Clinical and Experimental Studies on Cerebral Hypernatremia

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MINETA, T., TSUTSUMI, E., SUZUKI, H. and KASAI, M. Clinical and Experimental Studies on Cerebral Hypernatremia. Tohoku J. exp. Med., 1971, 104 (3), 233-249 — Electrolyte disturbances, especially hypernatremia, which are not uncommon in cerebral injuries or diseases, are usually attributed to water depletion and sodium retention. The authors observed hypernatremia in 9 of 37 neurosurgical patients. In 2 of them, water depletion and sodium retention were denied by the balance study and estimation of the sodium space and total exchangeable sodium, and hypernatremia was considered to be due to damage to the central nervous system itself. Experimental injury of the brain also caused hypernatremia in 3 of 44 dogs. Analysis of tissue electrolytes suggested the shift of electrolytes between intra- and extracellular compartments. Decrease of muscle sodium was confirmed in these patients, while bone sodium did not change. Release of muscle sodium was regarded as contributing to hypernatremia.

In 1939, Allot reported 5 cases of hypernatremia and hyperchloremia, of which 4 had cerebral lesions. Since then many cases of cerebral hypernatremia have been reported and experimental researches concerning cerebral hypernatremia were published.

Taylor (1962) reported 6 cases of cerebral hypernatremia and reviewed 30 cases from the literature. He suggested that there was an interruption of the pathway between frontal cortex, hypothalamus and brain stem, which brought forth the hypernatremic-hyponatruic response. MacCarty and Cooper (1951), Gilbert and Glaser (1961), Welt (1962), Avioli et al. (1962), Kastin et al. (1965), Pleasure and Goldberg (1966) and Goldberg et al. (1967) suggested that cerebral hypernatremia was due to brain damage itself. On the other hand, Borst (1951), Engstrom and Liebman (1953), Moore (1962), and Christie and Ross (1968) denied the existence of cerebral hypernatremia. They suggested that cerebral hypernatremia was secondary to water depletion and brain damage itself was not a causative factor. However, Stevenson et al. (1950) had reported hypernatremia following experimental lesions in the hypothalamus in rats. Further, Ganong et al. (1961) reported hypernatremia following destruction of the diencephalon and frontal lobe.

Although many arguments as to cerebral hypernatremia have been made, its

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precise mechanism has not been cleared. In the present report, observations on clinical cases and experimental studies on this problem are described to clarify the mechanism of cerebral hypernatremia.

**MATERIALS AND METHODS**

*Clinical research*

Thirty-seven patients, whose major brain lesions located in the frontal lobe or brain stem, were selected and serum electrolyte level was studied for 7 days after operation. Eighteen had brain tumor, 9 aneurysm, 7 head injuries and 4 miscellaneous. Nineteen of them were male and 18 female. Their mean age was 34 with a range of 4 to 58 (Table 1).

Estimation of serum and urinary electrolytes, and their balance study were carried out for 7 post-operative days. Sodium space and total exchangeable sodium (\(Na_e\)) were estimated in selected cases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain tumor</td>
<td>18</td>
</tr>
<tr>
<td>Glioma</td>
<td>11</td>
</tr>
<tr>
<td>Meningioma</td>
<td>2</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>2</td>
</tr>
<tr>
<td>Neurinoma</td>
<td>1</td>
</tr>
<tr>
<td>Vascular tumor</td>
<td>1</td>
</tr>
<tr>
<td>Congenital tumor</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>37</strong></td>
</tr>
</tbody>
</table>

(Male 19, female 18)

*Experimental research*

Forty-four mongrel dogs were used for the experiments. They were divided into two groups as follows:

First group (29 dogs); after the optic chiasma and the internal carotid artery were exposed through osteoclastic craniotomy, bone wax, weighing about 1.5 g, was placed on the cranial basis to compress the piriform area and anterior perforated substance (Fig. 1).

Second group (15 dogs); hypothalamic lesions were made stereotaxically by the method of Hume and Ganong (1965). Fig. 2 showed the destroyed areas in animals of this group.

Urinary bladder cannulation was made with the equipment described by Zeman (1966) after the brain lesions had been made. Estimation of serum and urinary electrolytes were carried out for 7 postoperative days by the same method as used in the clinical research.
Analytical procedures

1) Serum and urinary electrolytes

Serum sodium and potassium were measured flamephotometrically with the use of Hitachi EPF-2 flamephotometer by external standard method. Serum chloride was measured by Schales and Schales’ method (1941). Urinary electrolytes were measured by the same method as for serum electrolytes.

2) Tissue electrolytes

a) Muscle. A small piece of skeletal muscle was taken from the sartorius muscle. This sample was weighed and dried for 24 hr at 100°C. The total content of water was calculated by subtracting the dry weight from the wet weight.

Sodium and potassium were measured by the method of Graham (1967) as follows: One hundred milligrams of dry muscle powder were extracted in 5 ml of 1 N nitric acid overnight and then the supernatent was obtained. Sodium and potassium were measured by flamephotometry with external standard method.
Chloride was measured by the method of Wilson and Ball (1928) as follows: Fifty milligrams of fat free wet muscle were extracted in 0.2 ml of 0.03 N silver nitrate and 1 ml of concentrated nitric acid overnight. One drop of 30% hydrogen peroxide was then added to this solution and the mixture was maintained at 100°C for 1 hr. After cooling in a cold room, 2 drops of saturated ferric alum were added. This solution was titrated with 0.01 N ammonium rhodanide.

b) Bone. Sodium and potassium were measured by the method of Bergstrom and Wallace (1954) as follows: Bone cortex was heated for 48 hr at 105°C. The ash was dissolved in 11 ml of 10% nitric acid. Five milliliters of oxalic acid and 10 ml of water were added and the pH was adjusted to 8 to 9 by concentrated ammonia. Most of bone sodium was extracted and a small amount of sodium coprecipitated with calcium in this solution, so the precipitates were separated and then redissolved in nitric acid. This process was twice repeated. The specimens of supernatent fluid obtained by these procedures were mixed, and sodium and potassium were measured by flamephotometry with internal standard method.

Chloride was measured by the method of Wilson and Ball (1928).

3) Sodium space and total exchangeable sodium (Nae)

Radioactive sodium solution (24NaCl), of which radioactivity was about 100 μCi, was injected intravenously. Three and 24 hr after injection, blood and urine were sampled, and then radioactivity of each specimen was measured with the use of Shimazu well-type scintillation counter. Sodium space and Nae were calculated by the following formula:

\[
\text{Sodium space} = \frac{24\text{Na injected} - 24\text{Na excreted}}{24\text{Na in spot specimen of urine} - \frac{\text{Serum sodium content}}{\text{body weight}}} - \text{body weight}
\]

\[
\text{Nae} = \frac{24\text{Na injected} - 24\text{Na excreted}}{24\text{Na in spot specimen of urine}} \times \frac{\text{Serum sodium content}}{\text{body weight}}
\]

4) Balance study

In clinical research, patients were nourished by pernasal intragastric tube for 7 post-operative days. In experimental research, the diet was prepared with Gaines (General Food Co.). Twenty-four hour urine specimens were collected completely. Stool collection was not made. The water and electrolyte balance was calculated by subtracting the daily output from the daily supply.

RESULTS

Clinical research

The preoperative serum electrolyte values in 37 patients averaged as follows: sodium 138±5.1 mEq/L, potassium 4.4±0.4 mEq/L, and chloride 105±1.3 mEq/L. There were no abnormalities of electrolytes in all the patients before surgery.

After surgery abnormalities of electrolytes appeared in 16 patients. Hypernatremia occurred in 9 of 16 patients. Four of them were male and 5 female. Their mean age was 34 with a range of 28 to 58. Four of them had suffered from brain tumor, 3 aneurysm and 2 head injury (Table 2). Three patients died within 14 days after surgery and other 6 patients were discharged in good health.

Case 1. The patient (Y.S.), a 25-year-old female, complained of headache, nausea and vomiting a month prior to admission. Her complaints were not
TABLE 2. Serum sodium in nine hypernatremia patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease</th>
<th>Sex</th>
<th>Age</th>
<th>Serum sodium (mEq/liter)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brain tumor</td>
<td>F</td>
<td>25</td>
<td>165 153 152</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Head injury</td>
<td>M</td>
<td>29</td>
<td>163 158 152</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>Aneurysm</td>
<td>F</td>
<td>31</td>
<td>165 153 164 158 152</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Aneurysm</td>
<td>F</td>
<td>31</td>
<td>177 160 128 132</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>Aneurysm</td>
<td>M</td>
<td>40</td>
<td>170 131 126 128 127</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>Head injury</td>
<td>F</td>
<td>58</td>
<td>156 145 156 151</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>Brain tumor</td>
<td>M</td>
<td>28</td>
<td>154 146 166 158</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>Brain tumor</td>
<td>M</td>
<td>33</td>
<td>145 145 160 163 164</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>Brain tumor</td>
<td>F</td>
<td>35</td>
<td>148 148 160 160</td>
<td></td>
</tr>
</tbody>
</table>

* Postoperative day 1 2 3 4 5 6 7

improved by treatment and became worse gradually. Neurological examination showed bilateral choked disc. Carotid angiogram showed mass lesion of the anterior cerebral lobe. Brain tumor in the left frontal lobe of cerebral hemisphere was diagnosed and left frontal craniotomy was done. Astrocytoma containing multiple tiny cysts was extirpated. It weighed 90 g. Hypotension or shock did not develop during and after operation.

Serum sodium level rose to 175 mEq/L on the 1st postoperative day and it was 165 mEq/L on the 2nd day. Serum electrolytes were restored to normal on the 3rd day. In the course of hypernatremia her consciousness was clear, and she was afebrile and did not vomit (Fig. 3). Water balance was +600 ml on the 1st day and +700 ml on the 2nd day and she was not dehydrated clinically. Sodium balance was -33 mEq on the 1st day, +17 mEq on the 2nd day and +8 mEq on the 3rd day, that is, sodium was not retained (Fig. 4). Sodium space and Na_e were

![Fig. 3 Changes of serum electrolytes in Case 1.](image)
estimated on the 4th day when serum sodium was 152 mEq/L. Their values were within normal limits; sodium space was 287 ml/kg and Na\textsubscript{e} 43.7 mEq/kg (Fig. 3).

**Case 3.** The patient (M.W.), a 31-year-old female, suddenly fainted away and lost her eyesight, but she became well soon after the attack 3 months prior to admission. Neurological examinations disclosed no abnormal signs. Carotid angiogram showed aneurysm of the anterior cerebral artery which located in the portion of A1. Craniotomy was performed under hypothermia (25°C) and the neck of aneurysm was clipped. Hypotension or shock did not develop during and after surgery.

Serum sodium rose to 175 mEq/L on the 1st day and then it gradually lowered. It again rose to 164 mEq/L on the 4th day and 158 mEq/L on the 5th day. In the course of hypernatremia she was clear and afebrile and did not vomit. Na\textsubscript{e} was 53.0 mEq/kg on the 3rd day when serum sodium was 153 mEq/L (Fig. 5). Balance study was not done.

**Case 6.** The patient (T.I.), a 58-year-old female, encountered a traffic accident and was admitted to our hospital in coma 6 hr after the accident, and epidural hematoma was aspirated. Hypotension or shock did not develop before, during and after operation.

Six hours after surgery, serum sodium rose to 185 mEq/L, but it was restored to a normal level on the 2nd day. She was clear on the 1st and 2nd days, but gradually fell into delirium, and incontinence of urine and feces appeared on the
3rd day, and right hemiplegia occurred on the 5th day. Corresponding to her physical conditions, serum sodium again rose and hypernatremia continued (Fig. 6). Balance study had been carried out only from the 1st to the 3rd days, \( N_{ae} \) was 49.8 mEq/kg on the 1st day when serum sodium was 156 mEq/L (Fig. 6). Water and sodium balance had been negative from the 1st to 3rd days (Fig. 7).
Case 7. The patient (Y.S.), a 28-year-old male, complained of headache, nausea and vomiting 2 months prior to admission. He gradually lost his eyesight. Neurological examinations showed unilateral facial paresis and disturbance of hearing on the right side and bilateral choked disc and anopsia. Left temporal craniotomy was done. Brain tumor was found in the deep layer of the temporal lobe infiltrating into the lateral ventricle. Therefore, radical operation was not done. Histologically the tumor was a glioblastoma. Hypotension or shock did not develop during and after surgery.

Serum sodium rose to 154 mEq/L on the 1st day and 171 mEq/L on the 2nd day. On the 3rd day it lowered to 146 mEq/L, but it again rose to 155 mEq/L and then hypernatremia continued till he died on the 7th day. During the period of hypernatremia he was afebrile and did not vomit, but fell into coma since the 5th day (Fig. 8). Water balance was +1,000 ml on the 1st day and +2,800 ml on the 2nd day and he was not dehydrated clinically. Sodium balance was -7 mEq on the 1st day and -1 mEq on the 2nd day, that is, sodium was not retained (Fig. 9). Sodium space and Naₐ were within normal limits on the 2nd day when serum sodium was 171 mEq/L; sodium space was 280 ml/kg and Naₐ was 43.3 mEq/kg (Fig. 8).

Case 9. The patient (Y.H.), a 35-year-old female, complained of headache and disturbance of eyesight since 5 years. Two months prior to admission, tinnitus and clouding of consciousness appeared and at times she fell into coma.
Neurological examinations showed bilateral homonymous anopsia and optic atrophy. Cepharometric roentgenogram revealed destruction and expansion of the sella turcica, and pneumoventriculogram showed enlargement of the lateral
ventricle. Diagnosis of hypophyseal tumor was made and bilateral coronal craniotomy was done under hypothermia (29°C). Hypophyseal tumor, almost hen egg size, which compressed the optic chiasma and invaded the third ventricle,

Fig. 10. Changes of serum electrolytes in Case 9.

Fig. 11. Balance study in Case 9.
was extirpated intracapsularly. Histologically it was a chromophobe adenoma. Hypotension or shock did not develop during and after operation. She died on the 12th day.

Serum sodium rose to 160 mEq/L on the 4th day and hypernatremia continued till she died on the 12th day. In the course of hypernatremia she was delirious, but she was afebrile and did not vomit (Fig. 10). Water balance was +1,300 ml on the 1st day, +2,500 ml on the 2nd day and +800 ml on the 3rd day. From the 4th to the 6th day water balance was nearly zero. Sodium balance was negative excepting the 6th, 7th and 8th days (Fig. 11). Polyuria occurred since the 1st day, though the Carter-Robbins test (1947) proved secretion of ADH. We examined free water clearance in order to confirm the existence of dehydration. Its value was −0.15 on the 6th day, +0.17 on the 8th day, +0.68 on the 10th day and +0.34 on the 12th day.

Muscle electrolyte content was measured on the 11th day. Muscle sodium was 98 mEq/kg dry muscle. Intracellular sodium was nearly 0 mEq/L and intracellular water was 1,817 ml/kg dry muscle. A rib was obtained at autopsy on the 12th day. Its sodium content was 290 mEq/kg dry bone, potassium 20 mEq/kg dry bone and chloride 25 mEq/kg dry bone (Table 3).

### Table 3. Tissue electrolytes in Case 9

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Case 9</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total water*</td>
<td>2,485</td>
<td>3,197</td>
</tr>
<tr>
<td>Extracellular water*</td>
<td>673</td>
<td>710</td>
</tr>
<tr>
<td>Intracellular water*</td>
<td>1,817</td>
<td>2,471</td>
</tr>
<tr>
<td>Total electrolytes†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>98</td>
<td>148</td>
</tr>
<tr>
<td>Potassium</td>
<td>340</td>
<td>414</td>
</tr>
<tr>
<td>Chloride</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Intracellular electrolytes‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Potassium</td>
<td>210</td>
<td>167</td>
</tr>
<tr>
<td>Chloride</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

| Bone                    |         |              |
| Total electrolytes†     |         |              |
| Sodium                  | 290     | 310          |
| Potassium               | 20      | 26           |
| Chloride                | 25      | 15           |

* ml per kg dry weight. † mEq per kg dry weight. ‡ mEq per liter.

### Experimental research

The normal value of serum electrolytes was determined in 50 dogs. Serum sodium averaged 141 ± 3.4 mEq/L, potassium 4.3 ± 0.4 mEq/L and chloride 94 ± 8.9 mEq/L (Table 4).

Forty-four dogs were used for the experiment and their preoperative serum electrolytes were within normal limits. After operation 21 survived more than
Hypernatremia occurred in 3 dogs of the first group, but in none of the second group. The figure 12 showed changes of serum sodium in 3 dogs. Hypernatremia appeared on the 1st day and continued until they were sacrificed on the 8th day. During the period of hypernatremia they were clear and did not vomit and had good appetite. It was confirmed at autopsy that bone wax just compressed their brain stem (Fig. 1).

Experimental animal (No. 3). A mongrel dog, male, 7 kg, was anesthesized intravenously with pentobarbital and tracheal tube was inserted. Osteocrastic craniotomy was done and the optic chiasma was exposed with gentle maneuver. A piece of bone wax, weighing 1.5 g, was put near by the optic chiasma and the wound was closed primarily. A urinary bladder cannula was placed with Zeman’s apparatus.

Serum sodium rose to 171 mEq/L on the 1st postoperative day and hypernatremia continued until the animal was sacrificed on the 8th day (Fig. 13). During
the postoperative course the dog was clear and had good appetite. Water balance was positive throughout the postexperimental course. Sodium balance was slightly positive from the 1st to 3rd days, and since the 4th day on sodium was
retained much more (Fig. 14). At autopsy, it was found that bone wax destructed brain substance around the piriform area and the anterior perforated substance. There were no abnormalities in other organs.

**DISCUSSION**

Taylor (1962) suggested that brain damage in the frontal lobe, hypothalamic pituitary region or brain stem frequently caused hypernatremia. In the present study hypernatremia was observed in 9 neurosurgical patients (Table 2). In 7 of them the lesion located in the brain stem (Cases 1-5, 8 and 9). It was glioma of the left frontal lobe in Case 1, left optic lesion in Case 2, aneurysm of the right anterior cerebral artery in Case 3, aneurysm of the left posterior communicating artery in Case 4, aneurysm of the anterior communicating artery in Case 5, craniopharyngioma and meningitis in Case 8, and hypophyseal tumor in Case 9. Our results of clinical investigation proved the same correlation between cerebral hypernatremia and location of the cerebral lesion as Taylor's report. A number of patient with hypernatremia, who have had lesions in or around the hypothalamus and frontal lobe, have been reported. However, the precise localization of lesions responsible for hypernatremia, has not been well settled.

Stevenson et al. (1950) experimentally produced hypernatremia following lesions in the ventromedian nucleus of the hypothalamus in rats. Ganong et al. (1961) noted transient hypernatremia after destruction of the diencephalic and frontal lobe in 8 dogs. We also produced hypernatremia in 3 dogs by destruction around the piriform area and anterior perforated substance. These experiments suggested that hypothalamic lesions might contribute to cerebral hypernatremia.

Patients with hypernatremia could be divided into two groups. In the first group, hypernatremia occurred soon after surgery and the sodium level was gradually restored to normal. In the second group, hypernatremia did not occur immediately after surgery, but it occurred after the 4th or 5th day of operation and usually continued until death. Cases 1-7 belong to the first group and Cases 8 and 9 to the second (Table 2). In experimental study hypernatremia occurred soon after surgery and it continued till sacrifice (Fig. 12).

Figs. 3 and 4 are the charts of serum electrolytes and balance study of Case 1. Hypernatremia occurred on the 1st day and continued to the 4th day. The patient was clear and afebrile and did not vomit during the period of hypernatremia. Water balance including insensible water loss was positive from the 1st to the 4th day. Sodium balance was negative from the 1st to the 2nd day and slightly positive after the 3rd day. Sodium space and Nae on the 4th day were within normal limits; reduction of extracellular fluid and increase of exchangeable sodium were not proved. It was suggested from these data that dehydration and sodium retention were not the cause of hypernatremia in this patient.

Figs. 13 and 14 are the charts of results of the experimental study in the dog. Hypernatremia occurred on the 1st day and continued till sacrifice on the 8th day. Water balance was positive from the 1st to the 3rd day and 16 mEq of sodium
accumulated in 3 days; 8 mEq on the 1st day, 4 mEq on the 2nd day and 4 mEq on the 3rd day. Serum sodium level averaged 6±0.8 mEq/L in 5 healthy dogs after intravenous administration of 20 mEq of sodium in one shot. Therefore, such sodium retention as described above did not seem to be the cause of elevation of sodium level in this dog in which sodium level gained nearly 20 mEq/L.

Recently the existence of cerebral hypernatremia has been in dispute. Some authors believed that most, if not all, reported cases of hypernatremia were secondary to dehydration produced by various mechanisms. These mechanisms may include water loss in diabetes insipidus, inadequate water intake and hypodipsia from poor thirst mechanism due to impaired consciousness or lesions near the thirst center in the hypothalamus. On the other hand, others considered that there were cases with hypernatremia where dehydration was not present and where the electrolyte disturbances must be the result of damage to the central nervous system itself. Welt (1962) advanced the hypothesis that the ‘setting’ of the osmoreceptor was altered.

The results of the present study showed that dehydration, reduction of extracellular fluid and sodium retention were not found in Cases 1 and 7 and in 3 experimental dogs. We believe from these results that hypernatremia in Cases 1 and 7 was not secondary to water depletion, but belonged to primary cerebral hypernatremia as described by Logothetis (1966).

In Cases 2 and 6, sodium space was normal in spite of negative water balance. It seemed that water depletion did not reduce the volume of extracellular fluid and was not the cause of hypernatremia. It seemed, therefore, that some mechanisms other than dehydration would have produced hypernatremia in these cases. In the cases other than Cases 1, 2, 6 and 7, hypernatremia seemed to be secondary to dehydration and sodium retention.

The bone consists of both organic and inorganic materials and about 40% of the total body sodium are contained in the bone tissue. It was reported that most of sodium in the deep layers of the bone cortex were in combination with inorganic materials and the maximum exchangeable sodium is only 25% of the sodium content of the bone (Casey and Zimmermann 1960). Forbes et al. (1965) suggested that bone sodium changes in equilibrium with the extracellular sodium, and the bone functions as a reservoir of sodium and plays a significant role in sodium metabolism.

A rib specimen obtained at autopsy in Case 9, in which hypernatremia continued until death, contained 290 mEq of sodium/kg dry bone, 20 mEq of potassium/kg dry bone and 25 mEq of chloride/kg dry bone (Table 3). These values were within normal limits.

Muscle electrolytes were analyzed in Case 8 when its serum sodium was 150 mEq/L and in Case 9 when its serum sodium was 166 mEq/L. Muscle sodium content was 82 mEq/kg dry muscle in Case 8 and 98 mEq/kg dry muscle in Case 9 (Table 3). The results showed decrease in muscle sodium in spite of hypernatremia. In contrast with bone sodium, it was mentioned that muscle sodium easily changed
and had more close correlation with the volume of extracellular water (Graham et al. 1967, Muldowney 1963). The results obtained were coincident with a Kasai's report (1956) as to the changes of muscle electrolytes in posttraumatic hyponatremia.

It was concluded from these results that primary cerebral hypernatremia might be induced through release of muscle sodium into extracellular fluid by hypothalamic lesions.

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