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DIALYSIS ENCEPHALOPATHY AND ALUMINUM EXPOSURE: AN EPIDEMIOLOGIC ANALYSIS

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Abstract—We identified 55 patients with dialysis encephalopathy in six dialysis centers studied by means of a uniform clinical classification. Dialysis encephalopathy was the direct cause of death in most cases, and the disease appeared to significantly shorten survival. The overall attack rate of dialysis encephalopathy was 4% and varied among dialysis centers from 2.2% to 14.7%. In two centers with adequate data, the attack rate for dialysis encephalopathy rose significantly with increasing cumulative aluminum exposure via dialysate, and the mean cumulative aluminum exposure for patients with the disease was significantly higher than that for all other patients at risk. We further demonstrated that the cumulative level of aluminum tolerated by the patient before onset of symptoms was inversely related to the average aluminum concentration of dialysate water.

INTRODUCTION

Dialysis encephalopathy (DE) was first described in 1972 [1], adding another known complication to the many already associated with chronic renal failure and its treatment. Since that time, additional cases have been described and various etiologies postulated [2, 3]. In this report we present the results of an investigation designed to define better the clinical syndrome, develop and apply a uniform means for classifying it and examine possible contributing factors.

METHODS

Dialysis center selection and population at risk

From a telephone survey of 36 university-related dialysis centers, we selected six centers for investigation on the basis of (1) reported number of cases; (2) geographic proximity, and (3) willingness to participate. The centers studied were located in Denver, Colorado; Salt Lake City, Utah; Chicago, Illinois; Minneapolis, Minnesota; and Alma, Michigan. The population at risk was defined as all renal failure patients undergoing chronic dialysis or transplantation at the selected centers at any time during the specified study period (1968–1976).

Data acquisition

From each center's dialysis logs we obtained the following data in all patients at risk: age at start of treatment, sex, race, cause of renal failure, date of initiation and mode of treatment, and dates of all changes in status of modes of treatment during the study

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period. Additionally, the charts of all patients in the population at risk who died during the study period were reviewed. During the chart review, we recorded all neurologic or psychiatric complications in terms of episodes—typically hospital admissions. The data included those for all neurologic or psychiatric symptoms and signs on admission, the in-hospital course, and the pertinent work-up. When they were available, we reviewed such material as autopsy reports and death notes dealing with the circumstances of the patient's death. The medical staff at each center reviewed information on all their dialysis patients as of December 31, 1976, in order to identify any with dialysis encephalopathy who were still alive at the end of the study period.

At each center, we obtained month-specific data on the configuration of the water treatment systems, dialyzers, and dialysis machines. Although we attempted to obtain municipal water chemistries from the plants supplying each dialysis center, serial determinations of mean composite monthly aluminum concentrations of municipal water treatment plant effluents were available for only Chicago and Minneapolis. Aluminum determinations in Chicago and Minneapolis were by the Eriochrome cyanine R method [4].

Derivation of major treatment modality

We defined treatment modalities for renal replacement therapy as: "incenter" hemodialysis (hemodialysis in the hemodialysis center under study), home hemodialysis, peritoneal dialysis, hemodialysis in a satellite facility, and transplantation. Since the study period covered 9 years and 64% of the patients changed modes of therapy at least once, we attempted to simplify these data by relating risk of dialysis encephalopathy to the major treatment modality (MTM). The MTM is defined as the mode of treatment accounting for the majority of the patient's treatment course from initiation to death, transfer, or the end of the study period.

Case definition

Three different groups of objective findings were used in the case definition:

(1) speech impairment—stuttering, stammering, dysnomiona, hypofluency, mutism;
(2) seizure disorder—generalized tonic–clonic, focal, or multifocal seizures;
(3) motor disturbance—myoclonic jerks, motor apraxia, immobility.

A patient was classified as having dialysis encephalopathy on the basis of having at least two of the above neurologic group findings on any single admission, or signs of speech impairment or motor disturbance on two or more separate admissions. Two or more admissions with seizure disorder alone were insufficient to define a case of dialysis encephalopathy. In applying the classification, an admission was said to include the events precipitating the admission as well as the entire hospital course. If the patient had evidence of speech impairment or motor disturbance and seizures during the same admission, speech impairment and motor disturbances had to clearly antedate the onset of seizures by at least 7 days. Finally, any plausible cause for neurologic problems found during the patient's work-up was sufficient to disqualify that entire episode from consideration in the classification process.

ELECTROENCEPHALOGRAM

In order to evaluate the utility of the electroencephalogram (EEG) in diagnosing the dialysis encephalopathy syndrome, we searched for all EEGs done on all patients whose charts were reviewed; one of us (JRH) reviewed them in random order without knowing the patients' neurologic findings. EEG's were then classified individually as characteristic of dialysis encephalopathy on the basis of a subjective interpretation of the entire tracing, but with special emphasis on the presence or absence of bilateral synchronous spike and wave activity.

Derivation of cumulative aluminum exposure

Enough water quality data were available in Chicago and Minneapolis to justify estimating total cumulative aluminum exposure via the dialysate for each patient at risk. In order to estimate this exposure, we assumed a constant three dialysis treatments per week for the period of incenter hemodialysis and a constant exposure of 125 l. of dialysate water per treatment. The mean monthly composite effluent of the water treatment plant supplying the dialysis center was assumed to approximate the aluminum concentration of the dialysis water unless it was deionized (DI) or treated with reverse osmosis (RO). Either RO or DI was assumed to remove 100% of the aluminum from the dialysate water. If the RO or DI units were known to be malfunctioning, it was assumed that no aluminum was removed from the water while they were being repaired. Consequently, these data can be used to estimate the dialysate aluminum exposure for each week a patient is on dialysis.

In order to compare patients with dialysis encephalopathy to all other patients at risk, each patient's aluminum exposure was summed from the start of "incenter" hemodialysis to the end of treatment. The result is expressed in terms of grams of aluminum per patient per treatment course. The patient's average level of aluminum exposure was derived by dividing the patient's cumulative aluminum exposure by the period in which this exposure occurred and is expressed as micrograms of aluminum per liter of dialysis water.

Statistical methods

We used simple two-dimensional tables to examine possible relationships between attack rates of dialysis encephalopathy and various risk factors, with statistical significance determined with the χ^2 statistic. Since multiple analyses were attempted in exploring the data, statistical significance is assumed only if the p values associated with the test statistic is less than or equal to 0.01. In examining the relative contribution of aluminum exposure and average aluminum concentration of dialysate to the risk of dialysis encephalopathy, we used discriminant analysis with significance determined by Wilks Lamnda [5]. In determining the significance of differences in the means of cumulative aluminum exposures and average level of exposure for patients with and without the syndrome, we used the Mann–Whitney U-test [6]. The significance in differences in mortality rates for patients and controls was determined by the log-rank method [7]. Controls were patients dialyzing in the same center as the case, matched by age at start of hemodialysis and duration of hemodialysis prior to the onset of DE symptoms in the case.

RESULTS

Dialysis encephalopathy cases

Using the case definition derived in this investigation, in the charts we reviewed, we identified 50 deceased patients and 5 patients who were alive as of December 31, 1976, whose neurologic symptomatology in 1976 fit the case definition. Descriptions of patients from centers in Denver, Chicago, and Alma, Michigan have been previously published by investigators at these centers [1, 9, 10, 12, 18]. Table 1 shows the findings used in classifying patients as having or not having cases. Only the data for patients deceased during the study period are included in this Table. The 50 patients with DE had a total of at least 87 episodes of neurologic complications that required hospitalization or were associated with admissions for other reasons. The 429 patients not classified as having dialysis encephalopathy had 10 similar admissions. Patients with DE most frequently had myoclonic jerks and seizure disorder combined; speech impairment alone and myoclonic jerks alone occurred less frequently. Only 12% of the patients with DE had seizure disorder alone, as did 10.7% of the patients not classified as having DE.

TABLE 1. NEUROLOGIC FINDINGS DURING HOSPITAL ADMISSIONS FOR PATIENTS DECEASED DURING THE STUDY PERIOD

	Patients with DE		Patients without DE	
Neurologic findings during admission	Number of patients with 1 or more admissions with neurologic findings*	Percentage of total patients with DE manifesting findings	Number of patients with 1 or more admissions with neurologic findings*	Percentage of total patients without DE with neurologic findings
SP–SE–MJ**	14	28.0	2	0.4
SP–SE	7	14.0	2	0.4
SE–MJ	18	36.0	5	1.1
SP–MJ	8	16.0	5	1.1
SP	12	24.0	22	5.1
SE***	6	12.0	46	10.7
MJ	11	22.0	21	4.9
Total number patients in category	50		429	

*SP—speech impairment, SE—seizure disorder, MJ—myoclonic jerks.
**Note: Admissions with neurologic findings are not exclusive. Patients may present with different complexes of findings on different hospital admissions or similar findings on repeat admissions.
***Note: Multiple admissions with seizures alone are insufficient for DE classification.

Also included in this Table are data for 29 patients whose neurologic findings fit the case definition, except that other possible causes for these findings were documented during the patient's work-up. The findings for 11 patients could be accounted for on the basis of the following metabolic disturbances: 5 patients had hyperglycemia (peak recorded glucose = 280, 406, 412, 660, 800 mg/dl), 1 patient was markedly uremic (BUN = 179, not first time dialysis), 3 patients had hypercalcemia (calcium = 11.4, 12.1, 12.9 mg/dl), 1 patient had hypermagnesemia (Mg = 4.6 mg/dl), and 1 patient had hypophosphatemia (phosphorus = 0.5 mg/dl). Six patients had medical complications excluding them from classification: 3 were septic, 2 had hepatic insufficiently, and 1 had a possible chlorpromazine overdose. The remaining 12 patients had diagnosed neurologic problems causing their symptoms: bacterial or fungal meningitis (3) chronic subdural hematoma (3), intracranial hemorrhage (2), occlusive stroke (1), and cerebrum pseudotumor (1).

Other neurologic findings besides those used to classify these patients were frequently present. 66% of the patients with DE and only 17.2% of those not classified as having DE had concomitant confusional episodes. 44% of patients with DE and only 3.7% of those without had impaired memory, and 30% of the former group and only 9% of the latter had behavioral disturbances. Patients with DE were infrequently noted to have hallucinations and paranoid ideations. Depressed level of consciousness was present in 26% of the patients with DE vs 22.3% of those without DE. Dialysis disequilibrium syndrome, arbitrarily defined as any compatible neurologic condition appearing within 7 days of initial dialysis, was not significantly more common among patients with DE than those without DE (10% patients with DE vs 6.0% patients without DE, $p < 0.25$).

The 50 DE patients received various degrees of antemortem workup. Three types of neurodiagnostic procedures were recorded: one or more EEG's, one or more neuroradiologic procedures to rule out mass lesions (isotope brain scan, computerized axial tomography, or carotid angiogram), and one or more cerebrospinal fluid examination to rule out central nervous system infection. Only those procedures performed after the onset of findings compatible with dialysis encephalopathy were considered. Additionally 26 of the 50 patients with DE had postmortem examinations. Of 25 patients who had one or more of all three types of procedures, 13 had postmortem central nervous system examinations.

Of 17 patients who had some combination of two of these three types of diagnostic procedures, 10 had postmortem examinations. Of 7 patients who had only one of the three types of procedures, 4 had postmortem examinations. One patient who had no neurodiagnostic procedures had a postmortem examination. None of the abnormalities found at postmortem were sufficient to account for the patients' neurological conditions. All antemortem diagnostic procedures were normal or nondiagnostic so that the cause of the patient's neurologic condition remained idiopathic. All EEGs obtained after the onset of symptoms were originally read as abnormal, although in only two centers whose neurologists retrospectively reviewed the EEGs, were any read as diagnostic of dialysis encephalopathy.

Since many of these EEGs were interpreted before the dialysis encephalopathy syndrome was generally recognized, we attempted to have all EEGs on dialysis patients at these centers reinterpreted. We obtained 173 electroencephalograms on 77 patients for reinterpretation: 26 of these 77 were classified as having DE on the basis of the clinical classification.

Of the 97 tracings done on these 26 patients with clinical DE, 82 (85%) showed bilateral spike and wave activity characteristic of DE, and 20 of the patients (77%) had one or more EEGs diagnostic of DE. Six of the 26 patients with DE had 15 tracings, none of which was thought to be diagnostic of DE. These 6 patients had similar clinical syndromes to those with EEG confirmation of DE.

We reinterpreted 76 EEG records for 51 patients not classified clinically as having DE. Only one patient's tracing had bilateral spike and wave activity once during photic stimulation.

We located and reviewed notes pertaining to the circumstances of the patient's death in 42 of the 50 cases. In 11 of the 42, dialysis was discontinued after the patients' mental status deteriorated, another 11 died with uncontrolled seizures, 4 patients died of diagnosed cardiovascular insults, and another 4 of sudden death. 6 others died of infectious complications directly attributable to a depressed level of consciousness, and the others died of one or more complications unrelated to their neurologic condition. Discontinuance of dialysis because of abnormal mental status was more common for patients with than without DE (26.2% vs 5.3%, $p < 0.001$) as was status seizure activity (26.3% vs 10.5%). Sudden death, death resulting from diagnosed cardiovascular insults, and infection were no more frequent for patients with DE than those without.

Not included in the above analysis of deceased patients are 5 patients still alive on December 31, 1976, whose conditions in 1976 met the case definition. In order to describe patient survival after the onset of symptoms of DE, these 5 patients are included in the case group. Figure 1 gives patient survival after the onset of findings compatible with dialysis encephalopathy. Patients with DE had a significantly shortened survival. Although 90% of the patients with DE died within 12 months of the onset of symptoms, 5 patients survived longer than 1 yr.

Analysis of risk factors

Fifty-five of 1380 patients at risk had neurologic complications sufficient to classify them as having DE, reflecting a gross attack rate of 4.0%. The case attack rate among all patients at risk was not found to be significantly related to the patient's age at initiation of treatment, sex, or etiology of renal failure. Race was significantly related to the attack rate for DE—caucasians 42/1095 (3.8%) and non-caucasians (13/99 (13.1%), $p < 0.001$. However, more than 50% of the non-caucasians were treated in a single center that had a high attack rate for DE. Exclusive of this center, non-caucasians had no higher attack rate than caucasians.

Major treatment modality

When we classified patients at risk by their major treatment modality, the case attack rate for hemodialysis-center patients was 5.9%, significantly higher than the 2.6% for home hemodialysis patients (Table 2). Although there are significant differences in attack

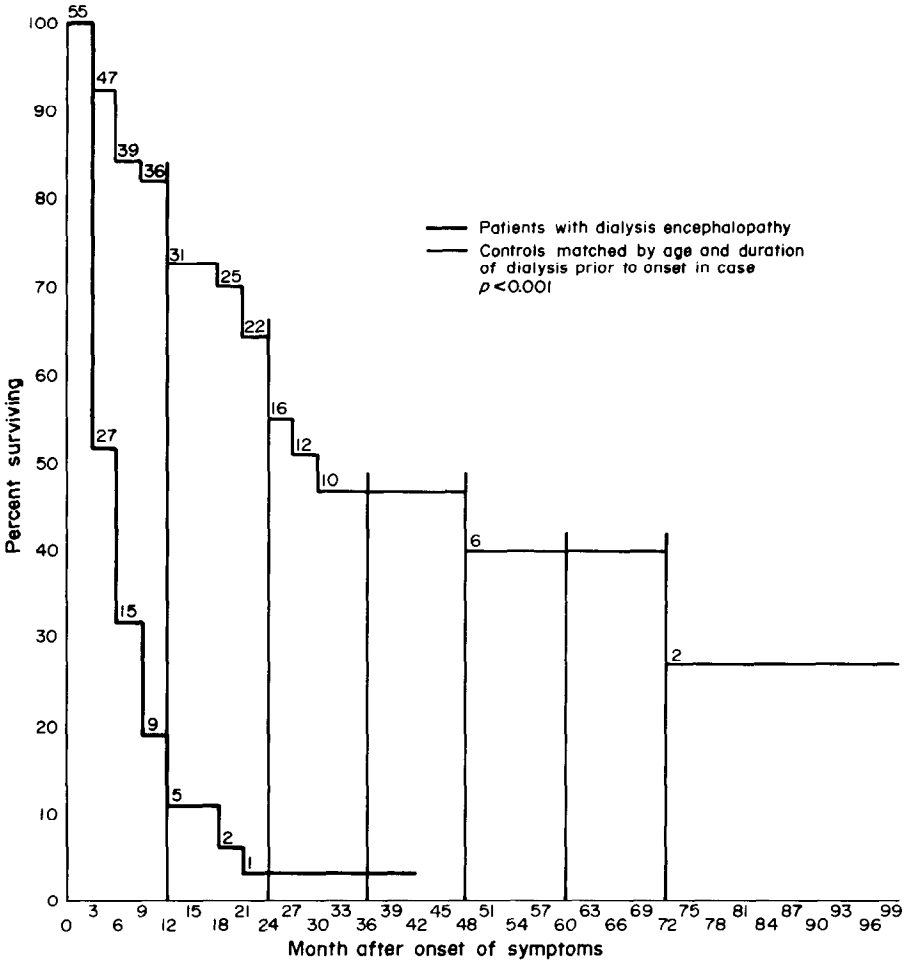

FIG. 1. Cumulative survival of patients with DE after onset of symptoms compared with matched controls.

rates associated with various modes of treatment, this method of classification does not completely describe the relationships between the treatment modalities and the risk of DE. Of the 9 patients with major treatment modalities of home hemodialysis or transplantation, 6 had symptom onset while dialyzing "incenter". Of the remaining three, two were satellite hemodialysis patients, and one had onset of symptoms after 13 months of

TABLE 2. DIALYSIS ENCEPHALOPATHY ATTACK RATES BY THE CLASSIFICATION OF THE MAJOR TREATMENT MODALITY

Major treatment modality	Number of patients with DE	Number of patients at risk	Attack rate (%)*	Number of patients/ cases at risk in treatment modality	Incidence/ per 100 patient years**
Incenter hemodialysis	46	779	5.9	1137.6	4.0
Home hemodialysis	6	226	2.6	613.5	1.0
Transplantation	3	171	1.7	697.4	0.4
Satellite hemodialysis	0	195	0	350.8	0
Peritoneal dialysis	0	8	0	3.2	0
Total	55	1380	4.0	2802.5	2.0

*$\chi^2 = 48.2$, 4 *df*, $p < 0.0001$; **$\chi^2 = 64.1$, 4 *df*, $p < 0.0001$.

TABLE 3. ATTACK RATE OF DIALYSIS ENCEPHALOPATHY AMONG INCENTER HEMODIALYSIS PATIENTS BY DIALYSIS CENTER

Dialysis center	Number of patients with DE	Number of patients at risk	Attack rate (%)	Number of "incenter" years at risk	Incidence per 100 patients years at risk
1	9	61	14.7	164.1	5.5
2	2	89	2.2	113.8	1.8
3	2	78	2.6	97.0	2.1
4	13	129	10.1	147.3	8.8
5	15	356	4.2	557.7	2.6
6	5	50	10.0	37.7	13.24
Total	46	763	6.0	1137.6	4.0

$\chi^2 = 19.4$, 5 *df*, $p < 0.005$; $\chi^2 = 23.4$, 5 *df*, $p < 0.001$.

peritoneal dialysis. Also, although "incenter" hemodialysis was the MTM with the highest attack rate, this was not the case in every center. Center No. 2 had a 2.2% attack rate "incenter", whereas among home hemodialysis patients the attack rate was 3.6%.

Intercenter differences

Among patients whose MTM was "incenter" hemodialysis, we found that the case attack rate varied markedly by center (Table 3). Centers No. 1, No. 4 and No. 6 all had attack rates over 10%, whereas Centers No. 2, No. 3 and No. 5 had attack rates for DE of less than 5%. In the three centers with attack rates over 10%, we found significant and consistent increase of attack rate with increasing duration of "incenter" hemodialysis (Table 4).

In two of the three centers with high attack rates and in one center with a low attack rate, there was significant clustering in the occurrence of DE during the period 1974–1976 (30 of the 33 (91%) DE cases in these centers) which reflected a real increase in the incidence over this period. In one center with a high attack rate, the cases occurred approximately uniformly during the entire study period. In the two remaining centers with low attack rates, the occurrence of DE appeared to be sporadic without suggestion of clustering.

All three centers with high attack rates used municipal water treated by alum coagulation and had "incenter" water treatment systems in which neither DI nor RO was used for most of the study period. Of the three centers with attack rates less than 5%, Center

TABLE 4. ATTACK RATES OF DIALYSIS ENCEPHALOPATHY AMONG INCENTER HEMODIALYSIS PATIENTS BY DURATION OF INCENTER HEMODIALYSIS

Duration of hemodialysis	Centers numbers 1, 4, 6 only Number of patients with DE	Number at risk	Attack rate (%)
7 days–6 months	3	75	4.0
6–12 months	3	41	7.3
12–24 months	7	64	10.9
24+ months	14	60	23.3
Total	27	240	11.2

$\chi^2 = 13.3$, 3 *df*, $p < 0.01$.

*Total duration of incenter hemodialysis from initiation of treatment to diagnosis (cases), death, transfer or end of study period.

No. 2 used water from deep wells which was not alum coagulated; this center used only softening as a treatment prior to dialysis. Center No. 3 used water which was exclusively treated by municipal alum coagulation but used the treatment systems of DI and RO in series for the entire study period. Center No. 5 used municipal water which was alum treated and deionization to produce water for dialysis until September 1974; at that time recurrent technical difficulties with their water treatment equipment resulted in more than 50% of their dialysis water being treated with neither DI nor RO. 13 of the 15 "incenter" cases occurred during this period of technical difficulties with water treatment systems.

CUMULATIVE ALUMINUM EXPOSURE VIA DIALYSIS WATER

We next examined the importance of aluminum exposure via the dialysis water as indicated by the cumulative aluminum exposure and the average level of aluminum exposure via dialysis water in Centers No. 4 and No. 5, the only two centers with sufficient data to justify such an approach. Among patients with the DE syndrome, the cumulative and the average aluminum exposures did not vary significantly by center, so the data for the two centers are combined in the analysis.

Of all factors assessed in this investigation, the attack rate of DE was most strongly related to the cumulative dialysate aluminum exposure (Table 5). The attack rate was less than 0.7% among 316 patients with less than 4.0 g of aluminum exposure, and rose thereafter to 18.6% for patients with more than 12.0 g of exposure.

Although the relationship between the DE attack rate and the cumulative aluminum exposure is strong and statistically significant, we were unable to determine a specific level of cumulative aluminum exposure which would clearly differentiate patients with DE from those who were exposed but did not develop the syndrome. The mean cumulative aluminum exposure for patients with DE was 10.23 g vs 3.67 g for the comparison groups ($p < 0.002$). However, 60 (7.6%) of patients in the comparison group had cumulative aluminum exposures higher than 10.2 g, and two or 7.1% of persons with DE had cumulative aluminum exposures less than the 3.6 g mean of the comparison group.

In an attempt to identify other factors which would better differentiate patients with DE and controls, we examined age of the patient, duration of "incenter" hemodialysis, and the average aluminum concentration of the dialysate water to which the patient was exposed by step-by-step discriminant analysis. Once cumulative aluminum exposure was considered, neither age nor duration of "incenter" hemodialysis was found to significantly relate to the occurrence of DE. However, the average aluminum concentration to which the patient was exposed was significantly related to the occurrence of the disease syndrome ($p < 0.008$) even after cumulative aluminum exposure was considered.

TABLE 5. ATTACK RATES OF DIALYSIS ENCEPHALOPATHY BY ESTIMATED CUMULATIVE ALUMINUM EXPOSURE FROM DIALYSATE, CENTERS 4 AND 5, ALL HEMODIALYSIS-CENTER PATIENTS AT RISK

Cumulative aluminum exposure (g)	Number of patients with DE	Number of patients at risk	Attack rate (%)
0	1	137	0.7
0.01–4.0	1	179	0.5
4.01–8.0	8	77	10.3
8.01–12.0	7	40	17.5
12.01+	11	59	18.6
Total	28	492	5.7

$\chi^2 = 47.1$, 4 *df*, $p < 0.001$.

*Estimated cumulative aluminum exposure from initiation of hemodialysis to diagnosis (cases), death, transfer, or end of study period.

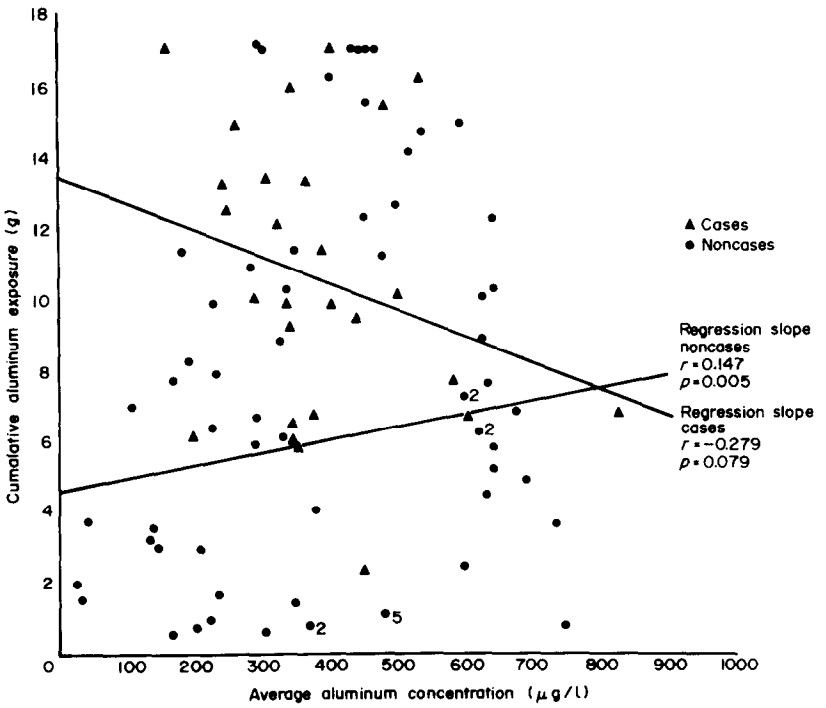

FIG. 2. Patients with and without dialysis encephalopathy plotted by cumulative aluminum exposure and average aluminum concentration of dialysate.

We further examined the relationship between cumulative aluminum exposure, average aluminum concentration of dialysate, and the occurrence of DE by plotting the date for DE cases and for a random 25% sample of the comparison group with respect to these two factors (Fig. 2). Among all patients cumulative aluminum exposure and average aluminum concentration are positively correlated ($r = 0.29$, $p < 0.001$). For the comparison group alone, this positive correlation remains ($r = 0.47$, $p < 0.002$). However, for persons with DE, cumulative aluminum exposure is inversely related to average dialysate aluminum concentration ($r = -0.27$, $p = 0.07$), and significantly so when compared to the data for the control group. This indicates that the higher the aluminum concentration to which the patient is exposed, the less cumulative aluminum is tolerated before death.

DISCUSSION

In this report we applied a uniform case definition of DE and established marked and significant differences in attack rates for the six centers studied and for the various modes of treatment. These centers were selected because of reported cases and, therefore, even greater variation in attack rates can be expected for centers that recognize cases and those in which the syndrome has not been identified. We do not conclude from these data that "incenter" hemodialysis *per se* is generally associated with the highest attack rate of DE, but rather that there is a real and significant variation in attack rate with the site of dialysis—or more specifically, with the origin of the patient's dialysis water and variations in the methods of dialysis water treatment.

Previous reports have implicated aluminum in dialysis water in the etiology of the syndrome. Flendrig reported on an outbreak of DE and postulated that the dialysate water was contaminated with aluminum [8]. Dunea correlated the occurrence of cases in Chicago with an elevated aluminum content in the municipal water supply [9], and Rosas *et al.* described clustering of cases in a period when their dialysis center used no DI and gave evidence that their dialysis aluminum concentration was probably in the range of 600 μg/l. [10]. Utilizing an epidemiologic approach, Platts and her associates showed that DE occurred significantly more frequently in areas with higher water

aluminum concentrations than in those without [11]. We take the association with aluminum in dialysate water a step further and show that the risk of developing DE is significantly related to cumulative aluminum exposure via the dialysate water. Since we used precise days of initiation and cessation of treatment and monthly composite mean aluminum concentration, we believe that these data are of sufficient accuracy to justify the method of derivation of cumulative aluminum exposure and its interpretation. Alfrey's report of a higher aluminum concentration in gray matter of dialysis patients with DE than of those with no evidence of DE [12] leads to the question of whether aluminum was indeed the toxic agent or whether its presence was simply incidental to alterations in the blood-brain-barrier observed in uremic patients [13]. However, one must take into consideration that: (1) patients with DE have a significantly higher aluminum content of central nervous system (CNS) gray matter than dialysis patients without the syndrome, (2) there is real variation in attack rates related to site of dialysis, and (3) cumulative aluminum exposure for patients with cases is significantly higher than for patients without the syndrome. We believe that the above observations support the theory that aluminum absorption from dialysate water plays a major role in causing DE.

If the significant association between cumulative exposure to waterborne aluminum and DE shown in this study is not a demonstration of cause and effect, we must conclude that the aluminum is acting as a highly correlated marker for the true cause. Such a conclusion would suggest that we look for another waterborne substance which has not been routinely measured and recorded but which varies directly with the aluminum levels used in our analysis. In both Minneapolis and Chicago the levels of aluminum in treated water were higher than in raw water, suggesting that the source of the aluminum was the filter alum, or aluminum sulfate, used in water treatment. The aluminum may be present in treated water as a soluble salt, a colloid, or an insoluble compound [4]. The chemical form and level of aluminum in treated water result from a process of chemical coagulation that involves complex equilibria among a number of variables including the colloids, the water, and the coagulating chemical [14]. Less complex factors of sedimentations and filtration may also come into play. Because of this overall complexity we could not identify another substance, nor do we think it likely that the concentration of another substance varies directly with that of aluminum in the treated water. (We also considered the possibility that some contaminant of filter alum might be present in treated water in rough proportion to the level of aluminum. However, commercial alum is reported to be 99.5% pure [15], thereby greatly reducing the possibility that even trace amounts of other impurities would be present in a finished water containing only microgram quantities of aluminum per liter.

Although we present data implicating aluminum absorption from dialysate water in the etiology of DE, we do not conclude that there is a simple relationship between the amount of aluminum to which the patient is exposed and the occurrence of the clinical manifestations of the disease. The data presented in Fig. 2 suggest that aluminum exposure is a significant factor related to the clinical manifestations of the syndrome, but that even accounting for cumulative aluminum exposure and the average level of exposure, there is considerable overlap for patients with and without the syndrome. When these data are examined with regard to cumulative exposure and the average level of exposure of patients with the syndrome, an inverse relationship is suggested between the two (Fig. 2). In other words, the higher the concentration to which the patient is exposed, the lower the cumulative aluminum exposure tolerated before death. This result is consistent with data presented by Ward [16] relating a lower concentration of aluminum in municipal water to a longer dialysis course before symptoms of DE developed among patients reported on in Newcastle, England. Kaehny's [17] observations of virtually no minimum threshold for aluminum absorption from dialysate water would indicate that an observed difference in attack rate as related to average level of exposure would not depend on a threshold of absorption but more likely on differences in distribution of absorbed aluminum, on differences in CNS tolerance of deposited aluminum, or both. Ward [16] has postulated that a lower aluminum exposure for a longer period results in

significant bone aluminum deposition and metabolic bone disease before symptoms of DE occur, whereas patients exposed to higher dose manifest CNS toxicity without evidence of significant bone disease. We did record evidence of pathologic fractures among patients with DE, but found no differences in the frequency of pathologic fractures among DE patients and other patients whose charts were reviewed.

The clinical classification of DE used in the investigation was designed to be used in a retrospective chart review. As such, the emphasis was on findings that would typically necessitate an admission for diagnostic workup and objective documentation on the patient's chart. The emphasis was on specifically, not sensitivity, and since intercenter comparisons were anticipated, on uniformity of criteria for classification. Consequently, we used three types of neurologic complications found to be the most frequently and objectively documented in the patient's chart. Although impaired memory and behavioral disturbances were frequently present, they were typically incompletely described. Furthermore, inclusion of impaired memory as a criterion in the clinical classification did not seem to increase the sensitivity of the classification, and did lead to classifying patients as having DE when their neurologic conditions were probably from other causes.

We used seizure and motor disturbance manifested by myoclonic jerks as two different neurologic findings even though they may both be manifestations of the same underlying neurophysiologic disturbance. Although this may introduce an element of nonspecificity into the clinical classification, only 6 of the 55 patients were classified as having DE on the basis of seizures and motor disturbance, and 5 of the 6 had the myoclonic jerks for more than a month before having seizures.

In this investigation we chose not to use the EEG findings as a basis for the diagnosis of DE, but rather to compare the syndrome as defined clinically with the EEG interpretation. The reasons for this were twofold. First, the original EEG interpretation seldom mentioned the possibility of DE since the existence of the DE syndrome was not widely appreciated during much of the study period. Consequently, in order to be usable, the EEG had to be re-interpreted, and many could not be located for re-reading. Secondly, although the EEG has been reported to be distinctive in the DE syndrome [1, 2, 10, 18–20], its specificity has not been sufficiently evaluated. This is the first report comparing the EEG interpretation to a uniform clinical classification. These results indicate that a properly interpreted EEG is highly suggestive of (quite specific) the clinical syndrome of DE, but that the absence of the characteristic bilateral synchronous spike and wave pattern on one tracing does not rule out DE. Although the sensitivity of the EEG in the diagnosis of DE might be increased with more frequent tracings, or EEGs obtained during symptomatic periods or after hemodialysis, these results suggest that some patients with otherwise identical clinical syndromes do not have these characteristic EEG changes.

The mortality rate for patients with DE described in this investigation approached 50% at 3 months, 80% at 8 months, and 90% at 1 yr after onset of overt symptoms (Fig. 1). Although dialysis patients are at risk of a number of diseases that may significantly shorten survival, it is apparent from these results that survival of patients with DE is significantly curtailed relative to that of appropriately matched controls. However, most of these cases occurred before the widespread recognition of the DE syndrome, and in no instances were effective measures taken to eliminate possible aluminum exposure via dialysate water or oral antacids. Consequently, these results should be assumed to represent mortality for patients with DE who continue to be exposed to aluminum. There have been several reports of remissions and significant symptomatic improvement among patients with DE when oral antacids were discontinued and the patients were dialyzed with aluminum-free water [21, 22]. Consequently, survival of patients with DE after the onset of overt symptoms may not be as curtailed as was observed in this investigation if the offending agent is identified and eliminated early in the patient's course.

In the six dialysis centers participating in this study, there appeared to be two distinct epidemiologic patterns of disease occurrence: sporadically occurring cases and cases

occurring in an outbreak or epidemic. The outbreak or epidemic pattern was characterized by high attack rate, a positive relationship between duration of dialysis and the attack rate, and a relationship to cumulative aluminum exposure via dialysis water. However, nine cases occurred in centers postulated to have a low aluminum exposure via dialysate water. Although the clinical findings in these cases were similar to that of the outbreak pattern of diseases occurrence, these patients may have had a different clinical syndrome, or if the same syndrome, a different route of exposure. The simplest explanation for the sporadic cases occurring in centers with low postulated aluminum concentrations is simply that the water treatment system did not remove all of the incoming aluminum, and a lower aluminum concentration in dialysis water resulted in a lower attack rate. Since there were no dialysate aluminum determinations made in these centers during the study period, this explanation cannot be refuted.

An alternative explanation is that the patients with DE in centers with few and sporadically occurring cases had other neurologic conditions similar to DE. In this regard 4 of the 6 patients who were clinically classified as having DE and whose EEGs were reviewed but found not to be diagnostic of DE were dialyzed in the two centers with the lowest attack rates. It is therefore possible that the clinical pattern of DE reflects more than one etiology and that other agents may cause similar syndromes.

A third interpretation is that the same causative factor may be involved but by a different route of exposure. In this investigation we were unable to determine retrospectively the amount of aluminum hydroxide administered to patients; however, all centers routinely used aluminum hydroxide gel in what seemed to be equivalent amounts. Consequently, it is doubtful that the epidemic pattern of dialysis could have been related to oral antacid use, even if these data were available. An apparent lack of association with orally administered antacids notwithstanding, Berlyne [23], Thurston [24] and Elliott [25], reported significant gastrointestinal absorption of aluminum for renal failure patients on hemodialysis, and Clarkston *et al.* [26] demonstrated that uremic patients had a positive aluminum balance after receiving aluminum hydroxide gels. If aluminum absorption from dialysate water is indeed neurotoxic, it is difficult to conclude that gastrointestinal absorption of aluminum among patients with renal failure is risk free. The observed difference in risk of parenteral exposure and oral exposure may relate to the chemical state of the aluminum absorbed, the peak rate of exposure as it may influence the body's ability to distribute aluminum, or to patient factors not yet assessed.

In conclusion we believe that DE is a distinct syndrome that is definable with adequate specificity; that, if no intervention is taken, it significantly shortens survival and is a direct cause of death in most cases. Further, the centers had significantly different attack rates and the difference can be explained by aluminum exposure in dialysate water. In two centers with adequate data we showed that patients with DE had a significantly greater cumulative aluminum exposure than did those without evidence of the syndrome and that the mean level of aluminum to which the patient was exposed was inversely related to the cumulative amount tolerated. We believe that these data are sufficiently convincing to recommend routine evaluation of hemodialysis water for aluminum concentration and adoption of 10 μg/l. maximum allowable aluminum concentration currently being recommended by the Association for the Advancement of Medical Instrumentation [27]. Although we believe that these data implicating aluminum absorbed from the dialysate are convincing, we suggest that there are other as-yet unidentified factors involved in the pathogenesis of the syndrome. Finally, we present data which suggest that there may be more than one epidemiologic presentation of the DE syndrome and that aluminum toxicity from dialysate absorption is difficult to implicate for patients with sporadic cases whose symptoms appear soon after they begin to have hemodialysis. Although aluminum absorption from dialysate has been clearly implicated in the outbreak pattern of this disease, the role of aluminum-containing antacids in the DE syndrome is not yet understood.

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