Temporal lobe epilepsy

Genetics of temporal lobe epilepsy

L Vadlamudi, I E Scheffer, S F Berkovic

Our traditional understanding is that TLE is an acquired condition, but only now are we beginning to understand the extent of genetic involvement.

In the second half of the 19th century, John Hughlings Jackson proposed the concept of partial epilepsy, including “uncinate seizures”, based on clinico-pathological observations from patients with structural lesions and further supported by pioneering brain surgery.

With the discovery of EEG in the early 20th century, the concepts of temporal lobe epilepsy (TLE) were further elucidated. Gibbs et al. described widespread slow activity during “psychomotor attacks”; they proposed a diffuse underlying cerebral disturbance, which was not in line with Jackson’s observations. Jasper and Kershman then described focal temporal sharp waves in patients they diagnosed with “temporal lobe seizures”. By the middle of the 20th century, the term TLE was widely utilised and much of the subsequent understanding of this disorder was based on pre-surgical studies of intractable cases. Traditionally, TLE has been considered to be an acquired disorder secondary to lesions such as hippocampal sclerosis, tumours, trauma, vascular malformations, and neuronal migration disorders.

Falconer et al., however, studied the aetiology of TLE in 110 refractory cases and demonstrated 95% of cases had aetiology of TLE in 110 refractory cases.11,12 The concept of partial epilepsy, including “uncinate seizures”, based on clinico-pathological observations from patients with structural lesions and further supported by pioneering brain surgery.11,12

AETIOLOGY OF TEMPORAL LOBE EPILEPSY

Familial mesial temporal lobe epilepsy

In 1994, we described familial mesial temporal lobe epilepsy (FMTLE) as a benign syndrome with onset in the second to fifth decades of life, no temporal lobe or hippocampal abnormalities on MRI, and no association with febrile seizures (table 1).

The initial descriptions of ADPEAF and more common syndrome of FMTLE led to the idea of a clinicoradiological distinction between these benign TLE syndromes, without preceding febrile seizures or hippocampal sclerosis, and patients with severe “sporadic” TLE with hippocampal sclerosis and frequently preceding febrile seizures. Subsequently, it has become apparent that the relationship between FMTLE syndromes, hippocampal sclerosis, and febrile seizures is far more complex.

FMTLE often associated with hippocampal sclerosis

Heterogeneity of FMTLE was shown when multiple TLE families with more severe syndromes were described with onset in the first to third decades of life, frequent hippocampal sclerosis, and a variable association with febrile seizures (table 1).12-21 Inheritance in some families is autosomal dominant, but mapping studies are yet to be reported.

These new data add to the puzzle of the aetiology of hippocampal sclerosis. There remains debate as to whether hippocampal sclerosis is the consequence of an early childhood injury (such as prolonged febrile seizures and encephalitis),24 a consequence of ongoing seizures,25 or an early developmental lesion.26 Genetic factors have been implicated since Falconer’s pioneering studies and these large families with hippocampal pathology suggests a major genetic component to its aetiology, at least in certain cases.

FMTLE often associated with febrile seizures

Two large families and some smaller kindred’s have been described with many individuals with both TLE and febrile seizures. The TLE syndrome begins in the first to second decades of life, there are no temporal lobe or hippocampal abnormalities on MRI and the course is benign (table 1).27-29 Digenic inheritance was suggested for the French family, one locus with significant linkage at chromosomes 18pter and one with supportive linkage at 1q25-q31.28 Linkage was not found in the Belgian family to known candidate loci.27

Febrile seizures often associated with mesial TLE

It is more common to find families where there are multiple individuals with febrile seizures and a few with TLE. A large
study of such families demonstrated a strong association between prolonged febrile seizures and hippocampal sclerosis. Another family has been described with generalised epilepsy with febrile seizures plus, with a few family members with TLE. The proband had TLE with hippocampal sclerosis. All affected family members had a sodium channel mutation (SCN1A).

**Familial mesial (FM) TLE syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>ADPEAF**†**</th>
<th>FM TLE no HS no FS**†**</th>
<th>FM TLE often HS / - FS**†**</th>
<th>FM TLE with HS usually no HS**†**</th>
<th>FPEVF**†**</th>
<th>PEPS**†**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age of onset†</td>
<td>8 years to 4th decade</td>
<td>10 years to 4th decade</td>
<td>1 year to 3rd decade</td>
<td>1 year to 2nd decade</td>
<td>1 year to 4th decade</td>
<td>2 years to 2nd decade</td>
</tr>
<tr>
<td>Characteristic features</td>
<td>Auditory, sensory aura</td>
<td>Psychic, autonomic aura</td>
<td>Occasional temporal parietal spikes</td>
<td>Occasional temporal parietal spikes</td>
<td>Seizures with different focal origin in family members</td>
<td>Multiple seizure types in the same individual</td>
</tr>
<tr>
<td>EEG</td>
<td>Rare temporal discharges</td>
<td>Rare temporal discharges</td>
<td>Frequent temporal discharges</td>
<td>Occasional temporal parietal spikes</td>
<td>Frequent pericentral spikes</td>
<td></td>
</tr>
<tr>
<td>MRI Outcome</td>
<td>Normal</td>
<td>Generally benign</td>
<td>HS</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Genes</td>
<td>LGI1</td>
<td>–</td>
<td>–</td>
<td>Variable</td>
<td>18q1,1q (7)</td>
<td>–</td>
</tr>
<tr>
<td>Genotype</td>
<td>LG1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*These divisions are preliminary and they are probably overlapping mesial TLE syndromes. †Range of onset ages reflects the majority of reported cases. Some “outliers” may begin earlier or later, but most family members fall within the stated ranges.

ADPEAF, autosomal dominant partial epilepsy with auditory features; HS, hippocampal sclerosis; FS, febrile seizures; FPEVF, familial partial epilepsy with variable focus; PEPS, partial epilepsy with pericentral spikes.

**Familial partial epilepsy with variable focus (FPEVF)** was first described by our group (in an Australian family) with onset in the first to third decades of life, heterogeneous seizures types including TLE within the same family, and without associated MRI abnormalities or febrile seizures (table 1). There was a suggestion of linkage to chromosome 2q. In 1999 a more definite linkage at chromosome 22q11–q12 was found in two large French–Canadian families with similar clinical features.

Partial epilepsy with pericentral spikes (PEPS) was described in a single Brazilian family as a generally benign syndrome with onset in the first to second decades of life, partial seizures including TLE, characteristic pericentral spikes on EEG, without associated MRI abnormalities or febrile seizures (table 1). Linkage was demonstrated to chromosome 4p15.

**SUSCEPTIBILITY GENES**

The syndromes described above appear to segregate major autosomal dominant genes; these are studied by linkage analysis, a robust technique depending on large families. Many patients with TLE do not have such a strong family history, yet genetic factors are likely to be involved to some extent. Such susceptibility genes have been studied by association studies. Association studies involve large numbers of sporadic cases to determine if there is significant association of epilepsy with a particular polymorphism within a gene.

Identifying susceptibility genes remains challenging, as there is no single locus of large effect, but rather multiple loci probably exist. Determination of such genes by association studies has many methodological problems and replication of the initial observation is often negative. Methodological issues include power of the study, false positives and differing ethnic background. Currently four polymorphisms have been suggested as susceptibility genes for TLE.

There has been a reported increased risk of TLE in those with a family history of seizures with polymorphisms of the prodynorphin gene, which encodes dynorphin (anticonvulsant peptide), a strong candidate for a seizure suppressor gene, which has not been reproduced by other investigators.

Polymorphisms of interleukin-1β (IL-1β), IL-1α, and IL-1 receptor antagonist genes have been studied, which encode proinflammatory cytokines that modulate neurotoxic neurotransmitters. Functional polymorphisms in the IL-1β gene associated with TLE and hippocampal sclerosis have been described, but not reproduced by others. Polymorphisms of IL-1 receptor antagonist have been described in susceptibility to febrile convulsions, but not found by other investigators.

Polymorphism of Apolipoprotein E (APOE) ε4 allele, promotes deposition of β-amyloid, and evidence from animal studies suggest the brain’s ability to repair damage is impaired by its presence, hence may result in an epileptogenic focus. It was found that the presence of APOE ε4 allele may shorten latency between initial injury and seizure onset in TLE, however associations between APOE polymorphism and TLE were not found in other studies.

Polymorphisms of the GABAB (B) receptor 1 gene, which encodes the major inhibitory neurotransmitter in the CNS, have been studied and an association between the G1465A polymorphism and increased susceptibility to TLE was recently described. To date, this is the only published study of this association.

We are only beginning to understand the genetics of TLE. Our traditional understanding was that it was an acquired condition, but only now are we beginning to understand the extent of genetic contribution to this condition. In the future we need to continue to find large families to perform linkage analysis in order to determine further candidate genes as well as continue the search for susceptibility genes through association studies.

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**Author’s affiliation**

I. Vadamudi, E. I. Scheffer, S. F. Berkovic,
Epilepsy Research Institute, University of Melbourne, Australia

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Correspondence to: Professor S. Berkovic, Epilepsy Research Institute, University of Melbourne, Austin Health, First Floor, Neurosciences Building, Banksia Street, Heidelberg West, VIC 3081, Australia; s.berkovic@unimelb.edu.au
Chronic fatigue syndrome

Enteroviruses in chronic fatigue syndrome: “now you see them, now you don’t”

M C Dalakas

Can enteroviruses infect human muscle and cause persistent infection that affects only the metabolic machinery of the cells without muscle destruction?

REFERENCES

such metabolic impairment is more common in patients with enteroviral sequences in the muscle. The paper raises a fundamental question: can enteroviruses infect human muscle and cause persistent infection that affects only the metabolic machinery of the cells without muscle destruction? If so, is this clinically relevant to CFS patients?

Although coxsackieviruses in mice cause acute myositis, there is no convincing evidence that they also infect human muscle. Cases of epidemic pleurodynia, myoglobinuria, or myocarditis attributed to coxsackieviruses, remain unsubstantiated. The evidence is even weaker for chronic diseases, such as CFS or inflammatory myopathies. Unfortunately, the application of modern molecular virology techniques has not cleared the field; instead, they keep the controversy alive. Furthermore, data on viral persistence emerging from the mouse model and tissue cultures, fuel the scientific interest. After an acute enteroviral infection, mice develop a chronic, T cell dependent, myositis; viral RNA is detectable in the muscle but declines over a 12 month period, as the inflammation resolves. Non-dividing cells, such as myofibres, if survived the acute cytopathic damage, regenerate and may harbour viral RNA, trapped in the cytoplasm. These viral material mutate, become less lytic or infective and under certain conditions, may produce interferon or other cell mediators that upregulate transcription of cytokine genes through activation of nuclear factor kappa B (NFκB). The induced nitric oxide synthase and cytokines, such as tumour necrosis factor alpha or interleukin 1, may either cause a slow muscle fibre injury or deprive the cells of their luxury functions, resulting in indolent metabolic dysfunction.

Accordingly, the findings of Lane et al are theoretically relevant to CFS even though a causal relationship between viral persistence and reduced muscle endurance was not demonstrated. In the past, such findings have turned out to be epiphenomena because enteroviruses are ubiquitous in humans and technical flaws inherently connected to contamination in laboratories working with these viruses are inevitable. Lane et al have performed a careful study and their findings deserve attention because, if proved to be specific, they will provide the first indirect indication of a viral related fatigue in a subset of CFS patients.

CFS is a common problem and any clues regarding its cause are welcome. The authors need, however, to demonstrate enterovirus within the muscle fibres by in situ PCR; prove that viral persistence alters the metabolic machinery of the cell; and show that such abnormalities cause clinical symptomatology. This is a laborious, but worthwhile effort that may prove rewarding for the millions of CFS patients because anti-enteroviral agents are now available (pleconaril) or in the offing. The authors may be on the right target but there are no shortcuts in pursuing it.

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**References**


They quote only one other study with a follow up period of equivalent length. In that study, 19 essential tremor patients were followed for six to seven years after unilateral thalamic deep brain stimulation. The benefits for postural and action tremor were well maintained over 6.5 years (SD 0.3) although, again, some slippage of effect was seen, for example for action tremor of the legs. The stimulator output increased from 2.0 V (SD 0.7), initially to 2.4 V (SD 0.9) after two years, and was 2.3 V (SD 1.0) after six to seven years.

These and other studies have shown that unilateral deep brain stimulation is as effective as unilateral thalamotomy in the management of severe essential tremor and it may be that bilateral deep brain stimulation is better than unilateral deep brain stimulation, particularly for those with a generalised tremor syndrome. Had there been poor durability of long term deep brain stimulation, the marginal superiority of stimulation over thalamotomy would have been lost, especially considering the cost and the more intense follow up regime required for deep brain stimulation. However, these two long term studies show well maintained symptomatic benefit over six to seven years, and any trend for recurrent tremor was scarcely detectable by statistics and may reflect the natural progression of the disease.

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Author's affiliation
J P R Dick, Department of Neurology, Greater Manchester Neuroscience Centre, Hope Hospital, Stott Lane, Salford M6 8HD, UK

Correspondence to: DR J P R Dick; Jeremy.Dick@srht.nhs.uk

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M C Dalakas

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