Intracranial calcification in survivors of childhood medulloblastoma

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SUMMARY Computerised tomography scans of the brain have been performed on 5 children who have survived at least 5 years after treatment with surgery and radiotherapy for medulloblastoma. Intracranial calcification of varying degrees of the basal ganglia and of the frontal and parietal cortex was detected in the 3 children who were irradiated under age 5 years.

Now that survival rates seem improved after combined treatment of medulloblastoma in childhood, attention is focused on the quality of life of the survivors.1–3 In some intellectual function and growth are impaired. However, no structural changes observed on the computerised tomography (CT) scan have been related to these changes in function. We performed CT scans on five, 5-year survivors of medulloblastoma to detect morphological changes in the central nervous system (CNS).

Patients

Between 1968 and 1976, 31 cases of medulloblastoma were notified to the Northern Region Children's Malignant Disease Registry (A W Craft, unpublished data) of whom six patients are still alive at least 5 years after treatment. Five of them were studied. Details of their treatment are shown in Table 1. All children in addition received spinal irradiation.

Results

The CT scan findings, intelligence quotients, and recent clinical details are shown in Table 2, and examples of the CT scans are shown in Figs 1 and 2.

Three patients, those treated under age 5 years, had evidence of intracranial calcification in varying

Table 1 Details of operative and cranial radiotherapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years) at presentation</th>
<th>Operation</th>
<th>Postoperative course</th>
<th>Details of radiotherapy</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose (Gy)</td>
<td>Fractions</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Subtotal removal</td>
<td>Ventricular peritoneal shunt</td>
<td>36*</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Subtotal removal</td>
<td><em>Staphylococcus aureus meningitis, Ventricular peritoneal shunt, Temporary Rickham's reservoir</em></td>
<td>39*</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Subtotal removal</td>
<td></td>
<td>30*</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Subtotal removal</td>
<td>Ventricular peritoneal shunt</td>
<td>45†</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>Total macroscopic removal</td>
<td></td>
<td>34*</td>
<td>25</td>
</tr>
</tbody>
</table>

*These children received an additional 15 Gy to the posterior fossa.
†Received at the London Hospital.
### Table 2  Current clinical details and appearances on the CT scans

<table>
<thead>
<tr>
<th>Case</th>
<th>Years survival</th>
<th>School performance</th>
<th>Clinical details</th>
<th>IQ</th>
<th>CT scan findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>Poor attention span. Hyperactive</td>
<td>Growth hormone deficient. Minor seizures. Abnormal EEG</td>
<td>77</td>
<td>Extensive calcification in frontal and parietal lobes and basal ganglia. Lateral ventricles slightly dilated. Repeat scan 18 months later showed no change</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Poor attention span. Hyperactive</td>
<td>One year postoperatively obstructed ventricular peritoneal shunt. Normal CT scan one year postoperatively</td>
<td>71</td>
<td>Multiple areas of calcification in frontal lobes and basal ganglia</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Poor</td>
<td>Mild ataxia</td>
<td>66</td>
<td>Small areas of calcification in basal ganglia and left side of suprasellar cistern. Dilatation of lateral ventricles with some periventricular lucency</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Average. Poor memory. Managed at normal school</td>
<td>Episodes of anaesthesiae and weakness on right side. 'Transient ischaemic attacks'</td>
<td>---</td>
<td>Low density area in region of 4th ventricle. Lateral ventricles slightly dilated</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Average</td>
<td>Well</td>
<td>91</td>
<td>4th and lateral ventricles slightly enlarged</td>
</tr>
</tbody>
</table>

#### Discussion

In recent years attention has been paid to the side effects of radiotherapy to the brain in children, particularly in relation to the low-dose prophylactic cranial irradiation given for acute lymphoblastic leukaemia. Price et al. described two types of pathological changes in the brains of such children: a leucoencephalopathy with degeneration and demyelination of the CNS white matter related to methotrexate exposure, and a non-inflammatory mineralising microangiopathy often accompanied by necrosis and calcification in adjacent neural tissue. The calcification generally occurred in the basal ganglia and was less common in the cerebral cortex but only in those children who had received cranial irradiation and survived more than 10 months. The risk of its development was greater in children irradiated under age 10 years. It was concluded that microangiopathy resulted from cranial irradiation potentiated by systemic and intrathecal chemotherapy.
The various CT scan abnormalities noted in leukaemic children receiving cranial irradiation and chemotherapy are cerebral calcification, low density areas, ventricular dilatation, and cortical atrophy.6 7

The pathological changes that follow high-dose cranial irradiation are alterations in vascular permeability, delayed progressive fibrosis, and direct damage to neural cells.8–10 The vasculopathy consists of fibrinoid necrosis, endothelial proliferation, and extensive extravasation of fibrin into the neural parenchyma.11 In experimental animals the changes have been shown to be dose related.12 Certain areas of the cerebral microvasculature are especially susceptible to damage, particularly vessels in the basal ganglia.13 This vasculopathy results in slow necrosis of the surrounding neural tissue with accompanying dystrophic calcification of the necrotic tissue. In children who received higher doses of cranial irradiation for treatment of brain tumours there have been reports of isolated basal ganglia calcification occurring 3 to 14 years later.14–16 In addition Lee and Suh17 described a boy who, 14 years after receiving 43 Gy to the supratentorial region after removal of a medulloblastoma at age 2 years, developed minor seizures and in whom a CT scan showed calcification of the basal ganglia and cerebral cortex. Pure basal ganglia calcification detected 10 years after cranial radiation for a medulloblastoma at age 2 has also been reported.18

The children reported here had not received intrathecal or parenteral chemotherapy and therefore this cannot be implicated as a cause for the calcification. However, they had received many insults to the brain—the presence of a tumour, hydrocephalus, surgery, and irradiation—but with the knowledge of the pathological changes after radiotherapy and their distribution, it would seem that irradiation was the most likely cause of the calcification. The CT scans of the medulloblastoma survivors show no low density areas in the cerebral hemispheres, differing from methotrexate leukoencephalopathy in which these frequently occur.

There appears to be a correlation between the age at which the child received irradiation and the presence and extent of calcification on the CT scan. The infant brain is more vulnerable to insults than the mature brain.19 In children receiving cranial irradiation (24 Gy) and 3 years of chemotherapy for acute lymphoblastic leukaemia, Eiser and Lansdown20 found that those treated before age 5 years, although within the normal range, tended to perform less well in certain areas than matched controls. In a recent survey of 8 medulloblastoma survivors by Broadbent et al.21 2 of 3 children with severe disability had been treated under 2 years of age.

The calcification does not appear to be progressive in Case 1, in whom a repeat scan 18 months later showed no change. There may be a latent period before the appearance of calcification as Case 2 had a normal scan one year after treatment. The presence of calcification is not related to the length of survival.

The intracranial calcification appears to be associated with impaired intellectual function and behavioural alteration. Case 1, with the most extensive calcification, has minor seizures, an abnormal electroencephalogram, and hyperactive behaviour, as did the patient described by Lee and Suh.17

These findings suggest that intracranial calcification may occur in many of the survivors of medulloblastoma after treatment with radiotherapy and surgery alone. Cerebral cortical calcification is not therefore restricted to methotrexate leukoencephalopathy. The relationship between the age at irradiation and the presence of calcification seems further to stress the increased vulnerability of the younger child's brain and also the need for continued surveillance of children after treatment of malignancy to identify the late effects of such therapy.

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