Pathology of temporal lobectomy for refractory seizures in children

Review of 20 cases including some unique malformative lesions

Venita Jay, M.D., F.R.C.P.(C), Laurence E. Becker, M.D., F.R.C.P.(C), Hiroshi Otsubo, M.D., Paul A. Hwang, M.D., F.R.C.P.(C), Harold J. Hoffman, M.D., F.R.C.S.(C), and Derek Harwood-Nash, M.D., F.R.C.P.(C)

Departments of Pathology, Neurology, Neurosurgery, and Radiology, The Hospital for Sick Children/Bloorview Epilepsy Program, University of Toronto, Toronto, Ontario, Canada

Significant pathological abnormalities were encountered in a series of 20 temporal lobectomies in children with intractable complex partial seizures. In particular, "dual pathology" (mesial temporal sclerosis with other lesions) was found rather than mesial temporal sclerosis as the only lesion. Unusual pathological findings included capillary penetration of neurons in a neuronal heterotopia in one patient, and foci of extensive cortical disorganization in some cases of mixed tumors and gangliogliomas. A high proportion of neuronal migration disorders was also seen with overlapping pathological features between cortical dysplasia and tuberous sclerosis. In this correlative clinical, radiological, electroencephalographic, and pathological study, some of the pathological lesions in children did not fit the classical categories of neoplasia and malformation and transitional forms were rarely encountered.

Key Words: pathology, seizure, temporal lobe, neuron, tuberous sclerosis, heterotopia

Temporal lobe epilepsy has been the subject of numerous reviews from neurophysiological, neurosurgical, radiological, and pathological perspectives. The aim of this paper is to highlight certain unusual lesions encountered in a series of 20 pediatric cases. In contrast to the pathological surveys of epilepsy resections encompassing all age groups, where mesial temporal sclerosis is most frequently found (often as the only lesion), our series suggests that mesial temporal sclerosis is almost invariably associated with other lesions: the so-called "dual pathology group." Furthermore, in contrast to previous well-documented pathological studies of temporal lobe epilepsy, where some cases exhibit no discernible morphological abnormalities, all of the patients in our pediatric series had pathological lesions. Unlike the adult series, the pathological spectrum in children includes a higher proportion of neoplastic and malformative lesions. In this correlative clinical, radiographic, electroencephalographic (EEG), and pathological study, we wish to underscore that some of the pathological lesions in children did not fit the classical categories of neoplasia and malformation and transitional forms were rarely encountered.

Clinical Material and Methods

Case Material and Preoperative Findings

The clinical records of all 20 patients undergoing temporal lobectomy for refractory seizures at The Hospital for Sick Children over a 5-year period were reviewed. All 20 patients underwent thorough preoperative assessments according to published protocols, including multiple EEG recordings with special electrodes (zygomatic and sphenoidal) and video EEG telemetry. Neuropsychological assessments were routinely performed in children over 4 years of age, and developmental assessment was performed in younger children. A Wada test was performed to determine the language-dominant hemisphere in patients over 4 years of age, and especially for patients with left hemispheric abnormalities. All the patients underwent neuroradiological examination including computerized tomography (CT), magnetic resonance (MR) imaging and single-photon emission CT (SPECT) with 99mTc-hexamethylpropylene amine oxime (HMPAO). In selected patients without any structural lesion on CT or MR imaging, SPECT was performed immediately after the ictus. Surgery was carried out under neuroleptic anes-


**TABLE 1**

**Summary of clinical findings in 20 children with temporal lobe epilepsy***

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Duration of Seizures (yrs.)</th>
<th>Seizure Type</th>
<th>CT Findings</th>
<th>MR Imaging Findings</th>
<th>Postexcisional ECoG Grade†</th>
<th>Postop Seizure Grade‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>F</td>
<td>17</td>
<td>CPS, 2G</td>
<td>normal</td>
<td>ISI</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>9</td>
<td>PMS, CPS, 2G</td>
<td>LAA</td>
<td>cystic lesion</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>F</td>
<td>1</td>
<td>CPS, 2G</td>
<td>LAA, EH+</td>
<td>ISI</td>
<td>E</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>F</td>
<td>4</td>
<td>CPS, 2G</td>
<td>CA, EH+</td>
<td>ISI</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>M</td>
<td>1</td>
<td>CPS</td>
<td>CA, LAA</td>
<td>ISI</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>F</td>
<td>4</td>
<td>PMS, CPS, 2G</td>
<td>normal</td>
<td>loss of G-W</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>2</td>
<td>CPS, 2G</td>
<td>HDA, EH+</td>
<td>ISI</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>M</td>
<td>11</td>
<td>CPS</td>
<td>normal</td>
<td>asymmetry of temporal lobe</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>F</td>
<td>5</td>
<td>CPS</td>
<td>CA</td>
<td>CA</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>M</td>
<td>6</td>
<td>CPS, 2G</td>
<td>normal</td>
<td>ISI</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>F</td>
<td>9</td>
<td>CPS, 2G</td>
<td>normal</td>
<td>ISI</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>F</td>
<td>2</td>
<td>CPS</td>
<td>LAA, HDA, EH+</td>
<td>LSI, marked GD+</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>M</td>
<td>4</td>
<td>CPS, PMS</td>
<td>CA</td>
<td>CA</td>
<td>A</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>M</td>
<td>11</td>
<td>CPS</td>
<td>normal</td>
<td>normal</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>M</td>
<td>5</td>
<td>PMS, CPS, 2G</td>
<td>normal</td>
<td>midline shift</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>F</td>
<td>6</td>
<td>CPS</td>
<td>EH+</td>
<td>ISI</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>13</td>
<td>M</td>
<td>11</td>
<td>CPS, 2G</td>
<td>normal</td>
<td>ISI, marked GD+</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>F</td>
<td>5</td>
<td>CPS</td>
<td>LAA</td>
<td>atrophy</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>11</td>
<td>F</td>
<td>9</td>
<td>CPS, 2G</td>
<td>atrophy</td>
<td>ISI, GD=</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>7</td>
<td>F</td>
<td>1</td>
<td>CPS, 2G</td>
<td>CA</td>
<td>ISI, CA, mild GD+</td>
<td>C</td>
<td>NA</td>
</tr>
</tbody>
</table>

*CT = computerized tomography; MR = magnetic resonance; ECoG = electrocorticography; CPS = complex partial seizure; 2G = secondary generalized seizure; PMS = partial motor seizure; LAA = low attenuation area; EH+ = positive enhancement; CA = calcification; HDA = high-density area; ISI = increased signal intensity; loss of G-W = loss of gray and white matter differentiation; LSI = low signal intensity; GD+/- = gadolinium-diethylentriamine penta-acetic acid positive/negative enhancement.
†A = no residual epileptiform activity; B = mild residual activity; C = moderate residual activity; D = unchanged from pre-excisional ECoG; E = indeterminate due to effect of drugs.
‡For explanation of grading system, see text. NA = not available.

---

Thesia consisting of fentanyl and droperidol in children aged 5 years and older, and under general anesthesia for patients under 5 years of age. All patients underwent intraoperative pre- and postexcisional electrocorticography (ECoG), with a single depth electrode directed toward the hippocampus in the cases with seizure activity from the inferomedial temporal lobe, preselected by sphenoidal EEG studies. Patients over 5 years of age with left temporal lobe lesions and dominance on the surgical side were examined by cortical electrical stimulation under neuroleptic anesthaesia for mapping of speech.

**Surgery and Postoperative Review**

The lateral temporal lobe was removed en bloc; basically, 4.5 cm of the left temporal lobe and 5.5 cm of the right temporal lobe were removed in adolescents. The mesial temporal structures were removed for patients who presented with either seizure foci in the inferior mesial temporal lobe on EEG recordings confirmed by depth electrode findings at ECoG, or hippocampal abnormalities on MR imaging. The hippocampal gyrus was removed by subpial suction, thus preserving a pial envelope covering the third cranial nerve, brain stem, and tentorial notch.

Every patient was assessed at 1 week, 3 months, 6 months, and 1 year postoperatively by neurological assessment and EEG studies, with neuropsychological evaluation at 6 to 12 months as well as visual field perimetry testing. A follow-up CT scan was routinely obtained within 24 hours postoperatively. For the patients with tumors, MR imaging was scheduled 1 year after surgery.

**Pathological Examination**

The lateral temporal lobe was submitted en bloc for examination. The tissue was processed for conventional histological study and, where appropriate, immunohistochemical staining was performed by the avidin-biotin complex or peroxidase-antiperoxidase techniques using the following antibodies: glial fibrillary acidic protein (GFAP, polyclonal, 1:200); factor VIII (polyclonal, 1:50); synaptophysin (monoclonal, 1:5); phosphorylated neurofilaments (monoclonal, 1:25); and neuron-specific enolase (NSE, polyclonal, 1:250). The hippocampus specimen was processed for conventional histology and immunostaining with GFAP.

For electron microscopy, tissue was fixed in the universal fixative (equal parts of 4% formaldehyde and 1% glutaraldehyde) and postfixed in 1% OsO₄ and embedded in Epon. Semithin sections were stained with uranyl acetate and examined under a Philips 201 transmission electron microscope.

**Summary of Cases**

The clinical findings in these 20 patients are summarized in Table 1. The patients included 11 girls and nine boys ranging in age from 7 months to 17 years.
### Pathological findings in 20 children with temporal lobe epilepsy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pathology</th>
<th>Mesial Temporal Sclerosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>moderate subpial gliosis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>old hemorrhagic infarct</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>mixed glioma (astrocytic, oligodendroglial, &amp; ganglionic cell components) (2 resections)</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>4</td>
<td>cavernous hemangiomma</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>5</td>
<td>dysembryoplastic neuroepithelial tumor</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>6</td>
<td>grossly abnormal gyrus with marked enlargement &amp; increased thickness of cortex; focal cortical dysplasia with large abnormal neurons with malorientation, neuronal heterotopias in white matter</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>7</td>
<td>oligodendroglia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>scattered heterotopic neurons in white matter</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>demyelination, giant cells mostly in white matter, gliosis consistent with tuberous sclerosis, subpial gliosis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>grossly abnormal gyrus with blurring of gray-white junction, extensive cortical abnormalities with focal polymicrogyria, focal cortical dysplasia, extensive white matter heterotopias, &amp; a hamartomatous nodule in deep white matter with neuronal penetration by capillaries</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>minimal focal neuronal heterotopia in white matter</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>ganglioglioma with multifocal tumor nodules separated by normal cortex as well as cortex with abnormal neuronal layering and clustering</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>mixed glioma (oligodendroglial, astrocytic, &amp; ganglionic cell components); multifocal distribution, with tumor merging with disorganized cortex; extensive calcification</td>
<td>hippocampus infiltrated by tumor</td>
</tr>
<tr>
<td>14</td>
<td>microdysgenesis with some large neurons, clustering of neurons, &amp; scattered heterotopic neurons in white matter</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>15</td>
<td>focal cortical dysplasia with abnormal architecture &amp; arrangement of neurons, binucleate neurons, large bizarre neurons, numerous &quot;balloon&quot; cells with glasy eosinophilic cytoplasm in cortex &amp; white matter, heterotopic neurons in white matter, some containing neurofilamentous accumulations</td>
<td>hippocampus NA</td>
</tr>
<tr>
<td>16</td>
<td>ganglioglioma with oligodendrogial &amp; ganglionic cell components; multinodular pattern reminiscent of dysembryoplastic neuroepithelial tumor; in nontumorous areas, abnormal neuronal layering &amp; gliosis</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>focal astroglisis &amp; perivascular lymphocytic cuffing in white matter</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>two resections both showing diffuse expansion of white matter by neurons and oligodendrocytes; cortical extension very focally; no atypia, mitoses, or necrosis; cellularity in keeping with a ganglioglioma with oligodendroglial elements</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>changes of tuberous sclerosis with numerous pale eosinophilic cells in white matter, less often in cortex, associated with reactive gliosis; nodule in subependymal white matter histologically reminiscent of subependymal giant cell tumor</td>
<td>+</td>
</tr>
</tbody>
</table>

*NA = not available; + = mesial temporal sclerosis identified (defined as neuronal loss and gliosis in the Sommer's sector, end folium, dentate gyrus, or other parts of hippocampal formation/amygdala).

All patients presented with complex partial seizures prior to temporal lobectomy, and 12 patients had both complex partial and secondary generalized seizures.

**Neuroradiological and ECoG Findings**

Abnormalities were detectable by CT in 12 patients. With MR imaging, abnormalities were observed in 19 cases (Table 1).

All 20 patients had epileptiform discharge on preexcisional ECoG. At postexcisional ECoG, four patients were in Grade A (no residual epileptiform activity), 11 in Grade B (mild residual activity), three in Grade C (moderate residual activity), one in Grade D (unchanged from preexcisional ECoG), and one in Grade E (indeterminate due to drug effects). The patient in Grade D (Case 19) had a recurrent ganglioglioma with recurrent seizures consisting of complex partial seizures that secondarily generalized.

**Clinical Follow-Up Results**

The postoperative seizure outcome was graded as follows: Grade 1: seizure-free off medications; Grade 2: seizure-free with medications; Grade 3: 50% or greater reduction in seizures with medications; Grade 4: less than 50% reduction in seizures with medications; and Grade 5: no change in seizures.

The clinical follow-up period ranged from 12 to 42 months, with a mean of 29 months. Since the surgery, one patient (Case 5) has been seizure-free without antiepileptic drugs (Grade 1). The 11 patients in Grade 2 have remained seizure-free with medications for over 1 year. The five patients in Grade 3 have had a reduction in seizure activity greater than 50% with medications. Only one patient (Case 19), who underwent two operations for removal of a ganglioglioma, remains with a less than 50% reduction of generalized seizures after her second surgery (Grade 4). No follow-up data were available in two patients.

**Pathological Results**

The pathological findings are summarized in Table 2. A few salient features are highlighted below.

**Hippocampal Pathology.** The hippocampus was available for examination in 14 cases (Table 2). Mesial temporal sclerosis (defined as neuronal loss and gliosis...
in the Sommer's sector, end folium, dentate gyrus, or other parts of hippocampal formation/amygdala was identified in 12 cases. Of the remaining two cases, the hippocampus was infiltrated by tumor in Case 13 and was involved by a hemorrhagic infarct in Case 2. In all 12 patients with mesial temporal sclerosis, an associated cortical/white matter abnormality was found (dual pathology).

**Cortical Microdysgenesis and Other Lesions.** Cases 2, 4, and 7 showed pathological changes consistent, respectively, with old hemorrhagic infarct, cavernous hemangiomata, and oligodendroglioma. Case 1 revealed moderate subpial gliosis but no other focal pathology. Scattered heterotopic neurons in the white matter were seen in three patients (Cases 8, 11, and 14), with microdysgenesis of cortex (defined as subtle/minimal abnormalities of neuronal clustering and orientation) in Case 14. Minimal degrees of subpial gliosis were disregarded, as these may be encountered in normal subjects and cannot be regarded as abnormal without detailed quantitative studies utilizing age and site-matched controls.

In one patient (Case 18), focal astrogliosis with scattered perivascular lymphocytic cuffing was seen in the temporal white matter underlying the active spiking cortex defined by ECoG. There were no microglial nodules or other evidence of encephalitis, and the observed changes in themselves were insufficient for an unequivocal diagnosis of Rasmussen's encephalitis.

**Focal Cortical Dysplasia.** Tissue from Cases 6 and 15 revealed changes consistent with focal cortical dysplasia (Fig. 1) as described by Taylor, et al.38 Both specimens revealed extensive abnormalities of neuronal size, shape, and orientation with clusters of heterotopic neurons in the white matter. In Case 15, both cortex and white matter contained atypical neuronal and glial cells as well as numerous “balloon cells,” which were unreactive for GFAP and neurofilament and weakly positive for NSE.

**Focal Cortical Dysplasia With Capillary Penetration of Neurons.** Case 10 (described in a previous case report16) revealed changes of focal cortical dysplasia, focal polymicrogyria, extensive white matter heterotopias, scattered “balloon cells” in the cortex and white matter, as well as a heterotopic nodule in the deep white matter which revealed numerous abnormal neurons showing penetration of somata by capillaries (Fig. 2). This was not associated with gliosis or scarring. Electron microscopy of this nodule revealed abnormal Nissl material in these neurons and intracytoplasmic capillaries with intact basal laminae.

**Tuberous Sclerosis.** Cases 9 and 20 represented the formae frustes of tuberous sclerosis, with no cutaneous or other stigmata of the disease. The large pale cells in the cortex and white matter (Fig. 3) in both cases were strikingly vimentin-positive and variably positive for GFAP and NSE. On electron microscopy, the pale cells constituting the cortical tuher in Case 20 revealed numerous dense bodies, lysosomes, and abundant intermediate filaments. In this specimen, a deep white-matter nodule had the histological appearance of a subependymal giant cell tumor/"candle garners." The cells in this nodule were positive for GFAP and NSE, and had punctate synaptophysin positivity in the vicinity of these cells, indicating aberrant synapses.

**Mixed Tumors**

The most enigmatic cases were those with mixed tumor: for the sake of clarity in the ensuing discussion, the tumors with only oligodendrogial with ganglionic components or only astrocytic with ganglionic components have been designated as "gangliogliomas" (Cases 12, 16, 17, and 19) and those with oligodendrogial, astrocytic, and ganglionic components as "mixed gli-

---

**FIG. 1.** Studies in Case 6, a 7-month-old girl with partial motor, complex partial, and secondary generalized seizures. *Left:* Magnetic resonance T₁-weighted image showing marked enlargement and increased thickness of the cortex and loss of gray and white differentiation over the right temporal lobe. *Right:* Photomicrograph of a cortical section showing focal cortical dysplasia with large abnormal neurons of variable size and shape, and an abnormal Nissl pattern (arrow). H & E, × 136.
Pathology of epilepsy in children

Fig. 2. Case 10. Photomicrograph showing a heterotopic nodule in the white matter containing large aberrant neurons with capillary penetration of neuronal cell bodies (arrow). H & E, × 136.

omas" (Cases 3 and 13), recognizing that semantically these are all a form of mixed tumor. Case 5 showed many of the features of the newly described "dysplasmatric neuroepithelial tumor," with multiple nodules and cystic areas in the cortex and white matter containing oligodendrocytes, atypical neurons, astrocytes, and cells (not classifiable as neuronal or glial) with abundant pink cytoplasm and nuclear atypia, as well as "balloon cells" with pale eosinophilic cytoplasm, extensive disorganization of cortex with abnormal neurons, and calcification (Fig. 4).

Besides Case 5, three further cases from the "mixed tumor" group showed varying degrees of cortical disorganization. Case 16 had a multinodular tumor with oligodendrogial and ganglionic components, again separated by normal cortex or cortex with abnormal neuronal layering and gliosis, and was reminiscent of the "dysplastic neuroepithelial tumor," without the component of atypical cells and the more widespread disorganization of cortex described in "dysplastic neuroepithelial tumor." Cases 12 and 13 also had multifocal tumors with the intervening cortex appearing normal or disorganized.

Case 19 revealed unusual pathology in that no discrete tumor nodule or mass was seen but, rather, the white matter was diffusely expanded by a proliferation of ganglion cells and oligodendrocytes, without mitoses, necrosis, or other features typical of anaplasia. Focally, there was extension of this process to the cortex, with satellitosis of cortical neurons.

Discussion

Mesial Temporal Sclerosis

Mesial temporal sclerosis is the single most common abnormality described in temporal lobectomies for refractory seizures, accounting for up to 65% of cases in various series. In the 857 cases reviewed by Mathieson at the Montreal Neurological Institute, mesial temporal sclerosis was seen as the only lesion in 67 cases, while mesial temporal sclerosis with cortical neuronal loss was found in a further 73 cases. Of the 249 cases reviewed by Bruton, 107 (43%) showed mesial temporal sclerosis; in 43%, mesial temporal sclerosis was the only lesion. In our series, the mesial temporal lobe structures were only removed in patients who presented with EEG seizure foci in the inferior mesial temporal lobe or manifested hippocampal abnormalities on MR imaging. This yielded hippocampal tissue in 14 cases, two of which had hippocampal involvement by tumor or infarct. The remaining 12 cases had evidence of mesial temporal sclerosis but, in contrast to the previous series, we found other associated lesions in every case. Thus, every patient in this

Fig. 3. Case 20, a 7-year-old girl with complex partial seizures. Left: Computerized tomography scan showing calcification in the right temporal lobe. Center: Gadolinium-enhanced magnetic resonance T1-weighted image showing the area as paradoxical increased signal intensity. Right: Photomicrograph showing clusters of large pale balloon cells in the white matter. H & E with Luxol-fast blue, × 135.
series who had mesial temporal sclerosis belonged to the "dual pathology" group, suggesting that this pattern predominates over isolated mesial temporal sclerosis in children. In contrast, in the series of 178 patients (mainly adults) with temporal lobe resections reported by Lévesque, et al., dual pathology was found in 30.3% of cases.

The 20 patients in this pediatric series had subtle or significant abnormalities of the lateral temporal lobe structures. A number of factors may be contributory to this significant difference between our series and those previously reported. An important factor is the selection criteria used by various authors. For example, in the series described by Bruton, these included refractory seizures, cases with a unilateral temporal lobe seizure focus (or, if bilateral, a clearly predominant spike discharge on the side of lobectomy), an absence of a space-occupying lesion determined by neuroradiological studies, and a preoperative intelligence quotient greater than 70. In contrast, our series included 20 consecutively treated children with refractory complex partial seizures who were considered for epilepsy surgery, most of whom had radiologically identified focal lesions.

The precise mechanisms responsible for this selective neuronal loss in the hippocampus remain unknown; however, one of the recognized associations is febrile seizures in childhood. The pattern of neuronal loss is different from that seen in hypoglycemic or hypoxic/ischemic injury. Bilateral but usually asymmetrical hippocampal gliosis has also been reported in an autopsy series of epileptic patients. In the large series of Lévesque, et al., the duration, severity, and type of seizures did not affect the severity of hippocampal damage. These authors reported that severe hippocampal neuronal loss was seen in over 88% of patients without extrahippocampal lesions, but in only 51.8% of patients with dual pathology. Furthermore, in the latter group, glioma patients had a milder cell loss as compared with patients with heterotopia, who suffered a severe neuronal loss. A mild-to-moderate degree of mesial temporal sclerosis was present in our cases, although due to the incomplete and fragmented nature of the specimen, detailed quantitative and comparative assessments of the degree of hippocampal neuronal loss and gliosis were not feasible.

Neuronal Dysgenesis/Microdysgenesis

Several recent publications have addressed the significance of minor neocortical abnormalities in epilepsy resections. These have been variably called "microdysgenesis," "microdysgenesis," and "neuronal dysgenesis." Hardiman, et al., evaluated 50 patients who underwent temporal lobectomies for intractable epilepsy for evidence of "neuronal dysgenesis," identified in this series by neuronal ectopia (presence of neurons in the subcortical white matter) and neuronal clustering and bare areas within cortical layers 2 to 6 as well as other lesions such as Chaslin's subpial gliosis. By comparing their patients with age- and sex-matched controls, they found that severe neuronal ectopia (more than eight neurons/2 sq mm of white matter) was
Pathology of epilepsy in children

present in 42% of patients with epilepsy, with neuronal clustering in 28% and Chaslin's subpial gliosis in 38% of epilepsy cases. For appropriate evaluation of such neuronal irregularities, comparative studies utilizing controls as in the study of Hardiman, et al., are required. Although we did not perform detailed quantitative studies, four cases in the present series fall under the category of microdysgenesis (Cases 1, 8, 11, and 14). In these patients, we found moderate subpial gliosis (Case 1), white-matter neuronal heterotopia (Cases 8, 11, and 14), and abnormal neuronal clustering (Case 14) along with mesial temporal sclerosis in the three patients from whom the hippocampus was available for assessment. In their study, Hardiman, et al., reported a favorable outcome after surgery in cases with severe neuronal ectopia and clustering. In our cases, postexcisional EcoG revealed Grade A findings (no residual epileptiform activity) in one patient and Grade B findings in three patients (mild residual epileptiform activity). A postoperative seizure grade of 2 was obtained in two patients, who were seizure-free with medications for over 1 year in follow-up evaluation. The remaining two patients had a reduction in seizure activity of greater than 50% while receiving medications. There was no significant correlation of the EcoG grade with the seizure outcome grade.

The pathological definitions of "microdysgenesis" and the significance attributed to some of the observed abnormalities have proved controversial.22,27,30 Prominence of subpial astrocytes, the very occasional heterotopic neuron in the white matter, and scattered neurons in the molecular layer are within the range of normal in the neocortex, and commonly observed in the brains of neurologically normal patients. More quantitative studies with larger numbers of subjects and a consensus among pathologists in accepting unified terminology for these changes will help in the interpretation of the more subtle abnormalities and their distinction from variations of the normal.

Focal Cortical Dysplasia and Tuberous Sclerosis

Two patients in this series (Cases 6 and 15) had changes of focal cortical dysplasia, as defined by Taylor, et al.38 The outcome of surgery has been reportedly variable in such patients.8,31-33,38 In one series, the variable most strongly correlated with surgical outcome was the amount of lesion removed.33 In both of our patients, postexcisional EcoG revealed Grade B features with mild residual epileptiform activity. Clinical follow-up evaluation in one patient (Case 6) showed a Grade 2 status (seizure-free with medications for over 1 year), while the other patient (Case 15) showed a seizure grade of 3, with reduction in activity greater than 50% while receiving medications.

The pathological spectrum of focal cortical dysplasia includes significant abnormalities of neuronal morphology and orientation with bizarre large neurons containing masses of Nissl substance, binucleate forms, aberrant neuritic processes, variable gliosis, as well as heterotopic neurons in the white matter. As observed in our cases, the presence of pale eosinophilic "balloon cells" akin to those seen in tuberous sclerosis is well recognized.12-20 Although the precise origin of the balloon cells remains undetermined, they are variably immunoreactive for glial and neuronal markers.20 In both of our patients with the forme fruste of tuberous sclerosis (Cases 9 and 20), the balloon cells were strongly immunoreactive for vimentin. In one patient (Case 20), a nodule reminiscent of a subependymal "candle guttering" showed synaptophysin positivity, indicating aberrant synaptic activity associated with these cells.

In a recent study of 22 patients with neuronal migration disorders including focal cortical dysplasia and forme fruste of tuberous sclerosis, Palmini, et al.,32 commented on the similarities in the histological features of the two entities and suggested that histological distinction was often difficult. These authors reported that differentiation between the two entities was based on a more marked extent of cytoarchitectural abnormalities in the forme fruste of tuberous sclerosis compared with focal cortical dysplasia, and on the presence of subpial clusters of giant astrocytes in tuberous sclerosis, which were apparently lacking in focal cortical dysplasia. In another recent communication, Ardermann and Palmini stated that the differentiation between the two entities is based on the degree of gliosis in the neopil and subcortical white matter, which is greater in tuberous sclerosis, as well as on the presence of microcalcifications and subpial astrogliosis in tuberous sclerosis and their absence in cortical dysplasia.

From our experience with the pathology of neuronal migration disorders both from the present series and over the last 20 years at The Hospital for Sick Children, we have been unable to confirm the above observations by Palmini, et al. We have not found the presence or absence of subpial astrogliosis to be a specific feature of either entity. Although there is overlap in the pathology, we have found a much greater degree of cortical neuronal disorganization in focal cortical dysplasia. The extensive collections of balloon cells with loss of myelin in the white matter have, on the other hand, been more typical of tuberous sclerosis. We have found astrogliosis in the cortex or white matter in both entities, and the degree and distribution of gliosis have not been helpful distinguishing features.

Focal Cortical Dysplasia With Capillary Penetration of Neurons

Most intriguing were the pathological findings in Case 10, reported in detail elsewhere.21 The patient, a 9-year-old boy with intractable complex partial seizures, had an enlarged left temporal lobe on MR imaging with diffuse high signal intensity over the cortex and poor differentiation of gray and white matter on T2-weighted MR imaging as well as decreased blood flow on a SPECT scan. Active epileptiform discharges were identified in the left temporal lobe with focal slow waves and generalized epileptiform paroxysms. The temporal lobectomy specimen revealed unusual abnormalities, including focal polymicrogyria, focal cortical dysplasia, widespread neuronal heterotopias in the white matter, as well as a heterotopic nodule in the deep white matter which contained giant abnormal neurons with intraneuronal penetration by capillaries. Penetration of neu-
ronal soma by blood vessels was described previously by Kepes, et al., in a 60-year-old man with a history of seizure disorder, in this patient, the phenomenon was attributed to glial scarring secondary to chronic inflammation associated with limbic encephalitis. In our patient, the pathology is suggestive of an unusual developmental disturbance affecting neuroectodermal and vascular elements. In one single neuron in our Case 20 (forme fruste of tuberous sclerosis), we observed a similar intraneuronal penetration by a capillary.

**Mixed Tumors and Dysembryoplastic Neuroepithelial Tumor**

Also of great interest are the mixed tumors in this series. Four patients (Cases 5, 12, 13, and 16) revealed major or minor degrees of malformed cortex in direct continuity or adjacent to the tumor region. Case 5 represents the newly described entity, "dysembryoplastic neuroepithelial tumor," a term proposed by Daumas-Dupont, et al., for supratentorial tumors which are typically multinodular with a heterogeneous cell composition including oligodendrocytes, neurons, astrocytes, and other atypical cells. Similar tumors were described in 1958 by Cavanaugh, who referred to them as "certain small tumors of the temporal lobe" and speculated that these may be hamartomas with potential for neoplastic transformation. The lesions described by Daumas-Dupont, et al., had a similar histological appearance, although, in one-third of patients, a focal cranial deformity was found indicating a slow-growing lesion of long-standing duration. Sixty-two percent of these tumors occurred in the temporal lobe and, typically, these lesions had a good prognosis with no evidence of recurrence on long-term follow-up examination. Our patient with the dysembryoplastic neuroepithelial tumor remains seizure-free without medication 1 year after follow-up evaluation (seizure Grade 1).

In the present series, there were three further examples of multinodular tumors associated with disorganization of the neocortex (Cases 12, 13, and 16). These tumors had some of the features described in the dysembryoplastic neuroepithelial tumor (namely, multinodularity and abnormal neuronal layering in some parts of the cortex), but did not have all the pathological features and radiological components described as typical for this entity. Thus, it would appear that there may be other "mixed tumors" similar to those described by Cavanaugh, which defy precise classification and represent hamartomaticus or neoplastic foci with transitional zones. The presence of transitions from malformed dysplastic cortex into neoplastic foci was described by Daumas-Dupont, et al., and documented in our series. Two (Cases 12 and 16) of our three patients with multinodular mixed tumors and cortical disorganization remain seizure-free with medication at follow-up evaluation. The third patient (Case 13) has not returned for follow-up review and his seizure status remains unknown.

One patient (Case 19) illustrates the difficulties in distinguishing between low-grade neoplasm and a hamartomatic or malformative process. This 11-year-old girl with complex partial seizures had temporal lobe pathology which was distinctive in having no discrete tumor mass, but rather a diffuse expansion of the white matter with a proliferation of ganglion cells and oligodendrocytes. The overall cellularity and excess of these cells was more in keeping with a neoplasm. The abnormality extended to the surgical margins of resection, indicating residual tumor. This patient had a Grade D status on postexcisional ECoG (unchanged from preexcisional grade) and on follow-up evaluation had a less than 50% reduction in seizures (Grade 4).

**Neuroradiological Studies**

A greater sensitivity of radiographic diagnosis with the advent of MR imaging allows preoperative recognition of focal abnormalities and better localization of a number of lesions, notably, mesial temporal sclerosis, focal cortical dysplasia, other migrational abnormalities such as pachygyria, polymicrogyria, and tumors. The SPECT and positron emission tomographic scanning techniques provide further information about functional abnormalities corresponding to the epileptogenic foci. In our study, the SPECT findings correlated favorably with localization of the seizure focus by EEG studies, demonstrating interictal hypoperfusion and a corresponding immediate postictal hyperperfusion. The SPECT scan shows regional cerebral blood flow changes and contributes to functional localization of the epileptic focus. In our Case 14, no abnormality was seen on either CT or MR imaging, but interictal and postictal change in regional cerebral blood flow was observed on SPECT with Tc-HMPAO, corresponding to the epileptic focus on the EEG recordings. The analysis of interictal and postictal SPECT using Tc-HMPAO recordings can therefore aid in delineation of the epileptic focus, particularly in patients without structural lesions. Most cases in the present series were "lesional" and had abnormalities on CT and MR imaging, which contributes to a higher incidence of "dual pathology" lesions. Nonetheless, compared with adult series, there was a higher proportion of lesions other than mesial temporal sclerosis. While the seizure outcome may be partially dependent on the duration of seizures, over one-half of the patients in the present series remain seizure-free with medication at 1 year of follow-up study.

**References**

5. Berkovic SF, Andermann F, Olivier A, et al: Hippocampal sclerosis in temporal lobe epilepsy demonstrated by mag-
Pathology of epilepsy in children

25. Lyon G, Gastaut H: Considerations on the significance attributed to unusual cerebral histological findings recently described in eight patients with primary generalized epilepsy. Epilepsia 26:365-367, 1985

Manuscript received March 16, 1992. Accepted in final form January 21, 1993. Address reprint requests to: Venita Jay, M.D., Department of Pathology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario MSG 1X8, Canada.