

Dialysis disequilibrium syndrome

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First described in 1962, [the dialysis disequilibrium syndrome \(DDS\)](#) is a central nervous system disorder that remains an important clinical problem in dialysis patients. It is characterized by neurologic symptoms of varying severity that are thought to be due primarily to cerebral edema. New patients just being started on hemodialysis are at greatest risk, particularly if the BUN is markedly elevated (above 175 mg/dL or 60 mmol/L). Other predisposing factors include severe metabolic acidosis, older age, pediatric patients, and the presence of other central nervous system disease such as a preexisting seizure disorder.

CLINICAL MANIFESTATIONS The classic DDS refers to acute symptoms developing during or immediately after hemodialysis. Early findings include headache, nausea, disorientation, restlessness, blurred vision, and asterixis. More severely affected patients progress to confusion, seizures, coma, and even death. It is now recognized, however, that many milder signs and symptoms associated with dialysis such as muscle cramps, anorexia, and dizziness developing near the end of a dialysis treatment are also part of this syndrome. The incidence of DDS varies according to the patient population and the attention paid to the preventive measures described below. Severe DDS is now rare in adults because of the standard use of the preventive recommendations made below. However, **children may remain at increased risk**. A retrospective analysis of 180 children and adolescents on maintenance dialysis found that 13 (7 percent) had dialysis-associated seizures. All but one of these patients were treated with hemodialysis. The development of the above symptoms during dialysis is strongly suggestive of DDS. Nevertheless, there are a number of other disorders that must be excluded including uremia itself, subdural hematoma, metabolic disturbances (hyponatremia, hypoglycemia), and drug-induced encephalopathy. Drug accumulation is a particular problem in renal failure with drugs that are normally excreted by the kidney.

PATHOGENESIS The symptoms of DDS are caused by water movement into the brain, leading to cerebral edema. Two theories have been proposed to explain why this occurs: a reverse osmotic shift induced by urea; and a fall in cerebral intracellular pH. Hemodialysis rapidly removes small solutes such as urea, particularly in patients who have marked azotemia. The reduction in BUN lowers the plasma osmolality, thereby creating a transient osmotic gradient that promotes water movement into the cells. In the brain, this water shift produces cerebral edema and a variable degree of acute neurologic dysfunction. The loss of extracellular water can also cause extracellular volume depletion which can contribute to the development of hypotension. The pathogenetic importance of urea in the DDS has been demonstrated by experiments in uremic rats. In one report, for example, rapid dialysis lowered the BUN from 200 to 95 mg/dL (72 to 34 mmol/L) in 90 minutes. This change was associated with a six percent increase in brain water. Neither undialyzed rats nor those rats dialyzed against a bath to which urea was added to prevent a fall in BUN developed cerebral edema. Furthermore, the retention of brain urea appears to be account for most of the increase in

brain water. Urea is generally considered an "ineffective" osmole, because of its ability to permeate cell membranes. However, this effect may take several hours to reach completion. Thus, **there is insufficient time for urea equilibration when hemodialysis rapidly reduces the BUN**; as a result, urea transiently acts as an effective osmole, promoting water movement into the brain. In the above experiments, for example, the 53 percent acute reduction in BUN was only associated with a 13 percent reduction in brain urea nitrogen. Intracerebral acidosis Some investigators have suggested that the reverse urea effect cannot account for the development of cerebral edema in the DDS, since urea movement out of the brain is sufficiently rapid to prevent a large osmotic gradient between the brain and extracellular fluid . They have proposed that a decrease in cerebral intracellular pH, occurring via an uncertain mechanism, is of primary importance. Both displacement of bound sodium and potassium by the excess hydrogen ions and enhanced production of organic acids can increase intracellular osmolality and promote water movement into the brain. However, an increase in brain organic osmolytes has not been confirmed in all studies. In most reports, the reverse urea effect appears sufficient to explain most of dialysis disequilibrium.

TREATMENT Prevention is the mainstay of therapy in the DDS, particularly in new dialysis patients who are at highest risk. The initial dialyses should be gentle, but repeated frequently. The aim is a gradual reduction in BUN, which will be protective but may not prevent mild symptoms such as headache and malaise. Slow urea removal can be achieved by one of the following methods: With hemodialysis, therapy can be initiated with two hours of dialysis at a relatively low blood flow rate of 150 to 250 mL/min with a small surface area dialyzer. This regimen, which is repeated daily for three or four days, is different from the standard every other day four-hour regimen at high flow rates. If the patient shows no signs of DDS, the blood flow rate can be increased by 50 mL/min per treatment (up to 300 to 400 mL/min) and the duration of dialysis can be increased in 30 minute increments (up to four or more hours, as necessary for adequate solute removal). Patients who also have marked fluid overload can be treated with ultrafiltration (which removes less urea per unit time) followed by a short period of hemodialysis. The patient can be started on peritoneal dialysis in which the low rate of peritoneal blood flow results in a urea clearance per unit time that is much lower than that with hemodialysis. The DDS has not been reported with continuous peritoneal dialysis. Some physicians recommend prophylactic phenytoin (1000 mg loading dose followed by 300 mg/day until uremia is controlled) and/or the administration of 12.5 g of hypertonic mannitol intravenously every hour of dialysis in high-risk patients with marked azotemia (BUN above 150 to 200 mg/dL [54 to 71 mmol/L]) or an underlying alteration in mental status. Symptoms of DDS are self-limited and usually dissipate within several hours. Severe DDS with seizures can be reversed more rapidly by raising the plasma osmolality with either 5 mL of 23 percent saline or 12.5 g of hypertonic mannitol.

