Background: The pathogenesis of posthaemorrhagic hydrocephalus (PHHC) following intraventricular haemorrhage (IVH) in premature infants includes a fibroproliferative reaction leading to arachnoidal fibrosis, ultimately causing malresorption of cerebrospinal fluid (CSF) at the arachnoid villi.

Aims: To determine whether an increased concentration of the carboxyterminal propeptide of type I procollagen (PICP) in the CSF of neonates after IVH reflects the activation of collagen synthesis preceding the manifestation of PHHC.

Methods: From 20 neonates with PHHC (median birth weight 740 g, median gestational age 25+1 weeks), 52 CSF samples were collected. CSF samples of four neonates (median birth weight 2170 g, median gestational age 32+4 weeks) with congenital non-haemorrhagic hydrocephalus served as controls. PICP was measured by radioimmunoassay.

Results: PICP in CSF taken at the start of external CSF drainage (median day 21, range 17–25 days postnatal age) was significantly increased (median 153.5–1944 µg/l) compared with controls (median 136.1, range 33.8–169.5 µg/l). CSF concentrations of PICP declined until permanent shunt placement (median day 70, range days 41–113).

Conclusion: In neonates who develop PHHC, significant elevation of PICP concentration in the CSF is present 3–4 weeks after IVH. It reflects the increase of local type I collagen turnover, thereby correlating with manifestation of PHHC.

**ORIGINAL ARTICLE**

Procollagen I C-propeptide in the cerebrospinal fluid of neonates with posthaemorrhagic hydrocephalus

A Heep, B Stoffel-Wagner, V Soditt, C Aring, P Grones, P Bartmann

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**Conclusion:** In neonates who develop PHHC, significant elevation of PICP concentration in the CSF is present 3–4 weeks after IVH. It reflects the increase of local type I collagen turnover, thereby correlating with manifestation of PHHC.

**Abbreviations:** CSF, cerebrospinal fluid; IVH, intraventricular haemorrhage; PHHC, posthaemorrhagic hydrocephalus; PICP, carboxyterminal propeptide of type I procollagen; PIIICP, carboxyterminal propeptide of type III procollagen; PIIINP, aminoterminal propeptide of type I procollagen; PIIINP, aminoterminal propeptide of type III procollagen; SAH, subarachnoid haemorrhage
immediately centrifuged and stored at −40°C until analysis. PICP was measured with a commercially available radioimunoassay (Orion Diagnostica, Espoo, Finland). The sensitivity of the method was 1.2 µg/l. The intra-assay coefficient of variation was 3.2% (mean 451 µg/l, n = 16), and the interassay coefficient of variation 4% (mean 435 µg/l, n = 8).

Data analysis
For statistical analysis, the Mann–Whitney U test was used, with two sided p values to compare groups of values, as the distributions were non-Gaussian.

RESULTS
The median concentration of PICP in the CSF of the patients with PHHC taken at week 3 after IVH was raised (median 851.5 µg/l, range 153–1944 µg/l). When compared with controls (median 118 µg/l, range 33–169 µg/l), this difference was statistically significant (p < 0.001). PICP concentrations in the PHHC group further decreased at week 4 (552 µg/l, 83–1588 µg/l) and week 5 (255 µg/l, 67–628 µg/l), and at the time of shunt placement (300 µg/l, 52–946 µg/l) (fig 1 and table 2).

DISCUSSION
The activation of collagen biosynthesis and collagen deposition in the brain after IVH has been shown in humans and in experimental studies in animals (table 3). It was shown that up regulation of extracellular matrix protein synthesis in the local mesenchymal cells (dural, leptomeningeal), which are composed of different collagen proteins (type I, type III) was induced as a consequence of cerebral bleeding. Several experimental models show the time course of collagen synthesis activation and fibroproliferative reaction in the brain following SAH. In a rat model of artificial SAH, a threefold increase of meningeal prolyl 4 hydroxylase activity, the major intracellular enzyme of collagen synthesis, was measured one week after induced SAH. In the same study, increased collagen synthesis resulted in an accumulation of type 1 collagen fibres within the meningeal tissue at three weeks after SAH. In a dog model of experimental SAH, leptomeningeal fibrosis was documented after two weeks by histopathology. In an experimental model of induced lung fibrosis, messenger RNA coding for type 1 procollagen was detected and reached a maximum accumulation two to three weeks after treatment. Proliferation of leptomeningeal cells and deposition of extracellular matrix in the arachnoid granulation after aneurysmal SAH was shown on human autopsy. Thus, experimental and human data suggest that IVH may induce collagen synthesis in the CSF and that it is a potential trigger of meningeal fibrosis.

Although most PHHC develop rapidly within two to four weeks after IVH in premature infants, some develop slowly over a period of weeks or months. In a recent study, we showed that normalisation of total CSF protein values under daily external ventricular CSF drainage was reached not later than week 5 after IVH. Procollagen propeptide concentrations decline until permanent

Table 1 Neonatal profile of the patients

<table>
<thead>
<tr>
<th>Neonatal profile (n=20)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>740 (470 to 1685)*</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>25±1 (22±3 to 33±2)*</td>
</tr>
<tr>
<td>No. boys</td>
<td>7/20 35</td>
</tr>
<tr>
<td>Respiratory distress syndrome &gt;2°</td>
<td>16/20 80</td>
</tr>
<tr>
<td>Seizures</td>
<td>9/20 45</td>
</tr>
<tr>
<td>Apgar-bradycardia syndrome</td>
<td>19/20 95</td>
</tr>
<tr>
<td>Necrotizing enterocolitis &gt;2°</td>
<td>1/20 5</td>
</tr>
<tr>
<td>Retinopathy of prematurity &gt;2°</td>
<td>3/20 15</td>
</tr>
<tr>
<td>Intraventricular haemorrhage, grade III°, IV°</td>
<td>19/20 95</td>
</tr>
<tr>
<td>Bilateral</td>
<td>17/20 85</td>
</tr>
<tr>
<td>Unilateral</td>
<td>2/20 10</td>
</tr>
<tr>
<td>Periventricular leucomalacia</td>
<td>9/20 45</td>
</tr>
</tbody>
</table>

*Mean (range).

Table 2 PICP concentration in the CSF in 20 neonates with PHHC and four control subjects

<table>
<thead>
<tr>
<th>Study group</th>
<th>PICP (µg/l)*</th>
<th>No. of analyses</th>
<th>Controls PICP (µg/l)*</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 3</td>
<td>851 (153–1944)</td>
<td>14</td>
<td>118 (33–169)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>552 (83–1588)</td>
<td>13</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>255 (67–628)</td>
<td>8</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td>300 (52–946)</td>
<td>17</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

*Median (range).

**Significantly higher in patients than control subjects.

Figure 1 Time course of PICP concentrations in the CSF of 20 neonates with PHHC and four control subjects. Values are median and 25th and 75th centiles (boxes), and 5th and 95th centiles (whiskers).

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shunt placement after the start of external CSF drainage, but remain above control concentrations despite normalisation of the CSF protein concentration. As CSF protein content is not an adequate marker for active fibroproliferation, which should therefore be monitored more specifically by determination of PICP. Our data provide evidence for the induction of intrathecal collagen type I turnover by IVH and the involvement of arachnoid fibrosis in the pathogenesis of PHHC in neonates. The results are in accordance with experimental data from animal models (table 3). Raised PICP concentrations in the CSF samples taken at different times show that the increased collagen turnover is not a transient self-limiting reaction of tissue repair following injury. It is related to chronically increased collagen turnover and deposition, interfering with CSF drainage and leading in all our patients to at least PHHC.

As all the CSF samples in this study were withdrawn with therapeutic intention, no further serum samples were taken to determine the CSF:serum ratio.

Further investigations are needed to describe the pathophysiology of the activation of collagen turnover after IVH in order to develop therapeutic strategies to prevent malresorptive hydrocephalus caused by meningeal fibrosis.

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REFERENCES

Table 3 Measurements of collagen turnover in the brain after IVH

<table>
<thead>
<tr>
<th>First author</th>
<th>Specimen</th>
<th>Organ</th>
<th>Measurement</th>
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</thead>
<tbody>
<tr>
<td>Sajanti</td>
<td>Rat</td>
<td>Brain</td>
<td>Prolyl 4 hydroxylase</td>
</tr>
<tr>
<td>Pang</td>
<td>Dog</td>
<td>Brain</td>
<td>Collagen deposition</td>
</tr>
<tr>
<td>Suzuki</td>
<td>Dog</td>
<td>Brain</td>
<td>Collagen deposition</td>
</tr>
<tr>
<td>Motohashi</td>
<td>Human</td>
<td>Brain</td>
<td>Collagen deposition</td>
</tr>
<tr>
<td>Sajanti</td>
<td>Human</td>
<td>Brain</td>
<td>PICP, PIIICP (RIA)</td>
</tr>
</tbody>
</table>
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