

REFERENCES

- 1 Horsley V. Brain-surgery. *BMJ* 1886;ii:670-5.
- 2 Jackson H. On a particular variety of epilepsy ("intellectual aura"), one case with symptoms of organic brain disease. *Brain* 1888;11:179-207.
- 3 Gibbs FA, Gibbs EL, Lennox WG. Epilepsy: a paroxysmal cerebral dysrhythmia. *Brain* 1937;60(4):377-88.
- 4 Jasper H, Kershman J. Electroencephalographic classification of the epilepsies. *Archives of Neurology and Psychiatry* 1941;45:903-43.
- 5 Bruton CJ. *The neuropathology of temporal lobe epilepsy*. Oxford: Oxford University Press, 1988.
- 6 Falconer MA, Serafetinides EA, Corsellis JAN. Etiology and pathogenesis of temporal lobe epilepsy. *Arch Neurol* 1964;10:233-48.
- 7 Ottman R, Risch N, Hauser WA, et al. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet* 1995;10:56-60.
- 8 Winawer M, Ottman R, Hauser WA, et al. Autosomal dominant partial epilepsy with auditory features: defining the phenotype. *Neurology* 2000;54:2173-6.
- 9 Poza JJ, Saenz A, Martinez-Gil A, et al. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. *Ann Neurol* 1999;42(2):182-8.
- 10 Brodtkorb E, Gu W, Nakken KO, et al. Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22-q24. *Epilepsia* 2002;43(3):228-35.
- 11 Kalachikov S, Evgrafov O, Ross B, et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. *Nat Genet* 2002;30(3):335-41.
- 12 Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol, et al. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. *Hum Mol Genet* 2002;11(9):1119-28.
- 13 Bissulli F, Tinuper P, Marini C, et al. Partial epilepsy with prominent auditory symptoms not linked to chromosome 10q. *Epileptic Disorders* 2002;3:183-7.
- 14 Pizzuti A, Flex E, Di Bonaventura C, et al. Epilepsy with auditory features: a LGI1 gene mutation suggests a loss-of-function mechanism. *Ann Neurol* 2003;53:396-9.
- 15 Kullmann DM. Genetics of epilepsy. *J Neurol Neurosurg Psychiatry* 2002;73(Suppl II):ii32-ii35.
- 16 Berkovic SF, Howell A, Hopper JL. Familial temporal lobe epilepsy: a new syndrome with adolescent/adult onset and a benign course. In: Wolf P, ed. *Epileptic seizures and syndromes*. London: John Libbey & Company Ltd, 1994:257-63.
- 17 Berkovic SF, McIntosh A, Howell A, et al. Familial temporal lobe epilepsy: a common disorder identified in twins. 1996;40:227-35.
- 18 Aguglia U, Gambardella A, Le Piane E, et al. Mild non-lesional temporal lobe epilepsy a common, unrecognized disorder with onset in adulthood. *Can J Neurol Sci* 1998;25(4):282-6.
- 19 Regesta G, Tanganelli P. Temporal lobe epilepsy of adult age of possible idiopathic nature. *Seizure* 2002;11(2):131-5.
- 20 Gambardella A, Messina D, Le Piane E, et al. Familial temporal lobe epilepsy Autosomal dominant inheritance in a large pedigree from Southern Italy. *Epilepsy Res* 2000;38:127-32.
- 21 Brewster Smith W, So N, Thompson K. Familial temporal lobe epilepsy. *Epilepsia* 1996;37(Suppl. 5):34.
- 22 Cendes F, Lopes-Cendes I, Andermann E, et al. Familial temporal lobe epilepsy: a clinically heterogeneous syndrome. *Neurology* 1998;50:554-7.
- 23 Kobayashi E, Lopes-Cendes I, Guerreiro CAM, et al. Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy. *Neurology* 2001;56:166-72.
- 24 Mathern GW, Babb TL, Vickrey BG, et al. The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy. *Brain* 1995;118:105-18.
- 25 Kalviainen R, Salmenpera T, Partanen K, et al. Recurrent seizures may cause hippocampal damage in temporal lobe epilepsy. *Neurology* 1998;50:1377-82.
- 26 Fernandez G, Effenberger O, Vinz B, et al. Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis. *Neurology* 1998;50:909-17.
- 27 Depondt C, Van Paesschen W, Matthijs G, et al. Familial temporal lobe epilepsy with febrile seizures. *Neurology* 2002;58:1429-33.
- 28 Baulac S, Picard F, Herman A, et al. Evidence for digenic inheritance in a family with both febrile convulsions and temporal lobe epilepsy implicating chromosomes 18qter and 1q25-q31. *Ann Neurol* 2001;49:786-92.
- 29 Ward N, Evanson J, Cockerell OC. Idiopathic familial temporal lobe epilepsy with febrile convulsions. *Seizure* 2002;11(1):16-19.
- 30 Maher J, McLachlan RS. Febrile convulsions. Is seizure duration the most important predictor of temporal lobe epilepsy? *Brain* 1995;118:1521-28.
- 31 Abou-Khalil B, Ge Q, Desai R, et al. Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation. *Neurology* 2001;57(12):2265-72.
- 32 Scheffer IE, Phillips HA, O'Brien CE, et al. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Ann Neurol* 1998;44(6):890-9.
- 33 Xiong L, Labuda M, Li D-S, et al. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. *Am J Hum Genet* 1999;65(6):1698-1710.
- 34 Kinton L, Johnson MR, Smith SJ, et al. Partial epilepsy with pericentral spikes: a new familial epilepsy syndrome with evidence for linkage to chromosome 4p15. *Ann Neurol* 2002;51(6):740-9.
- 35 Botstein D, Risch N. Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nat Genet Supplement* 2003;33:228-237.
- 36 Stogmann E, Zimprich A, Baumgartner C, et al. A functional polymorphism in the prodynorphin gene promoter is associated with temporal lobe epilepsy. *Ann Neurol* 2002;51:260-3.
- 37 Tilgen N, Rebstock J, Horvath S, et al. Prodorphin gene promoter polymorphism and temporal lobe epilepsy. *Ann Neurol* 2003;53(2):280-2.
- 38 Kanemoto K, Kawasaki J, Miyamoto T, et al. Interleukin (IL) 1 β , IL-1 α , and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy. *Ann Neurol* 2000;47(5):571-4.
- 39 Buono RJ, Ferraro TN, O'Connor MJ, et al. Lack of association between an interleukin 1 beta (IL-1 β) gene variation and refractory temporal lobe epilepsy. *Epilepsia* 2001;42(6):782-4.
- 40 Heils A, Haug K, Kunz WS, et al. Interleukin-1 β gene polymorphism and susceptibility to temporal lobe epilepsy with hippocampal sclerosis. *Ann Neurol* 2000;48(6):948-50.
- 41 Tsai F-J, Hsieh Y-Y, Chang C-C, et al. Polymorphisms for interleukin 1 β exon 5 and interleukin 1 receptor antagonist in Taiwanese children with febrile convulsions. *Arch Pediatr Adolesc Med* 2002;156:545-8.
- 42 Briellmann RS, Torn-Broers Y, Busuttill BE, et al. APOE e4 genotype is associated with an earlier onset of chronic temporal lobe epilepsy. *Neurology* 2000;55:435-7.
- 43 Poirier J. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. *Trends Neurosci* 1994;17:525-30.
- 44 Bluemcke I, Brockhaus A, Scheiwe C, et al. The apolipoprotein E epsilon 4 allele is not associated with early onset temporal lobe epilepsy. *Neuroreport* 1997;8:1235-37.
- 45 Gambardella A, Aguglia U, Cittadella R, et al. Apolipoprotein E polymorphisms and the risk of nonlesional temporal lobe epilepsy. *Epilepsia* 1999;40(12):1804-07.
- 46 Gambardella A, Manna I, Labate A, et al. GABA(B) receptor 1 polymorphism (G1465A) is associated with temporal lobe epilepsy. *Neurology* 2003;60:560-3.

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)¹ an 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,² 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.³ 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.³ Unfortunately, the application of modern molecular virology techniques have 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.^{3,4} 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.^{3,4}

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.

J Neurol Neurosurg Psychiatry
2003;74:1361-1362

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REFERENCES

- 1 Lane RJM, Soteriou BA, Zhang H, *et al*. Enterovirus related metabolic myopathy: a post-viral fatigue syndrome. *J Neurol Neurosurg Psychiatry* 2003; 74:1382-6.
- 2 McCully KK, Natelson BH, Iotti S, *et al*. Reduced oxidative muscle metabolism in chronic fatigue syndrome. *Muscle Nerve* 1996;19:621-5.
- 3 Dalakas MC. Viral related muscle disease. In: Engel AG, ed. *Myology*. New York: McGraw Hill, 2003 (in press).
- 4 Pelletier I, Duncan G, Pavia N, *et al*. Molecular mechanisms of poliovirus persistence: key role of capsid determinants during the establishment phase. *Cell Mol Life Sci* 1998;54:1385-1402.

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)¹ 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.²

A multicentre European trial had initially demonstrated the efficacy of thalamic deep brain stimulation (largely unilateral) in the management of essential tremor³ 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.⁴ 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.⁵ They comment that a bilateral procedure may have additional benefit for tremor of mid-line structures.⁵

In this study,¹ 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.