INTRACRANIAL LESIONS AS A CAUSE OF IMPAIRED RENAL FUNCTION*

C. DAVID SCHEIBERT, M.D.†

Department of Neurological Surgery, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee

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Experimental and clinical studies by others have emphasized increasingly the importance of the cerebrum in the control of water and electrolyte metabolism. However, organic renal damage has not been noted in these studies, and often significant azotemia has not occurred. Renal pathology and insufficiency, including nephrosis of the lower nephrons, as admirably described by Lucké, to the writer's knowledge have never been ascribed to intracranial lesions as the primary etiology.

The purpose of this paper is to describe a syndrome whereby intracranial lesions may cause severe renal damage and death.

During a 3-year period 108 patients suffering severe contusions of the cerebrum and brain stem and space-occupying traumatic lesions, or undergoing surgery for intracranial tumors and vascular anomalies, have had the following studies performed. Determinations of blood urea nitrogen, serum potassium, sodium and chloride, and CO₂ combining power, complete blood count and urinalysis were done 3 times weekly, or more often when abnormal, for at least 2 weeks after injury or intracranial surgery. Clearance of urea and urinary excretion of nitrogen and electrolytes were determined in some cases at varying intervals. A careful record of fluid intake and output, vital signs and clinical observations was made. More frequent laboratory determinations were done when there was any tendency to renal insufficiency or electrolyte abnormality in order to facilitate therapy.

In 21, or 19 per cent, of the 108 patients operated upon for intracranial tumor or aneurysm, or suffering from severe intracranial trauma, severe impairment of renal function developed, with death in 15, or 70 per cent. Seven of 15 deaths seemed to be caused by hyperkalemia or increase in serum potassium. In fact, all deaths in renal failure with intracranial traumatic lesions apparently were caused by increase in potassium, excepting 1 patient who expired with multiple pulmonary emboli. The remaining deaths apparently were caused by extensive deep-seated tumors of the brain. Table 1 reveals the cerebral pathology in the 21 cases: tumor 11, extradural hemorrhage 2, subdural hematoma 1, contusion of cerebrum and brain stem 6, and ruptured aneurysm 1. The number of deaths, and the number of patients who suffered severe retention of potassium, are noted. The average duration of life with renal failure following severe cerebral trauma or craniotomy for tumor was 9 days. It is interesting to note that in an additional 10 patients, 9 with tumor and 1 with trauma, a mild to moderate azotemia developed without other abnormalities.

Table 2 illustrates the type and location of the brain tumor in the 11 patients with renal

| TABLE 1 |

| Incidence of impaired renal function in 108 cases |

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Cases</th>
<th>Onset to Death (Days)</th>
<th>No. with Hyperkalemia</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Extradural hemorrhage</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral contusion</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ruptured aneurysm</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>(19%)</td>
<td>(79%)</td>
<td>15</td>
</tr>
</tbody>
</table>
INTRACRANIAL LESIONS AND RENAL FUNCTION

failure. Thus it is seen that, as in cases of traumatic lesions, these 8 gliomas, 2 metastatic tumors and 1 pinealoma had diversified locations. It seems that the severity of the lesion and sudden cerebral shifts or alteration of intracranial pressure are more important than the location and type of lesion.

Clinical observations have shown that renal insufficiency may follow marked cerebral shifts or increased intracranial pressure in cases of tumor, and develop after severe trauma, often manifested by extensor rigidity. The patient’s sensorium may improve for several days, but as renal insufficiency becomes obvious by elevation of blood urea nitrogen, the patient’s level of consciousness decreases to coma. Focal or general seizures usually occur with generalized edema in a few cases. The vital signs reveal almost consistently a persisting rapid pulse with little variation in blood pressure, which may be elevated or depressed. Shock, blood-transfusion reaction, anoxia and other causes of nephrosis of lower nephrons are usually absent.

Then, 1 or 2 days after operation, the urinary output increases and may average 2000 cc. of urine per day. This is the most outstanding manifestation of this syndrome, that of progressive renal insufficiency with output of normal volumes of urine. The urine usually is of clear yellow color but occasionally may be brown for several days. The specific gravity of the urine tends to fix at about 1.010. Clearance of urea is diminished. Albuminuria is present in varying amounts, usually accompanied by an increase in white blood cells, occasionally a large number of red blood cells and very occasionally granular casts. Chemical analysis of the urine reveals, as shown in Table 3, an almost complete absence of sodium and chloride ions in the urine with slight decrease in potassium. In cases of hyperkalemia there is a decrease in urinary potassium.

The blood usually reveals a polymorphonuclear leukocytosis with an occasional decrease in elements of the red cells. The first positive test is the elevation of nonprotein or urea nitrogen in the blood and this is progressive in the severe case. Marked elevation of serum potassium was found in one-third of the 21 cases and apparently was the cause of one-half the mortality. Significant deviation of serum sodium and chloride is unusual if the patient is maintained on glucose in water by infusion. CO₂ combining power may be decreased. The blood electrolyte changes are well illustrated by the following cases.

**TABLE 2**

<table>
<thead>
<tr>
<th>Type and location of 11 brain tumors in cases of renal failure following surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme 7</td>
</tr>
<tr>
<td>Temporal 2</td>
</tr>
<tr>
<td>Frontal 1</td>
</tr>
<tr>
<td>Ependymoma 1</td>
</tr>
<tr>
<td>Metastatic 2</td>
</tr>
<tr>
<td>Multiple 1</td>
</tr>
<tr>
<td>Pinealoma 1</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>Average daily urinary electrolyte excretion in mEq./l. for 15 days after craniotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case J.H.S.</td>
</tr>
<tr>
<td>Na 4.1</td>
</tr>
<tr>
<td>Cl 2.3</td>
</tr>
<tr>
<td>K 87.4 mEq./ l.</td>
</tr>
</tbody>
</table>

Average 1950 cc. urine vol./day

**Case 1.** R.B.B., a 26-year-old white male, was admitted in decerebrate rigidity 6 hours after sustaining a head injury. Immediate surgery relieved the patient of a left extradural hemorrhage. Decerebrate rigidity continued for 4 days and tracheostomy and left tentorial slit were done. Blood pressure during the 1st week ranged from 100/60 to 150/94 with pulse from 100 to 190. The course was moderately febrile.

With an initial limited intake of fluids, the average daily volume of urine was 705 cc. with mild to moderate albuminuria and hematuria. Blood studies, as shown in Fig. 1, revealed a progressive rise of nonprotein nitrogen from 38 mg. per cent to 333 mg. per cent and potassium from...
4.7 mEq./l. to 8.5 mEq./l. at time of death 10 days after admission. Serum chloride and CO₂ combining power remained normal. This was an early case in the series and no treatment was instituted.

Autopsy revealed contusion of the anterior part of the left temporal lobe. There was tubular necrosis of the lower kidney with heine casts and attempts at tubular epithelial regeneration.

Case 2. I.G., a 22-year-old colored male, was admitted March 28, 1955, with severe traumatic contusion of cerebrum and mid brain, in a state of decerebrate rigidity. Bilateral burr holes were nonrevealing. By the 8th hospital day the blood urea nitrogen and serum potassium had risen from normal to 128 mg. per cent and 6.9 mEq./l., respectively; these changes are shown in Fig. 2. Immediate intragastric administration of 2000 cc. of 20 per cent sucrose solution a day for 2 days resulted in prompt diarrhea with beginning correction of the above abnormalities. Renal function was able to then recover with return of blood studies to normal by the 20th hospital day and the patient did well thereafter.

Organic renal changes were noted in those patients who died with retention of nitrogen and potassium. These changes consisted of slight increase in weight, swelling, pallor of renal cortex and occasionally a white line at the corticomedullary junction. A patient who had undergone a bifrontal operative exposure of a large glioblastoma of the anterior corpus callosum died 9 days later with a nonprotein nitrogen of 266 mg. per cent and serum potassium of 7.9 mEq. The above gross changes were noted in the kidneys of this patient and, microscopically, they show predominantly swelling and necrosis of tubular epithelium with attempts at regeneration.

Allott,1 Sweet et al.,14 Peters et al.,13 Cooper,3 Higgins et al.,7 and others have described abnormalities of electrolyte metabolism associated with a variety of intracranial lesions. The changes have consisted of an increase in serum sodium and chloride, with a decrease in urinary sodium and chloride or a decrease in serum sodium and chloride and occasionally potassium. Azotemia may or may not be present. However, organic changes in the kidneys have not been described. The syndrome of nephrosis of the lower nephrons, as described by Lucké,11 and the described changes occurring with intracranial lesions vary chiefly in that severe oliguria and anuria present in nephrosis of the lower nephrons is absent in the cases presented herein. Also hypertension and heine casts are not the rule. It is also interesting to note that patients with intracranial lesions and renal insufficiency have had no previous history of renal disease and renal or electrolyte abnormalities.

Cort, as referred to by Livingston et al.,10 has described renal cortical ischemia caused by electrical stimulation of cortical area 13. Hoff et al.8 have demonstrated the same renal cortical ischemia in response to stimulation of the anterior sigmoid gyrus of the cat. This is not influenced by adrenalectomy,
but denervation of the kidney or section of the low cervical cord, as described by Kell and Hoff, eliminates the ischemic response. They have also described urinary abnormalities as well as tubular damage in the cat with more chronic stimulation. Brobeck et al. produced chronic glomerulonephritis with albuminuria and hematuria in rats by experimental hypothalamic lesions. Goodman has reported 2 cases of uremia following electroconvulsive therapy and McLardy, in analyzing 122 prefrontal lobotomies, found 7 patients who died in uremia. Each of these 7 had a bilateral lesion in orbital cortical area 47. However, the kidneys were not described by Goodman or McLardy. Weinberg et al. have described alterations in renal function, including hematuria, in man during intracranial air studies.

It is felt that the mechanism of the renal damage in the cases presented is a neural transmission of impulses from the abnormal brain through the hypothalamus, brain stem and lateral spinal cord resulting in renal cortical ischemia with irreversible changes in the kidney in some cases.

Treatment has been directed primarily toward reduction of serum potassium, when hyperkalemia occurs, together with the general treatment of uremia. Reduction of serum potassium has been brought about by causing diarrhea through a continuous intragastric drip of 20 per cent sucrose solution. Diarrhea results in 8 to 10 hours with reduction of serum potassium and electrolytes which may require administration of sodium chloride. Peritoneal lavage as described by Grollman has proved a more acceptable method for reduction of extracellular potassium. The use of cortisone in 1 case may have prevented a rise in serum potassium. Thorazine has been administered in 3 patients with the hope that it might result in sufficient autonomic blockade to prevent renal vasoconstriction. Experience with Thorazine is insufficient to allow any deductions as yet.

In summary, out of a series of 108 cases of severe varied intracranial traumatic lesions and tumors, 21 patients have evidenced severe renal damage and uremia, with death in 15. Ten additional patients have had mild to moderate retention of nitrogen alone. This syndrome is characterized by the onset of decreasing level of consciousness, tachycardia, seizures and occasionally edema, with a normal urinary output. The urine may show albuminuria, a tendency to fixation of specific gravity, red and white blood cells, occasional granular casts, and pronounced decrease of sodium and chloride and occasionally excretion of potassium. The blood shows leukocytosis, retention of nitrogen and increase in serum potassium in the severe cases. The most outstanding manifestation is the presence of a normal volume of urinary output which may lure the clinician into a false sense of security concerning the patient’s renal function and the downhill course is attributed to the intracranial pathology. The pathology and physiology have been discussed and treatment has been suggested. With proper therapy, aimed primarily at reduction of serum potassium, time for renal recovery may be allowed and the patient’s recovery insured.

REFERENCES


DISCUSSION

Dr. Joseph F. Kell, Jr.: I wish to congratulate Dr. Scheibert on his excellent clinical study of a large series of patients in which it is difficult to carry out functional studies.

The question of the neurogenic control of renal function has been the source of continued discussion between Dr. John Fulton and Dr. Homer Smith for some years. I would like to point out that Hughlings Jackson was the first to hypothesize that the autonomic or visceral nervous system is represented in the cerebral cortex and integrated similarly to the somatic motor and sensory systems throughout the central nervous system. Dr. Harvey Cushing noted that the disturbances of the autonomic nervous system associated with intracranial tumors may result in acute gastric ulceration. Many of the members of this Society have added to this information which has established Hughlings Jackson’s hypothesis. Doctors Poppen, Livingston and Chapman were some of the first investigators to definitely establish in man that there is cortical representation of the autonomic nervous system in the frontal as well as the temporal lobes. Dr. Lawrence Pool further verified this in his studies of the cingulate gyrus in man. Dr. Maurice Silver has demonstrated all stages of renal damage in canine epilepsy, and these renal changes appear to be secondary to prolonged central vasomotor stimulation. Today, Dr. Scheibert has presented in his study evidence that verifies that this mechanism of producing renal damage exists in man; and this mechanism undoubtedly is of major importance in the etiology of hypertensive cardiovascular renal disease in man.

Dr. Scheibert’s observation that decerebrate rigidity frequently is associated with this renal disorder is consistent with the observation that there tends to be an overactivity of the sympathetic discharges in the decerebrate state. Dr. Scheibert has certainly made a valuable contribution by pointing out the importance of treating the hyperkalemia and the renal disorders of vasoconstriction.

I should like to ask Dr. Scheibert if he has considered such sympatholytic medications as Dibenamine and tetraethylammonium chloride (Elaton), and such procedures as caudal anesthesia and bilateral paravertebral sympathetic blocks to release or block this vasoconstrictive mechanism. These procedures have been shown to be effective in acute nephritis and in toxemia of pregnancy.

Dr. W. Eugene Stern: Dr. Scheibert’s paper is certainly a provocative one. I would like merely to raise some questions as to whether any part of the syndrome that he presents could be explained on the basis of certain extrarenal changes. I believe, as I analyzed his paper and as he presented it, he has a satisfactory rebuttal to each objection that I might offer.

His study represents one of the very few providing data on certain of the metabolic changes that occur after severe intracranial trauma.

It is of interest that 13 per cent of these severely injured patients died of renal failure with hyperkalemia. We are assuming, I believe, that this was not caused by reactions to blood transfusions and similar obvious causes. He found azotemia in his patients and, as he has emphasized, a very reasonable volume of urinary output.

As one examines the possibilities in these cases, the question might be raised, what, if any, is the role of dehydration in such problems? Dehydration can reduce glomerular infiltration with retained potassium. Usually, however, in these circumstances the specific gravity of the urine is high and the volume is small. If deficit of water is profound, a deficit of salt may occur. That is to say salt may be lost in excess of water. That may produce hyperkalemia and azotemia, but also a hypotonicemia. It is of interest in Dr. Scheibert’s cases that the kidneys seemed to be conserving sodium very satisfactorily.

Dehydration, of course, may be aggravated in another way. If a high solute is given intravenously or by gastric tube, urinary volume may appear adequate if the volume itself is considered a criterion, but because of the obligatory loss of water via the kidneys to handle this extra solute there may be an appreciable volume of urine in the face of actual dehydration.

I ask Dr. Scheibert what solute load his patients were receiving in the preterminal phase.

On the other hand, hyperkalemia usually is not found in these examples of solute diuresis that have been reported.

The excessive metabolic response to severe stress is another possibility. This might be such as to raise the matter of adrenal hypofunction and, of course, the pituitary-adrenal axis may have been totally interrupted by the trauma. The strongest point against this is that he has is the preservation of the normal sodium in the blood. Dr. Scheibert did not administer salt to his patients, as I understand it.

Thirdly, one might ask did the stress act to produce severe hypotension with hypovolemic or oligemic shock which compromised renal function?
There should be a significant difference between the cases that Dr. Scheibert presented and those other cases of electrolyte disturbance that have been reported in the literature relating to cerebral disease. His patients do show most of the criteria of renal disease.

I just want to spice up the discussion a bit by suggesting that perhaps part of the response might be caused by excessive stress and an important degree of dehydration, perhaps masked by some solute diuresis.

This is a most enjoyable paper. I believe more balance studies will be of considerable interest in the future.

**DR. C. DAVID SCHEIBERT:** I wish to thank Dr. Kell and Dr. Stern for their discussion and questions.

As Dr. Kell has mentioned, the use of certain of the sympatholytic drugs or caudal or sympathetic or parasympathetic block might be of help in increasing the flow of blood to the kidneys. However, once this difficulty is picked up, the damage to the peripheral organ—that is the kidney—is well in progress, and certainly these things should be tried. I have not tried them. It may be that help can be gained through their use.

Dr. Stern has brought up some very interesting thoughts about further etiology of this complex problem and he in turn has answered some of his own questions. Very careful input and output studies were done on these patients and there was always more fluid administered than there was output. As stated, no electrolytes were given.

It was noticed if electrolytes, sodium chloride or potassium were given there was immediate rise in the serum levels and this is certainly contraindicated. This whole problem may be a part of stress in that the overactivity of so-called sympathetic pathways to the kidneys is certainly involved, and this is probably part and parcel of the stress reaction, but I don't believe that it is an hormonal one primarily, and can be explained through the excellent experimental work of others on the basis of direct neural transmission.