Microdysgenesis in surgical specimens from patients with epilepsy: occurrence and clinical correlations

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Abstract
Malformations of cortical development are commonly associated with epilepsy. In the first 139 consecutive patients in the Göteborg epilepsy surgery series, parenchymal malformations were found in 56.1% of the children and in 23.1% of the adults. Microdysgenesis (MDG), which was the most common parenchymal malformation, was found in 35.1% of the children and in 16.7% of the adults. The aim of this study was to identify clinical characteristics of patients with MDG. Mental retardation was found to be significantly more common in patients with major parenchymal malformations and in patients with MDG compared with patients without parenchymal malformations. Patients with major parenchymal malformations as well as patients with MDG also had a significantly earlier onset of seizures than patients without parenchymal malformations, also when adjusting for mental retardation. Patients with MDG were in these clinical aspects shown to closely resemble patients with major malformations. These findings suggest that MDG is a pathoanatomical entity of clinical relevance, with implications both in mental retardation and in epileptogenesis.

Keywords: epilepsy; microdysgenesis; mental retardation

Malformations of the cerebral cortex are being recognised with increased frequency as a cause of epilepsy and also of mental retardation and other neurodevelopmental disorders.1 As neuroradiological techniques develop, more subtle cortical malformations are demonstrated in patients with pharmaco-resistant epilepsy.1,2 However, there is still a proportion of patients in whom no structural correlates can be found despite high quality MRI.2,3 In these cases further histopathological analyses using modern techniques are of special importance to increase our knowledge of the aetiology of surgically treated epilepsy.

Meencke and Janz first described microdysgenesis (MDG) as a minor parenchymal malformation in patients with generalised epilepsy.3,4 It has also been found in epilepsy surgery specimens from patients with partial epilepsy.5–8 Nordborg et al described MDG in specimens from 42.4% of 33 patients operated on because of intractable partial epilepsy.9 Although the major parenchymal malformations are usually classified according to distinct macroscopical patterns11,12 the minor malformations are classified according to specific microscopical features.3–10

In an analysis of the clinical, radiological, and histopathological findings in the first consecutive 139 patients in the Göteborg epilepsy surgery series13 we found a high proportion of MDG. The series comprises children and adults (ranging in age from 0.9 to 62 years at the time of operation) subjected to a wide range of resective procedures. As there has long been a discussion about the pathophysiological relevance of the discrete histopathological findings of MDG,5–7,14–15 the purpose of the present study was to identify clinical characteristics of patients with this histopathological diagnosis. Our hypothesis was that if MDG, as well as major parenchymal malformations, is of pathophysiological importance in epilepsy, it might be possible to identify clinicopathological relations.

Patients and methods
From 1987 to 1995 139 patients (60 children ≤18 years old and 79 adults) underwent surgery for epilepsy. Most of the adults had pharmaco-resistant epilepsy of temporal lobe origin, without other neurological handicaps. Many of the children, however, had severe epilepsy as part of a multihandicap. In the adult population temporal lobe resections dominated (75.9%) followed by frontal lobe resections (15.2%). Among the children temporal lobe resections were less dominating but still the most common operation (25.0%), followed by frontal lobe and multilobar resections (21.7% each), hemispherectomies (13.3%), and callosotomies (11.6%).

In connection with the analysis of the surgical series, all specimens were re-evaluated by the first author, who was blinded regarding clinical data. Specimens from 57 children and 78 adults contained enough tissue for
histopathological analysis. A detailed methodological description of the histopathological analysis is given elsewhere.15 Eight main categories of lesions were recognised: parenchymal malformations, vascular malformations, low grade tumours, cysts, malignant tumours, infections, hippocampal sclerosis, and other atrophic-gliotic lesions. In total there were 59 different histopathological subgroups.

Major malformations included gross parenchymal malformations (all lesions displaying a disturbance of convolutional pattern or heterotopic islands of grey matter as well as schizencephalic defects), focal cortical dysplasia, and tuberous sclerosis. Focal cortical dysplasia was defined according to Taylor et al.16 In specimens considered as microdysgenetic five different morphological aberrations were found alone or in combination: supernumerary nerve cells in layer I, ectopic nerve cells in the white matter, indistinct cortical lamination, increased neuronal columnation, and increased clustering of nerve cells in the cortex. Balloon cells were, besides other MDG aberrations, found in only one case, which was, however, free from neuronal cytomegaly. There were no cases with marginal glioneuronal heterotopia and no cases displaying a loss of demarcation between layers I and II in the present material.15 As the border between what is considered as normal brain tissue and mild microdysgenesis is not quantitatively defined, there will, in a screening situation, by necessity be cases in which the changes are too subtle or the material too limited to allow an unequivocal diagnosis of MDG. In the present series there were 22 such patients (eight children and 14 adults) in which MDG was merely suspected. These patients have not been further considered in the statistical analyses.

Significance testing of correlations was performed with Pitman’s non-parametric permutation test.17 Mantel’s technique of pooling18 applied to Pitman’s non-parametric permutation test was used as a non-parametric partial analysis to study the correlation between two variables adjusted for a third variable. For comparisons between groups, the Mann-Whitney U test and the Kruskal-Wallis test were used.

Results
Specimens were achieved from 57 children and 78 adults. The main histopathological diagnoses are listed in table 1 (subgroups for the main diagnoses other than parenchymal malformations are detailed in table 3 in19). Most of the specimens from individual patients had more than one histopathological diagnosis. The mean number of diagnoses in the adults was 1.7 (range 1–3) and in the children 1.9 (range 1–3). The categories of lesions were the following: parenchymal malformations in 37.0% (n=50), vascular malformations in 9.6% (n=13), low grade tumours in 16.3% (n=22), one cyst, one malignant tumour, one infection, hippocampal sclerosis in 17.7% (n=24), and other atrophic-gliotic lesions in 78.5% (n=106).

Parenchymal malformations were found in 56.1% (n=32) of the children and in 23.1% (n=18) of the adults. Microdysgenesis was the most common parenchymal malformation in both groups and was found in 35.1% (n=20) of the children and 16.7% (n=13) of the adults. Histopathological characteristics of MDG are illustrated in the figure.

Table 1 Neuropathological diagnoses

<table>
<thead>
<tr>
<th>Neuropathological diagnoses</th>
<th>Total (n=236)</th>
<th>Children (n=108)</th>
<th>Adults (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal malformations</td>
<td>50</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Major malformations</td>
<td>17</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Gross malformations</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Focal cortical dysplasia</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Microdysgenesis</td>
<td>33</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>13</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Low grade tumours</td>
<td>22</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Cysts</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malignant tumours</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>24</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Atrophic-gliotic lesions</td>
<td>124</td>
<td>58</td>
<td>66</td>
</tr>
</tbody>
</table>

Discussion
The pathogenetic relevance of microdysgenesis in epilepsy has been a matter of controversy for many years.5,8,14,15 It has been argued that...
discrete aberrations in the cortical architecture can be seen also in subjects without epilepsy and might represent one end of the normal variation. According to published postmortem control series, MDG is, however, more common in epilepsy material. In one postmortem study, MDG was found in 37.7% of 591 patients with epilepsy and in only 6% of 150 controls. \textsuperscript{19} In another report severe neuronal ectopia (defined as more than eight dystopic neurons/2 mm\textsuperscript{2}) was found in 42% of specimens from the temporal lobes of 50 surgically treated patients whereas there were no microdysgenetic changes in 33 postmortem controls. \textsuperscript{8}

There are some independent data about the structure of microdysgenetic cortex in patients with epilepsy that can have a bearing on the pathogenetic relevance of MDG. In an earlier detailed study of specimens from 11 patients with epilepsy in our series, using confocal laser scanning microscopy, an increased number of dendritic abnormalities of single pyramidal and non-pyramidal cells could be demonstrated in the seven patients with MDG but not in those without MDG. \textsuperscript{20} This finding illustrates that MDG is not only a question of aberrant nerve cell distribution, but that individual neurons and neuronal connections may be abnormal. It seems reasonable to assume that such structural abnormalities and misconnections could lead to abnormal function.

Another way to test the possible pathogenetic relevance of MDG was used in the present investigation in which the relation between MDG and clinical variables was studied. In earlier studies patients with more severe malformations of cortical development, changes have been shown to have a higher incidence of mental retardation or developmental delay and a higher seizure frequency than those with less severe histopathological changes. \textsuperscript{2 4 10 12} In the one earlier study in which clinical correlates to MDG were studied, age at onset was not shown to relate to a histopathological diagnosis of MDG. \textsuperscript{8}

In the present study patients with MDG were shown to closely resemble patients with major malformations in several clinical aspects. They were significantly more often mentally retarded, and had a significantly lower age at seizure onset than the patients without parenchymal malformations. The age at seizure onset was still significantly lower for patients with MDG when adjusting for mental retardation and can hence not be attributed to some unknown underlying cause for mental retardation other than MDG. These findings support the contention that MDG is a pathoanatomical entity of clinical relevance, probably implied both in mental retardation and in epileptogenesis.

Because the difference in nerve cell distribution between normal and microdysgenetic brain is a matter of degree rather than quality, light microscopic screening of epileptic brain tissue will not enable an absolute delineation between microdysgenetic and normal brain. To
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