The concentrations of xanthine and hypoxanthine in cerebrospinal fluid as therapeutic guides in hydrocephalus

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Abstract. Xanthine, hypoxanthine, and total oxypurine levels were determined in the cerebrospinal fluid of 18 hydrocephalic patients and 8 healthy controls by high-performance liquid chromatography (HPLC). Eight of the hydrocephalic patients were self-compensated and 10 had shunts implanted during the course of the study. The mean xanthine, hypoxanthine, and total oxypurine levels in the normal children were 5.20, 5.94 and 11.29 μmol/1, respectively. In self-compensated hydrocephalics these levels were respectively 6.06, 6.50 and 12.57 μmol/1. In noncompensated hydrocephalics, they were 11.40, 10.79 and 22.19 μmol/1. The differences between the latter group and the first two are statistically significant (P<0.001). Fifteen days after implantation of shunts in the noncompensated hydrocephalics, the mean xanthine levels had fallen to 4.61 μmol/1, the mean hypoxanthine levels to 5.03 μmol/1, and the mean total oxypurine levels to 9.64 μmol/1. The change is statistically significant (P<0.001).

In light of these findings we propose that xanthine, hypoxanthine, and total oxypurine levels be used in cases of hydrocephalus as guides for therapeutic action and to monitor progress.

Key words: Hydrocephalus – Cerebrospinal fluid – Total oxypurines – Xanthine – Hypoxanthine – Guanine.

In treating infantile hydrocephalus it is frequently necessary to decide whether it is better to implant a shunt or to wait for spontaneous improvement. There are presently no universally accepted criteria on which to base this decision. Hagberg [9] has defended conservative management during the first months of life if there are no signs of psychomotor regression or neurological abnormality, and so long as the circumference of the skull tends to normality and ventricular dilation does not increase. In cases of hydrocephalus due to myelodysplasia, Zachary [20] recommended the use of criteria based on the thickness of the cerebral mantle and the pressure of the cerebrospinal fluid (CSF). We have previously [4] proposed criteria based on the absorption-pressure of the CSF. Our current clinical practice in cases of communicating hydrocephalus is to employ criteria based on Evans’ index and the mean weekly increase in cranial circumference [6]. When a shunt is necessary, we suggest adjusting its opening pressure to that of the CSF [5].

In recent years, high levels of xanthine and hypoxanthine have been measured in the CSF of newborn infants with cerebral hypoxia and in hydrocephalic children [1, 10, 13, 14]. This has prompted us to carry out a comparative study of the CSF oxypurine levels of hydrocephalic children and healthy controls, with the aim of evaluating the possibility of their use as criteria for therapeutic action.

Materials and methods

Eighteen hydrocephalic infants ranging from newborn to 4 years of age (mean age = 8 months) were monitored throughout 1985. The hydrocephalus was communicating in 9 cases and obstructive in the other 9. Shunts were necessary in all the obstructive cases and in one of the communicating hydrocephalics. No therapeutic action was required in the 8 communicating hydrocephalus patients with Evans indexes between 0.32 and 0.41, whose psychomotor development over the 12 months was considered normal, with no increase in ventricular size as measured by real time ultrasond and by computerized tomography (CT). They were, accordingly, deemed to have self-compensated.

The xanthine, hypoxanthine, total oxypurine, and guanine levels in the CSF of all hydrocephalic patients and 8 healthy controls to obtain the normal range (nonhydrocephalic emergency patients with normal CSF) were measured by HPLC [11]. Levels were determined again in all the children who required a shunt 15 days after its implantation. The results were analyzed statistically, using the Student's t-test.

Results

Xanthine, hypoxanthine, total oxypurine, and guanine levels in the CSF of patients and controls

The mean xanthine, hypoxanthine, total oxypurine, and guanine levels in the self-compensated hydrocephalic chil-
Table 1. Hypoxanthine, xanthine, total oxypurine, and guanine levels in the CSF of patients and controls. The differences between the hypoxanthine, xanthine, and total oxypurine levels of the non-compensated patients and those of the other two groups are statistically significant ($P < 0.001$)

<table>
<thead>
<tr>
<th></th>
<th>X±SD</th>
<th>Hypoxanthine</th>
<th>Xanthine</th>
<th>Total oxypurine</th>
<th>Guanine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (8)</td>
<td>5.94±0.74</td>
<td>5.20±0.87</td>
<td>11.29±1.11</td>
<td>7.23±2.34</td>
<td></td>
</tr>
<tr>
<td>Self-compensated (8)</td>
<td>6.50±0.86</td>
<td>6.06±1.62</td>
<td>12.57±2.30</td>
<td>8.57±3.36</td>
<td></td>
</tr>
<tr>
<td>Non-compensated (10)</td>
<td>10.69±1.55</td>
<td>11.40±1.54</td>
<td>22.19±2.89</td>
<td>7.95±2.32</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Hypoxanthine, xanthine, and total oxypurine levels in the CSF of patients with CSF pressures, respectively, less than and greater than 10 mmHg. The differences between the two groups are not statistically significant

<table>
<thead>
<tr>
<th>CSF pressure</th>
<th>X±SD</th>
<th>Hypoxanthine</th>
<th>Xanthine</th>
<th>Total oxypurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mmHg (6)</td>
<td>6.89±1.59</td>
<td>6.88±2.31</td>
<td>14.2 ±3.75</td>
<td></td>
</tr>
<tr>
<td>&gt;10 mmHg (12)</td>
<td>9.22±2.79</td>
<td>8.86±3.23</td>
<td>18.08±5.99</td>
<td></td>
</tr>
</tbody>
</table>

**Correlation between xanthine, hypoxanthine, and total oxypurine levels and CSF pressure**

The mean xanthine, hypoxanthine, and total oxypurine levels in patients with a CSF pressure of less than 10 mmHg were 6.88, 6.98 and 14.2 μmol/l, respectively. The levels in patients with a CSF pressure greater than 10 mmHg were, respectively, 8.86, 9.22 and 18.08 μmol/l (Table 2). The differences between the two groups are not statistically significant ($P > 0.05$).

**Changes in xanthine, hypoxanthine, and total oxypurine levels after the implantation of shunts**

In those patients in whom shunts were implanted, the mean xanthine level fell from 11.40 to 4.61 μmol/l, the mean hypoxanthine level from 10.79 to 5.03 μmol/l, and the mean total oxypurine level from 22.19 to 9.64 μmol/l (Fig. 1). These changes are statistically highly significant ($P < 0.001$).

**Discussion**

Adenine nucleotides may be overcatabolized as the result of faults in energy metabolism [2] in which case their metabolites, xanthine and hypoxanthine leave the cells in which they are produced to accumulate in extracellular fluids [2, 3, 7, 8, 15, 18, 19]. Thus, typically, tissue hypoxia that gives rise to increased catabolism of adenine nucleotides has the secondary effect of raising xanthine and hypoxanthine levels in plasma and CSF [2, 3, 10, 17]. The high levels of xanthine and hypoxanthine observed in the CSF of infants with hydrocephalus [1, 13] have been explained as the result of a reduction in the blood supply to the brain resulting from an increase in intracranial pressure, for it is known that a moderate rise in intracranial pressure can significantly reduce cerebral blood flow [12, 16]. Bejar et al. [1] have concluded that even when no increase in cranial circumference occurs, progressive ventriculomegaly is invariably associated with cerebral ischemia apparent in CSF hypoxanthine levels, which are exceptionally high but return to normality when the hydrocephalus is controlled. Levin et al. [13] have observed a close correlation between the CSF pressure and CSF