Relationship between Acidity and Swelling in the Brain

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Measurement of pH of the brain tissue, macroscopic observation of the brain volume and pathohistological examination were made upon a total of 86 brains removed at autopsy. The causes of death were various and the brains were without macroscopical pathological changes.

The values of pH ranged from 5.58 to 7.01; in the majority of cases, they were between 6.2 and 6.6. No definite relationship was found between the pH values, the cause of death, age, sex and postmortem interval. All 12 cases with a pH less than 6.0 showed remarkable brain swelling. Five out of these 12 cases died after attempts at artificial respiration or resuscitation. In 11 brains out of 55 cases with a pH between 6.0 and 6.6, remarkable swelling was seen in 4 cases and slight one in 7 cases.

The prominent finding noted in the swollen brain was edema of the white matter. This was in parallel with the degree of swelling and the value of pH in all cases except one case of CO poisoning. From the above results, the author inferred that the brain swelling was due to edema of the white matter caused by acidosis and sustained insufficiency of circulation.

It is well known that the acidity of the brain comes from accumulated lactic acid, which is not only due to hypoxic episodes in life but also due to postmortem changes. Lindenberg introduced the concept of edematous swelling of the brain and inferred that the fast-developed and sustained insufficiency of systemic arterial circulation produced edema of the white matter along with the acidosis, which occurred only when the anoxia was fast developed and of stagnant type.

The present study was made to know whether the swelling of the brain is closely related to its acidity and whether the insufficient circulation is also necessary to produce brain-swelling.

MATERIALS AND METHODS

This study was made on a total of 86 brains removed at autopsy. These brains were made available from the Office of the Chief Medical Examiner, State of Maryland, U.S.A. including various causes of death. Brains with hemorrhage, inflammation, softening or any other pathological findings were excluded. All
the examined brains were macroscopically intact.

The pH was measured with a Metrohm E300 pH-meter with a needle-type combined glass electrode. The white matter of the left parietal, frontal and temporal lobes, and the cerebellum were used for the measurement.

The brain was macroscopically observed and the tissue sections were microscopically examined after Nissl staining.

The history and the cause of death determined from autopsy were also analyzed.

**RESULTS**

The data of the representative cases are presented in Table 1, in which all cases showing very low values of pH and some other cases are included.

The number of cases and the causes of death verified from autopsy findings were as follows: 33 cases of cardio-vascular diseases, 10 cases of diseases of liver or pancreas, 9 cases of respiratory diseases, 8 cases of poisoning, 7 cases of drowning or asphyxiation, 5 cases of gunshot wound, 5 cases of multiple traumatic injuries, 4 cases of massive hemorrhage, and 5 cases of burns, electrocution or others.

The age of subjects varied from seven weeks to eighty-two years. Seventeen cases were female and 69 cases male.

In 79 cases, the subjects were found dead, or found unconscious and died on arrival (DOA). In 5 cases, the deceased had survived a few hours under medical treatments, and more than half a day in 2 cases.

A small difference such as less than 0.1 was found among the pH values measured at four parts of the left hemisphere. Accordingly, the author adopted only the value measured at the parietal lobe. The postmortem pH value of the brain

![Fig. 1. Diagram showing the number of cases according to the value of pH and the degree of swelling. Solid black: with remarkable swelling. Hatched area: with moderate or slight swelling.](image-url)
<table>
<thead>
<tr>
<th>Case No.</th>
<th>History and cause of death</th>
<th>Post-mortem period Hr.</th>
<th>pH</th>
<th>Swelling</th>
<th>Weight g</th>
<th>Pathohistological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>Female aged 44; known alcoholic, found unconscious in bed, DOA; fatty liver</td>
<td>4</td>
<td>5.60</td>
<td>#</td>
<td>1,380</td>
<td>Parietal lobe: “Acute changes” of neurons with visible dendrites over long stretches, large nuclei, breakdown of nucleoli. Early progressive changes in glia of cortex and white matter. Edema and plasma bleeding in white matter.</td>
</tr>
<tr>
<td>83</td>
<td>Female aged 3; collapsed, brought into hospital, resuscitation attempted; pneumonia</td>
<td>13</td>
<td>5.64</td>
<td>#</td>
<td>1,250</td>
<td>Parietal lobe: Early intravital necrosis of neurons in middle layers of cortex with paling and shrinkage. Mild progressive glial reaction. Dilatation of capillaries with beginning progressive changes of all elements. White matter: Mild edema and progressive changes in astrocytes. Pyknosis of oligodendroglia.</td>
</tr>
<tr>
<td>101</td>
<td>Male aged 2; found in water, completely arrested, given artificial respiration, the heart started to beat; drowning</td>
<td>13</td>
<td>5.64</td>
<td>#</td>
<td>1,260</td>
<td>Parietal lobe: Acute shrinkage of neurons with dilatation of pericellular spaces, seldom incrustations and vacuolization. Little edema and glial reaction in white matter. Midbrain: Acute shrinkage of most neurons, in some neurons vacuolization with paleness. Pyknosis of oligodendroglia. Little reaction of astrocytes. Medulla oblongata: Acute shrinkage of most neurons, beginning reaction of astrocytes, little interstitial edema.</td>
</tr>
<tr>
<td>8</td>
<td>Female aged 64; fell down, struck neck, survived 3 months; septicemia</td>
<td>15</td>
<td>5.68</td>
<td>#</td>
<td>1,290</td>
<td>Parietal lobe: Shrinkage of most neurons. No vacuolization. Edema in cortex with beginning reaction of astrocytes. Edema in white matter with glial reaction.</td>
</tr>
<tr>
<td>46</td>
<td>Female aged 6; pulled from water, given mouth-to-mouth resuscitation, taken to hospital, later went into cardiac arrest, resuscitation attempted; drowning</td>
<td>10</td>
<td>5.97</td>
<td>#</td>
<td>1,340</td>
<td>Parietal lobe: Shrinkage of large neurons in fifth layer. Slight paling of other neurons. Mild, early glial reaction. Congestion of vessels without cellular reaction. Edema with paleness in deep white matter. Little reaction of subcortical glia.</td>
</tr>
<tr>
<td></td>
<td>Case Description</td>
<td>Age</td>
<td>Width</td>
<td>Height</td>
<td>Score</td>
<td>Parietal lobe:</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>53</td>
<td>7 weeks female baby; found unconscious in crib; DOA; interstitial pneumonia</td>
<td>10</td>
<td>5.88</td>
<td>+</td>
<td>660</td>
<td>Many neurons normal, fuzzy dendrites. No vacuolization, no glial reaction. Edema and congestion in white matter.</td>
</tr>
<tr>
<td>1</td>
<td>Female aged 49; found lying on bed; hemorrhage from stomach</td>
<td>13</td>
<td>5.88</td>
<td>+</td>
<td>1,210</td>
<td>Cortex normal. Little edema in white matter (deep portion).</td>
</tr>
<tr>
<td>7</td>
<td>Female aged 55; was a passenger in an auto, the auto hit a wall; one month later, found dead in bed; bronchopneumonia</td>
<td>2</td>
<td>5.83</td>
<td>+</td>
<td>1,200</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Male aged 32; found dead in bed; previously had complained of chest pain; leukemia</td>
<td>5</td>
<td>5.79</td>
<td>+</td>
<td>1,440</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>Male aged 35; had convulsion, taken to hospital, given heart massage and placed under respirator; hypertensive cardiovascular disease</td>
<td>5</td>
<td>5.95</td>
<td>+</td>
<td>1,500</td>
<td>Shrinkage of all neurons. Edema in white matter. Early glial reaction in places. Some congestion.</td>
</tr>
<tr>
<td>47</td>
<td>16 months male baby; had a fever one day before death; while the mother was holding him, he went into a limp DOA; interstitial pneumonia</td>
<td>5</td>
<td>6.02</td>
<td>+</td>
<td>1,410</td>
<td>Normal neurons with fuzzy dendrites. No glial reaction. In white matter, little edema, slight regressive changes of glia in places.</td>
</tr>
<tr>
<td>100</td>
<td>Female aged 47; found unconscious in bed; pneumonia</td>
<td>5</td>
<td>6.02</td>
<td>+</td>
<td>1,410</td>
<td>Medium shrinkage of neuron. Some neurons normal. Increased glia in white matter. Some progressive changes and accumulation around vessels. Little edema. Beginning reaction of vascular elements.</td>
</tr>
<tr>
<td>16</td>
<td>Male aged 67; driver of a vehicle, it struck a tree; blunt impact to chest and abdomen</td>
<td>11</td>
<td>6.19</td>
<td>−</td>
<td>1,360</td>
<td>Acute shrinkage of some neurons, other neurons normal. No glial reaction. No edema.</td>
</tr>
<tr>
<td>26</td>
<td>Male aged 39; found lying on the floor alongside of his bed; pancreatitis</td>
<td>5</td>
<td>6.40</td>
<td>−</td>
<td>1,440</td>
<td>Acute shrinkage of many neurons. No edema. Regressive glia. Slight edema in white matter. Regressive changes of oligos.</td>
</tr>
</tbody>
</table>
tissue varied from 5.58 to 7.01, ranging from 6.2 to 6.6 in the majority of cases.

The term ‘brain swelling’ is based on macroscopic findings resulting from an increase in the brain volume. Such brain shows flattened gyri, narrowing of ventricular system, damp appearance of white matter or herniation. The relationship between the brain swelling and pH values is given in Fig. 1. From this diagram, the cases were classified into three groups, according to pH values of under 6.0, from 6.0 to 6.6 and over 6.6. All 12 cases belonging to the first group showed a remarkable swelling of the brain. Five cases, in which the subjects were placed under a resuscitator or the artificial respiration was attempted, were included in the first group with remarkable brain-swelling. In 11 out of 65 cases belonging to the second group, a remarkable swelling of the brain was seen in 4 cases and a slight swelling in 7 cases. Only one case of the third group showed a very slight swelling.

The postmortem interval to the time of measurement was within 24 hours and the corpses were being kept in a refrigerator at 6°C. No correlation was found between the values of pH and the postmortem interval. In two cases, for instance, in which the measurements were performed about four hours after death, one showed 5.62 and the other 6.34. Four cases about ten hours after death showed 5.88, 5.97, 6.34 and 6.52, respectively, and both of two cases about 24 hours after death showed 6.4.

The common microscopic finding was acute shrinkage of neurons. The cell body became angular and cytoplasm became acidophilic. Swollen neurons were not found. In the brains showing swelling and very low pH, early progressive changes and/or beginning degenerative changes were seen and the prominent change was commonly the edema in the white matter. In the brains showing moderate or slight shift of pH, there were no remarkable changes except small flaky structures in some cases. Those findings were in parallel with the swelling and the shift of pH in all cases except Case No. 54. The subject of this case died of CO poisoning in a car: There was a hole in the floor of the car and the exhaust gas invaded the car through the broken muffler. The value of pH was 6.35 in

|---|-----------------------------------------------------------------|-----|-----|---|-------|--------------------------------------------------------------------------------------------------|
the parietal, 6.32 in the frontal, 6.17 in the temporal lobes and 6.11 in the cerebellum. The brain showed macroscopical swelling and an increase of weight. Microscopically, spotty edema and early shrinkage of neurons were partly observed and edema of the white matter was also seen.

**DISCUSSION**

The values of pH observed in this study ranged widely from 5.58 to 7.01. There was no definite relationship between the values of pH and postmortem interval. For example, in two cases, of which the postmortem interval was four hours, the values of pH were 5.62 and 6.34. The corpses were kept in a refrigerator and the measurement were performed within 24 hours after death.

The pH value of brain tissues varies in accordance with the accumulation of lactic acid. In 1886, Langendorff reported that the brain was normally alkaline in its reaction but it became acid when the blood supply was cut off or when the brain was removed. Since then many investigators described the pH value and/or the concentration of lactic acid in the brain tissue. The pH value of the brain tissue is correlated with the concentration of lactic acid, and the amount of lactic acid is also correlated with postmortem glycolysis. The pH in normal and hyperglycemic animals measured immediately after sacrifice was low and fell in parallel with the postmortem decrease in sugar content and with the increase in lactic acid, while that in hypoglycemic animals was high and fell slowly. The curve of lactic acid accumulation in the brain after decapitation showed an abrupt rise during the first four minutes and gradually attained a plateau in the following 20 minutes. The curve for anoxic animals showed a more rapid rise than that for normal ones, and the acid production during oxygen deprivation was five times as great as that during sufficient supply of oxygen. Under the condition of ischemia, the pH went down rapidly during the first three minutes and the concentration of lactic acid increased.

It has been confirmed that the change of pH in the brain tissue is due to lactic acid produced. The important factors contributing to the final lactic acid concentration after death are the excessive acid in the brain at the time of death and the elevated blood sugar level. Hypoxic episodes such as asphyxia, severe hemorrhage or shock have been known to induce hyperglycemia. As mentioned above, the author inferred that the very low value of pH was not only due to the postmortem changes but also due to the acidosis and/or hyperglycemia in life.

In 1890, Roy and Sherrington observed that the brain volume increased when a small dose of free acid (nitric or sulphuric acid) was introduced into a vein, but there was no rise of blood pressure sufficient to cause the cerebral congestion. Wheatley reported an interesting experimental result that when NaCN in doses of 1.4 to 1.6 mg per kg was given to the paralyzed cat under artificial respiration,
there occurred a temporary inadequacy of circulation, and when the blood flow was restored, the brain volume increased by as much as a third of its volume.

Acidity enough to change the osmotic balance is necessary to produce swelling. If produced lactic acid is rapidly discharged into circulation, there would be no brain-swelling. If the production of lactic acid is continuous and the circulation is not sufficient to remove the acid but sufficient to supply water and sugar, acidosis would take place in the brain and cause brain-swelling.

In the present study, the cases of literally sudden death, in which the circulation cut off abruptly and there was no time to bring about the process described above, did not show an increase of the brain volume and low value of pH. In all cases with a pH value under 6.0, severe swelling was seen. And, all cases, in which resuscitation had been attempted, showed very low pH value and severe swelling.

These results support the above-mentioned concept that rapid interruption of oxygen supply and the poor circulation are the main factors to produce the swelling of brain.

The common microscopic finding was ischemic shrinkage of the neuron. In some cases, vacuolization or homogenization was observed. Such findings were similar to those observed by Lindenberg in human and experimental materials, in which death occurred either suddenly or within about ten minutes after the onset of hypoxia. The prominent change common to the brain with very low pH was edema of the white matter. This suggests that the increase of brain volume is caused by edema of the white matter.

From the above results, the author concluded that the brain-swelling was attributed to edema of the white matter caused by the acidosis and sustained insufficiency of circulation.

Acknowledgment

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