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Manganese elevations in blood of children with congenital portosystemic shunts

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Abstract Magnetic response imaging has demonstrated increased signal intensities within the basal ganglia in patients with hepatic encephalopathy; the densities are considered to represent manganese deposition. We measured whole blood manganese concentrations in nine children with congenital portosystemic venous shunts detected by screening tests for galactosaemia. Beyond 1 year of age, these patients showed significantly higher manganese concentrations than controls (2.40 ± 0.43 versus 1.48 ± 0.38 μg/dl; \( P = 0.0001 \)). Four of the nine patients were studied by magnetic response imaging. T1-weighted images showed increased signal intensities in the basal ganglia of those four patients, suggesting manganese accumulation.

Conclusion Children with congenital portosystemic venous shunts showed manganese elevations in blood and magnetic response imaging changes in the basal ganglia. These children should avoid excessive manganese intake.

Key words Basal ganglia · Congenital portosystemic venous shunt · Magnetic response imaging · Manganese

Abbreviations Mn manganese · MRI magnetic response imaging · PSVS portosystemic venous shunt

Introduction

Many cases of congenital portosystemic venous shunt (PSVS) are identified in the course of diagnostic investigation of hypergalactosaemia detected by newborn screening [3, 11–13]. In patients with PSVS, hepatic encephalopathy is the most feared complication. While blood ammonia concentrations are measured frequently as an indicator of hepatic encephalopathy [16], few investigations have considered other potential toxic agents in cases of congenital PSVS.

Increased signal intensities within the basal ganglia have been observed by magnetic response imaging (MRI) in patients with hepatic encephalopathy. Recently these abnormal signals have been attributed to manganese (Mn) deposition [1, 2, 7–9]. Even cases of congenital PSVS without hepatic dysfunction can show similar MRI changes [17], considered to have resulted from increased Mn concentrations in blood arising from PSVS. However, the issue of Mn metabolism in cases of congenital PSVS has, to our knowledge, not been addressed.

We detected high Mn concentrations in whole blood from children identified by newborn screening for galactosaemia who proved to have congenital PSVS.

Subjects and methods

Subjects in the present investigation included nine children ranging in age from 15 days to 11 years who were found to have congenital PSVS after newborn screening for hypergalactosaemia. The

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pathogenic anatomy of PSVS was as follows: connections between portal and hepatic veins via hepatic haemangiomas (four patients); absence of the intrahepatic portal vein with an open ductus venosus connecting the left portal vein to the inferior vena cava (one patient); hypoplasia of the intrahepatic portal vein with patent ductus venosus (one patient) and an abnormal canal between the left portal vein and the left renal vein (three patients) (Table 1). All patients had normal liver function and no instance of neurological symptoms. These patients presented with hyperammonaemia (patient 2 57–112 µg/dl, patient 3 79–260 µg/dl, and patient 5 39–184 µg/dl), but only patient 3 has shown persistent hyperammonaemia and taken a low-protein diet and the administration of lactulose. Seventy-one healthy children with no detected anomaly of the portal vein (age range 18 days to 18 years) were studied as controls.

Blood specimens were obtained during a visit to the Department of Paediatrics at the Hiroshima University Faculty of Medicine. Concentrations of Mn in whole blood were determined by flameless atomic absorption spectrometry. Cranial MRI was performed in four (patients 1–3 and 5).

Data were compared using the Mann-Whitney U test for independent groups. All values are presented as the mean ± standard deviation (SD).

Results

The four patients undergoing MRI all showed bilateral symmetric increases in signal intensity in the basal ganglia, especially the globus pallidus, in T1-weighted images (Fig. 1). T2-weighted images appeared normal.

As Figure 2 indicates, concentrations of Mn in whole blood from normal children are highest in neonates. With increasing age, these concentrations decrease until reaching a stable low level at 1 year. Respectful normal control values for Mn in neonates (n = 14), subjects 1 to 11 months old (n = 21), and subjects over 1 year old (n = 36) were 5.64 ± 1.64, 2.61 ± 1.89, and 1.48 ± 0.38 µg/dl, respectively.

Whole blood Mn concentrations in PSVS are shown in the Table 1 and Fig. 2. Above the age of 1 year, whole blood Mn concentrations in PSVS cases (n = 7) were significantly higher than those in controls (2.40 ± 0.43 versus 1.48 ± 0.38 µg/dl; P = 0.0001).

Discussion

Mn deposition has been considered a cause of MRI changes in the basal ganglia associated with hepatic encephalopathy. Some authors have noted that tissue Mn concentrations were increased in the basal ganglia in patients with cirrhosis who had similar MRI changes [1, 8, 9]. MRI similar findings were apparent in patients receiving long-term parenteral nutrition with excessive Mn content resulting in elevations of Mn in the blood [2]. In our congenital PSVS cases, we also found elevation of whole blood Mn concentrations and MRI changes in the basal ganglia. These observations suggest

Table 1 Clinical details of nine patients with PSVS. (ND not done)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>PSVS</th>
<th>Shunt rate (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Blood Mn (µg/dl)</th>
<th>Hyperammonaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>Haemangioma</td>
<td>45</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>Absence of portal vein</td>
<td>ND</td>
<td>2.6</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Patent duct venosus</td>
<td>70</td>
<td>3.2</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Portal-renal vein</td>
<td>14</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Haemangioma</td>
<td>57</td>
<td>2.0</td>
<td>+</td>
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<tr>
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<td>ND</td>
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<tr>
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<td>0.04</td>
<td>Portal-renal vein</td>
<td>ND</td>
<td>3.0</td>
<td>-</td>
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</tbody>
</table>

<sup>a</sup>The shunt rate was determined with 1123 iodoamphetamine per-rectal portal scintigraphy

Fig. 1 Cranial T1-weighted magnetic response images in the axial plane (patient 1). A Bilaterally symmetric hyperintensities in the globus pallidus. B Slightly hyperintense signal in the red nucleus and substantia nigra.