SHORT REPORT

Sex differences in patients with mesial temporal lobe epilepsy

Ivanka Savic, Jerome Engel Jr

Abstract
Possible sex differences in the pattern of interictal hypometabolism were investigated, and also seizure spread in patients with mesial temporal lobe epilepsy (n=48) and hippocampal sclerosis (MTLE). Male patients (n=21) more often had a frontal lobe hypometabolism ipsilateral to the seizure onset (p<0.0001) and a spread of epileptiform activity to this region (p=0.001). By contrast, female patients more often exhibited hypometabolism (p=0.0052) and an ictal spread to the contralateral temporal lobe (p=0.0097). These findings suggest sex differences in spatial distribution of brain dysfunction in MTLE, perhaps reflecting sexual dimorphism in regional cerebral connectivity.

Keywords: sex; brain; epilepsy; glucose metabolism; positron emission tomography

Sex differences are suggested in the functional and anatomical organisation of the human brain. Males perform better in visuospatial tasks, which can be attributed to their higher relative grey matter volume in the right temporoparietal area and, perhaps, stronger connections with the ipsilateral frontal cortex, which is coactivated during visuospatial tasks. Females show better verbal abilities and have a larger relative grey matter volume in the planum temporale. They also activate both hemispheres during language tasks, and show a better recovery after lesions in the language mediating structures.

These findings have led to the hypothesis about sex differences in interhemispheric and intrahemispheric cerebral connections, recently supported by a finding of a higher number of interhemispheric correlations in regional cerebral metabolic rate for glucose (rCMRglu) in women and intrahemispheric correlations in men. Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE) is pathophysiologically a well defined condition, often associated with complex partial seizures of mesial temporal lobe origin. Despite the stereotyped pathology, patients with MTLE show a variable seizure semiology, probably due to differences in seizure spread.

About 80% of patients with MTLE show an interictal hypometabolism within the areas of seizure onset. As seizure semiology and spread, its regional pattern varies in these patients.

Because seizure spread as well as the anatomical pattern of epileptogenic brain areas may result from inherently preferential intracerebral connections, and because these connections may differ between male and female subjects, we postulated the existence of sex differences in the pattern of hypometabolism in patients with MTLE.

The distribution of glucose hypometabolism was retrospectively analysed in 27 female and 21 male patients with postsurgically defined MTLE. The results were related to the data on regional spread patterns of ictal epileptiform activity recorded with EEG telemetry.

Methods

Patients
Among patients with mesial temporal lobe seizures who underwent surgical treatment at the UCLA Seizure Disorder Center between 1993 and 1997 we included patients with: (1) hippocampal sclerosis and absence of other brain pathology on morphological analysis of the resected tissue; (2) clinically and electrophysiologically well defined and stereotyped onsets and evolution of seizures. Exclusion criteria were: (1) diffuse or regional cerebral abnormality outside the area of seizure onset, determined by neuropsychological tests, EEG recordings, or MRI (1.5 tesla GE scanner, 3D SPGR sequences, TR 40 ms, TE 9 ms, Flip angle 9, slice thickness 1.7–1.9 mm); (2) secondarily generalised seizures (>three/year, or within 2 weeks before PET); (3) bilateral abnormality on the Wada test. Inclusion criteria were met by 48 patients (21 males). The area of seizure onset was right sided in 11 subjects in each group. Apart from having seizures the patients were healthy.

Positron emission tomography (PET)
In all the patients PET was preceded by a habitual seizure. Measurements with [18F]FDG PET were conducted according to the previously described procedure. Anatomical regions of interest (ROIs), with minimum size of 1.5 cm³, were drawn using a standardised template of anatomical regions. Three
Results from (A) PET and (B) EEG analyses. Some patients had several hypometabolic areas outside the seizure onset region

<table>
<thead>
<tr>
<th>Sex</th>
<th>II frontal</th>
<th>CI frontal</th>
<th>CI temporal</th>
<th>II parietal</th>
<th>CI parietal</th>
<th>No spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n=21)</td>
<td>13†</td>
<td>4</td>
<td>3††</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Female (n=27)</td>
<td>6</td>
<td>2</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

(A) Regions with hypometabolism outside the epileptogenic region:

(B) Spread of epileptiform activity during seizures:

<table>
<thead>
<tr>
<th>Sex</th>
<th>II frontal</th>
<th>CI frontal</th>
<th>CI temporal</th>
<th>II parietal</th>
<th>CI parietal</th>
<th>No spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n=21)</td>
<td>13*</td>
<td>3</td>
<td>5**</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Female (n=27)</td>
<td>4</td>
<td>1</td>
<td>17</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

II=ipsilateral; CI=contralateral. *p<0.001; ††p<0.0097; †p<0.0001; †††p=0.0052.

Discussion

**METHODOLOGICAL CONSIDERATIONS**

Because PET and MRI were not coregistered, possible partial volume effects were not corrected. Each ROI was delineated on several slices. Also, patients with MR abnormalities outside the epileptogenic zone were excluded, as were patients with visible hippocampal changes in the contralateral temporal lobe. Two male patients had slightly smaller contralateral hippocampi than normal. Because volumetric measurements were not available, possible sex differences in hippocampal atrophy cannot be excluded, although the Wada tests and neuropsychological battery indicated unilateral abnormalities, and bilateral interictal EEG spikes were found only in two male patients. A finding of bilateral hippocampal sclerosis in females would, however, be in favour of the present findings.
The scalp–sphenoidal EEG is not the optimal method for tracing seizure spread. Possible effects of its low resolution were minimised by using large regions in the comparisons, and by including all the regions involved in spread of the seizure. It is unlikely that low resolution would result in a systematically different spread pattern in males vs females.

**IMPLICATIONS OF THE GENERATED DATA**

Both the interictal hypometabolism and the pattern of seizure spread is thought to reflect epilepsy related synaptic reorganisation. Differential findings may be due to inherent sexual dimorphism in cerebral connectivity. 

This interpretation is suggested by the intra-hemispheric seizure spread and location of hypometabolism in male and corresponding interhemispheric dominance in female patients. The results are thus not surprising when considering available data on sexual dimorphism in healthy subjects. The present findings therefore encourage future studies on possible sex differences in partial epilepsy. Such studies may be of general interest, as partial epilepsy to some extent can be regarded as a human model for studies on cerebral connectivity.

This study was supported by the Swedish Medical Research Council, Karolinska Institute, Wenner-Gren Center Foundations, The Swedish Institute, The Swedish Medical Society, and NIH grants NS-02808, NS-15654, NS-33310, and GM-24839. We acknowledge Sandra Dewer and Jody Schmidt for technical assistance.