Neurobehavioral effects of recombinant human erythropoietin

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In the past, patients with end-stage renal disease (ESRD) commonly experienced a variety of debilitating symptoms that severely compromised their biological, psychological, and social adaptation. Because it was believed that these symptoms resulted from uremia, it was hoped that dialysis would largely alleviate these abnormalities.

However, dialysis — whether hemodialysis, intermittent peritoneal dialysis, or continuous ambulatory peritoneal dialysis (CAPD) — has proved only partially successful in accomplishing this goal. Although it has been relatively successful in clearing uremic toxins and reducing excess fluid, long-term dialysis, particularly hemodialysis, has not been successfully used to return hematocrit levels to the normal range, or to reverse many of the neurobehavioral abnormalities attributed to uremia.

The mode of dialysis in treatment efficacy

Patients receiving long-term dialysis usually experience a variety of debilitating symptoms. These symptoms include fatigue, decreased mental acuity, reduced appetite, impaired sexual interest and function, neuromuscular symptoms such as muscular twitching, peripheral neuropathy, and muscle cramps, a lowered exercise capacity, decreased cold tolerance, nausea, vomiting, and anorexia. Some patients may even experience angina and cardiac failure [1].

A study by Wolcott and Nissenson [2] found other differences between patients receiving CAPD and those receiving hemodialysis. Among 33 pairs of long-term CAPD and hemodialysis patients closely matched with respect to sex, age, diabetic status, ethnicity, and years of education, those receiving CAPD experienced a higher quality of life, lower illness-related and dialysis modality-related stress scores, and lower mood disturbance scores; this last difference was not statistically significant. They also reported more frequent participation in community and vocational activities and better relationships with dialysis physicians and other patients. Since the medical-status variables of both groups of patients were similar, including the hematocrit, medical status could not account for the differences found in psychological and social adaptation.

Quality of life for all patients receiving long-term dialysis is complicated by factors unrelated to dialysis modality. A study by Wolcott et al. [3] of 66 long-term dialysis patients showed that men and those patients over 51 years of age had poorer medical and psychological adaptation than did women and younger dialysis patients. Generally superior medical, psychological, and social adaptation was shown by the subjects who were actively employed, as compared with those who were not. This suggests that men may have poorer psychological adaptation than women as a result of greater distress associated with loss of capacity for physical activities and loss of vocational and sexual function. They may also have greater difficulty adjusting to the chronic dependence of the dialysis regimen.

It is clear from these studies that there are a number of factors that have an impact on the neurobehavioral manifestations of uremia, independent of medical status or anemia, including the modality of dialysis and patient age and sex.

Uremia as a neurobehavioral syndrome

Many of the symptoms of ESRD are related to the fact that ESRD is manifested primarily as a neurobehavioral syndrome [1, 4]. Included in the neurobehavioral dysfunction are abnormalities in electrophysiologic indices, clinical mental status, and neuropsychologic test performance. Neurobehavioral symptoms in the

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patient with ESRD may include confusion, decreased mental alertness, difficulty concentrating, impaired memory, and, occasionally, in patients with severe uremia, hallucinations, tremors, myoclonus, and seizures.

Effects of long-term dialysis

These neuropsychological and electrophysiologic abnormalities are only incompletely reversed with long-term dialysis [1]. For example, electrophysiologic function in hemodialysis patients, as measured by electroencephalographic analysis, rises to near-normal levels only briefly, approximately 24 hours after the most recent dialysis [5, 6].

A study by Marsh et al [4] examined the electrophysiologic indices of central nervous system function in 14 hemodialysis patients, 13 CAPD patients, and 10 healthy individuals matched by group for age and sex. A battery of evoked and event-related brain potential measures revealed differences between CAPD patients and hemodialysis patients in the electrophysiologic indices of central nervous system function. The majority of these differences occurred in the later brain waves associated with higher levels of cognitive processing, such as those that occur during tasks requiring selective attention, stimulus discrimination, and decision making on the part of the subject. In tasks involving easy discrimination, for example simple tone discrimination, patients receiving hemodialysis showed less efficient cognitive processing than controls, whereas patients receiving CAPD had test results similar to those of controls. However, when tested while performing more difficult continuous performance tasks, both CAPD patients and hemodialysis patients exhibited abnormally delayed later components [4]. This suggested that differences between the two modalities in removal of uremic toxins were significant and had an impact on brain function.

Erythropoietin and ESRD anemia

Most atients with ESRD continue to have a decreased quality of life while receiving dialysis. It is becoming apparent that many of the symptoms of ESRD result from the severe anemia that almost invariably accompanies chronic renal failure. Three primary mechanisms are responsible for this anemia: the failing kidneys' decreased production of erythropoietin (EPO), a hematopoietic growth factor, which stimulates the production of red blood cells in the bone marrow [7, 8]; the decreased response to EPO by the bone marrow because of the presence of uremic toxins (inhibitors of EPO action) [9-11]; and shortened red cell survival [12]. The production of EPO by the kidneys is particularly important since the kidneys produce more than 90 % of EPO found in a healthy adult, with the remainder produced by the liver [13].

Dialysis can improve hematocrit levels by reducing plasma volume in fluid overloaded patients, thereby creating a rise in hematocrit levels without a change in red cell mass. It can also improve hematocrit levels by clearing uremic toxins that may inhibit the action of EPO on the bone marrow [14, 15] or decrease the bone marrow's response to EPO. However, dialysis cannot compensate for inadequate EPO production by the diseased kidneys, which is the major cause of the anemia associated with ESRD.

In addition, the dialytic modality used plays an important role in the effect of dialysis on anemia. Patients undergoing CAPD have higher hematocrit levels and are less dependent on blood transfusions than patients undergoing hemodialysis [14, 16-18]. This difference may be related to CAPD's efficiency, up to ten times greater than that of hemodialysis, in removing inhibitors of EPO activity, some of which are in the «middle molecule» size range [4, 16, 17]. Continuous fluid removal with resultant hemoconcentration probably plays a role as well.

Anemia and the neurobehavioral syndrome

In recent years, there has been a growing understanding of the role of anemia in ESRD, and a number of studies have explored the effects of alleviating the anemia on a variety of symptoms. This research has been made possible by the development of recombinant human EPO (r-HuEPO), which has been shown to restore hematocrit levels to normal in almost all chronic renal failure patients with uncomplicated anemia (ie, without accompanying inflammation, aluminium toxicity, or iron deficiency) [19-21]. Treatment with r-HuEPO has largely ended the need for transfusions in long-term hemodialysis patients, thus removing the associated risks of infection, immunologic sensitization, and iron overload [16].

Improvement of the anemia resulting from treatment with r-HuEPO has also been associated with improvements in a number of clinical areas, including exercise tolerance, energy levels, appetite, sleep patterns, sexual function, and brain and cognnitive function. All of these are important factors in determining the quality of life for patients undergoing long-term dialysis.

Effects of r-HuEPO on brain and cognitive function

Some studies involving r-HuEPO have explored the

role that ESRD anemia plays in the neurobehavioral syndrome of uremia, as determined by changes in this syndrome brought about through increases in hematocrit levels [3, 22-25]. A study by Nissenson et al. [22] measured brain event-related potentials in 13 patients receiving long-term hemodialysis before and after at least 12 weeks of r-HuEPO treatment. The mean hematocrit level, which had been 22.7 % at the start of the study, increased to 36.6 % following treatment with r-HuEPO. In 9 of the 13 patients, improvements occurred in latency of the P300 EEG wave form with tone and vowel stimuli, indicating more rapid and efficient processing of information by the brain after correction of anemia.

Nissenson et al. [23] subsequently studied a group of 17 patients receiving long-term hemodialysis who were treated for at least 1 year with r-HuEPO. Before r-HuEPO treatment, the mean hematocrit level in the group was 23 %; at 1 year after the initiation of r-HuEPO treatment, it had risen to 37 %. Improvement in the speed of information processing, as measured by P300 latencies, had occurred in nine patients but not in the remaining eight patients. However, significant improvements in attention span, memory, and efficiency of cognitive function had occurred, as well as a significant ($P < .03$) increase in the amplitude of the P300 waves in the entire group, with 19 % improvement in parietal function, 63 % improvement in vertex function, and 160 % improvement in frontal brain area function.

Similar improvements in cognitive function associated with increased hematocrit levels, as measured by tests of visual, conceptual, and visuomotor tracking, auditory-verbal learning, symbol-digits modality, and trailmaking, were found in studies by Wolcott et al. [24, 25]. The investigators found improvements in scores for dialysis modality-related specific stress, self esteem (Simmons self-esteem scale), profile of mood states (POMS), vigor, and general treatment stress; they also noted decreased POMS fatigue scores and increased physical activity after correction of anemia [25].

Conclusions

The fact that treatment with r-HuEPO is associated with improvements in neuropsychologic and electrophysiologic abnormalities suggests that part of the uremic syndrome of patients with ESRD receiving chronic hemodialysis is directly attributable to the affects of anemia on the central nervous system. The improvement in abnormalities in brain function after correction of anemia in turn should contribute to an improvement in the patients' quality of life.

Future studies of the effects of anemia on brain function in uremic patients may enhance our understanding of the impact of these abnormalities on patients' social and vocational adaptation. In addition, they may provide important new insight into the metabolic effects of anemia on the brain. Especially for the young person with ESRD, subtle changes in the level of daily functioning may have a profound effect on the individual's overall sense of competency, autonomy, and life satisfaction. With correction of anemia, that component of the neurobehavioral abnormalities of uremia not attributable to retention of uremic toxins should largely be reversed.

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