Progressive Dialysis Encephalopathy

Role of Aluminum Toxicity

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In the article "Progressive dialysis encephalopathy" (Ann Neurol 4:199–204, 1978), Drs Lederman and Henry considered the role of aluminum in the origin of dialysis encephalopathy as speculative. We were astonished that aluminum blood levels were not reported for their 9 patients.

Like other authors [1, 3], we believe that aluminum toxicity probably plays a role in the production of dialysis encephalopathy, at least in some cases. The following arguments favor our belief. First, neuropathological studies have not shown major lesions even under electron microscopy [2], which suggests a metabolic mechanism. Second, demographically, dialysis encephalopathy has a higher incidence in regions where the aluminum dialysate content is increased [4]. Third, early interruption of aluminum intake has been reported to reverse the encephalopathy [5].

Recently we have observed 6 patients in whom the clinical and electroencephalographic findings were identical to those reported elsewhere in dialysis encephalopathy and to the 9 cases reported by Drs Lederman and Henry. In our 6 patients, psychic troubles and repeated somnolence were present in all, dysarthria in 5, myoclonic jerks in 4, and epileptic seizures in 1. In all 6 patients the EEG was disturbed and showed bilateral symmetrical, periodic, monomorphic, slow activity; in 3 patients, biphasic and triphasic spike configurations were noted. The average serum aluminum level was 407 μg per liter in the acute phase, 161 μg per liter in the remission phase with an average delay of six weeks, and 123 μg per liter three months later with maintained remission. (The normal serum aluminum level is 40 μg per liter as determined by flameless-oven atomic spectrophotometry.) Following interruption of the oral and dialysate aluminum intake, remissions were permanently maintained. In 2 cases, transient oral readministration of aluminum to treat hyperphosphatemia was followed by recurrent encephalopathy, reversed only when aluminum intake was stopped again.

References

1. Alfrey AC, Legendre GR, Kaehny WD: The dialysis encephalopathy syndrome: possible aluminum intoxication. N Engl J Med 294:184–188, 1976
2. Buge A, Escourolle R, Poisson M, et al: Un cas d'encéphalopathie dialysaire progressive: rôle de l'aluminum et étude neuropathologique. Nouv Presse Med 8:1071–1074, 1979
3. Cartier RF, Allain P, Gary J, et al: Encéphalopathie myoclonique progressive des dialyses: rôle de l'eau utilisée pour l'hémodialyse. Nouv Presse Med 7:97–102, 1978
4. Elliott HL, Dryburgh F, Fell GS, et al: Aluminum toxicity during regular haemodialysis. Br Med J 1:1101–1103, 1978
5. Poisson M, Mashaly R, Lebkiri B: Dialysis encephalopathy: recovery after interruption of aluminum intake. Br Med J 2:1610–1611, 1978

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Prevention through Control of Aluminum Levels in Water

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In the clinical review of progressive dialysis encephalopathy by Lederman and Henry (Ann Neurol 4:199–204, 1978), the evidence supporting aluminum as a toxic factor rather than as a consequence was limited.

We analyzed data from a small dialysis unit on 8 patients who developed typical progressive dialysis encephalopathy with fatal outcome [6]. These 8 patients represented a 38% incidence during the 22-month period in which aluminum was added to city water at concentrations of 200 to 1,000 μg per liter. In contrast, the incidence of this syndrome was zero for the five preceding years when no aluminum was added to the water ($p < 0.05$ for difference in incidence). During three years after a deionizer was installed that lowered the aluminum content to less than 1 μg per liter, no case suggesting this encephalopathy was observed, giving again a significantly lower incidence ($p < 0.0002$) [5].

The etiological importance of parenteral aluminum administration for aluminum-containing dialysate is further supported by several recent reports of dialysis encephalopathy developing during exposure to aluminum in dialysate [1, 2, 4]. Furthermore, the distribution of this syndrome has been uneven in dialysis units in the United States [3] despite the widespread oral use of aluminum-containing phosphate binders and despite partial intestinal absorption of aluminum.

We believe that outbreaks of dialysis encephalopathy can be prevented by maintaining dialysate aluminum levels below 10 μg per liter, as recommended in standards proposed by the Association for the Advancement of Medical Instrumentation in 1977 [3a]. This can be achieved through deionization of aluminum-containing water. Sporadic cases of this syndrome developing in the absence of aluminum in dialysate are apparently rare and might be related to an unusually high intestinal absorption of aluminum.

References

1. Dunea G, Mahurkar SD, Mamdani B, et al: Role of aluminum in dialysis dementia. Ann Intern Med 88:502–504, 1978
2. Elliott HL, Dryburgh F, Fell GS, et al: Aluminum toxicity during regular haemodialysis. Br Med J 1:1101–1103, 1978
3. Favero MS, Schreeder MT: Epidemiologic investigation of dialysis encephalopathy, in Proceedings of the 11th Annual Con-

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tractors' Conference, National Institute of Arthritis, Metabolic, and Digestive Diseases. Bethesda, MD, 1978, pp 206–213
3a. Hemodialysis systems standard (proposed) (AAMI HS-P 5/77). Arlington, VA, Association for the Advancement of Medical Instrumentation, 1977
4. McDermott JR, Smith AI, Ward MK, et al: Brain-aluminum concentration in dialysis encephalopathy. Lancet 1:901–904, 1978
5. Rozas VV, Port FK, Easterling RE: An outbreak of dialysis dementia due to aluminum in the dialysate. J Dialysis 2:459–470, 1978
6. Rozas VV, Port FK, Rutt WM: Progressive dialysis encephalopathy from dialysate aluminum. Arch Intern Med 138: 1375–1377, 1978

Endogenous Pain Control Mechanisms

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In their excellent paper on endogenous pain control mechanisms, Basbaum and Fields [1] have extended their concept of a pain-suppression feedback loop to one of the most common "essential" pain syndromes, the migraine headache. Although the pain in migraine is generally regarded as vascular in origin, the central nervous system may play an important role in determining the intensity of the pain perceived. Sicuteri's observation [4] of the development of spontaneous pains following treatment with *p*-chlorophenylalanine (pCPA), which has been reported for migraineurs but not for normal individuals, may serve as an indication of deranged pain processing in migraine sufferers. In the light of Basbaum and Fields' hypothesis, it may signify that migraineurs in normal life, i.e., when not experiencing an attack, are saddled with an activated pain-suppression system. Studies of the 5-hydroxyindoleacetic acid content of cerebrospinal fluid [3] do not, however, support this conclusion. The remarkable fact remains that migraineurs seem to do better during their migraine attacks when their activated pain-suppression system is interfered with: Sicuteri [4] described several patients who, despite distressing pains, persisted in taking pCPA for the prophylactic treatment of their attacks!

A very effective drug in migraine prophylaxis is methysergide, a putative serotonin antagonist. Methysergide has been shown to antagonize the analgesia produced by microinjection of opiates into the midbrain periaqueductal gray matter. Like lysergic acid diethylamide, which has been shown to antagonize analgesia produced by electrical stimulation of the PAG, methysergide inhibits spontaneous firing of serotoninergic raphe neurons when applied iontophoretically [2]. Thus, an alternative explanation for the counteraction of opiate analgesia by methysergide can be found in the inhibition of raphe neurons which mediate both opiate analgesia and stimulation-produced analgesia. The difference in mode and possibly site of action between methysergide and pCPA may account for the fact that, although both drugs turn off the "erroneously" activated pain-suppression system in migraineurs, spontaneous pains have not been reported for methysergide. When the pain-suppression system is put at rest, it may come into action at appropriate times and cope with a process which may otherwise result in a devastating headache.

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References

1. Basbaum AI, Fields HL: Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 4:451–462, 1978 1978
2. Haigler HJ, Aghajanian GK: Peripheral serotonin antagonists: failure to antagonize serotonin in brain areas receiving a prominent serotonergic input. J Neural Transm 35:257–273, 1974
3. Kangasniemi P: Biogenic amines and vasoactive peptides in the pathophysiology of migraine. Academic dissertation, University of Turku, Finland, 1975
4. Sicuteri F: Pain syndrome in man following treatment with *p*-chlorophenylalanine. Pharmacol Res Commun 3:401–407, 1971

Epileptic Drivers

In Illinois

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Dr Masland's editorial in the December, 1978, issue (The physician's responsibility for epileptic drivers. Ann Neurol 4:485–486, 1978) incorrectly includes Illinois with nine other states requiring physicians to report patients with epilepsy to the department of motor vehicles.

Illinois law does not require a physician to report a patient with epilepsy—the moral obligation is left up to the individual. It is only when the citizen has been honest in filing with the state and receiving a recommendation by his physician that the latter assumes a responsibility to notify the state of any detrimental change in the patient's condition.

The editorial is to the point, and our agency certainly concurs with Dr Masland's general conclusions.

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In New Mexico

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Contrary to the statement in Dr Masland's excellent editorial on epilepsy and driving, physicians in the state of New Mexico are not required by law to report epileptic drivers to the department of motor vehicles.

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