GL, Cerbo R, Fieschi C. Sumatriptan and daily headache. *J Neurol Neurosurg Psychiatry* 1995;**58**:508.

The reference to Osborne *et al* should be *BMJ* 1994;**308**:113.

Aramideh M, Eekhof JLA, Bour LJ, Koelman JHTM, Speelman JD, Ongerboer de Visser BW. Electromyography and recovery of the blink reflex in involuntary eyelid closure: a comparative study. *J Neurol Neurosurg Psychiatry* 1995;**58**:692–8.

In table 2 (bottom line) the mean R2 index (range) in the third EMG subclass should be 31 (28–37).