Temporal lobe epilepsy

Genetics of temporal lobe epilepsy
L Vadalamudi, 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 clinical-pathological observations from patients with structural lesions and further supported by pioneering brain surgery.1 2

With the discovery of EEG in the early 20th century, the concepts of temporal lobe epilepsy (TLE) were further elucidated. Gibbs et al3 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 Kershman4 then described attacks; they proposed a diffuse underlying cerebral disturbance, which was not in line with Jackson’s observations. Jasper and Kershman4 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.5

Falconer et al, however, studied the aetiology of TLE in 110 refractory cases and demonstrated 95% of cases had underlying cerebral pathology, but also astutely stated, “these lesions, however may develop on a soil already predisposed to convulsions”.6 In the past 20 years, what is becoming more evident is this evolving key role of genetics in TLE.

AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES

In 1995, Ottman et al7 described partial epilepsy with auditory features linked to chromosome 10q.8 Later termed the syndrome autosomal dominant partial epilepsy with auditory features (ADPEAF),9 similar families mapping to the same region were described with prominent visual features or sensory dysphasia, all suggesting a lateral temporal origin.10 ADPEAF is a benign syndrome with onset in the first to third decades of life, no abnormalities on MRI, and no association with febrile seizures (table 1).

Debate as to whether the families with somewhat differing clinical features were due to the same gene was settled when Kalachikov et al11 identified mutations in the leucine rich, glioma inactivated 1 (LGII) gene in five families with ADPEAF and mutations in this gene were also found in families with prominent visual or dysphasic features. LGII mutations are not found in all families with ADPEAF, suggesting genetic heterogeneity.12 13 Specificity of LGII to ADPEAF has been confirmed by the absence of mutations in different TLE phenotypes (unpublished data, Berkovic et al). LGII was first described in glial tumours where it may be deleted or rearranged, but glial tumours do not occur with increased frequency in ADPEAF. It has been suggested that LGII has a role in neuronal migration or cortical organisation.14 Given that the majority of LGII mutations cause protein truncation, loss of function is the likely underlying mechanism.15 16 All prior genes that have been discovered for idiopathic epilepsies have been associated with ion channels.17 This discovery suggests new neurobiological mechanisms for familial epilepsies.

FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

In 1994, we described familial mesial temporal lobe epilepsy (FMTE) 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).18 19 The nature of the aura, with prominent psychic and autonomic features, suggested mesial temporal origin. The commonest symptom was intense déjà vu; in some cases epilepsy had not been diagnosed and the intense déjà vu was regarded as “normal”. Inheritance is consistent with autosomal dominance with reduced penetrance, but no very large pedigrees have been reported and the disorder is yet to be mapped. The clinical features and good prognosis of FMTE have since been described by others investigating idiopathic TLE.19–21

FMTE, hippocampal sclerosis, and febrile seizures

The initial descriptions of ADPEAF and more common syndrome of FMTE 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 FMTE syndromes, hippocampal sclerosis, and febrile seizures is far more complex.

FMTE often associated with hippocampal sclerosis

Heterogeneity of FMTE 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).22–24 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 suggest a major genetic component to its aetiology, at least in certain cases.

FMTE 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–q31.29 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
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.

Polymorphisms of the GABA (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.

Table 1: Familial temporal lobe epilepsy (TLE) subtypes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>ADPEAF</th>
<th>FMTE without HS no FS</th>
<th>FMTE with HS and FS</th>
<th>FMTE with FS 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>Psychie, autonomic aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>Rare temporal discharges</td>
<td>Rare temporal discharges</td>
<td>Frequent temporal discharges</td>
<td>Occasional temporal discharges</td>
<td>Normal Variable 22q,2q (7)</td>
<td>Normal Generally benign</td>
</tr>
<tr>
<td>MRI Outcome</td>
<td>Normal</td>
<td>Generally benign</td>
<td>HS</td>
<td>Normal Variable</td>
<td>Normal Variable</td>
<td>Normal Generally benign</td>
</tr>
<tr>
<td>Linkage</td>
<td>10q</td>
<td>–</td>
<td>–</td>
<td>18q1,1q (7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Genes</td>
<td>LGI1</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 foc; PEPs, partial epilepsy with pericentral spikes.

More recently have been described that include seizures arising from the temporal lobe as part of their spectrum of clinical manifestations.

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 studies 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 only with a few family members with TLE. The proband had TLE with hippocampal sclerosis. All affected family members had a sodium channel mutation (SCN1A).

**TLE AS PART OF DOMINANT PARTIAL EPILEPSY SYNDROMES**

Other familial partial epilepsies have recently been described that include seizures arising from the temporal lobe as part of their spectrum of clinical manifestations.

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.

Polymorphisms of the GABA (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.

**Table 1: Familial temporal lobe epilepsy (TLE) subtypes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>ADPEAF</th>
<th>FMTE without HS no FS</th>
<th>FMTE with HS and FS</th>
<th>FMTE with FS 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>Psychie, autonomic aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>Rare temporal discharges</td>
<td>Rare temporal discharges</td>
<td>Frequent temporal discharges</td>
<td>Occasional temporal discharges</td>
<td>Normal Variable 22q,2q (7)</td>
<td>Normal Generally benign</td>
</tr>
<tr>
<td>MRI Outcome</td>
<td>Normal</td>
<td>Generally benign</td>
<td>HS</td>
<td>Normal Variable</td>
<td>Normal Variable</td>
<td>Normal Generally benign</td>
</tr>
<tr>
<td>Linkage</td>
<td>10q</td>
<td>–</td>
<td>–</td>
<td>18q1,1q (7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Genes</td>
<td>LGI1</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 foc; PEPs, partial epilepsy with pericentral spikes.
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?

In the paper by Lane et al (see pp 1382–1386) a new association was found between abnormal exercise lactate response and enterovirus sequences in the muscle of some patients with chronic fatigue syndrome (CFS). The paper rekindles the old saga of enteroviruses, muscle inflammation, and fatigue. CFS remains an elusive entity. When all known factors causing fatigue are excluded, a number of patients have organic disease. Because some CFS patients have impaired muscle energy metabolism, the cause of fatigue may not be “in their head” but “in their muscle”. Now, Lane et al propose that
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 to potential human pathogens 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 mutants, 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 (NFkB). 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.

REFERENCES


Author's affiliation
M C Dalakas, Neuromuscular Diseases Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Building 10, Room 4N248, 10 Center Dr. MSC 1382, MD 20892-1382, USA

Correspondence to: Dr M C Dalakas; dalakasmc@ninds.nih.gov

Essential tremor

Multicentre European study of thalamic stimulation in essential tremor

J P R Dick

Bilateral thalamic deep brain stimulation continues to show well maintained benefit in patients who have severe essential tremor after seven years with little increase in stimulation parameters

In their paper, Sydow et al (see this issue pp 1387–1391) have shown sustained long term efficacy of high frequency deep brain stimulation of the thalamus (Vim) for the management of severe essential tremor. This observation is of interest as certain authors had commented that its benefit may wane with time.

A multicentre European trial had initially demonstrated the efficacy of thalamic deep brain stimulation (largely unilateral) in the management of essential tremor and a subsequent comparison of bilateral Vim stimulation with unilateral thalamotomy suggested that deep brain stimulation was more effective and certainly associated with fewer side effects. In the latter study the outcome was slightly better for essential tremor patients (using either procedure) than for patients with Parkinson’s disease or multiple sclerosis. At 6 months some tremor had recurred in 7 of 34 patients (3 Parkinson’s disease, 4 multiple sclerosis) undergoing unilateral thalamotomy and in 3 of 34 (1 Parkinson’s disease, 2 multiple sclerosis) undergoing bilateral deep brain stimulation; no tremor had returned in any of the 13 patients with essential tremor. The greater efficacy of bilateral thalamic deep brain stimulation for essential tremor is highlighted by Deuschl et al in their review. They comment that a bilateral procedure may have additional benefit for tremor of mid-line structures.

In this study, 37 essential tremor patients managed with bilateral thalamic deep brain stimulation were reviewed after one and six years. While there was a non-significant trend towards increased tremor after six years, an excellent functional improvement was still maintained when comparing both activities of daily living and tremor scores, ON and OFF stimulation. This trend would, of course, be consistent with the natural history of essential tremor. The observed increase in stimulator output during the six year period largely arose in the first year (2.0 to 2.3 V). The authors speculate that the subsequent increase (2.3 to 2.6 V) was a reflection of disease progression, although acknowledge that it may have reflected an element of tolerance.
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.

REFERENCES

COMPETING INTERESTS: JPRD was sponsored by Medtronic to attend a two day workshop organised by the European Continuing Medical Training Group, on deep brain stimulation in Keil, Germany, January 2003.