

Epilepsy and Hippocampal Sclerosis: Cause or Effect?

Hippocampal sclerosis (HS) is the most common pathological finding in mesial temporal lobe epilepsy,¹ accounting for approximately 70% of cases in patients undergoing surgery for drug-resistant partial seizures.² Other focal lesions associated with partial epilepsy are listed in Table 1. The broader term mesial temporal sclerosis (MTS) acknowledges the frequent involvement of neighbouring limbic structures including the amygdala and parahippocampal gyrus.

Despite the strong association between hippocampal sclerosis and temporal lobe epilepsy, it remains unclear whether or not the relationship is causal – or if both conditions might reflect an underlying developmental abnormality of the hippocampus. In this article we will briefly review the pathological features of hippocampal sclerosis, before moving on to discuss some of the relevant experimental and clinical evidence.

Hippocampal sclerosis

The typical MRI features of hippocampal sclerosis, also known as Ammon's horn sclerosis (AHS), are unilateral volume loss and increased signal intensity on T2-weighted images. There is no sex or side preference and a proportion of cases are bilateral. Macroscopically the hippocampus is firm and shrunken, sometimes with visible collapse of the CA1 subfield (Sommer's sector). Microscopic findings include a characteristic pattern of neuronal loss and reactive gliosis (Figure 1) that varies in severity from case to case (Table 2).³ The mechanism of neuronal loss and selective vulnerability in MTS is likely to be excessive release of the excitatory neurotransmitters glutamate and aspartate, acting at calcium-permeable NMDA and AMPA receptors ('excitotoxicity').⁴ This leads

to intense depolarisation and calcium overload which triggers multiple cell death pathways. In addition to neuronal loss and gliosis, two commonly associated findings are mossy fibre sprouting and granule cell dispersion (Table 3).

Aetiology and pathogenesis

Several animal models of limbic status epilepticus demonstrate that HS can be acquired – and the pathological features in many cases are similar to those seen in humans.⁵ MRI and post-mortem studies also confirm that acute hippocampal damage may follow status epilepticus.^{6,7} An influential hypothesis suggests that an initial precipitating insult (IPI) in childhood such as a febrile convulsion may injure the hippocampus and that this 'first hit' at a critical period of development may act as a template for progressive neuronal loss and gliosis.⁸ It has been known for many years that more than half of patients with HS and temporal lobe epilepsy have a history of febrile convulsion or status epilepticus in infancy.^{1,9} This is typically followed by a variable 'latent interval' of around 7-10 years before the onset of spontaneous seizures. MRI studies in children with prolonged febrile convulsions have demonstrated acute changes in the hippocampus consistent with neuronal injury and oedema. Some follow-up studies have shown subsequent hippocampal atrophy⁷ or hippocampal sclerosis⁶ although the presence of a pre-existing abnormality cannot be excluded. It is important to note that most of these children do not develop epilepsy¹⁰ and that at least a third of patients with hippocampal sclerosis have no documented IPI.

Do seizures damage the brain?

It is often said that 'seizures beget seizures', but it has been difficult to demonstrate conclusively that patients with pharmacoresistant temporal lobe epilepsy suffer ongoing hippocampal damage. Some studies have shown a gradual deterioration in hippocampal volume, metabolism or memory performance over time¹¹ or evidence of progres-

Table 1: Common pathological findings in epilepsy surgical specimens

- Hippocampal sclerosis (HS)
- Malformations of cortical development (MCD)
 - focal cortical dysplasia (FCD)
 - mild malformations of cortical development (formerly 'microdysgenesis')
- Low grade glioneuronal tumours
 - ganglioglioma
 - dysembryoplastic neuroepithelial tumour (DNT)
- Vascular / traumatic lesions
- Dual pathology
 - usually mild HS in combination with a second pro-epileptogenic lesion

Table 2: Simple classification of hippocampal sclerosis

Subtype	Main pathological features
Classical	Neuronal loss and gliosis mainly in CA1, CA3 and end-folium
Total	Severe neuronal loss in all hippocampal subfields and the dentate gyrus
End-folium	Neuronal loss and gliosis restricted to the hilum of the dentate gyrus

Table 3: Features commonly associated with hippocampal sclerosis

Feature	Description	Possible significance
Mossy fibre sprouting (MFS)	New axons arising from granule cells extend upwards into the molecular layer of the dentate gyrus.	May contribute to epileptogenesis by forming potentially self-excitatory connections within the dentate gyrus.
	This can be demonstrated by immunostaining for the neuropeptide dynorphin (see Figure 1F).	However, inhibition of MFS in experimental models does not prevent spontaneous seizures.
Granule cell dispersion (GCD)	Increased width of granule cell layer, which is normally 4-5 cells thick, but is more than 10 cells deep in at least 40% of HS cases.	Also occurs in the opposite side, therefore may be a response to generalised seizure activity rather than signifying damage.
	Cells often have a spindle-cell appearance, reminiscent of migrating neurons (see Figure 1G-I).	Some animal models show increased neurogenesis in the subgranular layer, with upward migration of new neurons along radial glia.



Dr Paul Johns is a specialist registrar in neuropathology at the National Hospital for Neurology and Neurosurgery, Queen Square. His research interests have included neuroprotection in acute cerebral ischaemia and the pathology of focal epilepsy. In 2006 he won the Intercapital Prize in Epileptology.



Dr Maria Thom is a Senior Lecturer at the Institute of Neurology, Queen Square and an Honorary Consultant Neuropathologist at the National Hospital for Neurology and Neurosurgery. Her research has focused on the pathology of focal epilepsies.

Correspondence to:

Dr Paul Johns,
Specialist Registrar,
Division of Neuropathology,
National Hospital for Neurology
and Neurosurgery,
Institute of Neurology,
Queen Square,
London WC1N 3BG, UK.
Email: paul.johns@uclh.org
Tel. 0207 829 8731
Fax. 0207 676 2157

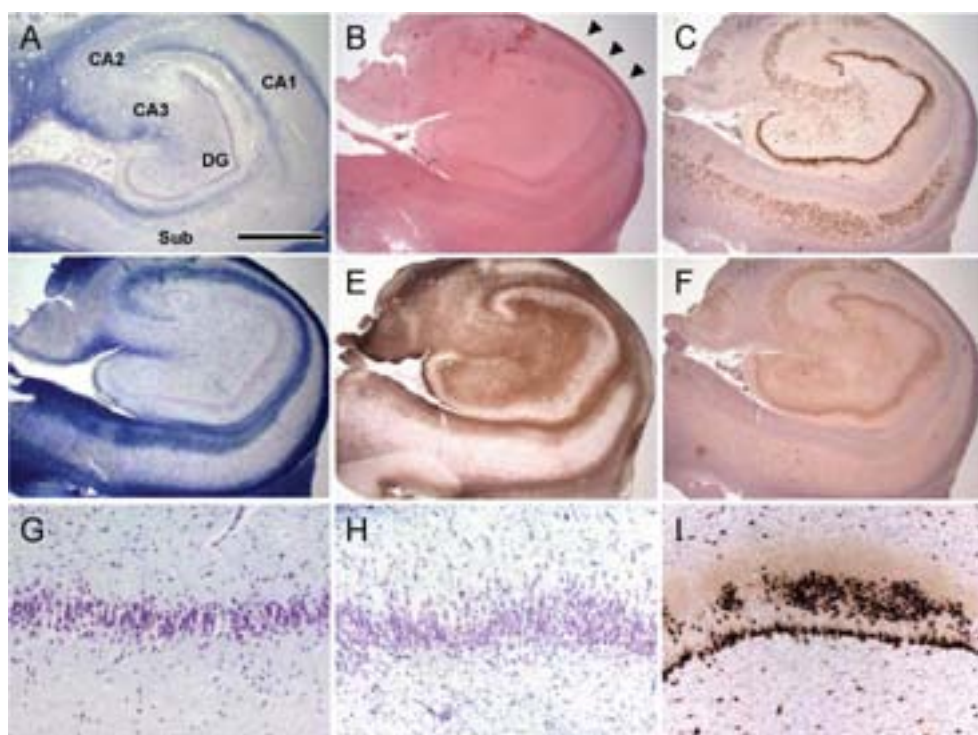


Figure 1: Microscopic appearances of (A) normal hippocampus and (B-I) hippocampal sclerosis. (A) Normal hippocampal anatomy. CA1-CA3=Ammon's horn (Latin: cornu ammonis). DG=dentate gyrus. Sub=subiculum. (B) In hippocampal sclerosis, collapse of CA1 (arrows) is evident even at low power. (C) Selective neuronal drop-out is highlighted by immunohistochemical preparations for the neuronal marker NeuN. (D) Reduced width of CA1 is more striking on a myelin preparation (Luxol fast blue/cresyl violet). (E) Reactive gliosis/astrocytosis generally parallels the degree of neuronal loss, demonstrated here (dark brown staining) by immunohistochemistry for the astrocytic marker glial fibrillary acidic protein (GFAP). (F) Mossy fibre sprouting is identified in diagnostic practice as a band of dynorphin-immunoreactivity (light brown) in the supragranular layer of the dentate gyrus. (G) The normal dentate gyrus contains a compact and sharply-defined layer of granule cells. (H) Granule cell dispersion is seen in at least 40% of HS cases. (I) The granule cell layer is focally bilaminar in up to 10% of cases, illustrated here by immunostaining for the neuronal marker NeuN. [Scale bar: A-F=2mm; G-I=200µm].

sive atrophy in the contralateral hemisphere¹² but the confounding effects of long-term exposure to antiepileptic drugs and seizure-associated head injuries should be borne in mind. In general, prospective MRI studies have failed to show a consistent relationship between the degree of hippocampal sclerosis and the duration/severity of epilepsy or the total number of generalised seizures.¹⁵ Furthermore, a quantitative post-mortem study has identified a subgroup of

patients with a life-long history of frequent seizures (including status epilepticus) but no significant neuronal loss in the hippocampus.¹⁴ Clearly, seizures do not inevitably damage the brain – and it is far from clear that hippocampal sclerosis worsens over time.

Developmental theories

An alternative possibility is that a pre-existing temporal lobe abnormality leads to hippocampal

sclerosis in adulthood and also increases risk of febrile convulsions in the early years of life. Examination of resected material in HS patients shows evidence for the persistence of Cajal-Retzius cells in the superficial temporal cortex and alterations within the reelin signalling pathway, both of which may signify a disturbance of neuronal migration.¹⁵ Further evidence to support this contention, derived from patients with pathologically-confirmed HS, includes: an increased incidence of subtle hippocampal malformations; excess ectopic white matter neurons in the mesial temporal lobe; and association with other lesions that may have a malformative origin (including low-grade glioneuronal tumours).¹⁶ Furthermore, subtle hippocampal malformations have been found in relatives of patients with HS (compared to age-matched controls) most of whom did not have a history of febrile convulsions or HS themselves.¹⁷ A maldevelopmental origin would perhaps also help to explain why hippocampal sclerosis is often unilateral.

Concluding remarks: chicken or egg?

The association between temporal lobe epilepsy and hippocampal sclerosis has been recognised for over a century, but despite many decades of basic and clinical research it is still not possible to assign an arrow of causality. One explanation is that hippocampal sclerosis may represent a phenotypically-similar manifestation of a heterogeneous group of pathologies with diverse pathogenesis, derived from a complex interplay of numerous factors (including genetic, developmental and environmental components). These same factors may also explain why some people are susceptible to seizure-associated hippocampal damage and others appear to be resistant. It is hoped that more light may be shed on this intriguing issue over the coming decades, perhaps facilitated by large-scale prospective neuroimaging studies which can be used to follow its evolution during the early years of life.

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