Medico-legal report

Re: Claire Roberts

Dob 10.1.1987

Prepared on behalf of:

Northern Ireland Inquiry into Hyponatraemia Related Deaths

By:

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I am Dr Waney Squier, Consultant Neuropathologist to the Oxford Radcliffe Hospitals and Honorary Clinical lecturer in the University of Oxford. I have been a consultant neuropathologist since 1984 having trained at the Institute of Psychiatry and Great Ormond Street Hospital for Sick Children. During my 28 years in Oxford, I have specialised in the pathology of the developing brain in the fetus and neonate. My other areas of interest are developmental causes of epilepsy and muscle pathology.

I have been involved in research into the nature and timing of brain damage due to intrauterine and perinatal insults, the effects of asphyxia on the immature brain, correlation of imaging and anatomic pathology in the pre-term human brain and the neuropathology of cerebral palsy in children. I have published widely on these subjects in peer-reviewed journals and have edited a book "Acquired Damage to the Developing Brain: Timing and Causation". I am a member of the British Neuropathological Society and the British Paediatric Neurology Association. I am a fellow of the Royal College of Physicians, (by election following membership by examination in paediatrics) and a fellow of the Royal College of Pathologists.

In the last ten to fifteen years, my experience with infant brain pathology has extended to many forensic cases and I have written reports and given evidence in court for both the prosecution and the defence in many cases of sudden unexpected death in infants.

My expertise is based on my experience in examination of the brain, spinal cord and dura after death and as such assists in the interpretation of the mechanisms of injury and the imaging of the brain.

I understand that my overriding duty is to the court in preparing reports and in presenting evidence. In preparing this report, I have attempted to be as accurate and as complete as possible and my opinions are restricted only to those subjects which are within my area of expertise. Wherever possible, my opinion is based on evidence derived from the peer-reviewed literature in addition to my personal professional experience. I believe that the facts I have stated in this report are true and that the opinions I have expressed are correct.

Dr Waney Squier MBCHB FRCP FRCPath

Consultant Neuropathologist

Honorary Clinical Lecturer

NP3/2012 Claire Roberts

I have received 16 tissue blocks and 22 stained sections. 16 are stained with H & E, and 5 with other stains (L26, CD68 and CD3) and one is a control. They are all labelled NPPM 114/96.

The sections are not numbered or labelled to denote the site in the brain from which they were taken. I have, for convenience, labelled the slides OX1-OX16.

I have stained certain blocks with additional methods. I have received a PDF with 10 pictures labelled "autopsy photographs."

The history is taken from the "Brief for Expert."

(1) Claire Roberts was born on 10th January 1987 and was admitted to hospital aged 6 ½ months with seizures. These were associated with abnormal posture & tone on the left side. She was investigated, no cause was found for her seizures but she was prescribed anti-epileptic medication. Convulsions ceased at the age of 4 years and anti-convulsant therapy was stopped.

(2) In May 1996, Claire was seen because of behavioural problems and was prescribed Ritalin. A number of head circumference measurements indicate that her head was growing along the 50th centile but had perhaps increased a little by the time of the last available measurement when she was 9 years 4 months old.

(3) 21.10.96 Claire was 9 years old with severe learning disability and had been seizure-free for 3 years. When she arrived home from school, she was said to have been very lethargic and vomited three times. Her speech was slurred. She was pale, did not like the light but had no neck stiffness. Her GP considered her tone increased on the right side and suggested an underlying infection. Claire was admitted to the RBHSC, she was drowsy, tired, apyrexial with increased left-sided muscle tone & reflexes. She had had a loose bowel motion three days previously but had repeated vomiting on admission. The admission diagnosis was:

1. Viral illness
2. Encephalitis

(4) Treatment was noted as IV fluids, IV diazepam if seizure activity.

(5) 22.10.96 Claire became lethargic and vacant. A diagnosis of status epilepticus, non-fitting, was made and diazepam given. Claire was apyrexial, her pupils responded sluggishly to light. 562mls of fluid (number 18 solution) were given over 8 hours.

(6) 15.10hrs Claire had a five-minute seizure. Dr Webb, consultant paediatric neurologist, examined Claire – she was afebrile with no meningism, she withdrew from painful stimulus, had mildly increased tone in her arms and symmetrical brisk reflexes, sustained ankle clonus and upgoing plantar responses. She did not have papilledema. Dr Webb thought that Claire had longstanding motor problems and that she had an acute encephalopathy, probably postictal in nature. Dr Webb prescribed antibiotics and antiviral drugs but did not think encephalitis was likely. He requested further samples to look for viral infection.

(7) 23.30hrs blood result from a sample taken at 21.00/21.30hrs showed serum sodium of 121mmol/L. A note of hyponatraemia was made.

(8) 22.10.96 Claire's neurological condition deteriorated and she no longer opened her eyes to speech, she was making incomprehensible sounds. Glasgow coma scale was 9 and thereafter 6 – 7. Her temperature rose to 38 degrees.

(9) At 02.30hrs on 23.10.96 a medical note states Claire had a respiratory arrest and developed fixed, dilated pupils. Claire was transferred to ICU, intubated and ventilated. Her pupils were fixed and dilated and bilateral papilledema was noted. Serum sodium was 121mmol/L. CT scan showed severe diffuse hemispheric swelling with complete effacement of the basal cisterns. No focal abnormality identified. Following two negative brain stem tests, ventilation was discontinued at 18.45hrs on 23.10.96 and a cause of death of cerebral oedema secondary to status epilepticus was given.

(10) Autopsy was requested. Investigations showed a sterile blood culture, blood virological studies were negative. CSF was blood stained. Protein 95g and no organisms were cultured.

(11) A brain-only autopsy was carried out on 24.10.96 by Dr Herron. The brain weighed 1606gms. He notes an expected weight of 1300g at this age.

Additional History from documents provided:

(12) 26.7 87 Discharge note: "Febrile convulsion secondary to chest infection." (099-046-060)

9.2.88 Letter from Dr Gleadhill: No fits since September. Concern for developmental delay. (099-039-053)

2.5.95 Letter from Prof Nevin, Geneticist: On day 2 of life Claire became blue and mucousy. He considered there was no genetic cause for her problems. The most likely cause is a degree of anoxia. (099-005-007)

24.8 87 Clinical notes: "Goes stiff extends right arm." (099-059-081)

16.2.95 Letter from Dr Major: No convulsions since September 1991 (112-034-050)

Summary of Main Neuropathological Findings

(The detailed neuropathological findings are appended below.)

(13) The submitted stained sections show a normally formed brain which is very swollen and congested. The brainstem is particularly swollen and distorted; more so than the cerebral hemispheres or the spinal cord. The cerebellum has not been sampled.

There is no evidence of trauma or of infection or haemorrhage. I can see no evidence of meningitis or encephalitis. There is no evidence of venous thrombosis. The most significant findings are of recent brain swelling. There is hippocampal sclerosis but no evidence of abnormal or failed neuronal migration. Specific features of diagnostic significance are described below:

Brain Swelling:

(14) All sections show brain oedema but swelling and distortion are most marked in the brainstem. The cerebellum is not sampled. Fragments of cerebellar cortex displaced round the spinal cord are an indication of very severe brain swelling which has forced cerebellar tissue out of the bony opening (the foramen magnum) where the base of the skull is attached to the upper part of the spinal column and into the spinal canal.

There are parts of the cerebral cortex which appear compressed but these are not labelled and their site of origin remains uncertain. These appearances are presumably due to severe brain swelling.

Neuronal eosinophilia:

(15) Nerve cells are eosinophilic[1]; this together with focal early nucleolysis indicates early cell death. There is reactive change in microglial cells, most marked in the brainstem, but there are no other cellular reactions and no endothelial[2] thickening is seen.

Leptomeningeal thickening:

(16) In block 9 the leptomeninges[3] appear focally thickened. This is, I believe, a result of artefactual folding. This area is adjacent to a fragment of bone which has probably been displaced into the surface of the brain during autopsy removal. This is an artefact which is almost unavoidable during brain removal when the brain is swollen. There is no local inflammation. In many sections, a few macrophages[4] are seen in the leptomeninges. They are particularly numerous in spinal cord sections. I do not consider them more numerous than normal and they do not support a diagnosis of meningitis.

Wide perivascular spaces:

(17) Wide perivascular spaces are seen in several sections. They are most likely to be a reflection of atrophy. There is no obvious old focal tissue damage to account for atrophy. This indicates that this has been a more generalised and very mild process which may be related to previous seizures, or could be part of a more generalised congenital brain disorder.

Perivascular cells:

(18) There is a scattering of small dark cells around occasional rare parenchymal vessels. There is no significant increase in inflammatory cells in most sections.

While the perivascular inflammatory cells are numerous in two of the submitted photographs and raise the suspicion of an inflammatory reaction, I did not see sufficient evidence of inflammation elsewhere in the tissue provided to establish a diagnosis of encephalitis. Staining with CD68 showed no increase in inflammatory cells in the leptomeninges or in the tissue of the brain, confirming the lack of evidence for meningo-encephalitis.

Hippocampal pathology:

(19) The hippocampus shows marked gliosis, predominantly in the hilum and CA1[5]. There is no obvious cell loss but without formal counting this cannot be accurately determined. Cell counting is not a routine diagnostic procedure but is undertaken in centres with specialised interest and which are involved in research into epilepsy.

The pattern of gliosis is that of mild (grade 1) hippocampal sclerosis and is seen in association with temporal lobe epilepsy (Martinian 2009, Blumcke 2012).

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1 Sections are routinely stained with haematoxylin and eosin. When cells preferentially take up eosin, they appear bright pink "eosinophilic." The nucleus (which stains blue) loses its integrity in nucleolysis. These two changes indicate the early stages of cell death and probably take from 1-8 hours to develop.

2 Endothelium is the thin cell layer lining blood vessels

3 The thin membranes covering the brain.

4 Macrophages and microglia are forms of reactive inflammatory cells. Microglia are normally resident in the brain. Macrophages are larger and a later stage of development of these calls and can take up and remove damaged brain tissue. They are scavenger cells.

5 The hilum and CA1 refer to anatomical areas of the hippocampus. The nerve cells here have differential sensitivities to deprivation of oxygen and are commonly damaged in epileptic syndromes.

Paraventricular structures:

(20) I can see no evidence of a neuronal migration defect. The irregularly clustered cells here are, I believe, the normal cells of this region and are part of the hypothalamus. The subependymal cells illustrated in image 10 are likely to be residual germinal matrix cells[6] and are normal at this site.

Timing of the pathology

(21) While timing by pathology cannot be accurate, the early neuronal changes in the absence of any reactive cellular infiltration indicate that the process began within several hours and up to a maximum of 1-2 days before death.

There are older changes in the hippocampus and temporal lobe, which are many weeks or even years old. There is also mild generalised brain atrophy.

Causes of the pathology

Cerebral oedema:

(22) The most significant pathology is of severe brain swelling (oedema). This may follow metabolic insults including lack of blood and/or oxygen supply, trauma, and cardio-respiratory arrest.

The acute reactive changes are non-specific and may be seen in similar circumstances.

It is not possible to determine the cause of the brain swelling from examination of the brain sections, and it may be due to hyponatraemia.

Perivascular cells:

(23) A few cells may be seen cuffing vessels in any brain which is swollen or hypoxic. In this case, the mild reaction seen may have resulted from the period of ventilation or from seizure activity.

Hippocampal pathology:

(24) Hippocampal sclerosis is associated with epilepsy. In most cases there is an "initial precipitating injury", usually a severe febrile convulsion in the early years of life [1] Claire suffered from febrile seizures when she was 6 months old (099-046-060). This condition may be associated clinically with a mesial temporal lobe syndrome in which a history of convulsions in infancy is followed by a phase of latency and a third phase of focal epilepsy (Aicardi 2009 Textbook "Diseases of the Nervous System in Childhood" page 617-8). There are other syndromes including genetic and metabolic conditions (channelopathies) which are also associated with developmental delay. This is not my expertise, but the history of which I am aware suggests that these syndromes should be considered by an expert in paediatric epilepsy.

[6] The germinal matrix is a mass of tissue which lines the ventricular system of the developing brain. New cells are generated here and migrate to form the cerebral cortex during the first 6-20 weeks of gestation. Small numbers of residual cells are seen in normal brains, particularly in young people.

Reactive Gliosis:

(25) There is diffuse gliosis in the white matter and the superficial cortex. It is difficult to time this accurately and so the effects of hypoxia or infection before or at the time of birth cannot be readily distinguished from the effects of later seizures, or even the terminal brain oedema. Babies who suffer from hypoxia and /or infection of the placenta or the fetal membranes may develop gliosis[7] of the white matter and developmental delay. I do not have any detail of the pregnancy or delivery and whether there was evidence of infection.

I have looked for a cause for Claire's developmental delay and for her anoxic event on day two of life (099-005-007). There is some gliosis and the suggestion of atrophy, but no clear structural cause is identified.

Neuropathology of status epilepticus:

(26) Seizures are due to hyperexcitation of nerve cells and make a huge metabolic demand on the brain; energy is required to support the hyperactive cells. There is a response of generalised increase in blood flow to the brain during epileptic activity. There may also be selective neuronal loss as the result of status epilepticus. Few studies of the neuropathology are available but several cases have been described [2, 3]. In these cases selective cell death in brain areas including the hippocampus, thalamus, cerebral and cerebellar cortex is described. No recent changes were seen in Claire's brain to suggest damage due to a seizure in the days prior to death.

<u>Opinion:</u>

- The recent neuropathology is of brain swelling.
- The cause for swelling is not apparent in the brain; there is no evidence of meningitis or encephalitis.
- There is no malformation or migration disturbance.
- There is mild old hippocampal scarring (sclerosis) which would explain the history of epilepsy.

Waney Squier

Consultant Neuropathologist

June 16th 2012

[7] Gliosis/ reactive astrocytosis is the equivalent of scar tissue in the brain.

Detailed neuropathological findings:

(a) Immunocytochemistry was submitted on blocks Ox15 and 16 with antibodies to L26, CD 3 and CD 68. All other immunocytochemistry was stained in Oxford. This includes GFAP, βAPP, LBCV and CD 68. The results are described with the individual sections.

Autopsy photographs:

(b) Several autopsy photographs have been provided.

Image 1: Two slices of fixed brain labelled NPPM 114/96 and with L and R marked with black ink. This is a normally formed brain with mild narrowing of the lateral ventricles in the upper slice. The ventricles are patent in the lower slice. The cortical gyri retain a degree of their normal rounded appearance in the upper slice although the sulci are compressed. The cortical gyri are more flattened in the lower slice. There is no evidence of medial temporal damage due to tentorial notching. The cortex is regular and well formed. The white matter appears normal, as do the deep grey nuclei. There is focal mild subarachnoid bleeding.

There are no pictures of the hindbrain.

(c) Nine H&E stained sections of brain tissue are submitted with no indication of the site in the brain from which they were taken. These images are labelled 2-10.

(d) Two (images 2 and 3) show blood vessels with dark cells cuffing them. No special staining to determine the cell types (immunocytochemistry) is provided to indicate the nature of these cells but they are probably lymphocytes. The inflammatory cells are not associated with damage to the vessel walls; this means there is no primary disease of the blood vessels (vasculitis). The cells are close to the blood vessel walls and are not seen infiltrating the adjacent parenchyma as would be expected to be seen in encephalitis. These cells are not sufficiently numerous to allow a diagnosis of inflammation of the brain to be made. It is not uncommon to see such small clusters of cells around one or two vessels in the normal brain.

(e) Images 3, 4, 5, 6, 7 and 9 are of swollen brain tissue. All show fine spaces in the tissue indicating fluid excess or brain swelling. Plump reactive astrocytes are seen in 5 and 6. Blood vessels are normal with no endothelial swelling. This indicates that the pathology is recent, as endothelial swelling takes several days to become apparent.

(f) Pictures 5 and 10 contain fragments of ependyma. These are from the ventricular wall and represent parts of the lining of the fluid-filled cavities within the brain.

(g) Picture 8 is of vascular and cellular tissue on the brain surface. The site is not identified. This resembles the tissue around the pituitary stalk in section Ox 8. While the tissue contains many cells there is no perivascular cuffing, which would be expected to be seen in meningitis.

(h) Image 10 Brain from the lining of a ventricle with a band of ependymal cells - the normal lining of the ventricle. Beneath the ependyma are clusters of small dark cells.

Histology:

(i) OX1:Two sections of spinal cord

The spinal cord is normally formed. The tissue is oedematous and nerve cells appear shrunken and pyknotic. The tissue is not distorted or fragmented. There is a mass of displaced cerebellar tissue outside the cord in the subarachnoid compartment. Macrophages are seen in the leptomeninges in normal numbers. ßAPP is expressed in nerve cells but not in axons.

(j) OX2: The cerebral cortex and underlying white matter is normally formed and mildly swollen. Some nerve cells are eosinophilic. The white matter is oedematous. The meninges and surface blood vessels are normal.

(k) OX3: As OX2 but very congested surface vessels. There is a small scattering of small dark cells around one parenchymal artery. They do not involve the vessel wall or extend into the parenchyma.

(l) OX4: Cerebral cortex. In some areas, the tissue is distorted and fragmented. There is no frank necrosis. There are wide perivascular spaces which may be a reflection of atrophy.

(m) OX5: Large areas of the cortex appear compressed and neurones are eosinophilic and shrunken. The tissue is oedematous.

(n) OX6: Cortex and white matter: swollen and congested. The lateral ventricle has a normal ependymal lining.

(o) OX7, 9: Swollen cerebral cortex and white matter. Perivascular spaces are wide. In block 9 the leptomeninges appear focally thickened. There is a fragment of bone in the adjacent cortex.

(p) OX8: Midline, corpus callosum and ventricles. Mildly swollen. This section includes the deep midline tissues around the third ventricle, including hypothalamus and a small part of the pituitary gland. The fornix, anterior commissure and optic chiasm are identified as well as lateral and third ventricles.

The paraventricular nuclei are seen on either side of the third ventricle. These nuclei are normally poorly defined and I do not think these represent a defect in neuronal migration. Further, their symmetry and the mature appearance of their neurones supports their normal structure.

There are also irregularly organised cells in the subependymal tissues. These are within normal limits.

(q) OX10-12: Three sections of hippocampus. The hippocampus is normally formed and shows old damage. There is one focus of irregularly displaced cells of the dentate gyrus. This is adjacent to a blood vessel and its absence on a further section from this block suggests that this is not a malformation. The dentate fascia appears otherwise well preserved. The cells of the dentate fascia and Ammon's horn are well preserved. There is no necrosis. GFAP shows extensive gliosis in the end folium and CA3 section of Ammon's horn. MAP-2 shows no dendritic change in the dentate cells. There is some superficial gliosis of the temporal lobe cortex indicating a degree of Chaslin's gliosis.

(r) OX13: Medulla. The tissue is very distorted and swollen. Nerve cells in the olivary nucleus are eosinophilic with early nucleolysis. There are many reactive astrocytes in and around the olive. CD 68 stain shows macrophages in the meninges in normal numbers and early microglial reaction in the parenchyma. ßAPP is expressed in bundles of fibres with few axonal swellings. The pattern is that of hypoxic-ischaemic or metabolic injury.

(s) OX14: Deep grey nuclei. Normally formed but very oedematous.

(t) OX15: Midbrain. The tissue is very swollen and distorted. The aqueduct is patent. Tiny fragments of cerebellum show a normal cerebellar cortex. Submitted special stains are L26 (a B cell marker) which in this section appears only to stain the smooth muscle walls of blood vessels, and CD68 (a macrophage marker) which stains a small numbers of cells around parenchymal blood vessels. There is no substantial tissue infiltrate.

(u) OX16: Pons. The tissue is normally formed but very swollen. CD3 stain (a T cell marker) is submitted and shows uniform background colour and little specific activity: the preparation may have faded. ßAPP shows a similar pattern to the medulla and is consistent with metabolic damage. CD68 stain shows widespread reactive change in microglia throughout the parenchyma and a few macrophages. There is no excess of macrophages in the meninges and no evidence of meningitis or encephalitis.

(v) Multiple blocks (Ox 2-6, 13 and 16) have been stained with LBCV to examine the state of myelin and the cortical structure.

(w) In all sections examined, the deep cortical margin is well defined and no subcortical heterotopias are seen. There is focally a mild increase in marginal layer cells or myelinated processes; these may be a reflection of previous seizures. Cortical lamination is within normal limits and I cannot identify focal or generalised dysplasia. Myelin is intact in all areas and no myelinolysis is seen in the cerebral or brainstem white matter.

(x) Blocks 4 and 5 (representative of the cerebral white matter and cortex) have been stained with GFAP to look for reactive glial cells and CD 68 to look for reactive microglial and macrophage cells. There are many reactive glial cells (astrocytes) mainly in the superficial cortical layers where they may represent Chaslin's gliosis, a reaction to seizures. Astrocytes are also numerous in the white matter, especially at the deep cortical border. It is difficult to age these cells; this may be a more recent response to brain swelling.

W Squier

16.6.12

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MINI-SYMPOSIUM: Etiologies of Focal Epilepsy

Defining Clinico-Neuropathological Subtypes of Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Abstract

Hippocampal sclerosis (HS) is the most frequent cause of drug-resistant focal epilepsies (ie, mesial temporal lobe epilepsy with hippocampal sclerosis; mTLE-HS), and presents a broad spectrum of electroclinical, structural and molecular pathology patterns. Many patients become drug resistant during the course of the disease, and surgical treatment was proven helpful to achieve seizure control. Hence, up to 40% of patients suffer from early or late surgical failures. Different patterns of hippocampal cell loss, involvement of other mesial temporal structures, as well as temporal neocortex including focal cortical dysplasia, may contribute to the extent of the epileptogenic network and will be discussed. An international consensus is mandatory to clarify terminology use and to reliably distinguish mTLE-HS subtypes. High-resolution imaging with confirmed histopathologic diagnosis, as well as advanced neurophysiologic and molecular genetic measures, will be a powerful tool in the future to address these issues and help to predict each patient's probability to control their epilepsy in mTLE-HS conditions.

HISTOLOGICAL CLASSIFICATION AND GRADING SYSTEMS FOR MTLE-HS

The earliest neuropathology study in epilepsy patients dates back to 1825, in which Bouchet and Cazauvielh described a hardened and shrunken hippocampus in autopsy brains from patients with clinical history of epilepsy (12). Wilhelm Sommer was first presenting microscopic features of hippocampal sclerosis in an autopsy brain from a patient with temporal lobe epilepsy (88). He observed loss of pyramidal neurons in a portion of the hippocampus that was later on termed "Sommer's sector," and corresponded to the sector CA1 of Lorente de Nó (52). Sommer already noted neuronal loss within the hilus of the dentate gyrus. In 1899, Bratz made available a detailed description of unilaterally atrophic hippocampus, illustrating severe loss of pyramidal neurons and gliosis in the Sommer's sector of the Ammon's horn, less severe neuronal loss in the hilus of the dentate gyrus and adjacent sector CA3, and preservation of neurons in the CA2, subiculum and the granule cell layer of the dentate gyrus (13). Of note, his illustration confirmed the boundary between lesional CA1 sector and a well-preserved subiculum as oblique, which represents the subicular-CA1 border zone or "prosubiculum" of Lorente de Nó. In 1966, Margerison and Corsellis defined two types of hippocampal damage (55). One was similar to that described by Bratz showing severe to total neuronal loss in CA1 and hilus of the dentate gyrus with sparing of CA2, termed "classical" Ammon's horn sclerosis. Another pattern of hippocampal damage that they described was characterized by neuronal loss confined to the hilus of the dentate gyrus or "end folium," termed "end folium sclerosis." In addition to those two patterns of hippocampal sclerosis, Bruton added, in his monograph published in 1988, the third pattern of hippocampal sclerosis called "total" Ammon's horn sclerosis showing almost complete neuronal loss in all sectors of the hippocampus (15). These specific patterns of hippocampal sclerosis could easily be assessed by qualitative observation; however, Bruton found no apparent correlation between any of those specific types of hippocampal sclerosis and the clinical history among 107 patients in his study.

The first systematic attempt to semiquantitatively evaluate the severity of hippocampal neuronal loss for the histological grading of hippocampal sclerosis was proposed by Wyler *et al* in 1992 (106). Four grades for hippocampal sclerosis along with a diagnosis of no hippocampal sclerosis were provided in Wyler's grading system. Grade I referred to mild mesial temporal damage (MTD) showing gliosis with slight (<10%) or no neuronal cell loss in CA1, CA3, and/or CA4; grade II presented moderate MTD and was characterized by gliosis with 10%–50% neuronal cell loss in CA1, CA3 and/or CA4, and "end folium" sclerosis if the lesion is limited to CA3 and CA4; grade III was classified as moderate to marked MTD equivalent to "classical" Ammon's horn sclerosis defined as gliosis with more than 50% neuronal dropout in CA1, CA3 and CA4, with sparing of CA2; and grade IV refers to marked MTD that is equivalent to "total" Ammon's horn sclerosis,

and defined as gliosis with more than 50% neuronal cell loss in all sectors of the hippocampus. Fascia dentata, subiculum and parahippocampal gyrus can also be involved in this category. Wyler's grading system revealed that classical and total Ammon's horn sclerosis were the most frequent pathologies in mesial temporal lobe epilepsy (mTLE). Inverse clinicopathological correlation has been reported between Wyler's grade and postsurgical memory impairment (43), as patients having the most postoperative memory loss were the ones with normal or grade I pathology, whereas those patients with high-grade pathology III and IV showed little postoperative memory decline. Mossy fiber sprouting in the dentate gyrus as demonstrated by Timm's staining can be observed in cases with Wyler's high-grade lesions (74). In terms of memory impairment, histological patterns of granule cell pathology in the dentate gyrus has been reported to be associated with learning dysfunction in addition to the higher age at epilepsy surgery and longer duration of illness (8). A more recent study has demonstrated that the *in vitro* capacity of proliferation and differentiation into neurons of neural stem cells isolated from the dentate gyrus in patients with pharmacoresistant mTLE was predictive for preoperative memory performance and the number of granule cells in the resected specimen (23). Another study has shown that the younger age at seizure onset was associated with Wyler's high-grade pathology (25). In 1996, Watson *et al* proposed a modification of Wyler's grading system (101). They introduced a six-tiered system by inserting an additional grade between Wyler's grades II and III, that is, Watson's grade III refers to gliosis with more than 50% neuronal loss in CA1 and 10%–50% neuronal loss in CA3/CA4, with sparing of CA2, and the definitions of grades IV and V are the same as Wyler's grades III and IV, respectively. Watson's grade II is defined as gliosis with 10%–50% neuronal cell loss in CA1 and/or CA4, indicating that, although not clearly mentioned in the literature, this category also includes end folium sclerosis and CA1 sclerosis (patient 5 in their 18 cases). In 2007, Blümcke *et al* proposed a clinicopathological classification system for hippocampal sclerosis, based on semiquantitative measurements of neuronal loss in CA1-CA4 (7). Based on the fact that extrahippocampal mesial temporal structures such as parahippocampal gyrus and amygdala may also be involved in pharmacoresistant mTLE (107), they used the term "mesial temporal sclerosis (MTS)" instead of "hippocampal sclerosis (HS)." A cluster analysis of the semiquantitative measurements revealed five distinct patterns of hippocampal pathology (Table 1), that is, no MTS refers to a group without histopathologically classifiable hippocampal sclerosis including no or only 10% neuronal loss that is within the first standard deviation of age-matched autopsy controls, corresponding to "no hippocampal sclerosis" and Wyler's grades I; MTS types 1a and 1b are equivalent to "classical" and "total" hippocampal sclerosis, respectively; MTS type 2 is identical with CA1 sclerosis; and MTS type 3 refers to "end folium sclerosis." They found that these patterns were associated with specific clinical histories and postsurgical outcome; for example, the age of the initial precipitating injury (IPI) appeared to be an important predictor of hippocampal pathology, as it was younger in patients with MTS types 1a and 1b (<3 years) than those with MTS types 2 (mean 6 years) and 3 (mean 13 years) as well as no MTS (mean 16 years). While successful seizure control was associated with MTS types 1a and 1b, MTS type 3 (end folium sclerosis) appears to be a predictor of poorer postsurgical seizure control. By contrast, Thom *et al* (99) found better outcomes for patients with end folium sclerosis and poorer outcomes for no HS group. Such differences in the results among various studies appear to be a major problem in elucidating the clinicopathological correlation of mTLE-HS, and seem to be associated, at least in part, with differences in the number of patients studied, inclusion and exclusion criteria, surgical procedures as well as postsurgical follow-up periods. Interobserver reliability would also affect the histological diagnosis and correlational studies, as anatomical boundaries between CA subfield and regions of interest are not uniformly applied. As mentioned above, trials for establishing the histological classification and grading systems for hippocampal sclerosis have begun with qualitative observations identifying several patterns of hippocampal injury, followed by semiquantitative evaluations for classifying the severity of neuronal loss with clinicopathological correlation studies. Current knowledge is to establish a classification of histological

Table 1. A neuropathologic grading system of hippocampal sclerosis.

	% neuronal cell loss				
CA1	≤10%	≥80%	≥80%	≥80%	≤20%
CA2	≤10%	≤30%	≤50%	≤30%	≤30%
CA3	≤10%	≤30%	≥70%	≤30%	≤30%
CA4	≤10%	≥40%	≥80%	≤30%	≥50%
Category	No HS	Classical HS	Severe HS	CA1 sclerosis	CA4 sclerosis

% neuronal cell loss: Semiquantitative microscopic examination of the human surgical hippocampus resected *en bloc* and evaluated at the midbody level. Formalin-fixed, paraffin-embedded sections at 4–7 μm thickness are recommended for H&E, CV/LFB, NeuN and glial fibrillary acidic protein (GFAP) stainings. Values refer to differences from age-matched post-mortem controls. Please note limitations of visual inspection, as first visible sign of cell loss is usually in the range of 30–40% (H&E stains, shown by quantified neuronal density measurements). Quantitative methods are, therefore, more reliable for scoring. CA1–CA4: Anatomical sectors of the human hippocampus according to Lorente de Nó (52). CA4: The center of CA4 was assessed but not the endfolium (bordering the polymorphic layer of DG). Dentate gyrus pathology was not predictive for postsurgical seizure outcome and relates rather to preoperative memory impairment (72). Granule cell counts were, therefore, not applied for this classification scheme. Scores best suited for differentiating HS subtypes are highlighted in gray. Modified from (7).

types based on the semiquantitative evaluation of neuronal loss. However, quantitative measurements for neuronal loss may require special equipments including computer and/or special technical support for labor-intensive, highly specialized examinations not readily available in most routine pathology laboratories.

Recently, the International League Against Epilepsy (ILAE) constituted a Task Force of Neuropathology within the Commission on Diagnostic Methods, which tries to compile an international consensus for the clinicopathological classification of hippocampal sclerosis. It is based on the agreement to define common terminology issues first and on the recognition of the importance to identify distinct morphological patterns. Further work will then allow us to clarify if these patterns relate to clinicopathological subtypes of mTLE-HS. Novel techniques including high-field imaging may be suitable to translate this knowledge into clinical perspectives and help to predict each patient's response to drug vs. surgical treatment as well as to related comorbidities, that is, memory impairment and mood disorders.

THE CLINICAL SPECTRUM OF MTLE-HS

In a large European series of 3311 patients suffering from temporal lobe epilepsies (TLE), HS can be identified in 48% (3). Within the entire cohort of 5392 epilepsy patients undergoing surgical resection for various etiologies, HS is recognized in 33.6%, with additional 5.1% presenting as dual pathology, that is, combination with tumors or scars (see also Blümcke and Spreafico in this issue). However, there is no reliable epidemiological information available for mTLE-HS. In a hospital-based study, 25% of TLE patients were reported to have hippocampal atrophy on magnetic resonance imaging (MRI) (83). There is evidence for familial history of seizures and familial forms of hippocampal sclerosis (18). There is no predilection for sex or affected hemisphere (14). It is important to note, however, that HS is present also in a non-epileptic elderly population and may be related to anoxic and/or ischemic injury or TDP-43-related neurodegeneration (108). Clinical histories in mTLE-HS patients often refer to an "initial precipitating injury" before the age of 4 years (6). In this patient cohort, complex febrile seizures are most frequently noted events. Birth trauma, head injury or meningitis were other early childhood lesions. The time between onset of habitual seizures and initial precipitating injury is the "latent period" (29). Seizures usually start by the end of the first decade although there are few reports for late onset (>50 years) (54). Seizure semiology often includes auras with psychic, perceptual or dysamnestic phenomena. Motor arrest with impairment of awareness and responsiveness and a blank staring appearance with pupillary dilatation are common in the beginning of a seizure. Seizures may either stop at this stage or semi-volunteered coordinated motor movements may follow (103). Contralateral posturing of the upper extremity indicating the involvement of basal ganglia, ictal speech (nondominant TL), ictal anomia and postictal dysphasia (dominant TL) are well-known lateralizing signs (49). Head and/or eye deviation is usually to the same side of seizure onset (at the early stage) where late and foreword deviation is generally contralateral (103). A seizure lasts typically less than 2 minutes, and is often followed by confusion and disorientation postictally, which resolves gradually over a period of minutes. Characteristic electroencephalogram (EEG) findings are blunt sharp waves with maximum field in sphenoidal and/or fronto-temporal T1/2 > F7/8 > T3/4 electrodes. EEG abnormalities may occur unilaterally, isolated or run at one per second repetition rates (10). They may be facilitated during drowsiness and non-rapid eye movement (REM) sleep stages 1–2, whereas REM stages are likely to exert inhibition. Ictal scalp EEG is usually characterized by secession of interictal spikes and flattening of background activity followed by rhythmic crescendo-like theta activity with decreasing frequency and increasing amplitudes (103, 105). Impaired declarative and episodic memory disturbances (long-term memory consolidation or recall of newly learned information) are frequent in mTLE-HS patients and will be discussed further below. MRI is highly sensitive and specific for the diagnosis of HS. Atrophy is detected in almost 90%–95% of patients when volumetric measurements are applied (17). T2 signals are increased in 80%–85%, T1 signals decreased in 10%–95% and loss of internal structure is visible in 60%–95% (103). There are also extrahippocampal abnormalities to be considered. However, all MRI modalities may fail to detect signal abnormalities in atypical HS variants, which can be demonstrated only by histopathology (see below). Functional imaging has become very helpful, with interictal ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography (mapping glucose metabolism) showing an ipsilateral anterior temporal hypometabolism. PET abnormalities may be visible on both hemispheres but usually aggravate on the HS side and with extratemporal involvement of insula, thalamus, basal ganglia, inferior frontal cortex and lateral parietal cortex (103).

Antiepileptic drug (AED) treatment may achieve favorable seizure control at the beginning of the disease, but most patients develop drug resistance during puberty or early adulthood (29, 32). The most recent definition of drug-resistant epilepsy has been proposed by an *ad hoc* Task Force of the ILAE Commission on Therapeutic Strategies and is described as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (50). For drug-resistant mTLE-HS patients, epilepsy surgery is beneficial as proven in a randomized, controlled trial (102). However, the analysis of our large database revealed a mean age at time of surgery around 34 years with a history of epileptic seizures for almost 23 years! There is no consensus protocol to evaluate postoperative outcome and a large range (33%–97%, median 70%) of seizure freedom has been reported so far (89). Favorable postsurgical seizure control can be usually envisaged when a distinct abnormality is visible on preoperative MR images, absence of status epilepticus, concordant lateralizing memory deficit and absence of seizures in the first postoperative week (22, 59). No significant differences were found regarding different resection types nor resection volumes (80, 81). However, neuropsychological testing usually reveals better postoperative results after limited resections compared with standardized procedures, especially with regard to attention level, verbal memory and calculated total neuropsychological performance (42). In a study where surgical failures were carefully reevaluated, no major risk factors, demographic, electrophysiological or radiological findings have been identified and seizure relapse occurred within 1 year in this patient population (76). Cure was defined to be totally seizure free for 2 years after AED discontinuation and was achieved in 36%–42.7% of patients (67, 104). Long-term relapse must also be taken into account and may affect 15% of operated patients (89).

DENTATE GYRUS PATHOLOGY IN MTLE-HS

It remains an intriguing observation that dentate granule cell loss significantly associates with deficient memory acquisition and recall in TLE patients (8, 23, 72). Indeed, the population of dentate granule cells is pathologically affected in the majority of HS patients. Lesional patterns in this anatomical distinct compartment range from granule cell dispersion (GCD), which occurs in almost 50% of patients (8) to severe cell loss in HS type 1a and 1b (Figure 1). Neuropathological criteria for granule cell alterations include increased granule cell lamination above 10 layers with smaller perikarya and larger intercellular gaps, as well as ectopic cluster and bilamination into the molecular layer. As grading scales for granule cell pathology are not yet internationally standardized, clinicopathological studies yielded complementary but also controversial results (8, 44, 58, 77, 97).

Our current understanding of these pathology patterns were much influenced from developmental neurobiology studies of the dentate gyrus and its propensity to generate neurons throughout life. Assembly of the granule cell layer follows different migration streams building first its internal limb, from which newly generated granule cells progressively expand into lateral direction, thus forming the external limb (1). Most intriguingly, the neurogenic capacity of the dentate gyrus maintains throughout life, also in human brain (30). Within the adult mammalian hippocampus, multipotent precursor cells have been characterized in the dentate gyrus, residing directly below the granule cell layer (34). These cells proliferate upon diverse functional and molecular stimuli, generate migratory neuroblasts and further differentiate into granule cells upon migration into the dentate gyrus (73, 84). Migratory guidance is provided by a scaffold of radial glial cells within the dentate gyrus as well as by Reelin molecules secreted by Cajal-Retzius cells (33, 47, 109). Newborn granule cells functionally integrate into the trisynaptic hippocampal pathway (37, 75, 100), expand dendrites into the molecular layer and axonal collaterals into the CA3 region (mossy fibers), where they form synaptic connections on large excrescences of pyramidal neurons within the stratum lucidum (41). The time period from proliferation to functional integration has been estimated in the range of 4 weeks in adult rodents, although maturation of newborn neurons extends over several months (100). In the mouse, axons reach the CA3 region about 2 weeks after neurogenesis (110). In adult rats, the number of newly added hippocampal neurons per day has been estimated to approximate 9000 or 250 000 per month, respectively (16), while cell proliferation in humans is likely to be much lower (27). The number of new and functionally integrated neurons is challenged by apoptosis and most of these cells die within 1–2 weeks after their generation (38).

The obvious association between HS and GCD led to the hypothesis that newly generated granule cells were aberrantly integrated into the dentate gyrus and compromised the trisynaptic hippocampal pathway, thereby increasing seizure susceptibility (69). Recurrent mossy fiber sprouting (mossy fibers are axonal projections of granule cells) has long been recognized in animal models of temporal lobe epilepsy (94) as well as in surgical human hippocampal specimens (92). Indeed, seizure-induced granule cell neurogenesis and/or dispersion may then represent a major pathomechanism underlying hippocampal seizure activity (69). Further studies on this intriguing topic challenged this assumption. Irradiation of hippocampal precursor cells did not abolish mossy fiber sprouting after experimental induction of status epilepticus (70) and fostered the discussion on the relevance of neurogenesis for architectural abnormalities within the epileptogenic hippocampus and the etiology of temporal lobe epilepsy (78). However, newly generated granule cells integrate not only anatomically and functionally into the granule cell layer (as destined) or ectopically into the molecular layer (GCD) but also ectopically into CA4 (71). Ectopic granule cells at the CA4/CA3 boundary have been first identified and functionally characterized in animal models for TLE (79). Using immunohistochemical preparations for Prox-1, a homeobox gene specifically expressed in postmitotic dentate granule cells (73), a significant number of ectopic granule cells can now be reliably recognized in rat models as well as human surgical specimens (71). These findings are compatible with the notion that aberrant anatomical organization of the epileptic hippocampus contributes to increased seizure susceptibility and that neurogenesis is critically involved in this process. The majority of findings points to a predominately young age of seizure-induced neurogenesis, which contributes to aberrant network integration and seizure progression. The decreased propensity of neurogenesis in chronic TLE stages, whether reflecting a depletion or exhaustion of the precursor cell pool (5), would rather result in the well-recognized cell loss patterns and severe cognitive deterioration (72) (see below). This hypothesis is in good agreement with a recently proposed pathogenic model on the "two faces" of seizure-related neurogenesis in human TLE (78).

The hippocampus serves a major role in all aspects of conscious, declarative memory, that is, semantic memory for facts and concepts, episodic memory and spatial memory (91). Notwithstanding, bilateral damage of both hippocampi induces profound anterograde amnesia in humans (82). Neuropsychological lesion studies, functional imaging in humans, as well as experimental animal models, linked memory function particularly to the dentate gyrus (46). Thus, standardized cognitive evaluation programs in epilepsy patients submitted to surgical treatment offer the unique opportunity to study such higher brain function in humans. Evidence has already been achieved pointing to the impact of dentate granule cell neurogenesis on learning and behavior in rodents (51, 85). We have studied this issue in human hippocampus obtained from epilepsy surgery. Comparing memory performance [tested by amobarbital anesthesia (WADA) in patients subsequently submitted to surgical resection of either the left or right hippocampus] with the extent of hippocampal cell loss identified granule cell density within the internal limb as the most significant predictor, accounting for 78% of the total memory capacity in an individual patient (72). It "suggestively" points to neurogenesis as the neurobiological substrate of memory acquisition (rather than seizure etiology) and that a rundown of the neurogenic propensity in chronic seizure disorders compromises higher cognitive brain functions. Indeed, we experimentally confirmed this hypothesis when isolating proliferating and differentiating adult human stem cells from the dentate gyrus of TLE patients with HS (23). There was a highly significant correlation between the proliferation and differentiation capacity of adult stem cells with the same patient's memory performance, when each hemisphere was tested separately using WADA. These results suggest that encoding new memories is related to the regenerative capacity of the hippocampus also in the human brain.

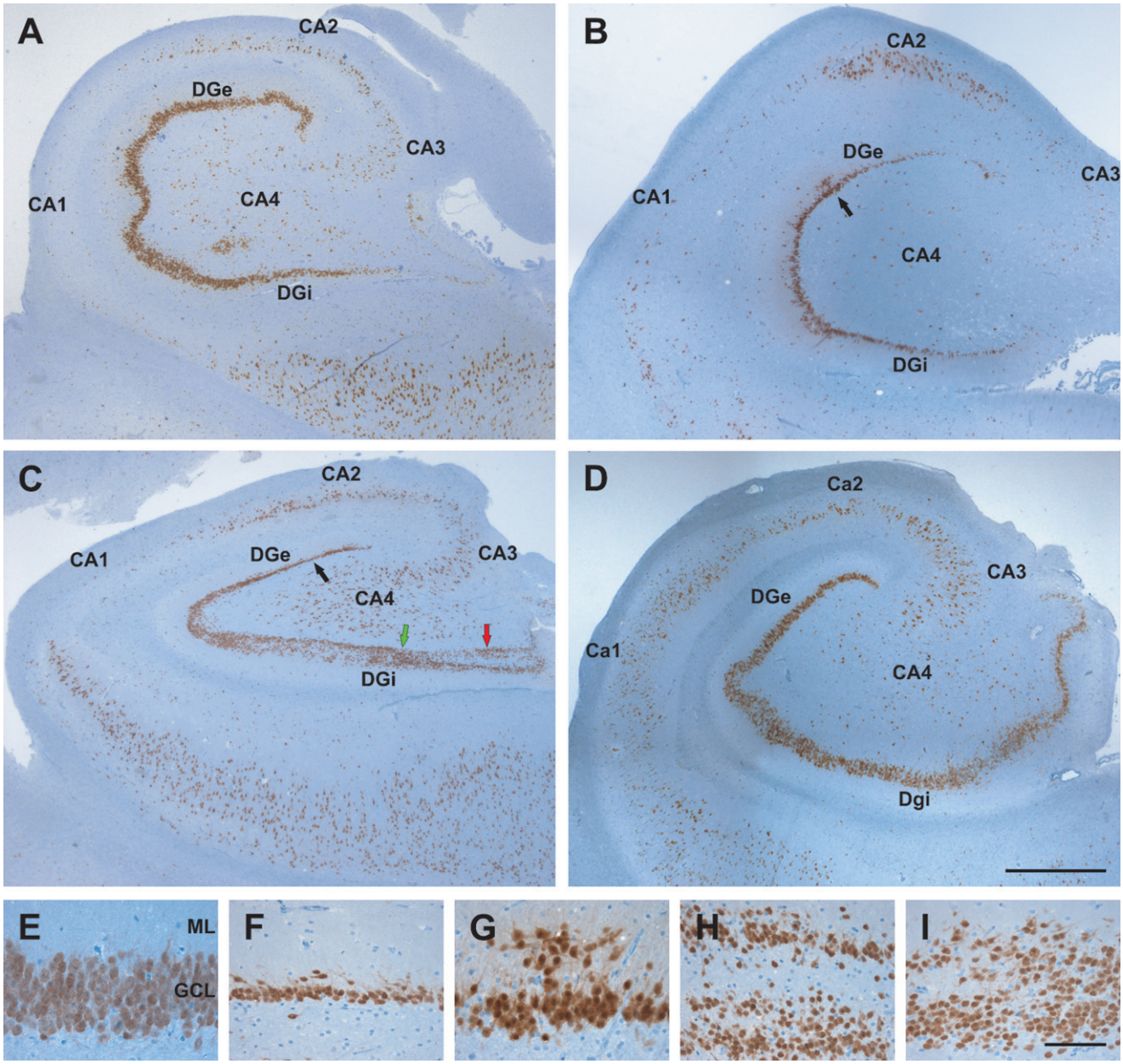

Figure 1. *Neuropathological subtypes of hippocampal sclerosis.* **A.** Classic hippocampal sclerosis with pronounced neuronal cell loss in CA4 and CA1. Note severe cell loss also in the internal limb of the dentate gyrus (DGi), compared to the mid portion or DGe area. Experimental data has shown that this patterns correlates with the patient's impairment to store and recall memory [WADA-testing of the isolated hemisphere; (23)]. **B.** Severe hippocampal sclerosis is characterized by abundant neuronal cell loss in hippocampal CA4, CA3 and CA1 sectors. **C.** CA1 Sclerosis is a rare and atypical HS pattern characterized by predominated cell loss in CA1. Semiquantitative measurements reveal pyramidal cell loss in other sectors as well, but at a lower extent that is not really visible by visual inspection (<30%; Table 1). Please also note the different patterns of granule cell loss in this patient (higher magnifications shown in **E**–**I**). Granule cell loss is evident at the external limb (black arrow). Granule cell dispersion visible at the mid portion (green arrow). Bilaminar architecture at the internal limb (red arrow). **D.** A patient with limbic encephalitis and late onset of her MTLE. The surgical specimen showed restricted cell loss within the CA4 region. This rare pattern is classified as atypical CA4 sclerosis (Table 1). **E.** Higher magnification of a normal human dentate gyrus with densely packed granule cells and sharp borders to subgranular and molecular layers. **F.** Granule cell pathology with significant granule cell loss indicated by layer thinning. **G.** granule cell dispersion with spreading of granule cell clusters into the molecular layer, as described by (44). **H.** Aberrant bilaminar architecture of the granule cell layer is visible. **I:** Granule cell dispersion with spreading of granule cells into the molecular layer. NeuN immunohistochemistry with hematoxylin counterstaining (4 μm thin paraffin-embedded section; applies to all Figure 1 images). GCL = granule cell layer; ML = molecular layer. Scale bar in **D** (applies also to **A–C**) = 1000 μm; scale bar in **I** (applies also to **E–H**) = 100 μm.

HIPPOCAMPAL SCLEROSIS AND ASSOCIATED FOCAL CORTICAL DYSPLASIA (FCD TYPE IIIA)

An intriguing issue remains in the association between mTLE-HS and focal cortical dysplasia (4). Despite the many published results, neither a distinct etiology nor a clinicopathological phenotype for HS with FCD has been identified, which elicits continuous debate (90). Notwithstanding, HS is frequently associated with other pathologies (6), and electroclinical as well as imaging abnormalities in mTLE-HS patients are often larger than the hippocampus, suggesting a more widespread substrate for the generation or persistence of seizures (19, 20, 31). An *ad hoc* Task Force of the ILAE diagnostic commission has classified, therefore, some distinct aberrant histopathological patterns in mTLE-HS patients as associated FCD type IIIa (9). It could yet not been clarified whether FCD type IIIa is an acquired pathology with accompanying reorganizational dysplasia resulting from hippocampal sclerosis, or a distinct developmental entity. The latter would favor the hypothesis that HS is the consequence of chronic epileptogenicity of the temporal lobe caused by the dysplasia. Several aspects argue, however, for a common etiology between HS and FCD type IIIa. Patients from both groups have a similar age at onset and a similar history of febrile seizures as an initial precipitating injury (56); no other clinical differences have yet been identified between isolated HS and HS/FCD type IIIa cases (98). Accordingly, postsurgical outcome is similar in patients with HS only and with FCD type IIIa (93).

Another well-recognized clinical challenge is that of ipsilateral temporal atrophy with temporo-polar gray/white matter blurring, visible by MRI in up to 70% of mTLE-HS patients (21, 60, 62). It is often regarded as a sensitive radiological FCD marker, although no reliable pathological substrate has been identified. Histopathologically proven cortical abnormalities in mTLE-HS patients are less frequent and usually present in two variants. In approximately 10% of temporal lobe surgical specimens from HS patients, an abnormal band of small and clustered "granular" neurons can be observed in the outer part of neocortical layer 2, and was classified as temporal lobe sclerosis (TLS) (35, 98). TLS is likely to present severe neuronal cell loss in layers 2 and 3 with associated laminar gliosis (GFAP-positive astrogliosis) and cortical reorganization (Figure 2). Horizontal bundles of myelinated axons can be observed to a variable degree in these cases. However, there is no correlation between this FCD variant and MRI findings from the same patients (36, 98). Small "lentiform" nodular heterotopias can be identified as another structural abnormality in the temporal lobe of patients with mTLE-HS. They usually remain undetected by MRI (61). Radial orientation along the gray/white matter junction is characteristic and cellular composition is usually formed by projecting neurons (61). These small "lentiform" heterotopias, which are distinct from the larger nodular heterotopias that are readily identified by MRI, may be present in any location of the white matter and are histologically characterized by projecting and local circuit neurons (61). A diagnostic pitfall results from a similar but normal anatomical structure located within the depth of the temporal lobe close to the claustrum. In addition, lentiform heterotopias should be separated from the frequent observation of "isolated" heterotopic neurons either at the gray/white matter junction or in deep subcortical white matter location. Both findings are very often encountered in surgical specimens obtained from epilepsy patients, although its pathogenic or epileptogenic significance remains undetermined (64). The nature and developmental stage of these heterotopic neurons have been addressed in previous studies (28, 40, 95, 96). They may also derive from resting adult stem/precursor

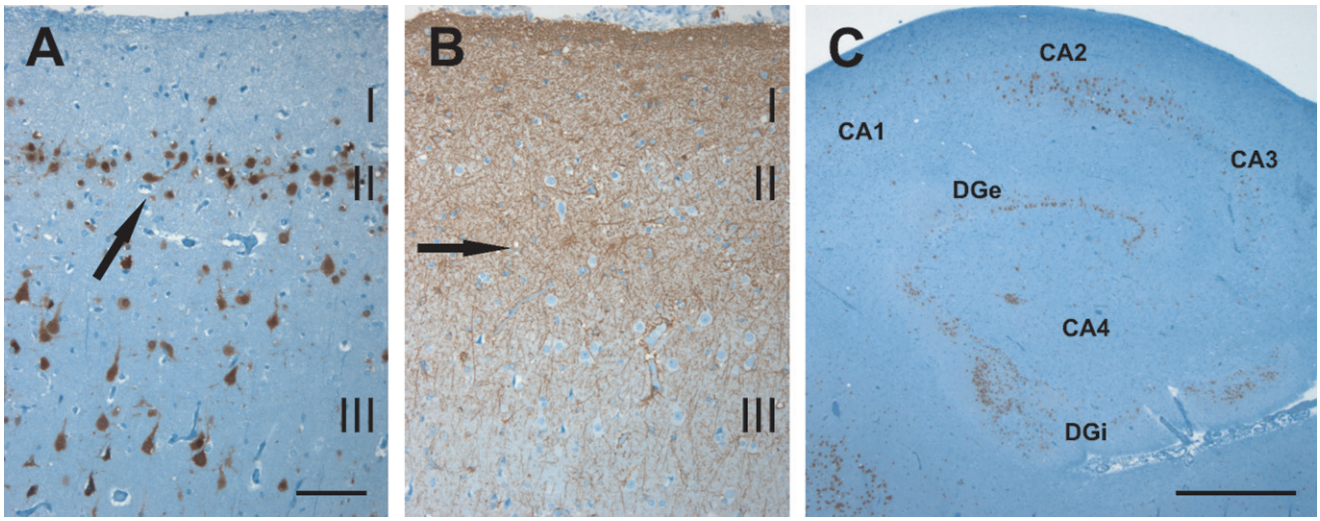

Figure 2. *Temporal lobe sclerosis (FCD type IIIa according to 2011 ILAE classification system).* **A.** "Temporal lobe sclerosis" (98) can be identified in approx. 10% of mTLE-HS patients and is characterized by an abnormal supragranular cell layer (arrow). This pattern should be specified as associated FCD (type IIIa) according to the 2011 consensus classification system for focal cortical dysplasias (9). **B.** Serial section to **A** identifies laminar astrogliosis below the aberrant supragranular cell layer (arrow), indicating severe neuronal cell loss in layers 2/3. Glial fibrillary acidic protein immunoreactivity. **C.** In the same patient, severe HS was evident following microscopic inspection at the midbody level of a NeuN stained and *en bloc* resected hippocampus. I–III = cortical layers; DGe/DGi = external and internal limbs of the dentate gyrus. Scale bar in **A** (applies also to **B**) = 100 μm; scale bar in **C** = 1000 μm.

cells, as recent neurodevelopmental studies provide evidence for neurogenic radial glia in the outer subventricular zone of human neocortex (39), a region that will turn into white matter at later maturation stages. In rat models as well as young children, increased hippocampal neurogenesis was shown following repetitive seizures (86). This may apply also to cortical epilepsies but remains to be shown. The functional impact of aberrantly located white matter neurons to seizure susceptible neuronal networks is another controversial issue, as seizure initiation from white matter location is not very well documented (53). Increased numbers of heterotopic neurons in white matter locations should still be diagnosed, however, as a mild form of cortical malformation using Palmini's classification system (mMCD type II) (68) if occurring as isolated finding without HS, tumors or other principal lesions (9).

MOLECULAR NEUROPATHOLOGY AND ANIMAL MODELS SPECIFYING HS SUBTYPES

It is beyond the scope of this review to illustrate and discuss cellular and electrophysiologic properties of "epileptic" neurons and glial cells in mTLE patients (2) or present the plethora of aberrantly expressed genes, molecules and proteins in this disease condition (87). It may be tempting to speculate, however, that a common trait of upstream regulatory events exists in mTLE. Such upstream regulatory events may involve epigenetic chromatin modifications (48) or the adenosine deficiency hypothesis of epileptogenesis (11). Both mechanisms are able to severely derange downstream gene expression profiles in affected brain regions and are closely related with each other. Animal models remain, therefore, important to study molecular and pathophysiologic sequelae of epileptogenesis (24). A single injection of pilocarpine (or kainic acid) into the animal's peritoneum or directly into the hippocampus elicits status epilepticus, which is most often used to experimentally study pathogenic mechanisms of TLE (65). Other models require subthreshold electrical stimulation of the limbic system following intrahippocampal or amygdala electrode implantation (63). Only few experimental paradigms have tried, however, to reproduce specific human hippocampus pathology or even establish different HS subtypes. Notwithstanding, very long disease duration in many mTLE-HS patients will make this attempt difficult to address in experimental animals. A recent study aimed at this specific issue postulating that classic hippocampal sclerosis results from a single excitatory event by producing prolonged hippocampal excitation in awake rats without causing convulsive status epilepticus (66). Briefly, they triggered two daily episodes of perforant pathway stimulation, which increased granule cell paired-pulse inhibition, decreased epileptiform afterdischarge durations during 8 h of subsequent stimulation, and prevented convulsive status epilepticus. Similarly, one 8-h episode of reduced-intensity stimulation produced hippocampal discharges without causing status epilepticus. Both paradigms immediately produced the extensive neuronal injury that defines classic hippocampal sclerosis, without giving any clinical indication during the insult that an injury was being inflicted. Spontaneous hippocampal-onset seizures began 16–25 days postinjury, before hippocampal atrophy developed, as demonstrated by sequential magnetic resonance imaging. Their results indicated that classic HS is uniquely produced by a single episode of clinically "cryptic" excitation (66), which may well correlate with the early onset hypothesis of classic HS (MTS 1a) in mTLE-HS patients (8).

In conclusion, the clinicopathological and molecular genetic spectrum of mTLE-HS suggests structural and functional disturbances to be more extensive than just affecting the hippocampus (103). We can clinically define subgroups ranging from very focal mesial to widely extended temporal plus types (45). Neuropathological investigations detected different patterns of neuronal cell loss within hippocampal subfields and adjacent temporal lobe structures (26, 57, 106). An intriguing issue will be, therefore, to identify the missing link between clinical and pathology patterns of mTLE-HS. A reliable consensus classification system will be also helpful to define terminology issues and to prospectively evaluate such clinicopathological HS subtypes with respect to postsurgical seizure control and amelioration/aggravation of frequent comorbidities, such as memory impairment and mood disorders.

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Severe amnesia: An unusual late complication after temporal lobectomy

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Abstract—A patient developed the severe amnesic syndrome 8 years after temporal lobe surgery for epilepsy. He underwent left temporal lobectomy (6 cm, 43.5 g; hippocampal sclerosis) aged 19, and remained seizure free for 8 years until a convulsion followed a head injury. He became severely amnesic after a fourth convulsion 16 months later. He was right-handed, pre-operative IQ was average, verbal memory poor and non-verbal memory normal. Post-operatively, these were unchanged. After the first post-operative seizure he began professional training. After onset of amnesia IQ was unchanged, anterograde memory severely impaired and retrograde amnesia dense for at least 16 months. He died 2 years later. Magnetic resonance imaging before amnesia showed absence of anterior left temporal lobe, atrophy of left fornix and mamillary body, and normal right temporal lobe. Four months after onset of amnesia, right hippocampal volume had reduced by 36%. Autopsy showed: previous left temporal lobectomy with absence of left amygdala and hippocampus, atrophy of fornix and mamillary body; neuronal loss in the right hippocampus, severe in CA1 and CA4; intact right amygdala and parahippocampal gyrus; recent diffuse damage associated with cause of death. A convulsion can cause severe hippocampal damage in adult life. Hippocampal zones CA1 and/or CA4 are critical for maintaining memory and the amygdala and parahippocampal gyrus cortex alone cannot support acquisition of new memories. © 1997 Elsevier Science Ltd.

Key Words: memory; hippocampus; epilepsy; MRI; neuropathology; hippocampal sclerosis.

Introduction

Severe anterograde amnesia is a well recognized but rare complication of temporal lobe excisions in the treatment of epilepsy [5, 14, 28, 29]. Severe and permanent anterograde amnesia resulting from surgery for epilepsy was originally reported after bilateral medial temporal lobe resection in the well-documented case of HM [34]. The assumption that when amnesia results from unilateral excision there is pre-existing abnormality in the non-operated temporal lobe has been confirmed at autopsy in two cases [27, 36], although in the second of these the authors comment that after 25 years it is difficult to state with certainty when any old damage occurred.

Professor Milner's publications over several decades have been seminal in establishing the importance of the medial temporal lobe structures as a substrate for memory and they have constituted one of the most major contributions to knowledge of brain–behaviour relationships. These medial temporal lobe structures include not only the hippocampus and amygdala, but also the cortex of the parahippocampal gyrus with the entorhinal cortex and the pararhinal cortex. All have been implicated as possibly playing a crucial part in memory [7, 20–22, 24, 38]. Surgery in humans, mostly as a treatment for intractable epilepsy, cannot, with the possible exception of stereotactic amygdalotomy, excise one of these structures without encroachment on others. Consequently, it has been difficult on the basis of post-operative studies alone to establish the relationship between an individual structure and function. An opportunity to achieve this is, however, provided by the occasional patient who suffers a pathological process largely restricted to one structure [26]. Notable examples are those described by Duyckaerts *et al.* [6] and Zola-Morgan *et al.* [38], leading to the conclusion that severe damage to the CA1 zone of the hippocampus alone is sufficient to cause severe amnesia. This does not, of course, exclude the possibility that damage restricted to some other structure, such as the entorhinal cortex, might also cause a similar amnesia.

We describe a case who developed the severe amnesic syndrome following a severe and prolonged seizure

8 years after successful left anterior temporal lobectomy, which had removed the amygdala, perirhinal cortex and most of the hippocampus, which was sclerotic, without causing significant memory change. The amnesia did not recover and the patient died 2 years later. Damage to the right hippocampus following the seizure was demonstrated by neuroradiological changes during life and by histopathological examination at autopsy.

Case history

CG, male, right-handed

When he was 4 years old he suffered a generalized convulsion which continued for approximately 20 min, affected the right limbs more than the left, and was not accompanied by fever. His habitual epilepsy commenced when he was 13 years old. The pattern of his seizures was: he would complain of feeling unwell and take to his bed; he would then become progressively more unresponsive; he would seem to be repetitively looking at his right hand, and, sometimes after a period of 1–2 hr, he would develop jerking of the right side of his face and then his right limbs and, ultimately, in approximately 50% of his seizures, a generalized convulsion. He suffered six to 10 such episodes in each of the three pre-operative years. These seizure symptoms suggest that each episode consisted of recurrent complex partial seizures, or a period of complex partial status, sometimes culminating in a secondarily generalized convulsion. Also, during the five pre-operative years his behaviour became physically aggressive. He was examined on a number of occasions between the ages of 13 and 19. Sometimes his right limb tendon reflexes were regarded as brisker than those on the left and his right plantar response was regarded as extensor, but on other occasions the examination findings were regarded as normal.

Electroencephalography. Electroencephalography (EEG) was undertaken on a number of occasions and consistently revealed slow waves over his left hemisphere down to 2–3 Hz most prominently, and sometimes phase reversing, at the left posterior temporal electrode. More extensive EEG investigation was carried out when he was 18 years old; there was a sustained slow wave abnormality with spikes/sharp waves over the left anterior temporal region, and a pharmacologically activated recording with sphenoidal electrodes showed 1–3 Hz phase reversing at the left anterior temporal electrode. Three cerebral computer tomography (CT) scans carried out when he was aged 13–18 years revealed enlargement of his left temporal horn and to a lesser extent of the whole of his left lateral ventricle.

Left temporal lobectomy. A 6-cm *en bloc* anterior temporal lobectomy [8] was carried out in 1983 when he was 18 years old. At operation the left temporal lobe appeared abnormally small. The superior temporal gyrus was spared. The excision specimen weighed 43.5 g and contained an estimated 2.5 cm of hippocampus [subsequent magnetic resonance imaging (MRI) and autopsy analysis (see below) indicated that the hippocampal removal was more extensive, which is understandable given that part of the removal is by suction]. The post-operative course was uncomplicated and the only abnormal physical sign detected post-operatively was a right homonymous upper quadrantic partial visual field defect.

Post-operative course. Post-operatively he was seizure free and medication was withdrawn 2 years after surgery, when he was 21 years old.

In 1986/87 he developed migraine, the attacks being characterized by throbbing left-sided headache and fortification spectra seen in the right lower quadrant of his visual field, relieved by a mixture of paracetamol, codeine phosphate and buclizine hydrochloride. In February 1991 he developed a migraine attack whilst driving and he was involved in an accident, sustaining a minor head injury. He was taken to the Accident and Emergency Department of the local hospital, where he had a generalized convulsion. A second generalized convulsion, preceded by abnormal sensation in his right arm and then focal jerking of the right arm, occurred 4 months later and treatment with carbamazepine was reinstated. One further convulsion occurred whilst he was taking carbamazepine and he experienced occasional ill-defined episodes in which he would have a feeling as of sound in his ears associated with an odd sensation around his mouth and a feeling down his right arm, without any alteration of awareness, lasting for up to 5 min. An EEG was reported as showing sustained low-amplitude slow waves over the left temporal region, with occasional high-amplitude slow waves focal in the left mid to anterior temporal region, but there were no definite spikes or sharp waves. An MRI scan (see below) showed no abnormality other than what is standard after left temporal lobectomy.

Then, one morning in June 1992, when he was 28 years old and 3 months after the MRI scan, he was found in his bedroom in a confused state with a bruised face and a bitten tongue. He had not been seen since the previous evening and it was assumed that he had suffered a convulsion. Unfortunately, there is no way of knowing how long this seizure lasted, or whether it caused severe anoxia or a period of cardiac arrest, but we presume that it was prolonged. His confusion had not resolved by the day after and so he was taken to the local hospital, where he was said to be alert, but restless, and making incomprehensible sounds, although he would obey commands; there was a haematoma over his left eye but no other signs were noted. Observations by psychiatrists during the next 3 days were that he was uncooperative, talking nonsense, repeating sentences and expressing strange thoughts that he could not explain. The initial view was that he was in a post-ictal psychosis, but at neurological review it was clear that he was suffering from severe amnesia.

During the next 23 months he suffered nine further convulsions, despite vigorous attempts to prevent them with medication. Some were prolonged, necessitating hospital admission, and some seemed to exacerbate his amnesia. He died in a convulsion that could not be terminated nearly 2 years after he had become severely amnesic.

Neuropsychology

Prior to temporal lobectomy

CG was first assessed at the age of 18 as part of the pre-operative investigations. Follow-up neuropsychology was performed at 6 weeks, 6 months, 2 years and 5 years post-operation. Results of pre-operative, and 6-month and 5-year post-operative assessments are shown in Table 1.

CG presented as a pleasant 18-year-old. He was consistently right handed with no familial sinistrality. He had finished school 1 year previously having done well in mathematics and physics examinations, but failing to achieve the same level in English language examinations, despite several attempts. He said he was a little forgetful about words and telephone messages. He was unemployed but applying for office jobs. The pre-operative

Table 1. Test results before and after temporal lobectomy and after onset of amnesia

	Pre-operation	Post-operation		Post-onset amnesia		
		6 months	5 years	1 month	6–12 months	2 years
WAIS*						
Verbal IQ	105	103	109	106		106
Performance IQ	114	120	129	129		127
Full-scale IQ	109	111	119	117		116
Language Function						
Oldfield–Wingfield Naming Test	18	23	—	23		
Shortened Token Test	32.5	35	—	—		
MAE Sentence Repetition	11	9	9	11	—	—
MAE Word Association	34	39	39	29	36	—
Verbal Memory						
Digit span: Forward	7	6	5	7	7	5
Backward	5	4	4	4	5	4
WMS Logical Memory						
Immediate	6.0	7.75	11.5	3.5	7.75	7.25
Delayed	3.25	8.0	11.5	0	0.5	0
WMS Paired Associate Learning						
Inital score	18.0	14.0	13.5	3.0	7.0	10.5
Delayed (max 10)	10	9	10	2	3	4
Combined Verbal Memory						
Immediate Ci	24.0	21.75	25.0	6.5	14.75	17.75
Delayed Cd	12.25	17.0	21.5	2.0	3.5	4
Non-verbal Memory						
Block tapping span	6	6	—	6	6	
Rey Osterrieth						
Copy	31	34	34	36	34	35
Delayed recall	28	23.5	27	8.5	9.5	9
Maze Learning Path II						
Trials to criterion	6	4	4	15	Failed in	—
Errors	4	1	1	19	25 trials	—
Benton Visual Retention Test						
Correct	9	7	9	5	—	9
Errors	1	4	1	9	—	1

*The WAIS was used at the first assessment in 1983 and this has been continued for the sake of consistency, despite the introduction of the WAIS-R.

results indicated average intelligence with a discrepancy between Verbal and Performance IQ of 11 points (age-scaled subtest scores were: Information 9, Comprehension 9, Arithmetic 17, Similarities 9, Digit Span 12, Vocabulary 9, Digit Symbol 10, Picture Completion 13, Block Design 17, Picture Arrangement 9, Object Assembly 13). Tests of language function revealed minor impairment in object naming and in verbal fluency tasks for objects and animals, but not for words beginning with a specified letter.

The verbal memory tasks used were the Logical Memory Paragraphs and the Paired Associate Learning Test of the WMS, Form 2. ('Form 3'—our own version on which we have normative data—was used at the early post-operative screening and Forms 1 and 2 alternated thereafter in order to minimize practice effects.) Logical memory was poor, particularly after a delay of 1 hr, while paired associate learning was good. The combined delayed verbal recall score (12.25) was moderately low. Non-verbal memory was tested using Taylor's complex figure [35], the Benton Visual Retention Test, a 10-choice point visually guided stylus Maze Learning task [25], and the Corsi Block Span. All these tasks were performed normally. (Post-operatively at 6 months, 2 years and 5 years the Rey figure was alternated with Taylor's figure and alternative versions of the Benton test were used.)

Overall, the results were considered to be compatible with dominant temporal lobe dysfunction in a right hander. They did not raise the likelihood of atypical cerebral dominance nor suggest that global memory impairment was a significant risk from left-sided operation and, in accordance with our practice at the time, carotid amytal studies were not done.

Post-operatively, prior to the onset of amnesia

At 6 months there was a slight increase in Full-scale IQ attributable to improved Performance IQ, possibly

partly due to practice effect. Language test performance had improved on several measures. Logical memory immediate recall was unchanged, but there was an improvement in delayed recall. Paired associate learning was reduced, although still within normal limits, and he reported a mild change in memory for verbal material in daily life. Non-verbal scores showed some fluctuation depending on the task, but all scores were within the normal range. At 5 years post-operation the picture remained essentially unchanged, with paired associate learning the only persistent mild loss and good performance on virtually all other cognitive and memory tasks, including improved logical memory scores. He had a satisfactory neuropsychological outcome. The psychosocial outcome was also satisfactory. He was employed full-time as a building society clerk. He was a car owner. He was still living with his parents but had an active social life. He had set up a computer club and was editing their magazine. He was attending evening classes, had gained some further successes in public examinations and was studying for a qualification in computer science.

At the time of his first post-operative seizure more than 7 years after surgery, he was employed as a driver for a parcel delivery company. He had to stop driving and took up office work in local government. A few months later he started a course of professional training (accountancy) and apparently followed this without difficulty until the onset of amnesia. There was no suggestion of memory impairment associated with the head injury and a further neuropsychological assessment was neither indicated nor performed.

After the onset of severe amnesia

He was admitted to the Radcliffe Infirmary 6 days after the onset of confusion and disturbed behaviour, following the presumed prolonged convulsion during the night. He was disoriented in time but not in place, recognizing that he was in the RI which he had, of course, known for many years. He also recognized some of us (J.O. and S.O.) for the same reason. He was totally unable to give any recent personal history and he asked questions repeatedly. He occasionally commented that he had "only just realized" that he had been talking to one of us, as if he was forgetting with only the slightest distraction the very activity in which he was engaged. At the simplest level, anterograde memory was assessed by the presentation of three items, two pictures and a sentence, with instruction to remember them. After a 2-min period of distraction first recall and then recognition were tested. None of the three items was either recalled or recognized. Questioned about personal history of the years since surgery he was repetitive, gave inconsistent answers to questions about his most recent past, and appeared to have no recall of events since the first post-operative seizure. He clearly had an extremely severe anterograde amnesia and a retrograde amnesia. A full standard assessment was carried out 3–4 weeks after the onset (Table 1).

General intellectual function as assessed by the WAIS was unchanged. Language function was not impaired. Standard memory tests showed that short-term memory as judged by the digit and block tapping span tasks was unaffected. There was severe impairment on all other memory tests. Thus, immediate recall of logical passages was markedly reduced and delayed recall was zero; paired associate learning was severely impaired, with none of the unassociated pairs recalled on any trial and delayed recall correct only for the very easily guessed associations (up–down, North–South); delayed recall of the Rey figure was very reduced, although not zero. He did not recall copying a figure that day, and although he made an attempt he thought he may have been remembering from a previous occasion (he had, indeed, been exposed to this figure more than once in the years prior to the onset of amnesia). Maze Learning was also impaired, in contrast to very rapid learning prior to the amnesia; although he mastered the route eventually it is not clear whether this 'new' learning was based on previous exposure to the route.

At about this time we were fortunate enough to have Professor Brenda Milner visiting Oxford. She spent some time with CG and presented some informal tests. Her view was that he did indeed have the severe amnesic syndrome, although perhaps it was not quite as severe as that of HM.

Additional tests (Table 2) showed that his recognition memory was severely impaired for both words and faces [37]. He did not, however, perform at chance on this test and it was noteworthy that he performed relatively well on the first half of the recognition items and then rapidly dropped back to chance level. One month after the onset of his amnesia recall of geometrical figures (WMS Visual Reproduction) was low to average immediately after presentation, but zero on delayed recall (40 min). His performance on the Rey Auditory Verbal Learning Test did not show any learning over five trials (scores = 5, 5, 5, 6, 5) and he recalled none of list A after the presentation of the distractor list B.

Performance was intact on the Wisconsin Card Sorting Test, with minimal perseveration. Questioned about categories immediately afterwards he said there were three ways of sorting (colour, form, number), but that he had only used number and form and certainly no more than once. In fact, he had used all three categories twice. In comparison, HM recalled only one category after completing three categories (Milner, personal communication).

Procedural learning was demonstrated by exposure to the Gollin figures. He improved and maintained his performance over several months. Unstandardized use of the Tower of Hanoi [3] suggested faster and more systematic solutions with practice. Similarly, in some daily routines he demonstrated procedural learning and quickly acquired the habit of using a notebook as an aid.

Table 2. Supplementary tests after onset of amnesia

		1 month	6–12 months	2 years
Recognition Memory Test				
Words	Score	35	33	33
	Percentile	< 5th	< 5th	< 5th
Faces	Score	36	40	37
	Percentile	< 5th	25th	< 5th
WMS Visual Reproduction				
Immediate (max 14)		9	13	
Delayed		0	6	
Rey Auditory Verbal Learning				
List A	Trial I	5		
	Trial II	5		
	Trial III	5		
	Trial IV	6		
	Trial V	5		
List B		6		
List A	Trial VI	0		
Three-Picture Test				
5 min delay				
Recall		0	0	1
Recognition		0	2	3
Wisconsin Card Sorting Test				
Categories		6	6	
Errors		5	2	
Perseverative errors		2	0	
Cognitive Estimations		—		
Score		5 normal		
Gollin Incomplete Pictures		Serial testing over 6 months		
No. of exposures for identification	Set B	19 11 11	11 10	10 10
	Set A		15 12	11 11

Retrograde amnesia

Clinical questioning revealed a dense retrograde amnesia (RA) for the 16 months from the first post-operative seizure in February 1991 to the onset of the amnesia in June 1992. Recall of the previous 5 years appeared impoverished. He repeatedly asked what had happened to him and whether he had been driving and had an accident (which was the case in February 1991). He had no recollection of his sister returning from working in Bermuda in August 1991 and for several months he could never remember that she was back, even though he saw her daily. Likewise, he had no recollection of the accountancy course he had been taking for 3 months: he would look at written work he had produced and realize that it was in his own handwriting, but have no recognition of the content or recollection of ever having done the work. There was some evidence for more extensive retrograde memory loss: for example, on one occasion he was found in tears in the kitchen having pressed his trousers and being unable to remember where to put away the ironing board, which had been kept in the same kitchen cupboard for 8 years.

There were no previous test results of remote memory. Administration of The Autobiographical Memory Interview (AMI) [13] in June 1992 (see Fig. 1) indicated Personal Semantic scores in the *acceptable* and *borderline* ranges respectively for Childhood and Early Adult Life, and a *definitely impaired* Personal Semantic score for Recent Life. The Autobiographical Incident score was similarly *acceptable* for Childhood but *definitely abnormal* for Early Adult Life and Recent Life.

Re-administration of the AMI 10 months later, in April 1993, suggested there had been some slight reduction in the extent of RA. Personal Semantic scores were in the *acceptable* range for Childhood, Young Adult and now Recent Life. Autobiographical Incidents were *acceptable* for Childhood, but *probably abnormal* for Early Adult Life and *definitely abnormal* for Recent Life. Clinical questioning suggested that a very few events, such as the wedding of a friend, had been recalled but that otherwise there had been little meaningful change in the dense 16-month RA from February 1991 to June 1992, although he had now re-learned certain key facts, such as that his sister had returned from working abroad. Some of the apparent improvement in Autobiographical Incidents scores on the AMI also appeared to be an artefact of his being tested a few days after an event that was salient and out of the ordinary for him, i.e. a weekend away in the country staying with a much-loved grandmother.

An additional attempt was made to check the sequencing and richness of his autobiographical memory via separate semi-structured interviews with him and his father in July 1992. In summary, these interviews strongly suggested impoverished and patchy autobiographical memory throughout his life span.

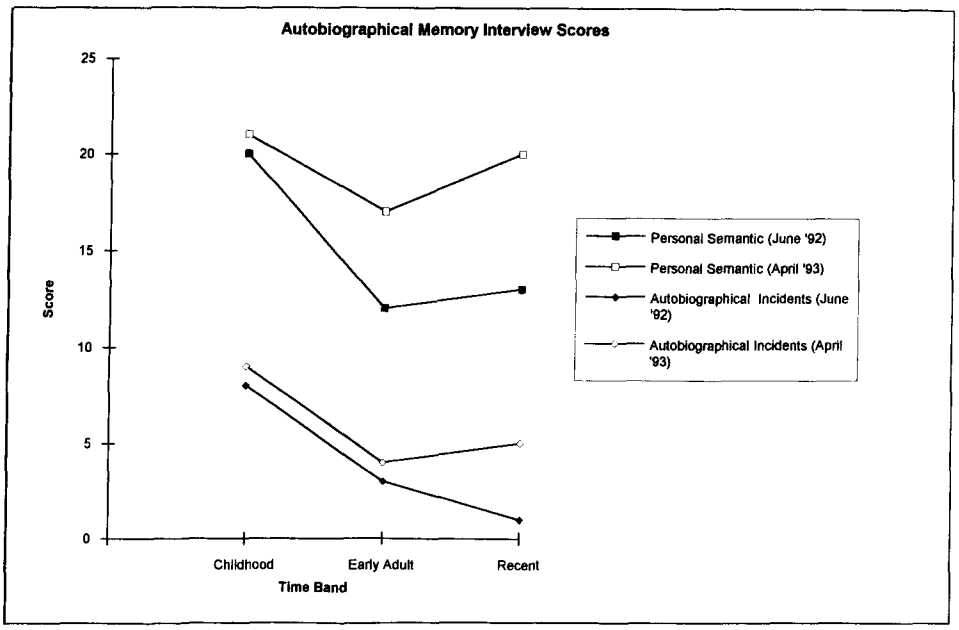

Fig. 1. Autobiographical Memory Interview scores obtained early after onset of the amnesia and at re-test 10 months later.

No formal public events tests were administered, but in June 1992 he thought Margaret Thatcher was still Prime Minister, whereas she had in fact resigned at the end of 1990 amidst considerable media coverage and prior to his first post-operative seizure in February 1991.

Progress

His amnesia was a severe and devastating handicap in daily living. He was unable to remember what he had done from day to day or earlier the same day unless prompted by the use of his notebook. Eventually he would learn or partially learn a new routine, such as that he was attending a rehabilitation centre, but could seldom say what he did there without referring to notes. For several weeks on arrival each day he would remain standing puzzled at the entrance unable to recall which door he should enter, but he eventually learnt. Particularly salient or unusual events were often partially recalled, such as a stay with relatives. There was some fluctation in his state related to continuing seizures, and after the worst ones his memory would sometimes appear to his family to be even worse and he would seem to have lost any small gains. There was one phase when he seemed to be making progress and an attempt was made to introduce some independence into his life by making him responsible for his own medication and encouraging him to travel to the rehabilitation centre by bus. The former worked quite well, with the use of a bleeper on his wrist watch twice daily, although this was never reliable because he did not hear the bleeper if he was asleep and did not remember the pills on waking. His relatives observed that it took more than 2 weeks for him to learn where the pills were kept in the family kitchen. He did manage to use public transport but frequently did not remember having done so, although he would deduce as much from finding a bus ticket in his pocket. He did quite well in some projects at the rehabilitation centre and, not surprisingly given his good non-verbal ability, he produced some beautiful woodwork. However, he was slow, constantly checking on what he was meant to be doing, and both in that setting and at home he was virtually unable to make and to execute plans without guidance. In the same way, a former computer enthusiast, he could no longer write programmes because the load on memory, in terms of the number of variables to be held in mind, was beyond him. His mood fluctuated and at times he was seriously depressed, requiring treatment.

Re-assessment on standard tests showed very little change. Slight improvement was seen in immediate but not delayed Logical Memory, Paired Associate Learning and Benton Visual Retention (Table 1). Other tests suggested some improvement in the Three-Picture Test (Table 2) and in one test of non-verbal delayed recall (Visual Reproduction), but not the Rey figure, and at the same time Maze Learning deteriorated. Despite other significant seizures said at the time to arrest or even reverse progress, there was no evidence of progressive impairment, either generalized or specific. He remained essentially a person with a severe anterograde amnesia and a limited retrograde amnesia until his death 2 years later.

Neuroradiology

All MRI examinations were performed using a 1.5-Tesla GE Signa Advantage scanner. T1W sagittal scans, fast spin echo (FSE) T2W axial scans, FSE dual echo coronal scans and, except on the examination carried out approximately 3 months before the onset of the severe

amnesia (scan 1), a three-dimensional volume acquisition spoiled grass (SPGR) coronal sequence with 1.5 mm slice thickness and with a flip angle of 35′, were obtained through the whole brain. The hippocampal outline was traced using a trackerball on each coronal slice of the SPGR sequence, and the hippocampal cross-sectional area was calculated by computer software. Measurements began posteriorly at the level of the crus of the fornix. The uncal recess of the temporal horn and alveus were used as the anatomic landmarks to separate the majority of the hippocampal head from the amygdala.

Figure 2(a) and (b) illustrate the scan (scan 1) carried out approximately 3 months before CG became severely amnesic. This scan was considered to show no abnormality beyond absence of the anterior part of the left temporal lobe, along with the amygdala and most of the hippocampus, as would be expected after an *en bloc* temporal lobectomy.

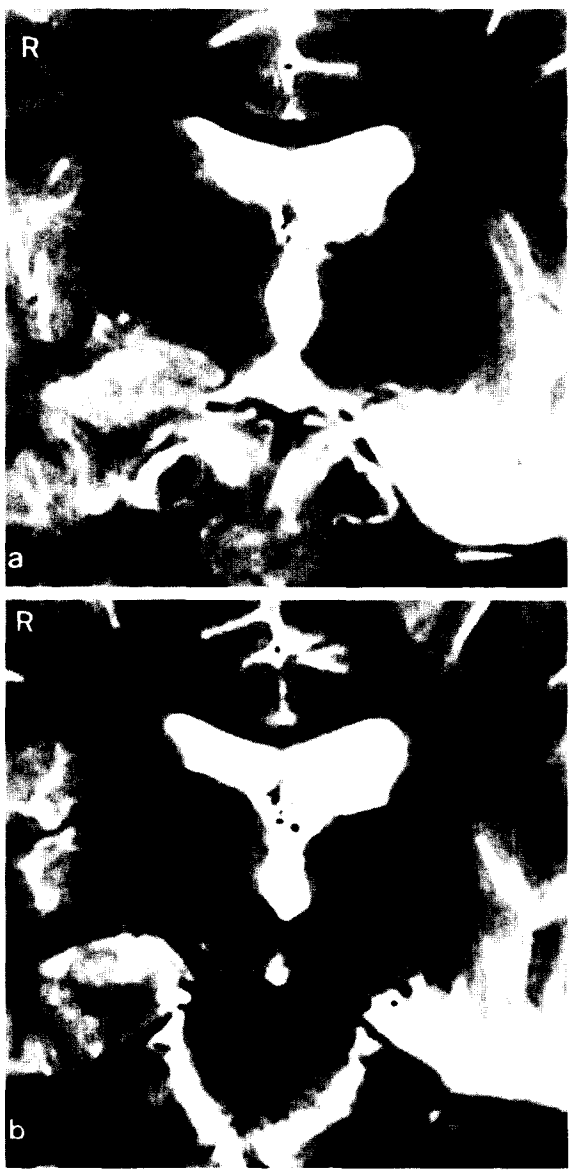

Fig. 2. FSE T2W coronal MR images, approximately 3 months before the onset of severe amnesia, demonstrate the normal head (a) and body (b) of the right hippocampus (arrows). There has been a left-sided anterior temporal lobectomy, with removal of most of the hippocampus and entire amygdala.

Figure 3(a)–(c) illustrate the MRI (scan 2) obtained approximately 2 weeks after the presumed prolonged seizure and amnesia onset. The appearances are similar to those seen on scan 1, with the additional finding from the SPGR sequence on scan 2 that the left fornix and mamillary body are atrophied, compared to those structures on the right, presumably secondary to the previous left temporal lobe excision. The volume of the right hippocampus measured 3034 mm^3. No direct comparison can be made, but this figure does fall within the normal range quoted by Ashtari *et al.* [1], and there is no reason to suppose that the appearances of the right hippocampus were abnormal on either scan 1 or scan 2, even though its function was almost certainly not normal by the time of the latter.

Scan 3, obtained approximately 4 months after the onset of the amnesia, showed that by then atrophy of the entire right hippocampus had developed (Fig. 4a, b). The volume was 1932 mm^3, a reduction of 36%. This is illustrated by plots of the right hippocampal cross-sectional areas seen on scans 2 and 3 (Fig. 5). The amygdala had not changed in size and measured approximately 1996.0 mm^3 on both occasions.

Neuropathology

The temporal lobectomy specimen weighed 43.5 g. It was fixed in 10% formalin before being sliced into five coronal slices, each 1 cm thick. Slices were embedded in paraffin wax, sectioned and stained with routine histological stains, including haematoxylin and eosin, Luxol Fast Blue and Cresyl Violet, and antibodies to glial fibrillary acidic protein. Histological examination revealed marked loss of neurones from the CA1 region of the hippocampus, with accompanying gliosis (Fig. 6). Other areas of the hippocampus were less severely affected.

Autopsy studies

General postmortem examination revealed no significant abnormalities. The brain weighed 1655 g and was removed and suspended in 10% formalin for 4 weeks prior to neuropathological examination. Macroscopic examination showed the absence of the left temporal lobe. Tissues around the resection site were grey and irregular. The brain was generally soft, with severe oedema causing parahippocampal grooving on the right side and cerebellar tonsillar herniation. Foci of cortical discoloration indicating recent haemorrhagic infarction were widespread, particularly on the left side of the brain.

Coronal slides confirmed cerebral oedema. The left fornix, mamillary body and thalamus were smaller than the right. There was dark discoloration of the left caudate nucleus and subaqueductal gray tissue. Blocks were taken

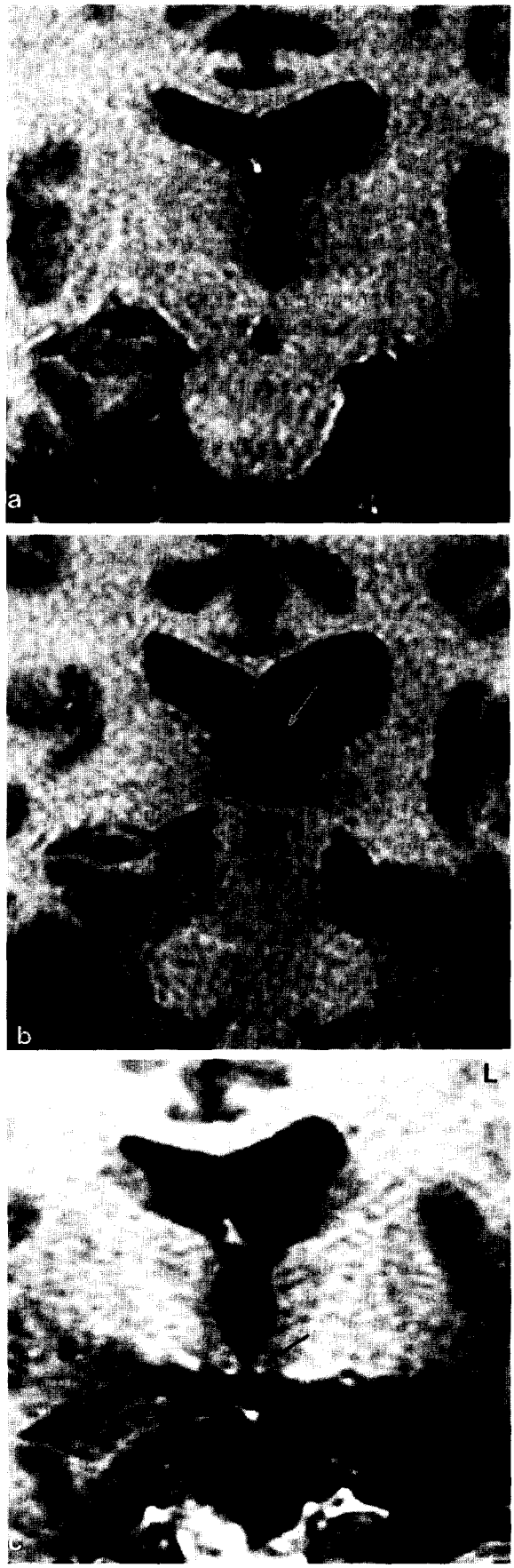

Fig. 3. Coronal SPGR MR images obtained approximately 2 weeks after the presumed prolonged seizure and amnesia onset again demonstrate a normal right hippocampus (a, head; b, posterior body; arrowheads) and post-operative changes in the left temporal lobe. The volume of the right hippocampus measured 3034 mm^3. (The coronal FSE T2W images, corresponding to those in Fig. 2(a) and (b), demonstrated no change in appearance of the right hippocampus.) Atrophy of the left mamillary body (c; black arrow) and fornix (b; white arrow) are secondary to removal of the left hippocampus.

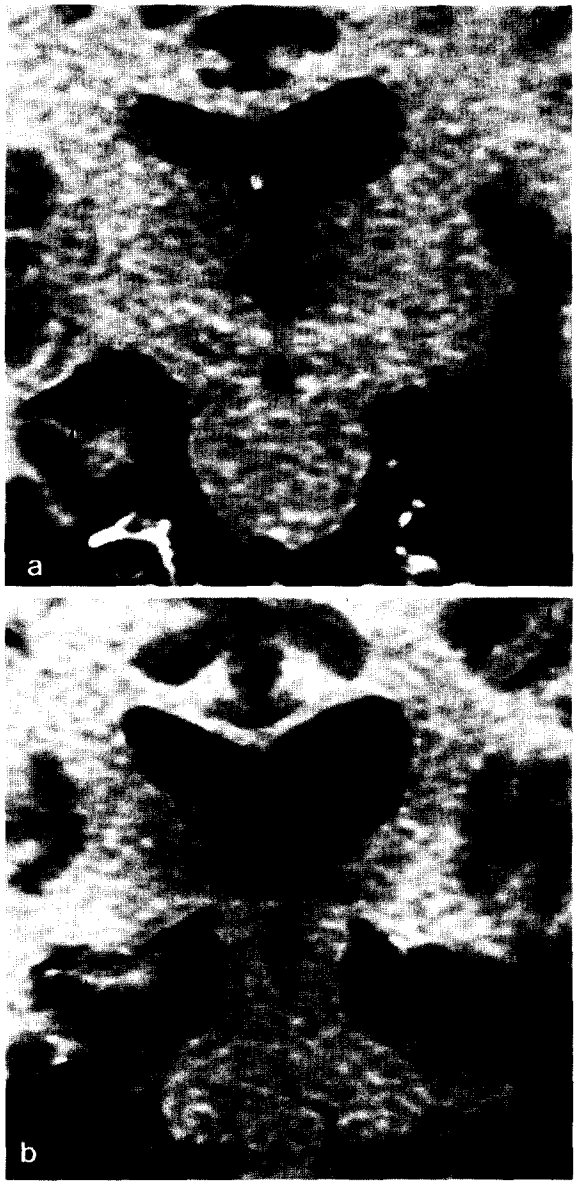

Fig. 4. Coronal SPGR MR images, 4 months after the onset of amnesia, through the head (a) and posterior body (b) of the right hippocampus, at comparable levels to Fig. 3(a) and (b), demonstrate atrophy of the entire right hippocampus. The hippocampal volume measures 1932 mm^3, a reduction of 36%.

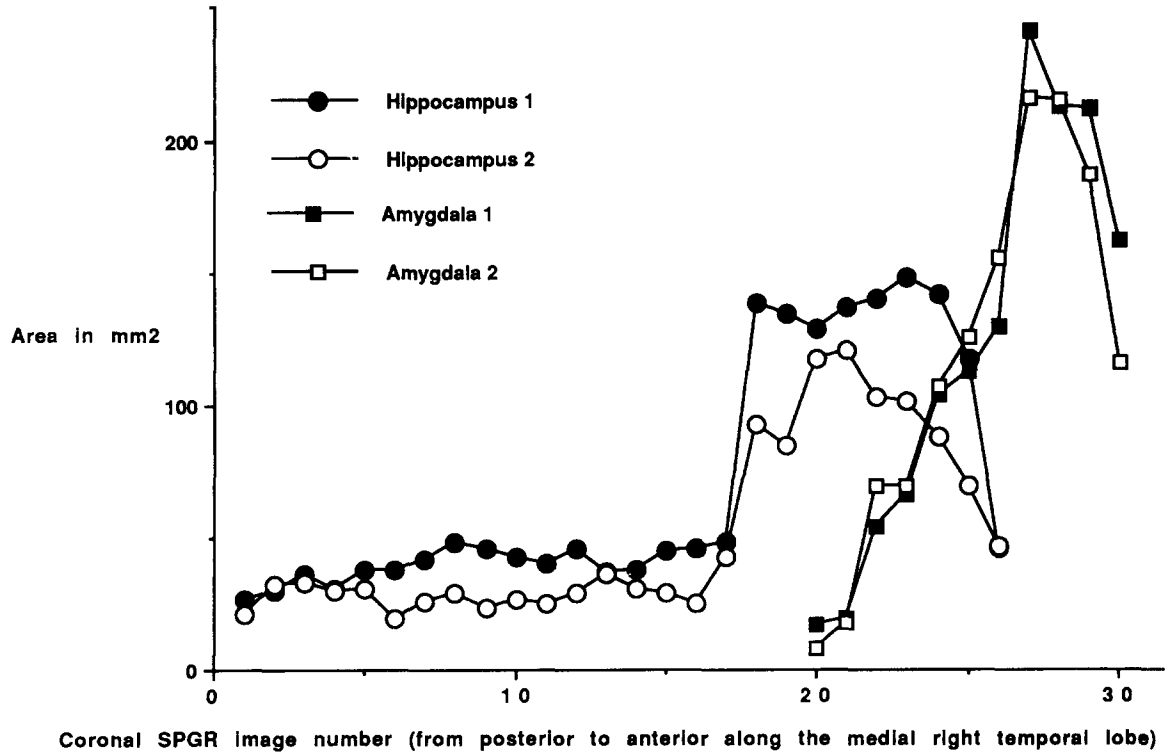

Fig. 5. Graph plotting the area of the right hippocampus and amygdala (y-axis) against SPGR MRI scan number (x-axis), 2 weeks after the prolonged seizure (hippocampus 1 and amygdala 1, black circle and square respectively) and 4 months later (hippocampus 2 and amygdala 2, white circle and white square respectively). The entire hippocampus is atrophied on the later scan. The amygdala has not changed in volume.

from all brain areas and embedded in paraffin wax. Sections of 5 μm thickness were stained as above.

Histopathology showed widespread change due to recent (terminal) hypoxia–ischaemia manifest by oedema and eosinophilic change in neurones of the cerebral cortex, both thalami, the right hippocampus, the brain stem and the cerebellum, and by small perivascular haemorrhages. There was extensive gliosis in the tissue adjacent to the old surgical resection of the left temporal lobe, and the left fornix and mamillary body were atrophied and gliotic compared to the right. There was mild long-standing neuronal loss in the left thalamus.

In the CA1 zone of the right hippocampus there was a complete loss of neurones with an intense gliosis, capillary proliferation and cuffing with macrophages (Figs 7 and 8). These changes indicate both old damage of at least several months duration and more recent or continuing damage occurring in the weeks or months before the terminal episode. Marked neuronal loss and gliosis indicative of old damage were seen in CA4, and to a

Fig. 6. Left temporal lobectomy. The pyramidal layer of the CA1 zone (between arrows) is thin and gliotic. Blood vessels are congested due to handling during surgery. D, dentate fascia. Haematoxylin and eosin, $\times 26$.

Fig. 7. Right hippocampus. The CA1 zone is densely gliotic (arrows). Some neurones remain in the CA2 zone (arrowheads), while only a few are seen in CA4 (open arrows). D, dentate fascia. Haematoxylin and eosin, $\times 26$.

Fig. 8. Right hippocampus. Higher power picture of the area of CA1 between arrows in Fig. 7, showing that almost all neurones have been lost and replaced by glial cells. Two calcified neuronal profiles remain (arrows). Collections of macrophages are seen around many capillaries (V), indicating recent damage. Luxol Fast Blue and Cresyl Violet, × 130.

Fig. 10. Right entorhinal cortex. The cortex is congested due to terminal asphyxia, but structure and neuronal content appear normal. Luxol Fast Blue and Cresyl Violet, × 26.

lesser extent in CA3, and there was mild gliosis in the dentate gyrus, indicating long-standing neuronal loss; there was no evidence of ongoing damage in these structures (Fig. 9). The entorhinal cortex showed no gliosis and neuronal numbers appeared to be within normal limits (Fig. 10), the only abnormality here being severe acute change due to terminal hypoxia. The right amygdala contained occasional glial cells without appreciable loss of neurones (Fig. 11a, b).

DISCUSSION

We have described the case of a young man, CG, who developed a severe anterograde amnesia with limited retrograde amnesia, following a presumed severe and prolonged seizure, 8 years after a successful left anterior temporal lobectomy. Memory function was essentially normal during the 8 years after the anterior temporal lobectomy, and MRI towards the end of this period, 1.5 years after he had developed a recurrence of occasional seizures following seven seizure-free years, showed a normal right temporal lobe, in contrast to the absent left temporal lobe. The left temporal lobe excision included the amygdala and most of the hippocampus, and had resulted in atrophy of the left fornix and left mamillary body. Shrinkage of the right hippocampus, but not of the amygdala, developed after the onset of the severe amnesia. Both were presumed to be the consequence of a prolonged convulsion. He died 2 years later. Histopathological examination of the brain showed sev-

Fig. 9. Right hippocampus. There is intense gliosis in CA4 and along the inner layer of the dentate fascia. Occasional astrocytes in the dentate fascia (arrows) indicate previous neuronal loss. Glial fibrillary acidic protein, × 130.

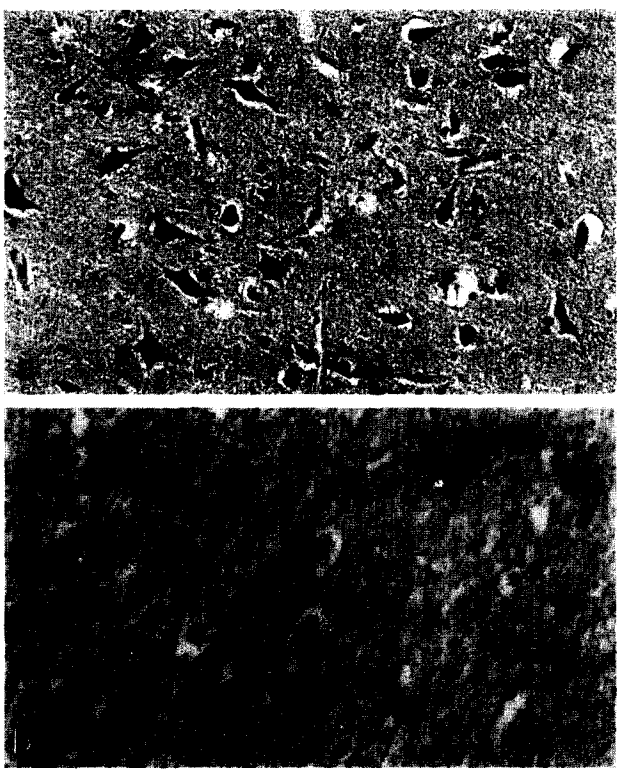

Fig. 11. Right amygdala. (a) All neurones show acute asphyxial damage, but their numbers are normal. Haematoxylin and eosin, × 130. (b) Only occasional glial cells can be demonstrated (arrows). Glial fibrillary acidic protein, × 130.

ere neuronal loss in the right hippocampus, with virtually no neurones remaining in the CA1 zone, and a severe depletion in the CA4 zone, but no obvious abnormality of the parahippocampal gyrus or perirhinal cortex. The amygdala was comparatively normal.

Detailed serial neuropsychological evaluation, prior to left anterior temporal lobectomy, during 5 years post-operative follow-up, and after the onset of the amnesia, demonstrated that the memory impairment was specific. Prior to surgery he was shown to be of high average intelligence. IQ scores did not change after the left temporal lobectomy nor after the amnesia onset. Furthermore, after amnesia onset he performed normally on other cognitive tasks, such as the Wisconsin Card Sorting Test. Memory was very little affected by the left anterior temporal lobectomy. Anterograde memory was, however, devastated by the presumed prolonged seizure and did not recover significantly. Immediate memory span was normal, but beyond this there was severe impairment. All delayed recall tasks were completely failed or virtually so (some material had been used more than once prior to the onset of the amnesia and this previous exposure almost certainly contributed to any recall after he had become severely amnesic). Learning tasks, such as word lists, provided no evidence of new learning and recognition memory was severely impaired. There was a limited retrograde amnesia for at least 16 months and evidence of patchy loss prior to that. Procedural learning appeared intact. These features are typical of the severe amnesic syndrome as described in well-documented cases with medial temporal lobe damage, notably HM [4, 34] and RB [38]. In terms of the severity, we suggest that our patient's anterograde amnesia was slightly less severe than that of HM and at least as bad as, and possibly rather worse than, that of RB. RB was reported to have a Wechsler Memory Scale Quotient of 91 compared to a WAIS IQ of 111. CG did not complete the whole of the Wechsler Memory Scale, but an extrapolated score suggests a Memory Quotient of approximately 70 compared to a WAIS IQ of 116.

Two aspects of CG's memory are worth further discussion: the adequacy of memory function after left temporal lobectomy and before the onset of the amnesia, and the nature of and problems of evaluation of his retrograde amnesia. CG had a left 6-cm *en bloc* anterior temporal lobectomy at the age of 19 years, which included the amygdala and most of the hippocampus. Subsequent MRI showed atrophy of the left fornix and mamillary body. Thus, much of the neuroanatomical substrate of memory in the left hemisphere was absent during the period of 5-year neuropsychological follow-up. He is presumed to have been left hemisphere language dominant, although this was not established by ISA testing, and there is no reason to change this view. What is worthy of comment is the remarkable memory function, at least in terms of standard psychological tests, that was sustained by the right temporal lobe alone. Not only was non-verbal memory intact, but verbal memory was far from seriously impaired. Surgery resulted in a mild impairment of verbal paired associate learning, but delayed logical memory improved. The neuropathological findings in the excision specimen included left hippocampal sclerosis, and the clinical history makes it highly probable that this had been present since early childhood. Removal of pathological hippocampus has relatively little effect on memory [9, 26], provided the other hippocampus is not damaged.

The case of CG appears to be broadly similar to those of HM and RB in showing a very significant but temporally limited remote memory impairment. Milner *et al.* [23] initially reported HM's retrograde amnesia to be restricted to about 2 years prior to operation. More probing objective test results have recently confirmed that the retrograde amnesia is circumscribed, but have extended the deficit back to 11 years prior to operation [31]. RB was also assessed on a range of public events and famous faces tests spanning four or five decades, and scored lower than six out of eight control subjects on detailed recall of public events of the 1970s (onset of RB's amnesia was in 1978). It was concluded that RB had little, if any, retrograde amnesia, except perhaps for a few years in the late 1970s. The extent of CG's retrograde amnesia appears to fall some way between the two, in being very dense for 16 months prior to onset of amnesia and certainly extending back in some form at least 8 years.

The fact that the beginning of the period of most dense retrograde amnesia appears to coincide with the first post-operative seizure suggests a possible relationship. It could be that the initial post-operative seizure resulted in minor right hippocampal damage which was subtle enough not to be evident on MRI scanning, but which nevertheless resulted in an impairment in the acquisition of new declarative information from that point forward. However, during this time CG was working in local government, embarking on professional training in accountancy, and there was nothing to suggest memory impairment. In addition, the retrograde amnesia was not entirely confined to this period.

CG presented particular problems for assessment of remote memory. There are considerable limitations to The Autobiographical Memory Interview [13], and in a young subject such as CG there is more overlap between the Early Adult Life and Recent Life sections than in an older subject. One Personal Semantic section on childhood was inapplicable and had to be omitted. CG had lived at the same address all his life, so the demands of the Personal Semantic sections were less than for someone in whom this was not the case. It is also difficult to check the veracity of autobiographical incidents and accurate time tagging of *early* events. The possibility of exploiting tests of public events and famous faces was also more restricted.

The MRI data indicated that neuronal loss leading to atrophy of his one remaining hippocampus, without any clear amygdalar or entorhinal change, was the pre-

dominant neuroanatomical consequence of the cerebral catastrophe which led to his severe amnesia. This was confirmed by the subsequent neuropathological finding of marked neuronal depletion and gliosis in the CA1 and CA4 hippocampal zones, with a lesser degree of depletion of the dentate gyrus granule cells, amounting to hippocampal sclerosis, without any obvious abnormality of the non-hippocampal right medial temporal lobe structures. The ability to image the structures subserving memory function so elegantly has depended upon the development of three-dimensional gradient echo sequences, such as spoiled grass (SPGR) and multiplanar rapid acquisition gradient echo (MPRAGE). These MRI sequences have provided a means of obtaining thin contiguous slices with superior gray/white matter differentiation and enhanced neuroanatomical detail. Thin slices maximize the accuracy of volumetric measurements and decrease partial volume averaging, and the use and accuracy of hippocampal volumetric measurements employing such sequences is now well established [1, 2, 10, 11].

We presume that CG developed severe hippocampal sclerosis as a consequence of a prolonged convulsion when he was 27 years old, 8 years after undergoing a left temporal lobectomy, although clearly cerebral ischaemia–hypoxia could have been a contributory etiological factor, and it is impossible to be certain that there was not a minor degree of pre-existing hippocampal sclerosis. There is compelling evidence that unilateral severe hippocampal sclerosis may result from a prolonged convulsion in early childhood [15–17, 32]. Likewise, it is well recognized that severe amnesia may develop as an immediate consequence of temporal lobectomy or amygdalohippocampectomy when there is unrecognized pre-existing severe sclerosis of the unoperated hippocampus [27, 36]. In contrast, we are only aware of one case description of unilateral hippocampal sclerosis developing in an adult as a consequence of a seizure [12], and we are not aware of any literature description of severe hippocampal sclerosis developing on the unoperated side late after temporal lobe epilepsy surgery and leading to severe amnesia. Clearly, this needs to be recognized as a rare hazard of the surgery.

The predominant right hippocampal neurone loss was from the CA1 zone, where virtually no neurones survived, and from the CA4 zone, where the depletion was severe. Various authors have shown correlations between neuronal density in each of these zones and both verbal and non-verbal memory [18, 19, 30, 33]. Furthermore, Zola-Morgan *et al.* [38] have described a patient with severe amnesia due to a profound bilateral depletion of CA1 neurones alone consequent upon cerebral hypoxia. This does not, of course, exclude the possibility that an equally severe amnesia could be caused by bilateral damage restricted to some other hippocampal zone or to the entorhinal cortex.

In CG, the marked depletion of CA4 neurones seemed quiescent in that it was not accompanied by capillary proliferation and cuffing with macrophages, indicative of an ongoing process. This suggests that it had occurred at least several months prior to death, possibly at the time of the presumed prolonged convulsion. In contrast, the virtually complete loss of CA1 neurones was accompanied by reactive changes, indicating that ongoing damage had been sustained during recent months, perhaps when seizures had occurred. If so, clearly the ongoing damage did not increase the severity of the memory impairment because neuropsychological examination during the month before CG died showed that his impairment was certainly no worse than it had been soon after its onset. Consequently, one cannot exclude the possibility that the onset of the amnesia was due to the sudden loss of CA4 neurones rather than specifically to the CA1 changes. Furthermore, there is some suggestion that the amnesia of CG was more severe than that of RB, the patient described by Zola-Morgan *et al.* [38], which might be due to CG having the marked CA4 zone neuronal depletion in addition to CA1 loss and complete loss of the left medial temporal lobe structures; Professor Brenda Milner suggested that the amnesia of HM may have been more severe than that of CG, which could, in turn, be due to the medial temporal lobe damage in HM having been even more extensive bilaterally than that of CG. It is difficult to define degrees of severe amnesia, but if such degrees do exist the differences could depend upon the overall mass of medial temporal lobe structures affected by the pathology.

CG's history and the detailed pre-amnesia neuropsychological data demonstrate very clearly the overwhelming difference between unilateral and bilateral hippocampal damage.

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ELSEVIER

Childhood Status Epilepticus and Excitotoxic Neuronal Injury

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This report describes the case of an 11-year-old girl with a prior history of epilepsy and multiple episodes of status epilepticus who presented with generalized convulsive status epilepticus and left hemiclonic seizures. Magnetic resonance imaging, including diffusion-weighted sequences and spectroscopy, and neuropathology at autopsy were consistent with excitotoxic neuronal injury to the hippocampus, cortex, thalamus, mammillary bodies, and cerebellum. Review of the literature revealed 11 similar cases that support the hypothesis of excitotoxic neuronal cell death after status epilepticus.

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Introduction

Childhood status epilepticus can cause significant morbidity and mortality. Animal models suggest that selective neuronal injury sustained after status epilepticus is a direct result of prolonged seizures [1,2]. Evaluating the consequences of status epilepticus in humans is difficult, because most cases of status epilepticus in humans are complicated by hypoxia, ischemia, hypoglycemia, encephalitis, lactic acidosis, and hyperpyrexia [1,2]. In addition, there is often no information about any pre-existing brain injury that might have caused the status epilepticus, rather than resulting from it. Imaging studies have demonstrated regional edema in the context of status epilepticus that can at times progress to atrophy. Serial diffusion-weighted imaging may be predictive of permanent brain injury [3]. Few reports include tissue confirmation of neuronal injury. Here, antemortem magnetic resonance imaging and postmortem neuropathology are presented for a case of status epilepticus uncomplicated by systemic abnormalities or underlying neurodegenerative disease.

Case Report

An 11-year-old female presented with an episode of status epilepticus in the context of febrile illness. She had a history of language regression at 1.5 years, mental retardation, autistic behaviors, megalencephaly, and partial epilepsy; a 1996 EEG reportedly exhibited frequent epileptiform activity most prominent over the left frontal region and an abnormally slow background diffusely. She had been in her usual state of health when she was found by her parents having a generalized convulsion. Treatment included 20 mg/kg valproate IV and 100 mg/kg ceftriaxone IV after 0.1 mg/kg diazepam rectally, 0.1 mg/kg lorazepam IV, and fosphenytoin 10 mg/kg IV had failed to stop her seizures. The total time of witnessed generalized and left-sided hemiclonic seizures was 45 minutes to 1 hour. She also had some breakthrough left clonic seizures and stimulus-sensitive multifocal myoclonus between 70 and 80 hours after she presented, which responded to additional phenytoin and lorazepam. She had an initial fever (40.6°C) in the emergency department but no other signs of illness. Her brother had signs of upper respiratory illness and a low-grade fever.

She had an obvious left hemiparesis within 12 hours after she presented and continued to have a low-grade fever without other signs or source of infection. She rapidly developed rhabdomyolysis and associated renal insufficiency, despite good urine output, requiring increased IV fluid and alkalinization. Abnormal laboratory values included valproate level of 17 μg/mL, mild disseminated intravascular coagulation, transaminase elevation to 2000 U/L, and an acylcarnitine profile notable for an elevated C4 such as can be seen in mild short chain acyl CoA dehydrogenase (SCAD) deficiency.

Computed tomography of the brain, obtained approximately 2-3 hours after she was found seizing, revealed no abnormality. Cranial magnetic resonance imaging done at 56 hours had mildly increased T_2 signal from the right pulvinar, insula, and bilateral hipocampi and possibly cortex. At 80 hours, there was progression to more diffuse right cortical edema and signal changes consistent with laminar necrosis, as well as left cerebellar edema. Diffusion-weighted imaging at 80 hours revealed reduced diffusion in the right cerebral cortex, right thalamus, and left cerebellum (Fig 1). A magnetic resonance angiogram at 80 hours suggested increased blood flow to the right hemisphere. Magnetic

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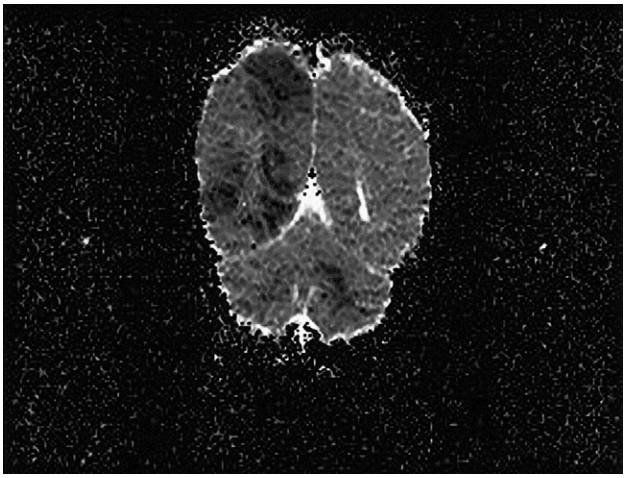

Figure 1. Apparent diffusion coefficient on diffusion-weighted magnetic resonance imaging performed 80 hours after presumed seizure onset reveals reduced diffusion (black) in right cortex and left cerebellum.

resonance spectroscopy at 56 and 80 hours over the basal ganglia and frontal white matter revealed normal N-acetylaspartate, creatine, and choline and no lactate peak. There was an increase in signal in the region of glutamine-glutamate.

Subsequent to her status epilepticus, the patient had a dense left hemiparesis, right gaze, left visual field cut, and possible body neglect. One month later she was seen in follow-up; her seizures were well controlled on valproate, except for a few episodes of complex partial seizures. Her left hemiparesis had improved such that she was able to ambulate independently. Her cognitive and language function had returned to baseline. Four months after her last admission to hospital, she had her only episode of nonconvulsive status epilepticus, which the parents described as at least 8 hours of unresponsive staring and irregular breathing pattern. This resulted in cardiorespiratory failure at home, and she failed resuscitation.

Past Medical History

The patient had epilepsy with left-side hemiclonic seizures and generalized seizures from 1-2 years of age. Prior to the addition of valproate at 3 years, she had multiple myoclonic and absence seizures per day. Approximately 1-2 times per year, she had a generalized convulsion for more than 10 minutes, often associated with left-side weakness postictally. She had approximately five total episodes of status epilepticus (>45 minutes with both generalized and partial seizures), the most recent occurring 1 year prior to her admission. Her anticonvulsant regimen at the time of admission was valproate at 17 (mg/kg)/day; she had received lamotrigine, phenytoin, and carbamazepine in the past. Because of noncompliance, she often had inadequate blood levels of all anticonvulsants. She had normal ophthalmologic (1993) and audiologic (1994) evaluations.

Family History

The patient's brother had a pervasive developmental disorder and brief generalized tonic-clonic seizures; magnetic resonance imaging showed no abnormalities, lactate and pyruvate levels were normal, no likely mutations were identified (i.e., for myoclonic epilepsy with ragged red fibers or mitochondrial encephalomyopathy lactic acidemia and stroke-like episodes), and ophthalmologic findings were normal. Two sisters had febrile status epilepticus and normal development. Her mother had seizures with illness that resolved by 5 years of age and has an orbitofrontal circumference of 60 cm. A paternal uncle has Down syndrome. The family had refused genetic testing on multiple occasions.

Post-mortem Pathology

At autopsy, gross pathology revealed megalencephaly and right superior frontal laminar necrosis. There was also diffuse mild brain swelling consistent with hypoxic injury. Microscopic studies revealed acute neuronal injury bilaterally in the cortex, mammillary bodies, thalamus, hippocampus, pons, medulla, inferior olivary nuclei, and cerebellum. There was striking asymmetry, with extensive astrogliosis and neuronal loss consistent with old injury unilaterally in the right frontal cortex, right thalamus, and left cerebellum (Fig 2). There was also extensive astrogliosis unilaterally in the right mammillothalamic tract. These neuropathological findings are consistent with acute diffuse hypoxic-ischemic injury superimposed upon prior focal neuronal injury in the left cerebellum and right-side supratentorial structures. There was moderate subcapsular and interstitial fibrosis in the kidney. Other organ systems, including liver, were normal on gross and microscopic examination.

Literature Review Methods

To identify other status epilepticus patients with neuropathology and imaging evaluations, a PubMed literature search was performed with search terms "brain damage" and "status epilepticus," "status epilepti-

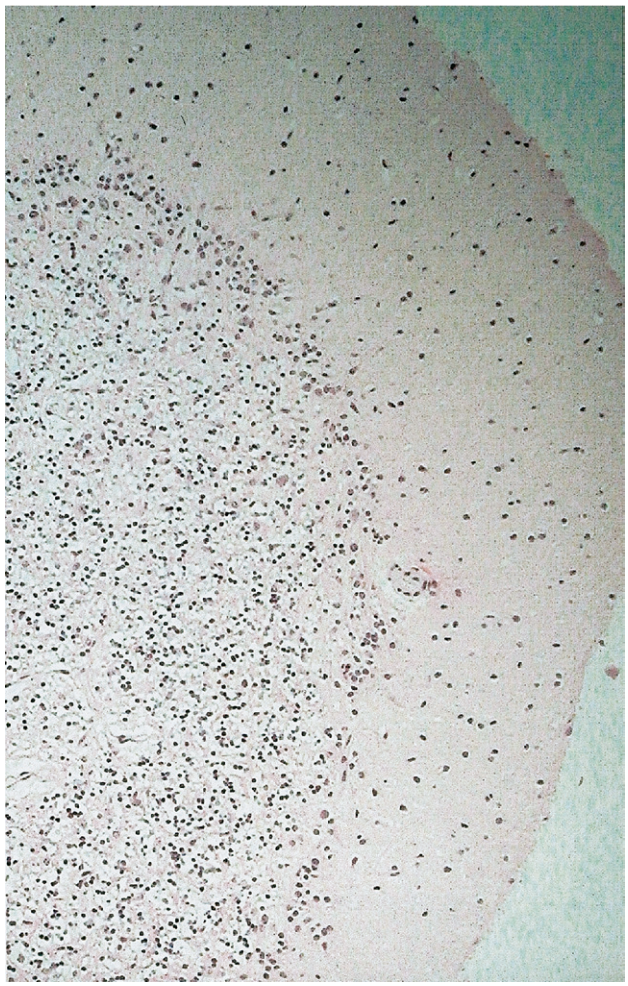

Figure 2. Chronic changes of neuronal loss and gliosis in the left cerebellum.

cus" and "neuronal necrosis," "status epilepticus" and "neuronal injury," "excitotoxicity" and "status epilepticus," and "status epilepticus" and "cerebellum." Additional articles were identified from the related articles lists accompanying PubMed references and from reference lists in the articles retrieved with the PubMed search. A number of cases were excluded because of concomitant hypoxic ischemic injury and status epilepticus.

Results

Eleven cases were identified with neuropathology after status epilepticus [3-11] (Table 1). Similar to our case, five patients had evidence for edema at least in the temporal cortex on imaging studies, and those areas later were demonstrated to have hippocampal neuronal necrosis. Patient 4 had imaging changes consistent with edema but no neuropathological evidence for neuronal injury [3]. Involvement of the thalamus was demonstrated in Patient 1 on both imaging and neuropathology, and Patients 3, 8, and 10 had neuropathological evidence for thalamic involvement [4,6,9,10]. Eight patients had cerebellar involvement on neuropathology (Patients 1, 3, 6-11) [4,6,8-11]. Patient 1 also had evidence for cerebellar involvement on neuroimaging [4]. Four patients had unilateral cortical (Patients 6, 7, 10, 11) or cerebellar (Patients 1, 6, 10, and 11) involvement on either imaging or pathology [4,8-11].

Discussion

The patient initially presented in status epilepticus due to anticonvulsant noncompliance. Although her course was complicated by systemic abnormalities associated with status epilepticus, she did not have sustained cardiorespiratory dysfunction until her terminal episode of status

Table 1. Patients with status epilepticus and neuropathology

Pt	References	Age, yr	Seizures, Complications	Medical History	Imaging	Pathology Findings
1	Men et al. [4]	24	SE; sepsis	Right **Hp** DNET or low-grade glioma	MRI—↑ T_2 left **Cx**, **Th**; abnormal diffusion in left **Cx**, **Th** and right **CB**	Neuronal necrosis left **Cx**, **Hp**, **Th**, right **CB**; right **Am** ganglioglioma
2	Kim et al. [5] (Pt 7)	60	Simple partial SE 5 days	None	MRI—↑ T_2 left temporal **Cx**, **Hp**; DWI ↓ ADC	Neuronal necrosis **Hp**; left temporal glioblastoma multiforme tumor
3	Soffer et al. [6]	20	Hemiclonic SE, sepsis	Complex partial sz after encephalitis	CT—left hemisph edema and midline shift	Left hemisph edema, neuronal necrosis left **Hp**, **Th**, deep gray; bilat **CB**
4	Lansberg et al. [3] (Pt 2)	82	SE >3 days	None	MRI—Right hemisph ↑ T_2; DWI ↓ ADC	Small hemorrhages; no neuronal loss, inflammation
5	Nixon et al. [7]	35	SE 6 days; ventilator support withdrawn	Prior mild flu symptoms	MRI—↑ T_2 mesial temporal structures and claustrum	Mild diffuse edema; neuronal necrosis bilat **Hp**
6	Leifer et al. [8]	58	Focal GTC sz; sepsis	Atherosclerosis risk factors	CT—Mild atrophy	Neuronal necrosis left **Hp**; nonvascular pattern of right Purkinje cell loss
7	Fujikawa et al. [9] (Pt 1)		Complex partial SE; died cardiac arrest	None		Neuronal necrosis bilat **Hp**, **CB**, **CPi** and unilat **Th**, entorhinal **Cx**
8	[9] (Pt 2)		Complex partial SE	None		Neuronal necrosis unilat **Cx** and bilat **Hp**, **Am**, **CPi**, **CB**, **Th**
9	[9] (Pt 3)		Complex partial SE	Carcinomatous meningitis		Neuronal necrosis right hemisph (nonvascular distribution), bilat **Hp**, **Th**, left **CB**
10	Tan and Urich [10]	4.5	Left focal motor SE	Resuscitation at birth		Neuronal necrosis right hemisph (nonvascular distribution) bilat **Hp**, **Th**, left **CB**
11	Vosskamper and Schachenmayr [11]	58	Died septic shock; no overt sz	GTC SE at 2 yr, right hemiparesis sequelae		Atrophy left **Cx**, right **CB**; neuronal necrosis left **Cx** layers 2-5 and **Hp**

Abbreviations (neuroanatomical sites are highlighted in bold);

ADC = Apparent diffusion coefficient
Am = **Amygdala**
bilat = Bilateral
CB = **Cerebellum**
CPi = **Piriform cortex**
CT = Computed tomography
Cx = **Cerebral cortex**
↓ = Decreased
DNET = Dysembryoplastic neuroepithelial tumor
DWI = Diffusion-weighted [magnetic resonance] imaging
GTC = Generalized tonic-clonic
hemisph = Hemisphere
Hp = **Hippocampus**
↑ = Increased
left = Left side
MRI = Magnetic resonance imaging
Pt = Patient
right = Right side
SE = Status epilepticus
sz = Seizure
Th = **Thalamus**
unilat = Unilateral

epilepticus. Imaging after the initial insult was consistent with evolving right cortical, right thalamic, and left cerebellar injury from status epilepticus rather than from ischemia (Fig 1). Her residual neurological deficits and neuropathology (Fig 2) support permanent neuronal injury secondary to her prior episode of status epilepticus.

Two patients in the literature (Patients 1 and 5 in Table 1) presented with similar evidence of neuronal injury due to status epilepticus [4,7]. For both patients, previous magnetic resonance imaging had revealed no abnormalities, and both had infrequent or no seizures, making it unlikely that the neuropathological changes were present prior to the episode of status epilepticus. The selective injury in neuropathological samples in other cases with a single episode of status epilepticus and one or fewer prior seizures is also consistent with an excitotoxic insult.

Other cases reported in the literature without neuropathology also suggest neuronal injury directly related to status epilepticus. In a case with simple partial status, new, persistently reduced N-acetylaspartate was demonstrated on proton magnetic resonance spectroscopy in an area with transient increased T_2 signal and no atrophy [12]. Other patients had progressive hippocampal atrophy in serial magnetic resonance imaging between 1 month and 4-12 months following their episodes of unilateral status [13-15]. The late development of hippocampal atrophy in these cases suggests that prolonged seizures rather than pre-existing hippocampal pathology caused hippocampal volume loss. This concept is supported by a longitudinal study on 12 patients with unilateral temporal lobe epilepsy in which progressive hippocampal atrophy occurred only in patients with ongoing seizures [16]. In another study, patients with longer epilepsy duration had reduced white matter volume [17]. Furthermore, patients with longer duration of epilepsy have been shown to have poorer performance in neuropsychological tests, suggesting ongoing long-term cerebral damage [17,18].

Convulsive status epilepticus in animal models produces characteristic patterns of selective neuronal injury most prominent in the hippocampus (especially the CA1 region and dentate hilus), amygdala, and piriform cortex. Neuronal injury also occurs in the thalamus and cerebral and cerebellar cortex, but to a lesser degree [1]. The neuronal injury is accompanied by acute astrocytosis, and chronically there is cell loss and gliosis. Involvement of these regions may be explained by glutamatergic corticothalamic, corticopontine, and afferent cerebellar pathways [1,4,10].

Animal models support an excitotoxic mechanism of injury in status epilepticus. When oxygenation and perfusion are maintained during status epilepticus, the same selective neuronal necrosis is observed. The regions most vulnerable to injury also have the highest density of excitatory amino acid receptors and neuronal necrosis after status epilepticus has been replicated with excitatory neurotransmitter application [19]. Further, necrosis can be prevented by blocking glutamate receptors [20]. Finally, seizures result in increased glutamate levels in both humans and rats [21,22].

In summary, the present case and other human cases from the literature support animal models implicating direct excitotoxic injury in the absence of hypoxia-ischemia. Understanding these mechanisms may provide clues to rational therapeutics for delayed cell death after status epilepticus.

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