REVIEW ARTICLE

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Dialysis Dementia: A Review

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ABSTRACT

Dialysis dementia is a rare syndrome that was first described by Alfrey *et al.* in 1972. This disease is an entity nowadays, however, in Europe, between 1976 and 1977; the prevalence of dialysis dementia was 600 per 100,000 dialysis patients, although there was a wide variation between centers. The clinical picture is characterized by an insidious onset of altered behaviour, dementia, speech disturbance, myoclonus, tremor, asterixis and convulsions. In this manuscript, an interesting case of dialysis dementia and review topic is presented.

Keywords

Dialysis dementia, Encephalopathy, Rapidly progressive dementia

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INTRODUCTION

Dialysis dementia is a rare syndrome with several other nomenclatures in literature including dialysis encephalopathy, progressive myoclonic dialysis encephalopathy, and hemodialysis encephalopathy. It was first clearly documented by Alfrey *et al.* in 1972 (Fig. 1)[1]. He described a distinctive, progressive, usually fatal encephalopathy which occurs in patients who are chronically dialyzed for periods that exceed three year[1]. Epidemic, sporadic, and childhood forms of dialysis dementia have been reported (Table 1).

FIGURE 1.
Allen C Alfrey (1932 - 2008).

TABLE 1.
Characteristics of Subgroups of Dialysis dementia.

Sporadic Endemic
No clear relation to aluminum intake
Worldwide distribution
No known therapy
Endemic
Often related to aluminum concentration in dialysis water
Geographic clusters
Treatment of dialysis water
Likely associated trace metal accumulation
Childhood
No clear relation to intake
May be secondary to effects of uremia on immature brain

CASE STUDY

A 59-year-old female was admitted with 2 years history of progressive speech difficulties and seizures. She developed slurring of speech, difficulty understanding others and doing activities of daily living for at least a year and a half prior to the current admission. She also developed slowly progressive cognitive decline which had been first noted four years back. Her seizures were generalized tonic clonic type (GTC) treated with phenytoin and clobazam. Family have noticed myoclonus and intermittent episodes of speech arrest, lasting up to 15 minutes, both of which continued to get worse over time.

The patient developed renal failure 20 years back secondary to polycystic kidney disease and was started on hemodialysis since that time. In addition, she was also known to have hypertension, ischemic heart disease, congestive heart failure, secondary hyperparathyroidism, renal osteodystrophy, anemia and chronic back pain. Past surgical history was remarkable for renal transplant rejection after bilateral nephrectomies, total parathyroidectomy and gastric carcinoma with Bilroth-I anastomosis. Her medications included domperidone 150 mg daily, epanutin 300 mg daily, losartan 50 mg daily, clobazam 15 mg daily, omeprazole 20 mg daily, folic acid 5 mg daily and erythropietin 10,000 units weekly.

Her physical examination showed BP 137/80 mmHg, temperature 36.7C°, heart rate (HR) 100 beat per minute, respiratory rate (RR) 14/minute and O2 saturation 99% on room air. No palpable lymphadenopathy or thyromegaly was present. Systemic examination of chest, heart, abdomen, skin and MSK was unremarkable. No pedal edema or raised JVP.

Neurologically, she was awake and initially mute, but later-on she started to say one or two words followed by incomprehensible sounds. She appeared to comprehend by answering yes and no to questions. She was able to say, name and repeat with some errors. She had severe dysarthria, apraxia and agnosia. Intermittently, she became very tremulous. No cranial nerve abnormalities were detected. She had a normal tone and power throughout. Deep tendon reflexes were 1 in the ankles and 2 elsewhere. Plantar responses were flexors. Sensory examination was unreliable. Balance and coordination examination was limited but seemed normal. Gait was not assessed.

She had a normal electrolytes (including calcium and magnesium), glucose, liver function tests and troponin levels. Urea was 13.6, creatinine 604, HCO3 29, WBC 3.2, hemoglobin 100, HCT 0.30, MCV 96.2, RDW 17.3, platelets 119000, INR 1.4 and PTT 34. Epanutin level was therapeutic and aluminum levels at 5485 (0-371 nmol/L). CT-head and gallium scans were normal. EEG showed severe encephalopathy with generalized epileptiform activity displaying no overt clinical seizure activity (Fig. 2). The CSF was normal. The final diagnosis was dialysis dementia syndrome, and she was started on desferoxamine due to elevated aluminum levels. The differential diagnosis includes other causes of dementia such as metabolic

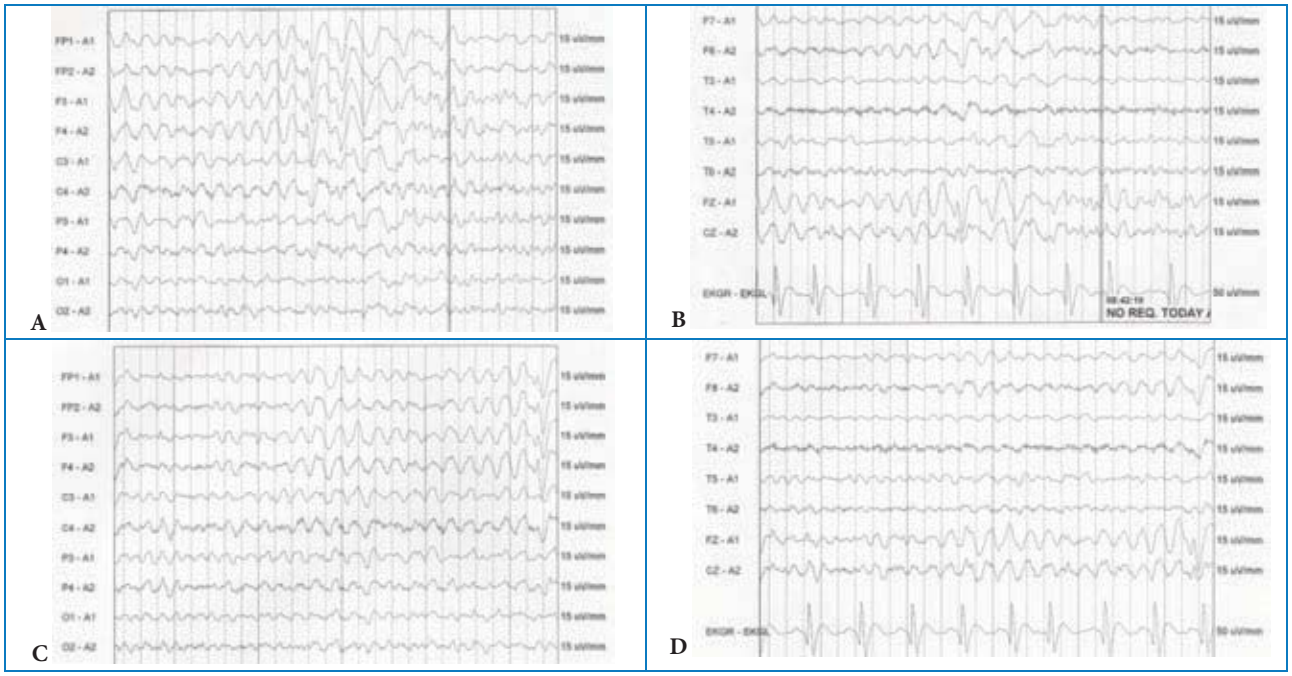

FIGURE 2 (A-D).
EEG of the case presented, show severe encephalopathy with generalized epileptiform activity.

TABLE 2.
Types of encephalopathy associated with renal disease.

Encephalopathy	Mechanism	Prevention and Treatment
Uremic encephalopathy	Accumolation of >100 neurotoxins including urea, purines, organic phosphates, oxalate, ascorbic acid, guanidosuccinic acid, hippuric acid, peptides and parathyroid hormone	Dialysis and/or kidney transplantation
Wernicke's encephalopathy	Thiamine deficiency	Thiamine supplementation
Electrolyte derangement	Hypercalcimic, hypermagnisimia, hypophosphatimia, hyponatrimia, osmolality changes	Correction of electrolytes imbalance
Dialysis disequilibrium syndrome	"Reverse urea" hypothesis causing cerebral edema versus 'idiogenic osmole" hypothesis.	Mannitol, addition of high glucose dialysate and mannitol or the substitution of sodium bicarbonate for sodium lactate in the dialysate
Hypertensiveencephalopathy/ reversible encephalopathy syndrome	Uncontrolled high blood pressure and autoregulation failure	Antihypertensive treatment
Dialysis dementia syndrome	Aluminum toxicity	Use of aluminum free dialysate, avoid aluminum-based phosphate binders, administration of deferoxamine.
Rejection encephalopathy	Cytokine production	Treatment of rejection
Drug-induced encephalopathy	Drugs metabolized or excreted by kidneys, immunosuppressive drugs.	Drug reduction or cessation

encephalopathy and structural lesions. Structural organic causes include subdural hematoma, normal-pressure hydrocephalus, hypertensive encephalopathy, multi-infarct dementia and stroke (Table 2).

She continued to have recurrent simple partial seizures with speech arrest and myoclonus; valproic acid was added with no significant decline in seizure frequency or severity. The patient continued to have bacteremia in spite of appropriate doses of several broad spectrum antibiotics. The patient's family elected to withdraw care and the woman pass away a year later.

BEGINNINGS

In 1972, a patient with renal failure on dialysis for many years at Cook County Hospital in Chicago began to have episodes of abnormal behavior, difficulty speaking, seizures and unconsciousness. At the beginning, these episodes would last several hours to days and she would recover. She was a depressed woman, her husband in prison, and she had numerous children to care for. Initially, her symptoms were thought to be functional; but in time, these episodes became more prolonged and eventually, she went into a terminal coma. Retrospectively, this case was a case of dialysis dementia and the diagnosis came after this syndrome has been described. Our case had a similar presentation but with a prolong course and several types of seizures.

EPIDEMIOLOGY

Although DCC is considered rare nowadays; however in Europe and between 1976 and 1977, the prevalence was 600 per 100,000 dialysis patients with a wide variation between centers[2]. In several large series, the mean age of affected patients was 50 years, with an age range of 21 to 68. In these studies, the mean onset of symptoms after hemodialysis had started was 35 months with range 0.5–112 months [3]. Since then, there has been a decrease in the incidence of this fatal progressive encephalopathy in which death usually occurred within 6 to 9 months from the onset of symptoms in most untreated cases[3,4]. Sporadic cases of dialysis dementia can still occur due to the use of aluminum hydroxide medication[5]. Table 3 shows the important neurological complications related to renal failure and dialysis.

PATHOPHYSIOLOGY

As mentioned before, high incidence of dialysis dementia cases occur in areas having aluminum-contaminated. This original observation has lead to enhancement of water-purification measures and elimination of aluminum in the dialysate. These maneuvers have caused a substantial reduction in the incidence of the disorder. Dialysis dementia results from aluminum accumulation in certain sites in the brain. Some early studies revealed an increase in brain aluminum content of 11-fold higher in dialysis dementia patients, compared to healthy persons, and 3-to-4 fold higher to those on hemodialysis but without dementia[6,7]. Hyperparathyroidism caused by phosphate retention in the course of renal failure may eventually lead to a reduction of the serum levels of phosphates. This condition is usually treated using phosphate binders. The use of non-mineral-containing phosphate binders and other binders as calcium carbonate and/or calcium acetate instead of aluminum-containing phosphate binders show substantial impact on the reduction of brain's aluminum content. The course of dialysis dementia has not been affected by parathyroidectomy, in spite the fact that, parathyroid hormone increases the gut absorption of aluminum. Disruption of basic cell processes like inositol phosphate system, calcium regulation, as well as facilitation of oxidative injury may occur as a consequence of toxicity with aluminum[7,8]. Patients with dialysis dementia have spongiform changes in the outer 3 cortical layers, with elevated aluminum levels in the cerebral cortex. In a previous study, frontal cortex of dialysis patients, treated with aluminum, showed post-mortem changes in tau-protein processing like those seen in Alzheimer's disease

TABLE 3.
Important neurological complications related to renal failure and dialysis.

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with no signs of dialysis dementia[7,9,10]. Other changes include neuronal loss, accumulation of lipofuscinpigment and neurofibrillary degeneration in the motor cortex and in the red, dentate and olivary nuclei.

CLINICAL FEATURES

Symptom usually begin with a mild cortical speech difficulty characterized by a stammering, hesitancy of speech that eventually progresses to speech arrest, dysarthria and expressive aphasia[10,11]. Speech disorder is worse during and immediately after dialysis and initially may occur only at these times. Other manifestations include myoclonus, tremor, asterixis and seizures. Dementia, auditory or visual hallucinations and delusional thinking become apparent as the disorder advances[10]. Neurological focal abnormalities are occasionally present (Fig. 3). The patient becomes, afterwards, increasingly demented and symptoms may eventually fail to resolve.

EEG

The EEG has become abnormal in all patients with DDS, and it is the most prominent laboratory test abnormality[12]. Abnormalities in EEG may precede clinically overt symptoms up to six months. Initially, EEG develops increasing amounts of, at first, theta, and then delta activities, gradually increasing in amplitude and often occurring in a periodic fashion, as in many metabolic encephalopathies. Bilaterally synchronous and asynchronous slow-wave discharges in the 2-4 Hz range may occur[12-14]. The high voltage paroxysmal nature of the slow-wave discharges in the theta and delta range, as well as the bursts of sharp, spiking, and slow waves, occasionally have a predominance frontocentrally[13]. Occasionally, these paroxysmal components may be precipitated by photic stimulation. In the early stage of the disease, the EEG may show a peculiar intermittent worsening, especially during and after dialysis; this may also be associated with symptomatic worsening as well[12,14]. The clinical and EEG changes tend to improve somewhat before the next dialysis.

TREATMENT

Diazepam is helpful, in early stages, treating myoclonus, seizures and also improving speech. This therapeutic effect became less effective later. The natural history of the disorder, with a fatal end within a year of onset of symptoms, has not been altered neither by increased dialysis time nor by renal transplantation[15]. Deferoxamine, an aluminum chelator can reverse acute encephalopathy, osteomalacia and anemia associated with aluminum overload. Side effects like visual and auditory toxicity as well as paradoxical neurological deterioration may occur because of acute aluminum toxicity, presumably due to rapid mobilization of stored aluminum. The need for treatment is unclear in patients with an asymptomatic increase in aluminum levels. Rapidly progressive and fatal systemic rhinocerebral mucormycosis may occur in some cases[16]. Animal studies suggested a role of deferoxamine in enhancing causative organism pathogenicity and compromising the amphotericin therapeutic effect[17]. However, deferoxamine is still the main line of treatment for established dialysis dementia and many cases have been stabilized or improved by deferoxamine. Several protocols have been proposed for the administration of deferoxamine guided by baseline serum aluminum levels (normal; 6 ± 3 µg/L)[11,18]. In clinically-suspected aluminum toxicity or in aluminum overload (60 to 200 µg/L); a low-dose deferoxamine test is performed by administering 5 mg/kg 1 hour before the end of dialysis. In symptomatic patients, deferoxamine is given in a single dose of 30 to 40 mg/kg,in the last hour of a dialysis, and once weekly. Deferoxamine is not given to patients with plasma aluminum levels exceeding 120 µg/L to avoid neurotoxicity, until aluminum level is first

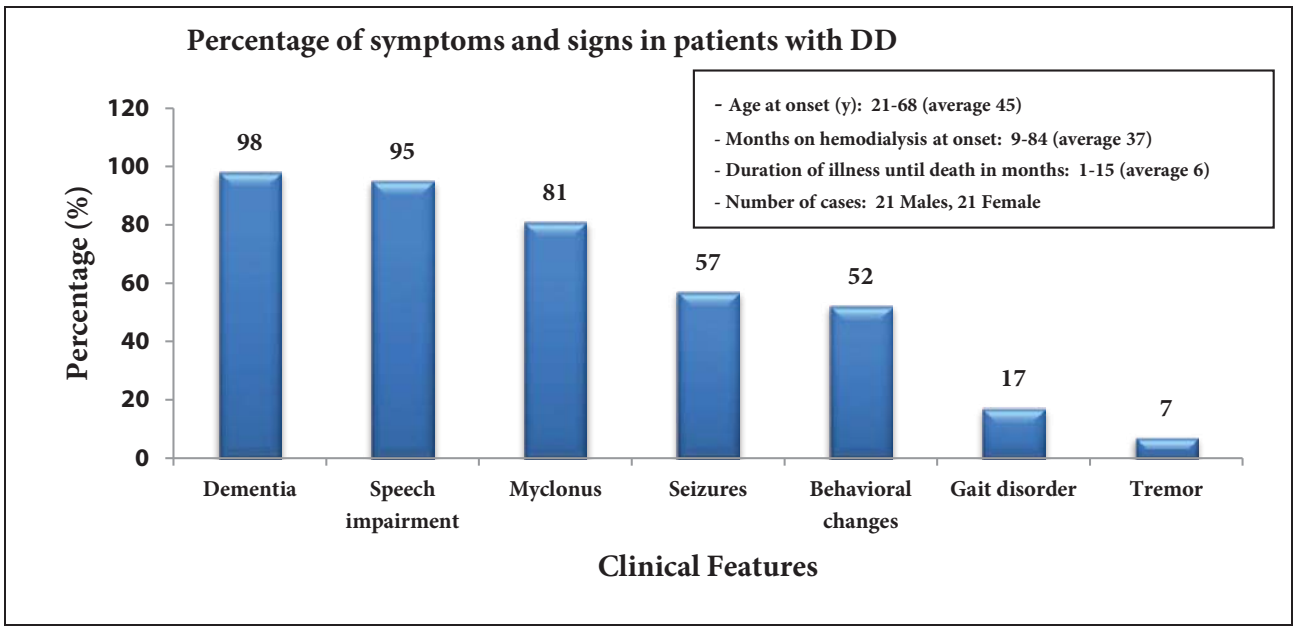

FIGURE 3.
Symptoms and signs of dialysis dementia.

lowered by reducing exposure. Daily hemodialysis is recommended in patients with serum aluminum levels above 200 µg/L, using high-flux membranes, low dialysate aluminum concentration, and withdrawal of all oral agents containing aluminum. A deferoxamine test dose of 5 mg/kg is given 4-6 weeks after such a treatment to set a time schedule for further intervention [18]. The duration needed to assure treatment is uncertain but it usually takes several months[19].

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الخرف نتيجة غسيل الكلى: مراجعة شاملة

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المستخلص:

متلازمة الخرف نتيجة الغسيل الكلوي، هي متلازمة نادرة الحدوث، أول من وصفها ، العالم الفري وزملاؤه في عام ١٩٧٢ م، وبلغ إنتشار هذا المرض في أوربا بين العام ١٩٧٦ و١٩٧٧ م حوالي ٦٠٠ حالة، لكل مئة ألف من مرضى الغسيل الكلوي، مع الأخذ بعين الإعتبار تفاوت هذا الرقم بين مركز وآخر، و تكون أعراض المرض على هيئة تغير مضطرد في السلوك مع خرف وتغير في الكلام ورعشة وتشنجات، و في هذا البحث نستعرض بالوصف حالة مريض بالخرف نتيجة الغسيل الكلوي، ونقوم بمراجعة الأدبيات المتعلقة بهذا الموضوع.