CASE REPORTS: Available On-line

CASE I:

A 42-year-old woman underwent a suboccipital craniotomy and C1/2 cervical laminectomy in 1969 for cerebellar ectopia and syringomyelia, involving the use of a human dura mater graft (brand uncertain). In 1978, she was re-admitted with a six week history of increasing lower limb stiffness and loss of balance. The neurological signs were felt generally to be consistent with syringomyelia but she continued to deteriorate with poor mobility and emotional lability. She developed myoclonus, akinetic mutism and died 6 months after onset.

Approximately 104 months elapsed between graft placement and the first symptom of CJD.

Investigations:

1 CSF examination was normal. 14-3-3 analysis not undertaken.
2 Serial EEG recordings were typical for CJD.
3 Cerebral CT was consistent with original diagnosis and surgery undertaken.
4 This case predates sequencing of the *PRNP* gene.
5 Autopsy was not performed.

Diagnostic Criteria: Probable Iatrogenic CJD.

CASE II:

A 36-year-old woman presented with headaches and visual problems. Further investigations revealed a left temporal/occipital meningioma which was subsequently excised; a Lyodura graft© inserted to repair the dura.

In December 1990, she developed difficulty with vision, word finding and emotional lability. By the late March, she had developed a right homonymous hemianopia,

dysphasia, a right upper motor neuron facial weakness, myoclonus, probable pyramidal signs and truncal ataxia.
Approximately 93 months elapsed between the surgery and the onset of CJD.

Investigations:

1 CSF examination was normal. 14-3-3 analysis not undertaken.
2 Three EEGs in March 1991 demonstrated non-specific slow wave change, with left sided predominance.
3 Cerebral CT demonstrated changes associated with previous surgery.
4 Limited sequencing of the *PRNP* gene demonstrated methionine homozygosity at codon 129.
5 Autopsy: Posterior temporal and occipital cortex on the left irregularly shrunken. Histological examination confirmed spongiform change with neuronal loss and gliosis throughout the cerebral cortex, basal ganglia and cerebellum, however, the features were most prominent in the occipital cortex.
Western blot analysis for protease-resistant prion protein (PrP^{res}) demonstrated a type 1 isoform. (Figure 1)

Diagnostic Criteria: Definite Iatrogenic CJD.

CASE III:

In late Jan 1985, this 54-year-old gentleman had a right acoustic neuroma surgically excised. In early February, a Lyodura graft© was necessary to repair a CSF leak.
In June 1989, he represented with a seven-week history of double vision and diminished ability at work. He continued to deteriorate, developing disorientation, echolalia, dyspraxia, nystagmus, impaired upgaze, profound truncal ataxia and extensor plantar responses. The deterioration was relentless and he died in June 1989.
51 months had elapsed from deployment of the dura graft to the onset of symptoms.

Investigations:

1 CSF examination normal. 14-3-3 analysis not undertaken.

2 An EEG showed only non-specific abnormalities.
3 A cerebral CT and MRI (T2 weighted MR sequence) were both normal but for old post-operative changes.
4 Genetic analysis of the *PRNP* gene was not undertaken.
5 Autopsy was not performed.

This case does not fulfil the diagnostic criteria for a definite or probable case but, on the balance of probability, CJD was felt to be the most likely diagnosis.

CASE IV:

In October 1985, this 27-year-old gentleman underwent a posterior fossa decompression and cervical laminectomy for cerebellar ectopia and syringomyelia. The defective dura was repaired using a Lyodura graft©.

He re-presented, in July 1989, with dysarthria and unsteadiness. Examination in September 1989 revealed left sided cerebellar signs, brisk reflexes and an extensor plantar response. Prior to his death in November 1989, he developed myoclonus and was akinetic and mute.

A period of 45 months had elapsed from exposure to clinical onset.

Investigations:

1 CSF- The only abnormality was a slightly elevated protein of 0.68g/l. 14-3-3 analysis not undertaken.
2 A cerebral CT was consistent with previous surgery.
3 EEG carried out was non-specifically abnormal.
4 Complete *PRNP* genetic analysis was not carried out; however, methionine homozygosity was demonstrated at codon 129.
5 Autopsy: Atrophic spinal cord with a crescentic cavity in the upper thoracic region consistent with syringomyelia. The cerebrum appeared normal, but there was asymmetry of the cerebellar tonsils. Histolopathological examination of the spinal cord confirmed syringomyelia. The cerebrum showed gliosis and

spongiform change predominately within the cerebral cortex and striatum. Moderate spongiform degeneration was present in the molecular layer of the cerebellum. The pathological features were consistent with a diagnosis of CJD. No frozen tissue was available for PrP^{res} analysis.

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Diagnostic Criteria: Definite Iatrogenic CJD.

CASE V:

A 39-year-old man presented with a history of three episodes of oscillopsia and a single generalised tonic-clonic seizure. Cerebral CT imaging revealed a left posterior parietal tumour and a meningioma was removed in July 1985, the dural defect being repaired with a Lyodura graft ©.

This gentleman represented with a bulge at the operation site and a second Lyodura © graft was inserted. He remained well until September 1992, when he developed oscillopsia, word finding difficulties, poor coordination and drowsiness. On examination, he was orientated in time and place but word finding difficulties and cerebellar features were noted. Treatment resistant right-sided focal seizures, myoclonus and decerebrate posturing were noted prior to his death in August 1993.

If one assumes that the original exposure resulted in transmission then the approximate incubation period is 86 months. If the second graft was responsible then the incubation period is 79 months.

<u>Investigations:</u>

1 CSF examination was normal. 14-3-3 analysis not undertaken.
2 Serial EEGs were carried out, eventually demonstrating features typical of CJD
3 Original MRI (Sequence unknown) showed cystic changes at the operation site and serial scans demonstrated generalised atrophy.
4 Sequencing of the *PRNP* gene was not undertaken.

5 Autopsy: Severe atrophy of cerebral cortex and cerebellum. Histopathological examination showed status spongiosus in the cerebral cortex. The cerebellum and brainstem also showed spongiform change and neuronal loss, but these features were less marked in the thalamus and basal ganglia. Immunocytochemistry for PrP showed widespread positivity, with a predominant synaptic pattern of accumulation. No frozen tissue was available for PrP^{res} analysis.

Diagnostic Criteria: Definite Iatrogenic CJD

CASE VI:

This 14-year-old female presented in 1984 with persistent headaches. Further investigations revealed an astrocytoma of the cerebellum. This was resected in 1986 with use of a Lyodura graft©.

In November 1994, she presented with unsteadiness. Examination revealed right-sided cerebellar features and a severely ataxic gait. Myoclonus developed and following a period of anxiety, agitation and hallucinations, she became cortically blind, akinetic and mute.

She died 33 months after onset.

103 months elapsed between graft exposure and clinical onset.

Investigations:

1 CSF examination was normal. 14-3-3 analysis not undertaken.
2 Repeat EEGs were carried out, the most recent being typical for CJD.
3 MRI brain (T1, T2, FLAIR sequence) demonstrated features consistent with previous surgery.
4 No mutation was identified following sequencing of the *PRNP* gene and at codon 129 methionine homozygosity was demonstrated.
5 Autopsy: Severe atrophy of the cerebral cortex, particularly in the occipital lobes. The cerebellum was asymmetrical, with severe atrophy of the right hemisphere.

Histopathological examination showed status spongiosus in the cerebral cortex, with associated gliosis and neuronal loss. Spongiform change and neuronal loss were severe in the cerebellum, particularly in the right hemisphere, and were also present in the basal ganglia and thalamus. Immunocytochemistry for PrP showed widespread positivity in a composite synaptic/perineuronal pattern. Western blot analysis for PrP^{res} demonstrated a type 1 isoform. (Figure 1)

Diagnostic Criteria: Definite Iatrogenic CJD.

Case VII:

In August 1987 this 18 year old right-handed gentleman noted a swelling in the right frontal/parietal region of his skull. The lesion responsible was excised and histology confirmed an eosinophilic granuloma. Lyodura© was used to complete the dural defect.
He presented, in December 2002, with right facial paresthesia, dysarthria and dysphagia. Examination revealed a right upper motor neuron seventh nerve palsy, absent gag reflex, deviation of the uvula to the right and decreased pinprick over the right arm and face. Formal cognitive testing failed to identify any deficit. The sensory features progressed to involve a right hemi-sensory distribution and cerebellar features were noted. The terminal stages of illness were characterized by multi-focal myoclonus and generalised seizures and he died approximately 5 months after onset.

177 months had elapsed from deployment of the graft until clinical onset.

<u>Investigations:</u>

1 CSF analysis was normal. 14-3-3=Negative, s100=0.38.
2 EEG carried out during the illness demonstrated non-specific slowing.
3 MRI brain (T1, T2, DWI, FLAIR sequence) was normal.
4 Sequencing of the *PRNP* gene demonstrated methionine homozygosity at codon 129 and no mutations were detected.

5 Autopsy: Mild cerebral and cerebellar atrophy. Histopathological examination showed spongiform change with neuronal loss and astrocytosis throughout the cerebral cortex, with predominance in the frontal lobe. Similar changes identified in the putamen, thalamus and cerebellar cortex. Immunocytochemistry for PrP showed widespread positivity in a predominantly synaptic pattern. Western blot analysis for PrP^{res} demonstrated a type 1 isoform. (Figure 1)

Diagnostic Criteria: Definite Iatrogenic CJD.

Porcine Graft Case:

A 61-year-old right-landed lady complained of headache, unsteadiness, tremor and nausea. Subsequent investigations revealed a large lesion in the right parietal region. Surgical excision, in November 1988, confirmed a meningioma and a Zenoderm (porcine) graft was used to complete the dura.

134 months later she became unsteady, complained of dull bifrontal headaches and cognitive impairment was apparent. Examination revealed abnormal posturing of the left arm, with pyramidal and cerebellar features. Within 3 weeks she was akinetic, mute, with stimulus-induced myoclonus, and died 3 months after onset.

Investigations:

1 CSF examination normal. 14-3-3 analysis not undertaken.
2 Serial EEGs recordings were carried out, the most recent typical for CJD.
3 Serial MRI brain scan (T2) was normal.
4 Limited sequencing of the *PRNP* gene demonstrated methionine homozygosity at codon 129.
5 Autopsy: Moderate cerebral and cerebellar atrophy. Histopathological examination showed spongiform change with neuronal loss and gliosis particularly in the frontal and temporal cortex. Similar features were identified in

the basal ganglia thalamus and cerebellum. Immunocytochemistry for PrP showed widespread accumulation in a predominantly synaptic pattern. Western blot analysis for PrP^{res} demonstrated a type 1 isoform.

Diagnostic Criteria: Definite Sporadic CJD.