Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study

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Summary

Interictal hypometabolism is commonly found in mesio-temporal lobe epilepsy (MTLE), but its pathophysiology remains incompletely understood. We hypothesized that metabolic changes reflect the preferential networks involved by ictal discharges. We analysed the topography of interictal hypometabolism according to electro-clinical patterns in 50 patients with unilateral hippocampal sclerosis (HS) and consistent features of MTLE. Based on electro-clinical correlations, we identified four groups: (i) mesial group (13 cases) characterized by mesial seizure onset without evidence of early spread beyond the temporal lobe; (ii) anterior mesio-lateral group (AML; 18 cases) with early anterior spread involving the anterior lateral temporal cortex and insulo-fronto-opercular areas; (iii) widespread mesio-lateral group (WML; 15 cases) with wide spread (involving both anterior and posterior lateral temporal and perisylvian areas); and (iv) bitemporal (BT) group (four cases) with early contralateral temporal spread. Results of [18F]fluorodeoxyglucose-PET imaging in each group were compared with those of 10 control subjects using statistical parametric mapping software (SPM99). MRI data and surgical outcome in each group were compared with metabolic findings. Hypometabolism was limited to hippocampal gyrus, temporal pole and insula in the mesial group. Gradual involvement of lateral temporal cortex, insula and perisylvian areas was observed in the AML and WML groups. The BT group differed from the others with mild bitemporal involvement, bilateral insular hypometabolism and longer epilepsy duration. MRI structural abnormalities outside of the mesial formations were detected in 65% of the cases. Neither the severity of HS nor temporal atrophy appeared related to the topography of hypometabolism. However, temporal hypometabolism was more extended when temporo-polar signal changes were detected. Among operated patients (n = 43), seizure-free outcome was obtained in 82%. Surgical outcome appeared more favourable in the mesial group. However, the difference between the four groups was not significant. Our results suggest that hypometabolism in MTLE may be related to ictal discharge generation and spread pathways, even if structural changes and epilepsy duration may also play a role.

Keywords: mesio-temporal lobe epilepsy; hippocampal sclerosis; EEG; cerebral metabolism; epilepsy surgery

Abbreviations: AML = anterior mesio-lateral; BT = bitemporal; [18F]FDG = fluorodeoxyglucose; FLAIR = fluid attenuation inversion recovery; HS = hippocampal sclerosis; MTLE = mesio-temporal lobe epilepsy; SEEG = stereo-electroencephalography; SPM = statistical parametric mapping; WML = widespread mesio-lateral

Introduction

Mesio-temporal lobe epilepsy (MTLE) is a localization-related syndrome identified during the last decade. Its identification has proven to be valuable for epilepsy surgery candidate selection. Diagnosis is based on a combination of past history (in particular complicated febrile convulsions), clinical presentation (complex partial seizures with vegetative aura), EEG (anterior temporal focus) and imaging findings (hippocampal sclerosis; HS) (French et al., 1993; Wieser et al., 1993; Williamson et al., 1993; Mathern et al., 1995; Engel, 1996). The place of PET imaging in MTLE diagnosis and determining surgical prognosis has largely been demonstrated (Engel et al., 1982a; Theodore et al., 1992; Hajek et al., 1993; Henry et al., 1993; Radtke et al., 1993; Spencer, 1994). MTLE has proven to be one of the most medically refractory localization-related epilepsy syndromes (Semah et al., 1998). It is now considered as the prototype of a surgically
remediable syndrome (Engel, 1998). However, so-called MTLE does not appear to be homogeneous from an electro-clinical point of view (Adam et al., 1996; Bartolomei et al., 1999). Moreover, recent studies have indicated involvement of structures beyond the limits of the mesial temporal area, particularly of the temporal pole (Mitchell et al., 1999) and insular cortex (Isnard et al., 2000; Bouilleret et al., 2002). In addition, widespread structural brain abnormalities associated with HS have been demonstrated (Sisodiya et al., 1997; Moran et al., 2001). Failure after anterior temporal resection in some patients also suggests that the epileptogenic zone is not always confined to mesial structures (Hennessy et al., 2000). These observations provide some evidence that the hippocampus, even though it is characterized by a lower threshold for seizure generation, is part of a larger regional epileptogenic network involving neocortical temporal cortex and extra-temporal areas. The organization of this network may differ from one patient to another despite an apparently identical seizure onset zone, but seems individually fixed, consistent with the observation that ictal semiology remains remarkably stereotyped for a given patient.

Whether cerebral metabolism studies provide further information about the neuronal network involved in MTLE remains open to debate. Intercortical temporal hypometabolism ipsilateral to the epileptic focus is detected in 80–97% of MTLE cases (Spencer, 1994; Semah et al., 1995; Adam et al., 1996; Ryvlin et al., 1998). However, various patterns in temporal and extra-temporal areas have been reported. Hypometabolism is usually much larger than the structural lesion and epileptogenic zone (Engel et al., 1982b; Sackellares et al., 1990; Ryvlin et al., 1991; Theodore et al., 1992; Hajek et al., 1993; Henry et al., 1993) and often spreads over extra-temporal cortical areas including subcortical structures (Arnold et al., 1996; Savic et al., 1997; Dupont et al., 1998). Despite intensive studies during the last two decades, the pathophysiology of interictal hypometabolism and its clinical relevance remain incompletely understood. It has been postulated that structural changes may account for hypometabolism mechanisms, but a strong relationship has failed to be demonstrated. Recent studies demonstrate that the topography of the hypometabolism may be related to brain areas which generate the clinical expression of ictal onset and spread (Savic et al., 1997; Dupont et al., 1998; Koutroumanidis et al., 2000). We hypothesized that interictal hypometabolism reflects the preferential networks involved by ictal discharges. The aim of this study was to compare the topography of hypometabolic areas with electro-clinical patterns and ictal discharge spread pathways in MTLE. The relationships between structural changes detected on MRI, electro-clinical and metabolic data and surgical outcome will also be included in the analysis.

Patients and methods
We studied a series of 50 MTLE patients investigated for epilepsy surgery at Sainte-Anne Hospital, Paris between 1996 and 2001. All patients underwent comprehensive pre-surgical evaluation including EEG-video monitoring, neuropsychological testing, Wada test and/or functional MRI. In addition, stereo-electroencephalography (SEEG) was performed in 14 cases. Selection criteria included isolated unilateral hippocampal atrophy demonstrated by MRI, consistent clinical features of MTLE confirmed by EEG and/or SEEG recordings, and an available interictal metabolic study with $[^{18}]$F-fluorodeoxyglucose (FDG)-PET. The population consisted of 31 females and 19 males, aged from 14 to 50 years (mean: 32 years). Age at epilepsy onset ranged from 1 to 24 years (mean: 9.7 years) and epilepsy duration ranged from 5 to 45 years (mean: 22 years). Febrile convulsions in childhood were reported in 35 patients (70%), early brain injury (infectious, neonatal or traumatic) in 19 patients (38%) and a familial history of epilepsy was reported in 16 patients (32%). Past medical history was unremarkable for seven patients. Mean seizure frequency ranged from one to 30 per month. Forty-three patients underwent surgical resection (three patients were excluded from surgery because of risk for memory, and four others refused an operation). The operation was performed on the right temporal lobe in 26 cases and on the left one in 17 cases. HS was confirmed by neuropathological examination in all operated patients, and no associated lesion other than gliosis was found in the cortical specimen.

Clinical ictal patterns were characterized on the basis of seizure description by the patient and his/her family, direct observation of seizures by caring physicians, and ictal and post-ictal examination during video-EEG recording. The following symptoms and signs were analysed: presence and type of aura; time and degree of loss of consciousness; staring; type of automatisms (oro-alimentary, gestural, verbal, simple or complex); dystonic posturing; salivation; type and lateralization of somatomotor manifestations; head and eye version (that must be distinguished from head deviation or orientating reaction); secondary generalization; post-ictal confusion; and language disorder duration (considered as brief when <1 min and prolonged when duration exceeded 1 min) taking into account hemispheric dominance for language. Careful attention was paid to the chronology of the appearance of each sign, with distinction between early manifestations (present during the first 30 s of seizure) and late manifestations occurring later than 30 s after the onset of ictal discharge. Seizure duration was calculated beginning at the first electrical changes on EEG preceding the clinical manifestations and consisting of suppression of interictal abnormalities followed by depression or low voltage fast activity. For each patient, the clinical pattern was compared with the site of abnormalities on interictal EEG and correlated with the ictal discharge pattern. A total of 114 seizures (1–6 per patient) were analysed and related to usual seizures as described by the patient and his/her family. Unusual features related to drug withdrawal during EEG monitoring were not considered in the analysis. Classification was based on the methodological approach described by Bancaud and colleagues (Bancaud, 1980, 1987; Bancaud et al., 1984) with
precise correlations established between ictal clinical symptomaticity and the ictal EEG pattern. Here, each electroclinical pattern is considered to be the expression of the neuronal network involved by the ictal discharges for a given patient. In the cases where SEEG was performed, analyses of interictal and ictal deep recordings were used to verify information obtained by surface EEG. Four groups were identified according to ictal spread patterns: (i) mesial without evidence of early spread beyond the temporal lobe: ‘mesial group’; (ii) mesio-lateral with anterior spread (involving the anterior lateral temporal cortex and insulofronto-opercular areas): ‘anterior mesio-lateral’ (AML) group; (iii) mesio-lateral with wide spread (involving both anterior and posterior lateral temporal and perisylvian areas): ‘widespread mesio-lateral (WML) group’; and (iv) mesial with early contralateral temporal spread: ‘bitemporal (BT) group’.

The electro-clinical criteria for each group are detailed below. Individual classification was based on clinical and electrical criteria but, when there was ambiguity or unexpected clinical findings, the EEG and, when available, SEEG data were determinant.

The mesial group is clinically characterized by the presence of an aura, incomplete or inconstant loss of consciousness (if present always secondary), brief post-ictal confusion and no or brief post-ictal language deficit even in the case of seizure origin in the dominant hemisphere. Staring can be observed and automatisms are always simple, mainly oro-alimentary. Head deviation is unusual, whereas dystonic posturing, salivation, somatomotor manifestations, head and eye version and secondary generalization are not observed. Interictal EEG shows anterior temporal localized spikes and slow waves, and the ictal EEG onset consists of a prolonged low-voltage discharge located on the anterior temporal areas followed by a rhythmic discharge restricted to the same territory or with delayed spread to anterior frontal areas, without contralateral involvement. On post-ictal EEG, slow wave activity is limited to the anterior or to the anterior and middle temporal areas.

The AML group is defined by a more complex symptomaticity with early or secondary frequent and usually complete loss of consciousness, staring, automatisms (oro-alimentary, verbal and gestural) that may be complex, dystonic posturing (mainly contralateral to the ictal discharge) and head deviation (mainly ipsilateral). Salivation and contralateral somatomotor manifestations (mainly facial) are frequent but delayed, and head and eye version is rare. Secondary generalization is possible, but only occasional. Post-ictal confusion is almost constant, but usually brief; post-ictal language deficit is constant when seizure origin is located in the dominant hemisphere, but mostly brief. Interictal EEG consists of regional (anterior temporal and temporo-frontal) spikes and slow waves predominating on one side. Ictal EEG consists of a low-voltage discharge starting in the anterior temporal area which soon becomes visible over a wide anterior temporo-frontal territory followed by a widespread anteriorly predominant rhythmic discharge with secondary contralateral involvement. Post-ictal EEG shows regional slow waves on the temporal or temporo-frontal areas with unilateral predominance.

The WML group differs from the AML group by the constant, total and frequently early nature of the loss of consciousness, early salivation, somatomotor manifestations and head and eye version. Secondary generalization is not uncommon. Post-ictal confusion is frequent and possibly prolonged; post-ictal language deficit is constant and prolonged in cases where seizures start in the dominant hemisphere. Interictal EEG consists of widespread temporal (anterior, middle and posterior) spikes and slow waves spreading to fronto-central or parietal areas with unilateral predominance. The ictal EEG consists of a low-voltage discharge located over temporal areas that soon becomes visible over fronto-centro-parietal areas, followed by hemispheric rhythmic discharge with secondary contralateral involvement. Post-ictal EEG shows hemispheric slow waves with temporal and unilateral predominance.

The BT group is characterized by early loss of consciousness and prolonged post-ictal confusion (usually exceeding 10 min). Post-ictal language deficit may be present even in cases of seizure origin in the non-dominant hemisphere, but is often difficult to assess because of the severity of the confusion. Simple automatisms and dystonic posturing are frequent, but salivation, somatomotor manifestations, head and eye version and secondary generalization are unusual. Interictal EEG shows bilateral asynchronous temporal spikes and slow waves. Ictal EEG consists of a low-voltage discharge briefly lateralized over one temporal lobe, rapidly recorded from the contralateral side and followed by a bitemporal rhythmic discharge. Post-ictal EEG shows bitemporal anterior slow waves. Patients with bitemporal independent seizure onset were not included in this study.

FDG-PET scans were performed using a high-resolution head-dedicated PET camera (ECAT 953/31B Siemens) with 5.8 mm in-plane and 5 mm axial resolution, allowing 31 transverse sections of the brain, spaced 3.37 mm apart. A set of contiguous 3.4 mm thick axial T1-weighted MRI slices was obtained for superimposition on the PET images. Also, coronal T2-weighted slices (perpendicular to the hippocampal plane) were performed in all patients, and coronal FLAIR (fluid attenuation inversion recovery) slices in 37 cases. FDG was injected intravenously at a mean dose of 220 MBq/70 kg body weight. Image acquisition started 30 min after injection and ended 20 min later. The subjects were studied in an awake and resting state, in a quiet, dimly lit environment and carefully monitored for head movements and ictal events. EEG was not performed during FDG uptake. Ictal studies cannot be entirely excluded, but were unlikely because no abnormal movement was detected and patients did not report isolated subjective manifestations occurring during the examination.

Reconstructed images were corrected for attenuation using ⁶⁸Ga–⁶⁸Ge transmission scans. The results were compared with the PET scans of 10 male healthy volunteers as...
previously described (Semah et al., 1995). Since the PET scans were performed as a part of a research protocol, informed consent was obtained from all subjects. The protocol was approved by the local ethics committee (CCPPRB Pitie-Salpetriere Hospital, Paris, France) and conformed with the Declaration of Helsinki on human investigation.

None of the patients presented other than the usual type of seizure (e.g. secondary generalized seizures) during the 7 days preceding the PET examination. Intensive EEG-video monitoring and drug withdrawal were likewise distant in time. SEEG, when performed, always followed the PET scan. MRI scans were visually analysed by three trained neurologists (F.C., F.S. and V.B.) blinded to clinical data in order to assess the side and degree of hippocampal atrophy (mild, moderate or severe), associated temporal lobe atrophy and signal changes (hypersignal with blurring between grey and white matter on T2-weighted and FLAIR sequences) in the temporal pole.

Statistical differences between the four electro-clinical pattern groups were assessed using the Kruskall–Wallis non-parametric analysis of variance test with $P = 0.05$. Tested variables included patient age, age at epilepsy onset, epilepsy duration, seizure frequency, febrile seizures, familial epilepsy, MRI data, delay between last seizure and PET scan, and Engel class outcome. When a difference between the four groups was detected for a parameter, each group was checked using paired comparisons for this parameter either by the Kruskall–Wallis non-parametric analysis of variance test or by the Fisher exact test.

For the metabolic study, comparison between each MTLE patient group and the control group was performed using statistical parametric mapping software with fixed effects analysis (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Individual SPM analysis was first performed in order to detect some potential variability within each subgroup that may affect the group analysis results. Subgroup SPM analysis was performed afterwards by pooling the patients with the epileptogenic zone on the same side (for a given subgroup, the patients with a right focus were studied separately from the patients with a left focus). In the two conditions, hemispheres were then reversed in order to detect potential differences in metabolic changes related to anatomical asymmetries. Finally, we performed the group analysis by pooling non-reversed and reversed hemispheres according to the most frequently represented side ipsilateral to the epileptogenic focus in each subgroup.

The resulting SPM ($Z$) maps were thresholded to $P = 0.001$ and corrected for extent to 20 voxels. The spatial coordinates of the maximal hypometabolic areas were used to identify the

### Table 1 Ictal semeiology in the different groups of patients and in the whole population

<table>
<thead>
<tr>
<th>Seizure characteristics/clinical patterns</th>
<th>Mesial ($n = 13$)</th>
<th>Anterior mesio-lateral ($n = 18$)</th>
<th>Widespread mesio-lateral ($n = 15$)</th>
<th>Bitemporal ($n = 4$)</th>
<th>Total ($n = 50$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td>10</td>
<td>16</td>
<td>14</td>
<td>3</td>
<td>43 (86%)</td>
</tr>
<tr>
<td>Vegetative (epigastric)</td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>3</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>Psychosensorial (dreamy-state)</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Affective</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Staring</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent or incomplete</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Complete early</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Complete late</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Automatisms</td>
<td>10</td>
<td>18</td>
<td>15</td>
<td>4</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>Simple</td>
<td>10</td>
<td>18</td>
<td>15</td>
<td>4</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>(oro-alimentary)</td>
<td>(7)</td>
<td>(18)</td>
<td>(13)</td>
<td>(4)</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Complex</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Dys tonic posturing</td>
<td>0</td>
<td>13</td>
<td>11</td>
<td>3</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Head deviation</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>3</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Salivation</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Early/late</td>
<td>2/10</td>
<td>4/5</td>
<td>0/1</td>
<td>6/16</td>
<td></td>
</tr>
<tr>
<td>Motor signs</td>
<td>0</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Early/late</td>
<td>3/10</td>
<td>3/6</td>
<td>0/1</td>
<td>6/17</td>
<td></td>
</tr>
<tr>
<td>Version</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Early/late</td>
<td>0/3</td>
<td>2/6</td>
<td></td>
<td>2/9</td>
<td></td>
</tr>
<tr>
<td>Post-ictal confusion</td>
<td>8/5/0</td>
<td>1/12/5</td>
<td>2/8/5</td>
<td>0/0/4</td>
<td>11/25/14</td>
</tr>
<tr>
<td>Language deficit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent/brief/prolonged</td>
<td>6/7/0</td>
<td>10/5/3</td>
<td>11/1/3</td>
<td>2/1/1</td>
<td>29/14/7</td>
</tr>
<tr>
<td>Hemisphere dominant</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Secondary generalization</td>
<td>0</td>
<td>6 occasional</td>
<td>9 not uncommon</td>
<td>1 unusual</td>
<td>16 (32%)</td>
</tr>
</tbody>
</table>

Metabolic patterns in MTLE
corresponding brain areas according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). In order to assess the role of structural MRI changes, we performed a second type of group analysis in which the studied variables were successively the degree of HS (mild, moderate or severe), the presence or absence of temporal atrophy, and signal changes in the temporal polar areas. For signal change analysis only, patients with normal T2-weighted MRI but lacking FLAIR sequences were not included for statistical treatment (n = 6). For a given structural change, each subgroup was compared with the control group using the same parameters as for the electro-clinical groups.

Results

Electro-clinical patterns

Thirteen patients were classified in the mesial group, 18 patients in the AML group, 15 in the WML group and four in the BT group (Table 1). Within these groups, SEEG was performed for two, three, seven and two cases, respectively. Cases without aura were present in all groups, but this was an unexpected finding in the mesial group. However, these patients satisfied all other criteria for classification in this group. Furthermore, SEEG was performed in two of them, confirming that ictal discharges were either confined to mesial structures or spread to neocortical areas after a delay. The mesial group presented with more subtle clinical symptomatology and significantly shorter seizure duration than the other groups (P = 0.01); *seizure duration significantly shorter in the mesial group compared with the other groups (P = 0.05).

Table 2 General data according to electro-clinical patterns

<table>
<thead>
<tr>
<th>Mesial (n = 13)</th>
<th>Anterior mesio-lateral (n = 18)</th>
<th>Widespread mesio-lateral (n = 15)</th>
<th>Bitemporal (n = 4)</th>
<th>Total (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): min–max (mean)</td>
<td>23–41 (34)</td>
<td>17–45 (31)</td>
<td>14–40 (28)</td>
<td>36–50 (42)</td>
</tr>
<tr>
<td>Sex: M/F</td>
<td>5/8</td>
<td>8/10</td>
<td>6/9</td>
<td>0/4</td>
</tr>
<tr>
<td>Age at epilepsy onset (years): min–max (mean)</td>
<td>1–24 (13.5)</td>
<td>3–16 (7.3)</td>
<td>2–20 (9.8)</td>
<td>2–14 (8)</td>
</tr>
<tr>
<td>Epilepsy duration (years): min–max (mean)</td>
<td>11–40 (20)</td>
<td>9–30 (24)</td>
<td>5–36 (18)</td>
<td>24–45 (34)</td>
</tr>
<tr>
<td>Seizure frequency (mean per months)</td>
<td>12</td>
<td>7</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Seizure duration (s): mean/min/max</td>
<td>90/50/140</td>
<td>105/60/180</td>
<td>98/90/115</td>
<td>115/30/180</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Other early events</td>
<td>4: infections 4</td>
<td>8: infections 2; neonatal 3; traumatic 3</td>
<td>7: infections 5; neonatal 1; traumatic 1</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>Familial epilepsy</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>MRI data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS side: R/L</td>
<td>4/9</td>
<td>10/8</td>
<td>12/3</td>
<td>3/1</td>
</tr>
<tr>
<td>HS degree: +/+/+++</td>
<td>5/6/2</td>
<td>2/13/3</td>
<td>5/9/1</td>
<td>2/1/1</td>
</tr>
<tr>
<td>Temporal atrophy: 0/+</td>
<td>6/7</td>
<td>9/9</td>
<td>9/6</td>
<td>2/2</td>
</tr>
<tr>
<td>Polar signal abnormalities 0/+</td>
<td>8/5</td>
<td>2/13</td>
<td>3/11</td>
<td>0/2</td>
</tr>
<tr>
<td>Last seizure before PET (days)</td>
<td>1–25 (6.6)</td>
<td>1–27 (5.1)</td>
<td>1–21 (5.7)</td>
<td>3–15 (10)</td>
</tr>
<tr>
<td>Surgery</td>
<td>13</td>
<td>16</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Type of resection</td>
<td>Limited 13</td>
<td>Limited 8; large 8</td>
<td>Large 12</td>
<td>Large 2</td>
</tr>
<tr>
<td>Follow-up &gt;2 years</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Engel class</td>
<td>IA, 7; IC, 1; IIIA, 1</td>
<td>IA, 6; IB, 2; IIA, 1; IIIA, 1</td>
<td>IA, 4; IB, 2; IIA, 2</td>
<td>I, 23 (82%); IA, 17 (60%)</td>
</tr>
</tbody>
</table>

HS = hippocampal atrophy: +, mild; ++, moderate; ++++, severe. Limited resection corresponds to the resection of the mesial structures and the temporal pole. Large resection includes mesial and polar resection extended to the basal and lateral temporal cortex. In the WML group, the lateral resection included the posterior part of the superior temporal gyrus in six patients and the temporo-parietal junction in three others. *Epilepsy duration significantly longer in the BT group compared with the other groups (P = 0.01); †seizure duration significantly shorter in the mesial group compared with the other groups (P = 0.05); ‡temporo-polar signal changes significantly less frequent in the mesial group compared with the AML and WML groups (P = 0.05).
MRI findings
Unilateral HS was found on the right side in 29 cases and on the left side in 21 cases. It was classified as mild (14 cases), moderate (29 cases) and severe (seven cases). There was associated mild to moderate anteriorly predominant temporal atrophy in 24 cases (48%). In addition, four patients presented with mild ipsilateral hemispheric atrophy. Temporo-polar signal changes were detected on T2-weighted sequences (20 patients: 40%) and/or FLAIR sequences (24 out of 37 patients who had both sequences: 65%). Temporal atrophy and polar signal changes were present simultaneously in 18 patients and found separately in 16 others (13 had only signal abnormalities and three had only atrophy). Ten patients had neither signal changes nor atrophy, and the remaining six had normal T2-weighted scans, but no FLAIR sequences, three of them with temporal atrophy. MRI data did not differ significantly between the four groups for degree of hippocampal and temporal atrophy. However, polar signal changes seemed more frequent in the AML and WML groups (Table 2) than in the mesial group; however, the difference was weakly significant ($P = 0.05$).

FDG-PET imaging
Individual data did not show significant heterogeneity within each group, making possible the group analysis. Non-reversed and reversed hemisphere studies demonstrated similar changes in the mesial and BT groups. However, posterior temporal involvement was slightly more extensive in the AML and WML groups when the hemispheres of patients with a right focus were reversed to the left. To reduce this effect, possibly related to the functional hemispheric lateralization, results were analysed by pooling the epileptogenic hemispheres on the side more frequently represented in each group (on the left side for the mesial group, on the right side for the other groups). We found that the degree and topography of hypometabolism clearly differed between the four groups. The most limited hypometabolism was noted in the mesial group where it was restricted to the hippocampal gyrus, the temporal pole, the anterior insula and the inferior frontal gyrus. The AML group presented with predominantly anterior hypometabolism, involving both mesio-basal and anterior lateral temporal cortex, the frontal and insulo-perisylvian areas (anterior cingulum, anterior part of insula,

Fig. 1 3D MRI representation of hypometabolic areas in MTLE patients (significant differences compared with 10 healthy volunteers using SPM99, threshold: $P = 0.001$, corrected for extent to 20 voxels) in the mesial group (A), the AML group (B) and the WML group (C). Note the gradual involvement of the neocortical temporal areas as well as the perisylvian areas.
inferior frontal gyrus, pre- and postcentral gyri and the anterior part of the lenticular nucleus); mild contralateral frontal hypometabolism was also found. The WML group was associated with an even more extended hypometabolism involving the whole temporal lobe as well as insula, putamen and perisylvian areas up to the temporo-parietal junction and the inferior parietal gyrus; contralateral frontal lobe involvement was more widespread than in the AML group (Fig. 1). In the BT group, a mild but bilateral hypometabolism was found in the temporal pole and the anterior part of the middle temporal gyrus on the side of HS and the contralateral middle temporal gyrus. It was associated with bilateral insular and inferior frontal hypometabolism. In contrast to the findings in the other groups, bitemporal involvement was associated with the mildest degree of ipsilateral hypometabolism. Insular hypometabolism was found in all groups, but most major involvement was observed in the AML and WML groups (Fig. 2). The severity of neither HS nor the temporal atrophy was clearly related to the topography of the hypometabolism. However, temporo-polar hypometabolism was more pronounced and widespread when signal abnormalities were visible on MRI, extending to posterior basal temporal areas. Extra-temporal hypometabolism was similar regardless of whether signal changes were present or not.

**Surgical data and outcome**

The extent of resection varied within each group, taking into account the extent of the epileptogenic zone and hemispheric dominance for language. It was limited to the mesial structures and temporal pole in all patients belonging to the mesial group \(n = 13\) and in half of the operated patients of the AML group \(n = 8\). It was larger in all other cases \(n = 22\), all patients but one having resection in the non-dominant
hemisphere. The cortical resection including the mesial structures and polar cortex was extended to the basal and anterior lateral temporal cortex in 13 patients (eight of the AML group, three of the WML group and two of the BT group). In the WML group, the resection also included the posterior part of the superior temporal gyrus in six patients and the temporo-parietal junction in three others. According to Engel’s classification (Engel et al., 1996) with a minimal follow-up of 2 years (28 patients, mean follow-up: 3.4 years), seizure outcome was class I for 23 patients (82%), 17 patients being in class IA (60%). Three patients (AML group, one; BT group, two) had rare seizures (partial in one patient and generalized in two, <2 per year) and achieved class II outcome. One patient of the mesial group had persistent complex partial seizures after a seizure-free interval of 2 years with an overall major reduction in seizure frequency (class III). Postoperative MRI demonstrated insufficient hippocampal resection. The other patient in class III (AML group) had persistent auras during the first two postoperative years followed by several generalized seizures after reduction of antiepileptic drugs. The resection was considered insufficient on both mesial and lateral cortex and the patient recently has undergone reoperation. Besides the patient in whom hippocampal resection was considered insufficient, all patients in the mesial group fell into outcome class I (eight patients), with seven of them in class IA. Conversely, despite larger resections in most cases, class IA outcome was obtained for only six of 10 patients in the AML group and for four of seven patients in the WML group. However, differences in outcome did not attain a level of statistical significance, perhaps due to the small size of the sample.

Discussion

The main finding of our study is the concordance between the observed electro-clinical patterns and hypometabolism topography in MTLE. Furthermore, our data indicate that different patterns can be distinguished in MTLE. Information provided by electro-clinical data, MRI structural changes and surgical outcome in relation to metabolic data are examined below.

Electro-clinical patterns

The three main patterns (mesial, AML and WML) described differed according to the absence or presence of extra-temporal involvement and the extent of suprasylvian and contralateral involvement. The BT pattern was clearly less frequent, possibly as a result of selection bias since such patients are considered less suitable candidates for surgery than patients in the other groups. The WML pattern was observed mainly in patients with an epileptogenic focus in the non-dominant hemisphere, in contrast to the mesial group where the dominant hemisphere predominated and the AML group where both hemispheres were equally represented. This may also be a result of selection bias because patients with a large focus in the dominant hemisphere are assumed to have a poor outcome after surgery. The variability of electro-clinical features that we observed in our study contrasts with the apparent homogeneity of MTLE in previously reported series. When focusing on clinical symptomatology, most studies emphasize the lateralizing and localizing value of certain signs (Delgado-Escueta and Walsh, 1985; Kotagal et al., 1989; Newton et al., 1992; Fakhoury and Abou-Khalil, 1995; Bleasel et al., 1997; Williamson et al., 1998; Dupont et al., 1999). However, except for a few studies (Adam et al., 1996; Savic et al., 1997; Bartolomei et al., 1999), little attention has been paid to the variability of clinical symptomatology and EEG ictal patterns. Interestingly, Savic et al. (1997) used the 1981 international classification for seizures originated from mesio-temporal structures: focal limbic, widespread limbic, complex partial seizure (CPS) with posturing and sometimes clonic jerks and secondary generalized seizures. This classification is consistent with our electro-clinical patterns, but does not integrate the chronological ordering of each symptom or post-ictal deficits. It therefore provides less information concerning the topography of the cortical areas disorganized by ictal discharges.

Hypometabolism topography

The temporal and extra-temporal hypometabolic areas observed in our series are concordant with previous reports (Hajek et al., 1993; Henry et al., 1993; Arnold et al., 1996; Savic et al., 1997). SPM software analysis has been validated in MTLE, for FDG (DeCarli et al., 1995; van Bogaert et al., 2000; Bouilleret et al., 2002) and flumazenil (Koeppe et al., 1996). Compared with other methods of quantification, this methodology allows a global analysis of brain metabolism independent of a priori hypotheses about the extent and localization of effects. Our results provide evidence that temporoo-insulo-perisylvian hypometabolism represents the most typical metabolic pattern. Moreover, as reported in prior series (Arnold et al., 1996; Savic et al., 1997; Dupont et al., 1998), basal ganglia involvement is also frequently observed. Insular hypometabolism in MTLE has already been reported, but without emphasis (Arnold et al., 1996; Savic et al., 1997). It has been described recently as a common feature in a study using SPM96 software (Bouilleret et al., 2002), and our data confirm this observation. However, to our knowledge, perisylvian hypometabolism has not been described previously in MTLE.

Relationship between electro-clinical patterns and hypometabolism

We demonstrated a good concordance between hypometabolism topography and ictal patterns, thus supporting the hypothesis that neuronal networks involved by ictal discharges and metabolic changes coincide. The more focal the ictal symptomatology, the more limited was the
hypometabolism, and vice versa. These findings are in agreement with some studies demonstrating that spatial patterns of interictal hypometabolism reflect the regions involved in generation and expression of partial seizures (Savic et al., 1997; Dupont et al., 1998). We found insular involvement in most of our cases, even in patients presenting with a mild symptomatic profile (mesial group). However, insular hypometabolism was restricted to the anterior part of insula in this group, whereas it was more severe and extended in the AML and WML groups. These findings can be related to the frequency of vegetative aura (considered to be related to the topography of extra-temporal hypometabolism) and the insular cortex (Isnard et al., 1999). It should therefore be possible to establish correlations between various metabolic patterns and different seizure spread pathways in MTLE. A common mechanism for ictal discharge spread and hypometabolism could be local neuronal inhibitory circuit failure resulting in a concomitant decrease in inhibitory synaptic activity and in corresponding energy requirements (Koutroumanidis et al., 2000).

Among the other clinical data analysed in this study, only epilepsy duration significantly differed between the four groups, being longer for the BT group than for other groups. Although the relationship between hypometabolism and epilepsy duration remains open to debate, some studies demonstrate a relationship between epilepsy duration and bitemporal hypometabolism (Jokeit et al., 1999; Koutroumanidis et al., 2000). Our findings are consistent with these data, showing that bitemporal-independent spiking and early contralateral temporal spread are associated with bilateral hypometabolism and longer epilepsy duration. However, hypometabolic changes in the BT group were surprisingly mild, in contrast to the patterns observed in our other groups. These findings may be related to the small size of this group with a high selected threshold of significance. Moreover, we must keep in mind that, when defining the BT group, we excluded patients with independent bitemporal seizure onset. This may explain the differences in our observations when compared with other reports.

It has also been postulated that hypometabolism topography may be influenced by the type of the last seizure preceding the PET examination, especially if the last seizure was stronger than usual (Savic et al., 1997), and the delay between the last seizure and the PET scan (Leiderman et al., 1994). However, it seems unlikely that the observed variability of hypometabolic patterns in our study is due to the lapse of time and the type of last seizure, because none of the patients had an unusual seizure before PET and the delay between the last seizure and the PET scan did not differ significantly between groups.

**Structural changes on MRI and metabolism**

We found an abnormal signal in the temporal pole ipsilateral to HS in 65% of our cases and some degree of temporal atrophy either isolated or associated with signal changes in half of the cases. These findings are consistent with previous MRI studies based either on visual assessment or on volumetric measurements in patients investigated for HS (Sisodiya et al., 1997; Mitchell et al., 1999; Moran et al., 2001). Some studies demonstrated that temporal hypometabolism is correlated with the severity of hippocampal atrophy (Gaillard et al., 1995; Semah et al., 1995), but no strong relationship with the metabolic pattern was found (O’Brien et al., 1997). Furthermore, neuronal loss in hippocampal resections was not correlated with metabolic data (Henry et al., 1994). According to these data, despite the fact that MRI structural changes were graded on a rating scale and that quantified measures were not available in our study, we found that the degree of hippocampal atrophy or associated temporal atrophy does not appear to be determinant for metabolic changes. However, we found that temporo-polar signal abnormalities are associated with more severe and posteriorly extended temporal hypometabolism compared with patients without such abnormalities. These findings have already been reported in a previous study (Choi et al., 1999). It has been postulated that MRI changes may indicate developmental lesions, especially an increase of ectopic neurons in white matter (Choi et al., 1999), but these findings remain debated (Mitchell et al., 2000). The fragmented specimens obtained in our series did not allow us to rule out subtle developmental abnormalities, but pathological examination did not identify the typical features of cortical dysplasia in resected tissue. These findings are in agreement with these reported by Mitchell et al. (1999) who noted no specific histopathological abnormalities which could be related to MRI signal changes. Considering the high frequency of temporo-polar signal changes in our series, a related incidence of dual pathology is unlikely. Nevertheless, we observed that these temporo-polar signal changes were not related to the topography of extra-temporal hypometabolism and therefore the variability of metabolic changes cannot be explained by their presence.
**Metabolic data and surgical outcome**

As the surgical resection was tailored according to individual variations in the extent of the epileptogenic zone, the prognostic value of metabolic patterns would be difficult to demonstrate in our series. However, class IA outcome was obtained in 78% of the cases for the mesial group, whereas it was 60 and 57% for the AML and WLM groups, respectively, despite larger resections compared with the mesial group. The BT group consisted of too few patients to allow conclusions to be drawn, but the class II outcome observed in the two operated patients suggests a less favourable outcome than for other groups. Our data suggest that electro-clinical patterns and related hypometabolism can influence surgical outcome, despite the lack of statistical differences between the four groups that may be related to the size of the sample. The surgical prognostic value of FDG-PET is now well established (Engel et al., 1982a; Hajek et al., 1993; Radtke et al., 1993), showing a positive correlation between ipsilateral hypometabolism and favourable outcome. Recent studies demonstrated that ipsilateral temporo-polar hypometabolism is a predictive factor for favourable surgical outcome in MTLE (Dupont et al., 2000), but insular hypometabolism does not appear to have prognostic value (Bouilleret et al., 2002). It can be postulated that the features of insular and suprasylvian area spread, in terms of rapidity and extent, may condition surgical outcome. From this point of view, it would be interesting to examine the prognostic value of metabolic patterns related to electro-clinical data in a population undergoing standardized anterior temporal lobectomy.

**Conclusion**

On the basis of electro-clinical correlations in a large series of MTLE patients, our findings suggest that interictal hypometabolism topography may be related to the neuronal networks involved by ictal discharge onset and spread pathways, although other factors such as structural changes and epilepsy duration may also play a role. Furthermore, co-analysis of ictal and metabolic patterns shows that several subtypes can be distinguished for MTLE. Whether surgical prognosis is related to these patterns or not remains to be investigated.

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