Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence


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Summary
Hemispherectomy has been performed in the treatment of epilepsy in association with hemiplegia for over 50 years. However, the optimal timing of surgery with respect to age at presentation and the influence of underlying pathology on outcome is only slowly emerging. This study reports on the clinical course and outcomes of 33 children who underwent hemispherectomy at Great Ormond Street Hospital, London, between 1991 and 1997. Age at surgery was 0.33±17 years (median 4.25) with 1±8 years follow-up (median 3.4). The underlying pathology was developmental in 16 (10 hemimegalencephaly, two polymicrogyria, two focal cortical dysplasia, one diffuse cortical dysplasia and one microdysgenesis), acquired in 11 (six middle cerebral artery infarct, three post encephalitis/trauma, and one each of hemiconvulsion–hemiplegia epilepsy and perinatal ischaemic insult) and progressive in six children (four Rasmussen encephalitis, two Sturge–Weber syndrome). At follow-up, 52% were seizure free, 9% experienced rare seizures, 30% showed >75% reduction in seizures and 9% showed <75% seizure reduction or no improvement. Seizure freedom was highest in those with acquired pathology (82%), followed by those with progressive pathology (50%) and those with developmental pathology (31%). However, seizure freedom, rare seizures or >75% reduction in seizures occurred in 100% of those with progressive pathology, 91% of those with acquired and 88% of those with developmental pathology, indicating a worthwhile seizure outcome in all groups. Hemiplegia remained unchanged following surgery in 22 out of 33 children, improved in five and was worse in six. No significant cognitive deterioration or loss of language occurred, and four children showed significant cognitive improvement. Behavioural improvement was reported in 92% of those who had behaviour problems pre-operatively.

Keywords: hemispherectomy; epilepsy; childhood

Abbreviations: DQ = developmental quotients; HHE = hemiconvulsion–hemiplegia epilepsy; IQ = intelligence quotients; MCA = middle cerebral artery; SPECT = single photon emission computerized tomography

Introduction
Hemispherectomy was described independently in 1928 by Dandy and L’Hermitte (Rasmussen, 1983) as a radical treatment for malignant glioma of one hemisphere, but with a failure to offer improvements in survival or quality of life compared with more conservative treatments. Further interest in the procedure followed the publication in 1950 (Krynauw, 1950) of a study of a series of 12 children with infantile hemiplegia, seizures and behaviour disorders who underwent hemispherectomy for epilepsy with good seizure outcome. The popularity of anatomical hemispherectomy subsequently declined in the late 1960s because of the delayed complications of the procedure (Oppenheimer and Griffith, 1966; Till, 1967; Brett, 1969), which included obstructive hydrocephalus, superficial haemosiderosis and intracranial haematoma in as many as 33% patients (Rasmussen, 1983). However, a modification of the procedure (Adams, 1983) and the development of the sub-total or functional hemispherectomy (Rasmussen, 1983; Tinuper et al., 1988) largely abolished these complications.

Hemispherectomy can be considered for those with seizures arising from one hemisphere where there is a pre-existing structural abnormality of that hemisphere. It is particularly suitable for those with a pre-existing hemiplegia and/or visual field deficit, a group in whom co-existing
cognitive and behavioural impairments are common. However, it may be offered to those without such disabilities in circumstances such as Rasmussen syndrome, where inevitable deterioration in epilepsy is accompanied by deterioration of both motor and intellectual performance (Vining et al., 1997) and where lesser resections are unsuccessful (Platt et al., 1988).

The effectiveness of hemispherectomy for epilepsy associated with congenital hemiplegia was initially evaluated by the degree of seizure relief it offered (the traditional outcome measure used in adult epilepsy surgery). Seizure outcome was impressive but positive effects on cognition and behaviour were increasingly reported and were replicated by other groups in the 269 published reports of the procedure by 1961 (Rasmussen, 1983). The cognitive and behavioural impairments associated with congenital hemiplegia may be profound, especially for those with very early onset epilepsy and dysplastic lesions in whom development appears to remain arrested until clinical and sub-clinical seizure activity is abolished. Such secondary impairments, which constitute the severe epileptic encephalopathy suffered by these children, are emerging as the main target for epilepsy surgery in childhood. The aim is to offer surgery at a younger age in order to maximise the beneficial effects on developmental trajectory. This aim challenges our ability both to predict outcome and to justify major surgery in very young children. In the context of clinical decision-making, it would be very difficult to randomise to early or late surgery. At this stage, therefore, we have to analyse our attempts to address these issues in the clinical setting and this is the main purpose of this study. We report the clinical outcomes of hemispherectomy for epilepsy at Great Ormond Street Hospital, London, between 1991 and 1997, where the practice is.

**Methods**

A retrospective case note study was undertaken of 33 children who underwent hemispherectomy at Great Ormond Street Hospital between 1991 and 1997. Patients had been assessed using a standard protocol involving clinical, neuroradiological, neurophysiological, neuropsychological, neuropsychiatric and developmental teams. The data were discussed at a multidisciplinary meeting and these reports form the prospective aspect of this study. Each child was evaluated using MRI, video EEG telemetry, with or without single photon emission computerized tomography (SPECT). A previous review of our data suggested interictal EEG to be more useful in lateralization over ictal EEG (Doring et al., 1999), although ictal video EEG telemetry was performed in all cases. Ictal/interictal SPECT were performed in children early in the series; however, review of practice has suggested little contribution of SPECT over EEG and MRI in children being evaluated for hemispherectomy, and no correlation with outcome (Hartley et al., 2002) All children had cognitive/developmental assessments and all families were evaluated by a neuropsychiatrist.

Seizure outcome was assessed using a modified Engel scale (Engel et al., 1993). This scale or slightly modified versions of it have been used in most other studies (Peacock et al., 1996; Wyllie et al., 1996, 1998; Vining et al., 1997; Duchowny et al., 1998; Sugimoto et al., 1999; Edwards et al., 2000; Carreno et al., 2001, 2002). There were four major outcome categories: seizure freedom, rare seizures, >75% reduction in seizures and <75% reduction in seizure frequency. Motor function pre- and post-operatively was documented by the presence and severity of the hemiplegia, and the quality of fine finger movements. Visual field deficits were assessed clinically and, where possible, on Goldman perimetry. Visual evoked responses were obtained in some cases. Formal pre- and post-operative cognitive assessments were carried out using standardized tests in 15 children. Developmental assessments were carried out in 10 cases and, in eight cases, evaluation was based on a clinical assessment by a consultant paediatric neurologist. Individual intelligence quotients (IQ) or developmental quotients (DQ) were calculated based on these assessments. Normal cognition/development was defined as an IQ/DQ of >85, mild impairment as an IQ/DQ of 75–85, moderate impairment as an IQ/DQ of 55–75 and severe impairment as an IQ/DQ <55. Behaviour was evaluated on the basis of parental report.

**Patients**

There were 21 males and 12 females aged 0.33–17 years (median 4.25 years) at surgery who were followed for 1–8 years (median 3.4 years) after surgery. Thirty functional and three anatomical hemispherectomy procedures were undertaken of which 17 were right-sided and 16 were left-sided. Functional hemispherectomy involved a modified approach with a limited suprasylvian window but a large temporal lobectomy. The insular cortex was undercut. Four patients had undergone previous surgery: one child with a congenital extradural cyst had a cystoperitoneal shunt placed; one child born at 29 weeks gestation suffered an intra-ventricular haemorrhage and hydrocephalus requiring a ventriculoperitoneal shunt at 3 weeks of age; one child with hemimegalencephaly had undergone a previous left frontotemporal resection; and one child with Rasmussen encephalitis had undergone both a right temporal lobectomy and a right frontal resection.

**Statistical tests**

Descriptive statistics were calculated using standard computer software and comparisons between groups were made using the non-parametric Mann–Whitney U test or the Kruskal–Wallis test for multiple group comparisons (Conover, 1980).
Table 1 Pre-operative population characteristics

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Median age at seizure onset in years</th>
<th>Duration of seizures in years</th>
<th>Seizure frequency at surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental Hemimegalencephaly (n = 10)</td>
<td>0 (0–0.66)</td>
<td>2.5 (0.33–13.8)</td>
<td>10 (3–50)</td>
</tr>
<tr>
<td>Others (n = 6)</td>
<td>0.12 (0–3)</td>
<td>3.7 (0.2–15.4)</td>
<td>23 (1–150)</td>
</tr>
<tr>
<td>Acquired Congenital MCA infarct (n = 6)</td>
<td>1.0 (0–3.5)</td>
<td>9.5 (1.9–12.3)</td>
<td>8 (0.15–20)</td>
</tr>
<tr>
<td>Others (n = 5)</td>
<td>2.2 (0.25–7)</td>
<td>6.75 (2.5–16.75)</td>
<td>11 (4–150)</td>
</tr>
<tr>
<td>Progressive Rasmussen syndrome (n = 4)</td>
<td>4.2 (3.25–8)</td>
<td>3.9 (0.6–7.75)</td>
<td>5 (2–8)</td>
</tr>
<tr>
<td>Sturge–Weber syndrome (n = 2)</td>
<td>0.25 (0.13–0.4)</td>
<td>1.9 (1.4–2.4)</td>
<td>13 (–)</td>
</tr>
</tbody>
</table>

EPC = epilepsia partialis continua

Results

Pre-operative data

The underlying pathology was ascertained both from imaging and pathological examination of the surgical specimens. Sixteen patients exhibited developmental pathology; 10 cases with hemimegalencephaly, two with polymicrogyria, two with focal cortical dysplasia, one with diffuse cortical dysplasia and one with microdysgenesis. Hemimegalencephaly was defined as MRI showing an enlarged hemicranium with associated malformation of the cerebral cortex, of which examples were pachygryria, polymicrogyria or cortical dysplasia. Eleven children had evidence of later acquired pathology of one hemisphere; six showed typical features of congenital middle cerebral artery (MCA) infarction, one had evidence of a perinatal ischaemic insult and two showed damage resulting from post-natal encephalopathy/encephalitis. Hemispheric damage was assumed to be the result of repeated attempts at amnioncentesis in one child and the final patient had suffered the hemiconvulsion-hemiplegia epilepsy (HHE) syndrome. In six children, the underlying condition was considered to be progressive; Rasmussen encephalitis in four and Sturge–Weber syndrome in two. No child showed an abnormality of the contralateral hemisphere on MRI.

Pre-operative population characteristics with regard to seizure history and timing of surgery are given in Table 1. Age of seizure onset was significantly different for each of the pathological subgroups. Those with developmental pathology showed a median age of seizure onset in the neonatal period, those with acquired pathology had a median age of onset of 1.5 years and those with progressive pathology had a median age of onset of 3.3 years (Kruskal–Wallis P = 0.0004).

The average number of anticonvulsant medications that had been tried was >4 and patients were on a median of three anticonvulsant medications at surgery. Patients experienced, on average, three seizure types prior to surgery; the most common of which were complex partial seizures (70%), simple partial seizures (52%) and secondary generalized tonic/clonic seizures (52%). Epilepsia partialis continua (EPC) was experienced at some time by nine out of 33 (27%) patients; four out of 16 (25%) of those with developmental pathology, one out of 11 (9%) of those with static pathology, one out of two with Sturge–Weber syndrome and three out of four (75%) of those with Rasmussen encephalitis.

All but one of the children exhibited a pre-existing hemiparesis. The child without an apparent hemiparesis had hemimegalencephaly and was profoundly delayed in the domain of motor performance, with an age equivalent performance of 9 months at a chronological age of 4.25 years. Fine finger movements of the hemiparetic side were absent in 23 and present in four, and 17 patients were walking whilst 10 were non-ambulant. Six children were <2 years of age at the time of assessment and were considered to be too young to be classified, in the presence of a hemiparesis, as definitely non-ambulant or without fine finger movements. A visual field deficit was present in 18 children and was characterized as a homonymous hemianopia in all but one case, in whom a quadrantanopia was present. A deficit was undetectable in 12 and three could not be tested, either due to young age or restricted developmental performance.

The cognitive category of the patients pre-operatively assessed according to IQ or DQ is shown in Fig. 1. Figure 1 shows that the majority of children (88%) with developmental pathology, including all 10 subjects with hemimegalencephaly, exhibited severe cognitive/developmental delay. The majority of patients with acquired pathology (64%) also showed severe delay and a further 27% showed moderate delay. Those with Rasmussen encephalitis were most likely to have normal levels of cognitive function (three out of four) whilst the two children with Sturge–Weber syndrome were in the severe and moderate impairment groups. Twelve children (36%) had shown evidence of developmental regression prior to surgery.

Particular difficulty with expressive language was noted in six subjects and was anticipated in two subjects with Rasmussen encephalitis of the left hemisphere who came to surgery at 3.8 and 4.2 years of age, respectively. One was developmentally normal and the other was only mildly developmentally delayed prior to surgery. One showed very slurred speech, which was reduced in quantity during formal assessment, but developed clear speech immediately prior to surgery and the other became aphasic two weeks prior to surgery. One further subject with left-sided pathology resulting from a congenital MCA infarction was 2.3 years at the time of surgery with severe developmental delay. The
three remaining subjects showed abnormal pathology of the right hemisphere and when assessed at age 1.5, 2.6 and 12 years, respectively, were thought to be severely developmentally delayed thereby making language assessment difficult particularly in the two younger patients. In the opinion of experienced examiners, however, these children exhibited expressive language difficulties beyond those which would have been predicted from cognitive performance and comprehension. The pathology was developmental in one, acquired in one and the other child had Sturge–Weber syndrome.

Behaviour difficulties were present in 12 children (36%). The most common problem was difficulty with concentration (75%), followed by fluctuating mood with or without socially intrusive behaviour (66%). Twenty-five percent showed temper tantrums or aggression. The duration of seizures prior to surgery (median 7.38 years) and hence age at surgery was significantly greater in those with behaviour problems compared with those without (median duration of seizures 2 years, Mann–Whitney U test $P = 0.0033$). The median duration of seizures prior to surgery in those with acquired pathology was significantly longer at 7.75 years compared with 2.6 years and 1.9 years in the developmental and progressive pathology groups, respectively (Kruskal–Wallis $P = 0.0004$). Behaviour problems were most common in the group with acquired pathology (73%), followed by the group with progressive pathology (33%) and least common in those with developmental pathology (12.5%). There was no apparent association between the category of cognitive performance and the presence or absence of behaviour problems.

Operative and perioperative morbidity

In this series, there were no perioperative deaths. However, life-threatening operative complications occurred in three children: all three patients were <18 months of age (two <9 months) and all had hemimegalencephaly. Two underwent anatomical hemispherectomy early in the series prior to the routine use of the functional procedure (Rasmussen, 1983) and one had a functional hemispherectomy. The complications were related to haemorrhage which necessitated completion of the procedure 5 days later in one patient and precipitated an air embolus requiring resuscitation followed by a 3 day stay in the intensive therapy unit (ITU) in another. In the last child, haemorrhage resulted in cardiac arrest and a 24 day stay in the ITU. In none was there any clear loss of neurological functions as a result of these events.

The most common perioperative complication was fever with no identifiable source in 23 patients, which resolved without treatment. The duration of stay was 8–16 days (mean 12.4) for those who experienced this as an isolated postoperative problem. Six children developed sub-galeal collections treated by tapping and/or pressure bandaging and six other patients developed an infection (chest infection in three, meningitis in one, wound infection in one and glandular fever in one). Ten children experienced seizures in the perioperative period, which were the same type as the pre-operative ones in eight cases and of a new type in two. The seizures responded to simple intravenous therapy in nine and in one responded to the third intravenous agent.

Late complications occurred in five patients, three of whom required ventriculo-peritoneal shunts at 6–18 months follow-
Several children experienced complications following surgery. Another child presented with bilateral iliac vein occlusion 6 months after surgery which was thought to be related to central venous access and the final patient experienced chronic osteomyelitis of the bone flap discovered 3 years after surgery which was treated by removal and antibiotics.

### Clinical outcomes

#### Seizure outcome

Table 2 illustrates the seizure outcome for each type of pathology at the most recent follow-up. Considering all types of pathology, 52% became seizure free following surgery, 9% experienced only rare seizures, a further 30% had >75% reduction in seizure frequency and 9% experienced <75% reduction in seizures (3%) or no improvement (6%). The seizure outcome category was significantly different for each pathology (Kruskal–Wallis \( P = 0.04 \)) and significantly poorer in those with developmental pathology compared with those with acquired or progressive pathology. Thirty-one percent of those with developmental pathology became seizure free compared with 82% of those with acquired pathology and 50% of those with progressive pathology. However, seizure freedom, rare seizures or >75% reduction in seizures occurred in 88% of those with developmental pathology, 91% of those with a progressive pathology and 100% of those with a progressive pathology, indicating a worthwhile improvement following surgery in all groups.

Table 2 gives more detail about seizure outcome with 1–3 years and >3 years follow-up periods for each pathology. Seizure frequencies in the rare seizures and >75% improvement groups are also given. Subdividing the population for pathology, two follow-up epochs and seizure frequency produces small numbers in each subgroup; statistical comparisons have to be viewed in this context. No statistical comparisons are possible for the acquired and progressive pathology groups as there is only one seizure frequency above zero in the acquired pathology group and only one patient in the progressive pathology group.

#### Table 2 Seizure outcome at 1–3 years and >3 years following surgery

<table>
<thead>
<tr>
<th>Duration of follow-up in years</th>
<th>Developmental pathology</th>
<th>Acquired pathology</th>
<th>Progressive pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Engel</td>
<td>Seizure frequency daily</td>
<td>Engel</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
<td>Number of cases (%)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>---------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>1–3 years (mean 1.7, range 1–2.8)</td>
<td>1</td>
<td>2 (40%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 (40%)</td>
<td>1.6 (0.14–3)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (20%)</td>
<td>14</td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>&gt;3 years (mean 4.7, range 3.2–8)</td>
<td>1</td>
<td>3 (27%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (10%)</td>
<td>0 (0 for the last 12 months)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6 (55%)</td>
<td>1.8 (0.025–5)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (10%)</td>
<td>3</td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Sixteen children who were found to be taking an anti-convulsant medication at follow-up were no longer taking anti-convulsant medication 1 year post-surgery. The remaining seven children were on a significant reduction in drug treatment compared with pre-operative levels. Sixteen children were no longer taking an anti-convulsant medication at follow-up, indicating a worthwhile improvement following surgery.
similar seizures to those described pre-operatively, two of whom suffered in addition, a new seizure type. The remaining five cases experiencing seizures suffered a new seizure type not seen pre-operatively. In five children, investigation with video EEG telemetry was thought to be warranted and performed. Two were thought to have continuing seizures from the operated hemisphere and had an anatomical hemispherectomy; one remains seizure free. The other continues to have seizures involving the hemiparetic arm despite removal of all structural tissue. In two children, seizures had changed in semiology and were found to arise from the contralateral hemisphere. The final patient was investigated in the first year post-operatively for apparent language regression; there was no evidence for an epilepsy basis for this. She has now made gains in language and remains seizure free 8 years on.

**Motor, visual, cognitive and behavioural outcome**

The hemiplegia remained unchanged following surgery in the majority of cases (22 out of 33). The hemiplegia worsened in six children; three from the group with progressive pathology (two Rasmussen encephalitis, one Sturge–Weber syndrome), two from the acquired pathology group (one congenital MCA infarction, one other) and one with hemimegalencephaly. The hemiplegia improved in five children immediately following surgery; two with progressive pathology (Rasmussen encephalitis), one with acquired pathology (congenital MCA infarction) and two with hemimegalencephaly. Eleven children experienced a transient worsening of the hemiplegia in the peri-operative period, which had resolved by discharge in one child, by 6 weeks in nine children and after 6 weeks in the remaining child. The outcome following surgery for motor, visual, cognitive and behavioural characteristics are shown in Table 3. Fine finger movements deteriorated in five children; three with progressive and two with developmental pathologies and improved in two children (one with Rasmussen syndrome and one with a congenital MCA infarction). As expected, the outcome for visual fields was either unchanged if already impaired or worse following surgery.

The overall developmental/cognitive category was unchanged following surgery in 23 out of 27 children in whom follow-up data were available (median of 2.25 years following surgery, range 1–8 years). Four children showed improvement in developmental performance following surgery. Two children showed a >15 point improvement in DQ/IQ following surgery and moved from the severely impaired to the moderately impaired developmental category. The first with cortical dysplasia was aged 15 years at the time of surgery and the second with hemimegalencephaly underwent surgery aged 0.4 years. Two further cases with acquired pathology and developmental abilities in the severely impaired range also experienced significant improvements in developmental abilities (>15 point improvement in DQ), but scores did not reach the moderately impaired category. In three patients, small changes in quotient resulted in a drop from the pre-operative developmental category to the one below; however, since none of these represented ≥15 point change, they were not considered to be significant.

Of the six who demonstrated particular difficulties with expressive language pre-operatively, five showed improvement post-operatively to the degree that abilities were consistent with overall development. One with right hemisphere hemimegalencephaly showed no improvement in expressive language post-operatively, with no improvement in seizures and underwent further surgery. Two with right hemisphere developmental pathology and severe developmental impairment and appeared to show more expressive language impairment relative to the rest of the developmental domains post-operatively than had been noted pre-operatively. However, one child had an age equivalent developmental level of 1.2 years (chronological age 4.6 years) at pre-operative assessment, and the other an age equivalent of 9 months (chronological age 18 months) making accurate assessments of expressive language skills difficult. No patient had reduced language as a result of surgery.

Of the 12 children with pre-operative behavioural problems, 11 were reported to have significantly improved post-operatively, some (n = 5) to the extent where parents no longer reported behavioural problems. In the remaining child, behaviour was unchanged. Nine cases with improved behaviour had become seizure free, with the remaining two suffering only rare seizures. The child with unchanged behaviour also experienced only rare seizures.

Five children without behavioural disturbance pre-operatively showed problems post-operatively; two had developmental, two acquired and one progressive pathology. Two became seizure free and three had >75% reduction in seizures following surgery. Problems described were temper tantrums, associated with aggression when thwarted, and mood swings.

### Table 3 Outcome of motor, visual, cognitive and behavioural characteristics following surgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unchanged</th>
<th>Improved</th>
<th>Deteriorated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiplegia (n = 33)</td>
<td>22</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Fine finger movements (n = 33)</td>
<td>26</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Visual fields (n = 30)</td>
<td>17</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Cognitive category (n = 27)</td>
<td>23</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Behaviour (n = 33)</td>
<td>11</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>
These might be interpreted as consistent with age equivalent developmental levels of 16–36 months. However, six children in whom behaviour had improved also showed developmental/cognitive age equivalent performances of 14–30 months and had similar Engel seizure outcome grades (Mann–Whitney U test P = 0.49). Comparing these two groups more closely reveals that there was no difference in age of seizure onset, duration of seizures, age at surgery and duration of follow-up since surgery. Seizure frequency pre-operatively was greater in the group with improved behaviour, two of whom suffered epilepsy partialis continua. The group with hemimegalencephaly contained all those who showed sustained improvement in post-operative behaviour and none of those with behavioural deterioration, but the reasons for this trend are not clear.

Further interventions and outcomes

Three children who had a poor seizure outcome following functional hemispherectomy went on to anatomical hemispherectomy aged 4.2, 6 and 12.3 years, respectively. Two children had developmental pathology (one hemimegalencephaly) and one acquired pathology (MCA infarction). One child with hemimegalencephaly is now seizure free after 1.5 years follow-up and the other child with developmental pathology has shown >75% seizure relief after 6 years follow-up. The remaining child with a congenital MCA infarction and >3 years follow-up has shown a >95% reduction in seizure frequency. There were no detrimental effects on motor, visual or cognitive function in these patients and none showed behaviour problems prior to surgery, although significant improvement in the desire to communicate and in eating behaviour was noted post-operatively in one child.

Discussion

Seizure outcome

This study has reviewed the results of hemispherectomy in 33 patients at our hospital. Results have shown an excellent seizure outcome with 52% of children becoming seizure free and a further 39% experiencing >75% reduction in seizure frequency. This compares well with the Johns Hopkins series (Vining et al., 1997) of 58 children who underwent hemispherectomy, in whom 54% became seizure free and a further 24% were regarded as having insignificant residual seizures after a mean follow-up of 6.2 years (range 0.5–27.3 years).

Comparisons with other series are difficult since the proportions of subjects in each pathological sub-group are not always described and, when given, are not necessarily compared with seizure outcome results. Therefore, although the overall seizure free rate appears comparable between series, our results have highlighted the relevance of underlying pathology to seizure outcome, with 82.5% seizure free seen post-operatively in those with acquired pathology compared with 31% in those with developmental pathology. The seizure free outcomes from other studies of hemispherectomy vary from 54–69% (Rasmussen, 1983; Lindsay et al., 1987; Peacock et al., 1996; Duchowny et al., 1998; Wyllie et al., 1998). The better seizure free outcomes of >60% are seen either when hemimegalencephaly constitutes a small proportion of the developmental pathology group or when the contribution made by developmental pathology to the whole group is small. Developmental pathology occurred in 48% of those in our study, which is similar to the 41% of the Johns Hopkins series (Vining et al., 1997). However, it is unclear from the latter study how many subjects had hemimegalencephaly, whilst in our study this constituted 63% of the cases with developmental pathology.

A more recent study of seizure outcome following hemispherectomy for malformations of cortical development (Carreno et al., 2001) reported on six cases with hemimegalencephaly with a mean follow-up of 19 months compared with 4.4 years for this pathology in our study. One of six (17%) became seizure free, which is comparable to our result (two out of 10) and at least four out of five of those with persistent seizures were reported as showing significant improvement although two proceeded to anatomical completion for persistent seizures. An earlier report (Vigevano et al., 1989) describes two patients who were both seizure free after anatomical hemispherectomy, but with only 5 and 11 months follow-up. Battaglia and colleagues report 10 children with mean follow-up of 5 years 2 months (Battaglia et al., 1999). Overall, this was a younger group of patients with only four patients >12 months of age at surgery, and seven of the 10 had an anatomical hemispherectomy. Six of the group overall were seizure free at follow up. Three had worthwhile improvement and, in one, there was no change. In contrast, 47% of the Johns Hopkins group suffered Rasmussen encephalitis compared with 12% in our population with a similar overall seizure outcome. Together with the review of other studies above, this suggests that the seizure free outcome from any study may be more influenced by the proportion of patients with developmental pathology than by the proportions with other pathologies. Logistic regression analysis of many pre-operative variables in an attempt to identify predictive factors for seizure outcome in each pathological subgroup would not be valid in a population of this size and probably requires collaborative multi-centre studies.

Motor and visual outcome

Although hemiparesis remained unchanged in the majority of our series, five demonstrated improvement. Improvement in hemiparesis in a few patients following hemispherectomy was reported in early studies (Krynan, 1950; McKissock, 1953), one of which reported that of 17 patients, 12 remained unchanged, two were worse and three improved (McKissock, 1953). These outcome proportions resemble our own. In the six cases we report where hemiplegia worsened, one suffered temporary loss of ambulation which was regained after a week. Others have reported that all ambulant subjects who
underwent hemispherectomy regained ambulation within 6 months (Duchowny et al., 1998) and that transient worsening of the hemiparesis occured in some subjects following hemispherectomy with recovery to baseline function after several weeks (Wyllie et al., 1998). Most studies are concordant with our results which suggest that, in this population, the hemiparesis is likely to remain unchanged in the majority, with fewer showing an improvement or deterioration (Krynauw, 1950; Wilson, 1970; Vining et al., 1997). The large number of children not walking prior to surgery would, providing they were beyond the age of 2 years, be surprising for simple congenital hemiplegia and indicates the adverse effect of high seizure rate and reduced cognitive function. The improvements seen in motor function are likely to be the result of seizure relief, but are nevertheless surprising in the context of a disconnected hemisphere. Deterioration of motor function is particularly a feature of Rasmussen syndrome and is discussed separately. The emergence of a hemianopic field defect in those without a pre-existing hemianopia is an acknowledged consequence of surgery (Krynauw, 1950; McKissock, 1953; Wilson, 1970; Duchowny et al., 1998; Tinuper et al., 1988).

Cognitive and language outcomes
The majority of individuals in this study demonstrated no apparent change in cognitive performance after a median follow-up of 2.25 years. However, four subjects showed significant improvements in IQ/DQ, indicating improvement in developmental trajectory. Early studies found that that intellectual deterioration and loss of language following hemispherectomy were rare (Wilson, 1970), and that surgery appeared to arrest the deterioration in cognitive function in some. In a more recent report from the Cleveland clinic (Wyllie et al., 1998), pre-operative full scale IQ measurements did not differ between those with or without a seizure free outcome, and those with severe developmental delay preoperatively were represented both in the seizure free and non-seizure free groups. This emphasises that the presence of severe developmental delay is not a contra-indication to surgery in this group of children.

In our study, developmental regression was seen in 12 children (36%) prior to surgery. This was also seen in the series from The Park Hospital, Oxford, UK (Lindsay et al., 1987), where hemispherectomy was performed later in life (the youngest just before the eight birthday) and where sequential pre-operative psychological assessments revealed losses of 10–29 IQ points, with no patient showing a pre-operative IQ >90. Improvement in psychological performance was seen in seven out 17 (41%) patients in the same study with up to 36 years follow-up. A later study (Tinuper et al., 1988) reported increases in IQ of 3–18 points (mean 10) in six out of eight patients, although the exact timing of the repeat psychological assessments during follow-up is unclear.

In our study and others, those with widespread cortical dysplasia consistently show developmental delay (Wyllie et al., 1996; Sugimoto et al., 1999). There are mixed reports of developmental outcome in this group despite worthwhile seizure improvement. Some report modest even marginal developmental gains (Wyllie et al., 1996; Duchowny et al., 1998), whilst others report significant improvements (Vigeiano et al., 1989). One study of 10 children who underwent hemispherectomy for hemimegalencephaly described only modest cognitive gains but significant improvements in quality of life (Battaglia et al., 1999). Our results support the view that, although developmental gains may occur for only a few, cognitive performance is likely to remain unchanged in this group particularly in those with hemimegalencephaly. The influence of seizure severity and duration cannot be determined from this study.

There was no significant loss of language function following either right-sided or left-sided hemispherectomy in this study, which is also the reported experience of others (Wilson, 1970; Peacock et al., 1996; Vining et al., 1997; Duchowny et al., 1998; Wyllie et al., 1998). Where injury/pathology involving the left hemisphere occurs, it is thought that language develops preferentially in the undamaged hemisphere to a level sufficient to sub-serve aspects of everyday verbal communication (Vargha-Khadem et al., 1991). Reports exist of language re-organization occurring at the age of 12 and 13 years in Rasmussen syndrome (Vining et al., 1997) and in a 9-year-old boy with Sturge–Weber syndrome (Vargha-Khadem et al., 1997). Two similar cases are included in this study, both of whom suffered Rasmussen encephalitis. One boy aged 4.2 years at surgery developed progressively slurred speech becoming virtually mute. Immediately prior to surgery, his language improved and speech was preserved even during seizures. The improvement was maintained post-operatively, suggesting that language had become reorganized in the non-dominant right hemisphere prior to surgery. The other child aged 3.8 years at surgery became aphasic 2 weeks before surgery and speech returned post-operatively following left hemispherectomy. Our results and those of others suggest that involvement of the dominant hemisphere in an acquired/progressive process, especially in young children, may not preclude hemispherectomy subject to specialist assessment.

Behavioural outcomes
Krynauw said of his group of patients with infantile hemiplegia that most patients showed episodic outbursts of violent temper tantrums and that in many it was the mental state and not the epilepsy or the hemiplegia that had led the parents to seek help (Krynauw, 1950). Wilson reported behaviour disorder with rages, screaming and poor attention in 72% of his series (Wilson, 1970). Therefore, the magnitude of the behavioural disorder in children with hemiplegia and epilepsy has long been recognized, as have the beneficial effects and indeed the aims of surgery (Till, 1967; Wilson, 1970; Lindsay et al., 1987).
Our study shows improvement in reported behaviour in 11 out of 12 patients in whom problems were described preoperatively. Although behaviour in this study was assessed by parental report rather than standardized questionnaire, similar improvements have been reported by other early studies with improvement in behaviour in 14 out of 17 (McKissock, 1953) and 35 out of 36 (Wilson, 1970) patients. Lindsay and colleagues confirmed that severe unmanageable rages and aggression subsided in every case in whom these were a problem and that six children previously excluded from their homes were able to return (Lindsay et al., 1987). Another study refers to reports from parents of a better family life, improved behaviour and a decrease in aggressiveness in all but one patient (Tinuper et al., 1988). However, five subjects in our study showed deterioration in behaviour with temper tantrums, aggression and mood swings whilst being either seizure free or experiencing >75% relief of seizures. It must be recognized therefore, that surgery may release some children from a placid, inert state that accompanies their epilepsy thereby producing a more challenging and active child.

Rasmussen syndrome

The management and outcomes of Rasmussen syndrome warrant separate consideration. Greater awareness of this condition means that it is suspected earlier in the natural history of the condition and is often diagnosed earlier following a biopsy from the affected area. This presents the clinician, child and family with a difficult decision since these children often have relatively preserved intellect and relatively unimpaired hand and visual function at presentation. Although the condition is usually progressive, the variable course and the reported remissions with corticosteroid and immunoglobulin therapy (Hart et al., 1994; Leach et al., 1999) result in uncertainty regarding the optimal timing of surgery. The dilemma is whether to perform surgery early and risk inflicting greater motor, visual and language impairments from which there may be greater recovery at a young age, or to pursue other therapies and delay surgery until the disease produces similar motor and visual deficits to those which would be inflicted by surgery. However, during the delay there may be progressive impairment of language and intellect in addition to deterioration in motor and visual abilities, with reduced potential for recovery in the older patient. Often the severity of the epilepsy along with the social and behavioural problems encountered in these patients push one into surgery but, in most hemispherectomy series, it is these patients in whom the highest rate of increased impairment is reported and for whom periods of rehabilitation are required. This, however, is not a surprise; it is a predicted consequence not just of surgery, but of the natural history of the disorder.

Morbidity and mortality

The morbidity and mortality of hemispherectomy has to be considered in the context of the likely natural history of the child’s disorder. Early seizure onset, particularly in the first year of life is associated with a poor prognosis in the majority of cases with a 6% mortality at 12 months in the series reported by Chevrie and Aicardi (Chevrie and Aicardi, 1978). A higher mortality occurs in those who are younger than 6 months at seizure onset, with symptomatic as opposed to cryptogenic seizures and with partial seizures. Such children are also more likely to suffer severe long-term epilepsy, significant neurological deterioration and seizures that are unlikely to respond to medication or remit spontaneously (Peacock et al., 1996; Wyllie, 1996). Thus, the patients in this study represent a group with a poor natural history (despite medical therapies) and who are at risk with regard to mortality and neurological deterioration if untreated surgically.

Perioperative complication rates in our study compare favourably both with those from the Johns Hopkins (Vining et al., 1997) and the University of California Los Angeles (UCLA) series (Peacock et al., 1996), each of which reported on 58 children. Perioperative deaths occurred in three of out 58 and one out of 58 in those series respectively. Significant operative haemorrhage occurred in eight (14%) of patients from the Johns Hopkins group and in three (9%) of children in our study, all of whom underwent surgery aged <18 months for treatment of seizures due to hemimegalencephaly. Both of the latter features are associated with increased risk of haemorrhage due to the anatomical distortion and increased blood flow to the megalencephalic hemisphere (Taha et al., 1994; Vining et al., 1997).

Three children in our series have required a ventriculoperitoneal shunt to date, all following hemispherectomy for hemimegalencephaly. This is a similar finding to that reported in the UCLA study (Peacock et al., 1996) and both sets of results compare favourably with the Johns Hopkins series (Vining et al., 1997), in which 16 ventriculoperitoneal shunts were placed. Fever without source was the most common perioperative observation in our study which has been reported by other groups, one of which describes an aseptic meningeal reaction with headache, high fever and stiff neck lasting up to 1 week as a common occurrence following functional hemispherectomy (Tinuper et al., 1988).

Outcome prediction

The subjects in this study have complicated compounding handicaps attributable to seizures, medication for seizures, pre-existing motor impairment, pre-existing cognitive and behavioural impairment and, in the case of the progressive pathologies, the potential for greater future impairment. All of these factors influence quality of life and the burden of illness for the child and his or her family. Seizure frequency can, therefore, not be the sole measure of outcome from this type of surgery particularly since deterioration in motor or visual function and alteration in cognitive and behavioural performance may occur.
It has been our practice to attempt to predict seizure outcome by classifying patients broadly into groups; group A in whom a cure can be anticipated, group B in whom significant improvement can be anticipated and group C in whom there is a possibility of improvement but the outcome is less certain (Taylor et al., 1997). A neuropsychiatrist assesses all children and their families prior to surgery and with them negotiates and develops the aims of surgery. The extent to which these aims are achieved can then act as an outcome measure that can be audited. The published evidence and our experience suggests that pure acquired unilateral lesions with concordant data were in outcome group A developmental defects and those with incompletely concordant data were in group B. Certainly the placement of patients with hemimegalencephaly in group B is supported by this study.

The future

The relatively few and small series reported from tertiary paediatric neurosurgical centres worldwide illustrates the time required to build up experience of this procedure. The risks of epilepsy surgery in very young infants should not be under-estimated and even in specialist neurosurgical centres, unforeseen complications can and do occur which is reflected in a mortality rate of 1.3–6% in other series (Vining et al., 1997; Duchowny et al., 1998; Wyllie et al., 1998). In addition, the magnitude and expertise of the multi-disciplinary team and the specialized imaging (Chugani et al., 1990; Sisodiya et al., 1996; Wyllie et al., 1996) and neurophysiological techniques required are generally only available in centres specializing in paediatric epilepsy surgery.

As a consequence of the limited experience in few centres, many questions remain unanswered including whether earlier surgery preserves cognition, improves developmental trajectory and prevents behaviour disorder. Objective improvement in cognitive function occurred in four children in this study, which appears unrelated to pre-operative seizure duration. However, with such small numbers it is impossible to reach a conclusion on the effect of earlier surgery on cognition, particularly in the presence of differing pathologies. Support for early surgery is afforded by our observation and that of others that significant developmental and behavioural deterioration occurs over time prior to surgery (Lindsay et al., 1987) and by the qualitative reports of improved development following surgery (Vigevano et al., 1989; Wyllie et al., 1996). Since behavioural disorder was more common in those with acquired pathology and a longer duration of seizures, it might be inferred that earlier consideration of surgery in this group might help to prevent or attenuate this most disturbing feature.

The vast majority of patients offered hemispherectomy have congenital hemiplegia (hemiplegic cerebral palsy), which consists of different phenotypes. The clearest separation is on the basis of the presence of cerebral cortical impairments such as epilepsy, cognitive delay and behaviour disorder. The group with these features present major management problems for families and education compared with the group without such impairments. The challenge for hemispherectomy as an early intervention is whether it can convert those with these cortical impairments into members of the less impaired group. Perhaps these questions may only be answered by larger prospective collaborative studies involving the major paediatric epilepsy surgery centres with agreed pre-operative and post-operative assessment tools and scheduling.

We conclude that hemispherectomy in childhood and adolescence has a good outcome for those with seizures arising from hemipathology with associated hemiplegia. Our results are comparable to those obtained in other tertiary centres with low morbidity and mortality. Seizure outcome and cognitive performance appear to be related to the underlying pathology, being most favourable in those with acquired or progressive pathology when compared with those with developmental pathology. We suggest that results from future studies should be analysed with respect to both surgical procedure and underlying pathology in order to develop a stratified model for predicting outcome on a more individual basis.

Acknowledgements

This work was undertaken by Great Ormond Street Hospital for Children NHS Trust, which receives a proportion of its funding from the NHS executive. The views expressed in this publication are those of the authors and not necessarily those of the NHS executive.

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