A Complication in Treatment of Nephrosis

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DR. SCAGLIONE: During the past 2 years in the Babies Hospital, two instances have been observed of severe disturbance of the central nervous system in patients in an edematous phase of nephrosis and undergoing rapid diuresis during adrenal steroid therapy.

The first patient to show this alarming reaction was a 6-year-old white girl who, while being treated with intramuscular adrenocorticotropin (ACTH), rapidly lost fluid and developed marked hypochloremic, hypokalemic alkalosis. She became comatose for several weeks and, since that time, has had a convulsive disorder resistant to therapy. She also underwent severe impairment of intellect and is now considered to be hopelessly retarded.

The second patient, to be presented in greater detail, is a child who reacted in a similar manner while receiving prednisone, but she has apparently suffered no permanent alteration in intellectual function.

Patty H. is an 8-year-old Negro female who had the onset of edema in July 1955. During the first 6 months of the disease, she was given two courses of prednisone therapy in a local hospital and this resulted in prompt diuresis, but there was equally rapid re-accumulation of edema following cessation of therapy. The urine showed persistent proteinuria, cylindruria and hematuria. In January of 1956 she was treated again with prednisone at the Duke University Hospital in North Carolina. A moderate diuresis was obtained but she required admission 3 months later because of marked anasarca. The patient was then treated with a 12-day course of ACTH-gel (20 units/day) following which she underwent a massive diuresis and lost approximately 14 liters of urine in 4 days. This rapid loss of fluid was well tolerated. An attempt to maintain this remission by giving cortisone 3 days a week failed, and the patient was admitted to the Babies Hospital for further therapy on August 3, 1956.

On admission the patient, now 8 years of age, was markedly edematous and had ascites and bilateral pleural effusion. She weighed 30.7 kg and the blood pressure was 120/90. Laboratory studies confirmed the impression of nephrotic syndrome; the urine showed 4+ proteinuria along with varying amounts of erythrocytes, leukocytes and casts in the centrifuged sediment. The erythrocyte sedimentation rate by the Westergren method was 137 mm in 1 hour. Partition of the serum proteins by paper electrophoresis revealed a marked nephrotic pattern.

After a 5-day period of observation, during which time the patient gradually gained weight to 32.5 kg, she was treated with prednisone, 10 mg every 6 hours, orally. Gantnisin prophylaxis was given concurrently. Persistent elevation in blood pressure to levels of about 140/100 was controlled with reserpine, 0.5 mg/day. After 1 week of therapy, prednisone was increased to 60 mg/day. On the thirteenth day of therapy, the patient began diuresis slowly. On the fourteenth and fifteenth days, 25 gm of salt-poor, human albumin was administered intravenously in an attempt to accelerate diuresis. At this time, potassium chloride, 3.0 gm/day orally, was added to the regimen.

Reference to Table I will be of help in following the subsequent course. On the morning of the sixteenth day of therapy, the patient complained of headache and blurred vision and vomited. When a transient Chvostek's sign was elicited, the patient was given supplementary calcium by mouth. Determination of electrolytes in the serum that morning were not considered abnormal and the patient was merely observed.

As the morning wore on, her sensorium be-
came depressed to the point of permitting response only to painful stimuli. Early in the afternoon she had the first of four grand mal seizures. The blood pressure was 140/110; cerebrospinal fluid was negative. Repeat determination of electrolytes in the serum revealed the pattern of evolving hypochloremic, hypokalemic alkalosis. Prednisone was discontinued and management consisted of control of seizures with phenobarbital and diphenylhydantoin along with electrolyte solution intravenously with emphasis on replacement of potassium.

The patient remained semicomatose for about 3 days. Abnormalities in electrolytes in the serum gradually were corrected. Electroencephalograms revealed marked disorganization of wave patterns with frequent bursts of seizure activity. The patient's sensorium cleared sufficiently on the fourth day after the first convulsion to permit her to answer simple questions. Electroencephalograms showed parallel progressive improvement. During the ensuing week the picture was one of an organic psychosis with inappropriate grinning, perseveration in thought and speech, impairment of recent memory and inability to make simple associations. Two weeks after the cerebral insult, she developed marked hallucinatory activity, tremors, ataxia and nystagmus. She improved rapidly on withdrawal of diphenylhydantoin and reverted to similar symptoms when this drug was re-administered. This episode was then considered to be in part ascribable to sensitivity to this drug and it was withdrawn from the anticonvulsant regimen.

From this point until the present, the child has improved steadily until her higher intellectual functions seem to be completely restored. She did have occasional brief episodes of paranoid behavior, but these have completely subsided. At present, she seems to be more impulsive and aggressive than she was prior to diuresis. The electroencephalogram remains abnormal, but the child has suffered no further seizures while continuing phenobarbital therapy.

In attempting to explain the mechanism underlying the sequence of events just outlined, I must first admit that all of the discussion will be purely speculative. And yet, some association of events is difficult to ignore. Two major mechanisms come immediately to mind as possible causes: One, a cerebrovascular phenomenon, and the other, an electrolyte derangement affecting cellular function.

Cerebrovascular accidents, such as thrombosis due to increased coagulability of the blood or hemorrhages because of hypertension, are possible in patients receiving adrenal steroid therapy. In this child, the lack of neuromotor deficits, rapid recovery and normal cerebrospinal fluid tend to minimize this as a possibility. Also the patient's blood pressure never was very high. The hematocrit remained relatively low throughout the diuresis.

Both of these patient's experienced difficulties only during active diuresis. It is known
that with large obligatory water losses, such as occurred here, large losses of potassium occur from the extracellular fluid compartment (ECF) into the urine. In an effort to defend the ECF, potassium leaves cells. This gives rise to normal or perhaps slightly decreased concentration of potassium in the serum and low intracellular potassium. It is believed that sodium and hydrogen ions enter the cells in an attempt to compensate for the intracellular hypokalemia. This situation is thought to give rise to an extracellular alkalosis and concurrent intracellular acidosis. When acidosis has persisted long enough, cellular function becomes disturbed. This situation in the renal tubules could make them incapable of reabsorbing chloride and might account for the hypochloremia.

It is logical to assume that cellular derangement is probably widespread in the body and could account for cerebral dysfunction if severe enough. Although these events have not been proved to have occurred here, this appears to be a plausible explanation and supplies a hypothesis to test in future patients.

Chairman Riley: We present this little girl not to show the dangers of prednisone therapy or adrenal steroid therapy in general, because I still believe this is about the only reasonably effective method we have for the treatment of nephrosis. But these two examples we have here, and one or two others I have heard of in other parts of the country, would seem to be predicated on some basic derangement of the chemistry of the body. Whether the explanation that Dr. Scaglione suggested is the correct one or not, I don't know.

When the neurologists saw this child they immediately said, “Oh, it is prednisone that has done it! We often see central nervous system disturbances with steroid therapy.” On the other hand, since this patient has recovered neurologically, her nephrosis has not been under control, and we administered another course of prednisone. I am happy to say there were no observable changes in the sensory nervous system this time. I think the most reasonable thought is that the disorder in the nervous system results from some kind of change due to the rapid diuresis, and, if this is true, it should be preventable. I think we are all alerted now so that if we ever see a child rapidly diuresing and then, as this one did, starts to vomit about the time of the diuresis, we are prepared to give potassium intravenously and hope we will be able to avoid this situation.
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