

Familial British dementia with amyloid angiopathy

Early clinical, neuropsychological and imaging findings

Simon Mead,¹ Merle James-Galton,¹ Tamas Revesz,² R. Bala Doshi,³ George Harwood,⁴ E. Lee Pan,⁵ Jorge Ghiso,⁶ Blas Frangione⁶ and Gordon Plant¹

¹Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery, ²Department of Neuropathology, Institute of Neurology, Departments of ³Neuropathology and ⁴Clinical Neurology, King's College Hospital, London, UK, ⁵Department of Clinical Neurology, Groote Schuur Hospital, Cape Town, South Africa and ⁶Department of Pathology, New York University School of Medicine, New York, USA

Correspondence to: Gordon Plant, Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Summary

Familial British dementia with amyloid angiopathy (FBD) is an autosomal dominant condition characterized by a dementia, progressive spastic tetraparesis and cerebellar ataxia with onset in the sixth decade. A point mutation in the *BRI* gene has been shown to be the genetic abnormality. Genealogical work with the large family originally reported by Worster-Drought and updated by Plant has identified nine generations dating back to the late eighteenth century. The pedigree now includes six living affected patients, 35 historical cases, and 52 descendants at risk of having inherited the disease. A common ancestor has been identified between the large pedigree and a case report of 'familial cerebellar ataxia with amyloid angiopathy'. An autopsy case from a separate family with an identical condition is described but no common ancestor with the large pedigree has been

found. Case histories have been researched and updated in each pedigree. Eleven individuals at risk of FBD, aged between 44 and 56 years, agreed to undergo a clinical and neuropsychological assessment along with MRI brain imaging in order to clarify early diagnostic features. Five of the eleven were thought to show early clinical signs of the disease. Neurological examination was abnormal in three, with limb and gait ataxia and mild spastic paraparesis. Three had impaired recognition and recall memory and another had mild impairment of delayed visual recall. All affected individuals had an abnormal MRI of the brain, consisting of deep white-matter hyperintensity (T₂-weighted scans) and lacunar infarcts, but no intracerebral haemorrhage. The corpus callosum was affected particularly, and in one patient it was severely atrophic.

Keywords: dementia; amyloid angiopathy; familial British dementia; BRI; Worster-Drought

Abbreviations: AMIPB = Adult Memory and Information-Processing Battery; CAA = cerebral amyloid angiopathy; FBD = familial British dementia with amyloid angiopathy; HCHWA-D = hereditary cerebral haemorrhage with amyloidosis–Dutch; HCHWA-I = hereditary cerebral haemorrhage with amyloidosis–Icelandic; NART = National Adult Reading Test; PrP = prion protein; WMH = white-matter hyperintensity

Introduction

The familial occurrence of gradually progressive dementia, spastic tetraparesis and ataxia was first reported by Worster-Drought 67 years ago (Worster-Drought *et al.*, 1933). Later, additional histological staining of brain tissue was performed, demonstrating a unique appearance comprising severe cerebral, cerebellar and spinal cord amyloid angiopathy, amyloid plaques and neurofibrillary tangles in the hippocampus (Worster-Drought *et al.*, 1940; McMenemey, 1970). An identical condition was later reported in two siblings (Griffiths

et al., 1982). Plant discovered that the two families were part of the same larger pedigree, by reference to a house physician's family history in the archive case notes of a patient seen at the National Hospital for Neurology in 1924 (Plant *et al.*, 1990). Case reports obtained by Plant from the combined kindred have formed the basis of our understanding of what is now known as familial British dementia (FBD). In 1990 the disease was called 'familial cerebral amyloid angiopathy with non-neuritic plaque formation'. We have recently decided to change

the name of the disease to familial British dementia (Vidal *et al.*, 1999). The reasons for this are two-fold. First, further neuropathological work has indicated that neuritic changes are associated with some of the hippocampal amyloid plaques, although not as prominently as in Alzheimer's disease. Secondly, we wish to emphasize that the disorder is a primary dementia involving neuronal loss, and thus we wished to separate this disorder from the hereditary cerebral haemorrhage with amyloidosis angiopathies (Dutch and Icelandic types, HCHWA-D and HCHWA-I, respectively) and the sporadic cerebral amyloid angiopathy (CAA), in which the amyloid angiopathy is the primary pathology and dementia occurs as a consequence of recurrent haemorrhage related to CAA itself. In both FBD and Alzheimer's disease there is an amyloid angiopathy and consequent ischaemic damage, but in both disorders there is severe hippocampal pathology unrelated to the vascular involvement. The familial amyloid angiopathy most closely related to this condition is known as hereditary ophthalmoto-encephalica (Stromgren, 1981) (for a recent review, see Plant and Esiri, 1997). This disorder has now been shown to be due to a different mutation of the BRI gene (a decamer duplication; Vidal *et al.*, 2000).

The molecular biology of FBD has been characterized recently (Vidal *et al.*, 1999). The subunit of isolated amyloid fibrils in FBD is a 4 kDa insoluble protein called ABri. This protein is the abnormal product of a gene which we have called *BRI* on chromosome 13. In FBD there is a point mutation in the stop codon of *BRI* resulting in a longer than normal 277-residue precursor protein. A 34-amino acid C-terminal fragment of this precursor protein goes on to form the pathogenic amyloid. *BRI* is widely expressed throughout the body but the precise origin of ABri found in the cerebral vessels and parenchyma remains unknown. The enzyme furin has been implicated in the lysis of ABri from its precursor protein (Kim *et al.*, 1999).

There were two aims of the present study: first to expand the large Worster-Drought pedigree, and secondly to describe the early diagnostic clinical, neuropsychological and MRI brain findings. More than 17 members of the Worster-Drought pedigree were known to be at risk of FBD in 1933, but were subsequently lost to follow-up. Consequently, it is likely that the condition has gone unidentified or unreported in the descendants of this one family. A second family with a pathologically indistinguishable condition has been reported recently (Doshi *et al.*, 1996). An autopsy case report of 'familial cerebellar ataxia with amyloid angiopathy' has an identical pathology (Love and Duchon, 1982). A recent study has compared the pathology in these three families (Revesz *et al.*, 1999). These families were the starting point for the genealogical work. At-risk individuals from the resulting extended pedigree allowed an assessment of the early clinical features of the disease.

Methods

Family study

Individuals were recruited to the study from the previously reported large pedigree and the family of a patient reported by

Love and Duchon (Love and Duchon, 1982). This pedigree has been expanded by research with family members, and through the Family Record Centre, London Metropolitan Archives, Surrey Record Office and Probate Centre. Where possible, a subject was approached via prior consultation with his or her general practitioner. A family member was said to be 'at risk' if his or her parent was known to be affected by the condition or if the parent was at risk but died of other causes prior to the expected onset of symptoms. Subjects chosen were in their fifth or sixth decade, prepresentation but not necessarily asymptomatic. Informed written consent was obtained from all participants. The results of the study were open to investigators and individual patients if they so wished following genetic counselling. Ethical approval was obtained from the National Institutes of Health, USA and the Ethics Committee of the National Hospital for Neurology and Neurosurgery, London, UK.

Clinical evaluation

Clinical history-taking, general and neurological examinations were performed in the patients' own homes.

Neuropsychology

Selection of tests was based on expected early deficits in memory from documented cases of FBD. Tests of general intelligence included the Wechsler Adult Intelligence Scale—Revised with verbal IQ prorated from four subtests (Vocabulary, Digit Span, Arithmetic and Similarities) and performance IQ prorated from three subtests (Picture Completion, Picture Arrangement and Block Design) (Wechsler, 1986) and the Advanced Progressive Matrices Test Set 1 (Raven, 1960). The National Adult Reading Test (NART) (Nelson and Willison, 1992) was used to provide an estimate of premorbid IQ. Tests of memory included Warrington's Recognition Memory Test for words and faces (Warrington, 1984), Visual Design and Story Recall Memory Test from the Adult Memory and Information-Processing Battery (AMIPB) (Coughlan, 1985) and the Paired Associate Learning Test (Warrington, 1996). Other tests included two of frontal lobe function—the Wisconsin Card Sorting Test (Nelson, 1976) and the Verbal Fluency Test—and a naming test—the Graded Naming Test (McKenna and Warrington, 1983). Perceptual tasks were included from the Visual Object and Space Perception Battery (Warrington and James, 1991).

These tests took a total of ~2 h to complete, and were performed by S.M. in the subject's home on the same day as the clinical assessment.

Imaging

MRI was performed on eleven subjects. Seven scans were conducted at the Queen's Square Imaging Centre, one at the Cabrini Medical Centre, Melbourne, one at the Hobart Hospital, Tasmania and two at Auckland Imaging Centre,

Auckland Hospital, New Zealand. All units were 1.5-T. The images included sagittal T₁- and T₂-weighted, axial T₂-weighted and FLAIR (fluid-attenuated inversion recovery) sequences.

Diagnostic criteria

FBD was excluded in family members older than 60 years who were symptom-free. In those younger than 60, a diagnosis of FBD was made in at-risk individuals with one of the following which could not otherwise be explained: (i) symptoms or signs of spastic paraparesis or ataxia; (ii) clear-cut memory impairment on neuropsychological testing; and (iii) deep white-matter high signal on T₂-weighted MRI of an extent or location that would not be expected in normal individuals of the same age.

Results

Family study

The Worster-Drought Pedigree (Fig. 1) has been enlarged from 188 to 372 individuals. A common ancestor was

identified between the Worster-Drought pedigree and a pedigree provided by the descendants of T, the autopsy case of ‘familial cerebellar ataxia with amyloid angiopathy’ (Love and Duchen, 1982). This couple (case A), born around 1780, had 11 children. The youngest son (1819–1875), died in the Workhouse Infirmary, Lambeth, and descends to the family described by Love and Duchen. The second daughter (1808–1862) died at the Union Workhouse, Battersea, the death certificate stating only ‘paralysis’. The second of this daughter’s nine children (1830–1884), who died at home of ‘paralysis and exhaustion from bed sores’, descends to the large Worster-Drought pedigree. No descendants of the other 22 at-risk individuals from the generations alive in the early nineteenth century are known.

A second affected family, reported in abstract form (Doshi *et al.*, 1996), has been studied in detail in an attempt to find a common ancestor with the Worster-Drought pedigree (Fig. 2). Only two siblings are affected in this family (2A and 2B). To try to demonstrate a common ancestor, the family was traced back to a generation born in the 1840s, as many of the family had died prematurely. The two members of the earliest generation identified were not affected and

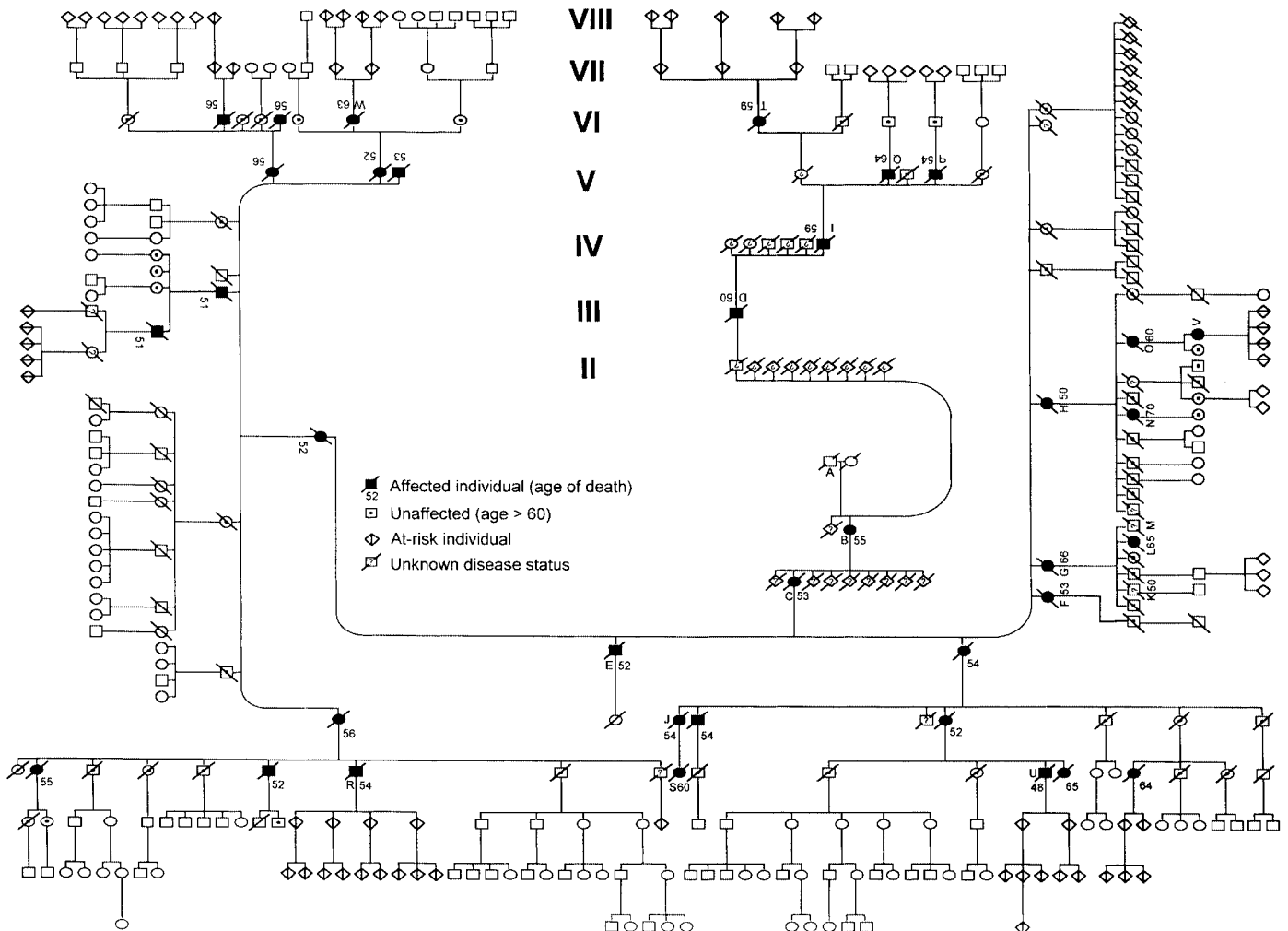


Fig. 1 Familial British dementia (Worster-Drought pedigree).

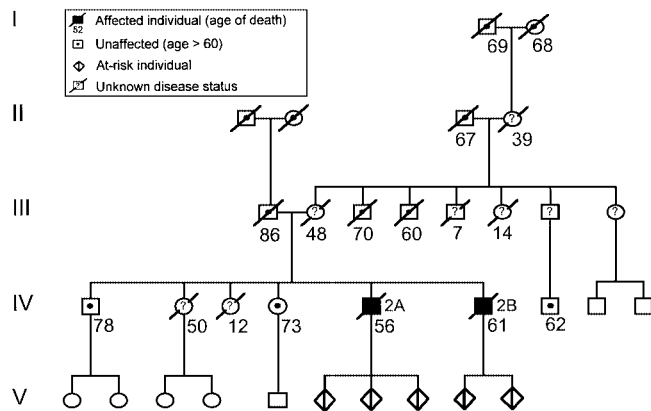


Fig. 2 Familial British dementia (second pedigree).

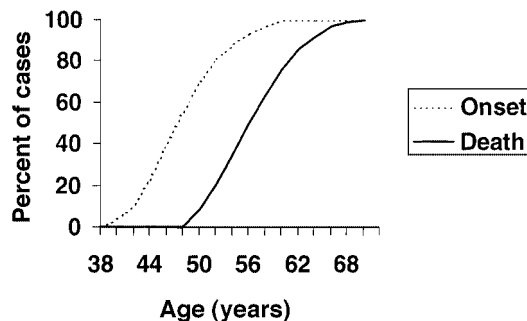


Fig. 3 Survival curve for familial British dementia with amyloid angiopathy ($n = 37$ for each curve, but information on onset and death was not available in every case).

died aged 68 and 69 years. It remains possible that the families are related through non-paternity.

Altogether, an additional 13 historical affected individuals have been identified. The conclusions from the previous work remain unchanged. The median age of onset 48 years (range 40–60) and the median age of death 56 years (range 48–70) are illustrated in a survival curve (Fig. 3). The mean length of illness is 9 years. The mode of inheritance is autosomal dominant and penetrance is complete by age 60 years.

The clinical features of the illness are presented in Fig. 4. In all cases, dementia and spasticity are the main clinical features. Cerebellar ataxia is very common. Information from living relatives has provided a more detailed history of the important autopsy case (T) than that available to Love and Duchon. It is clear from additional history that progressive memory impairment was a more important clinical feature of this case than was suggested in the original report (see Appendix).

There are three definite cases and one possible case of intracranial haemorrhage. Further history available from the two sons of case U, indicating that he had a progressive loss of memory and gait problems over the 2 years preceding his death, suggests that he was likely to have been affected by FBD. He died suddenly, and an autopsy showed a ruptured berry aneurysm, but the brain was not examined in detail. It remains possible that this haemorrhage was incidental. A daughter reported that case O was admitted to Atkinson-

Morley Hospital with a 'brain haemorrhage' in her sixth decade. She survived this but remained impaired, with progressive memory loss, gait problems, agoraphobia and headaches. One of her daughters has subsequently developed the disease. Case F died of a subdural haematoma in Banstead Asylum. Case 2B died of a large intracerebral haemorrhage; the post-mortem findings are described below. The stroke-like features that occurred in about a quarter of the historical case reports may represent small intracerebral haemorrhages. None of the five early cases seen described similar acute neurological episodes, and so the precise nature of these events remains uncertain.

Epilepsy may also be added to the clinical features of the disease. Myoclonus has previously been described in one case (Plant *et al.*, 1990). Generalized tonic-clonic seizures have been well described by living witnesses of historical case R. Case K, an at-risk family member, died of 'complications of epilepsy' aged 50 years, although it cannot be confirmed that he was affected as the coroner's post-mortem report has been destroyed and the subject had no children.

Headache and minor psychological problems such as mild depression, anxiety and sleep disturbances were found in most of the early case histories and some of the historical cases.

Pathology of case 2B

General post-mortem

The cause of the death was 'subarachnoid and intracerebral haemorrhage'. The brain was fixed in 10% buffered formalin and kept for detailed neuropathological examination.

Neuropathological examination

Macroscopical findings. The brain weighed 1380 g. The formalin-fixed brain showed a massive right intracerebral haematoma in the region of the anterior putamen and globus pallidus, which reached the right frontal horn and the basal surface of the brain (Fig. 5). The cerebral cortex appeared macroscopically normal, but the hemispheric white matter was extensively soft, grey and granular. The spinal cord was not available for neuropathological examination.

Histological examination. Tissue blocks from all major anatomical areas were processed in paraffin wax and tissue sections were stained with haematoxylin and eosin, luxol fast blue-cresyl violet, periodic acid-Schiff, Congo red and Bielschowsky's as well as Gallyas silver impregnation methods. In addition, immunohistochemistry was also carried out with antibodies to glial fibrillary acidic protein (GFAP) (Dako, UK, 1:400), tau (AO24, Dako, 1:150; AT8, Innogenetics, 1:200; AT180, Innogenetics, 1:50; AT270, Innogenetics, 1:500; TP70, courtesy of Professor B. H. Anderton, 1:2000; TP007, courtesy of Professor B. H. Anderton, 1:1000), ubiquitin (Dako, 1:150), A β -peptide

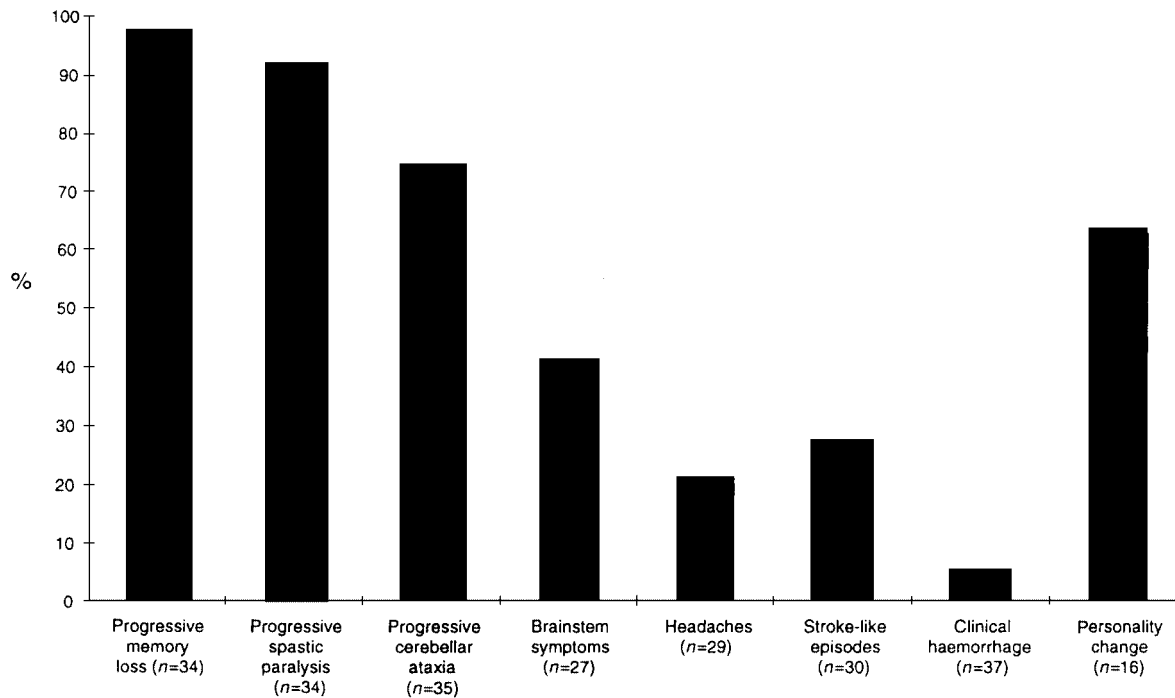


Fig. 4 Symptoms of familial British dementia with amyloid angiopathy, expressed as the percentage of individuals in whom the symptom or sign is known about (*n*).

(6F/3D, Dako, 1 : 60) and prion protein (PrP) (3F4, NYC Institute of Basic Research USA, 1 : 2000).

The neuronal cell population of the cerebral neocortex was, in general, well preserved throughout, although there were occasional small cortical scars. On the other hand, there was severe myelin pallor associated with axonal loss and gliosis in the hemispheric white matter, and these changes, in combination with the white-matter lacunae that were also present, were similar to those seen in Binswanger’s disease (Fig. 6A). In all anatomical areas there was deposition of periodic acid–Schiff- and Congo red-positive material into the leptomenigeal, cerebral, brainstem and cerebellar arteries and arterioles. It was also noted that the blood vessels of both the grey and the white matter were affected throughout the brain. The amyloid nature of the Congo red-positive deposits was confirmed by the characteristic apple-green birefringence that was noted in polarized light. The blood vessels affected often showed degenerative phenomena associated with amyloid angiopathy (Fig. 6B). Occasionally, affected blood vessels were found to be surrounded by chronic, inflammatory cell infiltrate.

There were numerous amyloid plaques of various morphological types, which were found most frequently in the hippocampal formation and cerebellum (Fig. 6C). The CA1 subregion of the hippocampus and also the prosubiculum were rich in relatively small (up to 30 µm), often star-shaped, amyloid plaques, some of which were also surrounded by abnormal neurites that were best demonstrated with the Gallyas silver impregnation method and tau immunohistochemistry. The amyloid plaques were less numerous in

CA2 than in CA1, whereas those characteristic of CA3 and CA4 had, in general, different morphological appearances. The maximum size of the CA3 and CA4 large plaques, which were relatively rarely seen in CA1, was ~150 µm, and these were occasionally seen to be associated with blood vessels. These plaques had a looser, filamentous structure and some contained a dense central core. The periphery of such plaques was faintly positive and their central core was strongly positive for periodic acid–Schiff and Congo red. Frequent astrocytes surrounded such plaques, and a rich meshwork of delicate, GFAP-positive astrocytic processes was noted within them. The large plaques were either negative on tau immunohistochemistry and Gallyas silver impregnation (‘non-neuritic’ plaques) or contained tau- and silver-positive filamentous material (Fig. 6D–F). Such large plaques were fewer in CA1 and the subiculum. It was a characteristic feature that there was a tendency for the vascular amyloid to spread into the surrounding parenchyma in a plaque-like fashion (perivascular plaques). The perivascular amyloid deposits often had a loose fibrillary texture and occasionally contained a dense central core. Amyloid plaques, mainly of the perivascular type, were numerous in the cerebellum, where they were seen in the cortex and white matter, and also in the dentate nucleus. The molecular layer of the cerebellar cortex showed severe isomorphic gliosis and there was loss of Purkinje cells and granule cells. Both the vascular and the plaque amyloid were negative on immunohistochemical staining for Aβ peptide and PrP.

Tau- and silver-positive neurofibrillary tangles were found in large numbers in the different subregions of the cornu

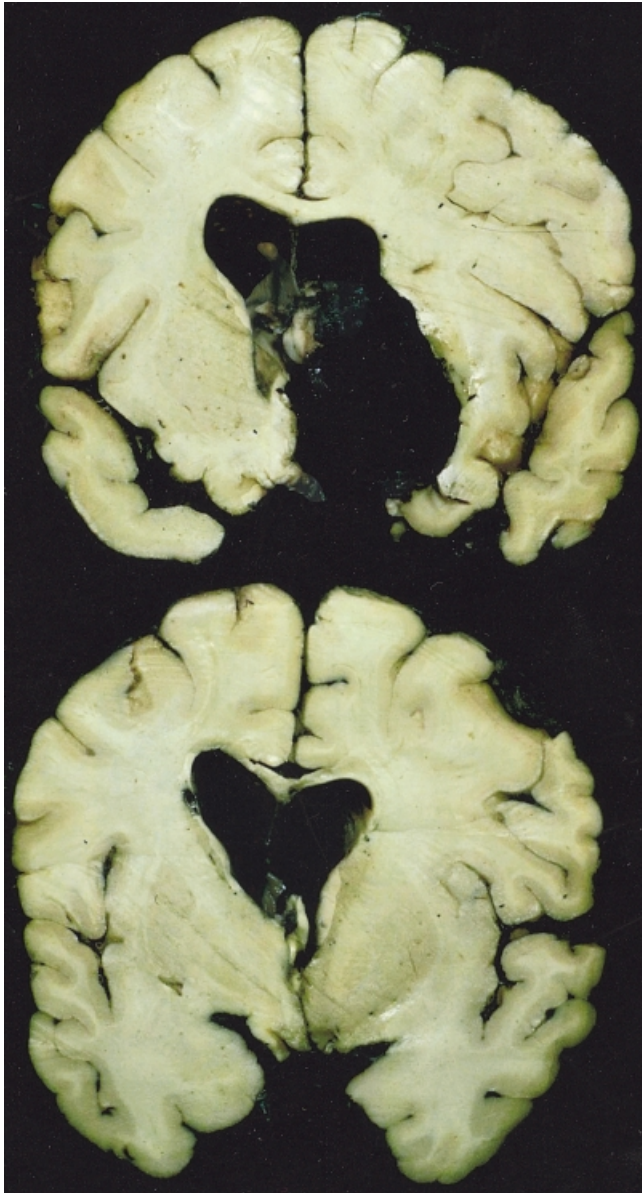


Fig. 5 Coronal brain slices showing extensive haemorrhage in the region of the right anterior basal ganglia. The hemispheric white matter has a granular appearance in several areas (Case 2B).

Ammonis (Fig. 6D–F) and the subiculum, entorhinal and transentorhinal cortices. Occasional neurofibrillary tangles were also noted in the cerebral neocortex, the locus coeruleus and the nucleus centralis superior of the pons. There were also frequent neuropil threads, best highlighted by Gallyas silver impregnation and tau immunohistochemistry, in the CA1 subregion of the hippocampus. The hippocampal neurofibrillary tangles, abnormal neurites and neuropil threads were shown by all phosphorylation-dependent and -independent antibodies used for the examination of this case.

Psychology

Neuropsychological assessment was performed on 12 at-risk subjects, aged 44–56 years, in order to identify early impairments in FBD. The results are detailed in Table 1. Two subjects had marked impairment of recall and recognition memory but there was no evidence of a decline in general intelligence, naming problems, frontal lobe dysfunction or perception. One had impaired recognition memory on Warrington's Recognition Memory Test for words, despite superior general intelligence. A further affected subject had equivocal neuropsychology profile, suggestive of early decline in recall memory, but preserved general intelligence, naming and frontal lobe function. The profile of one affected subject was normal. When the affected group was taken as a whole and compared with unaffected individuals from the same family, the most consistent impairment was in delayed-recall memory tasks. A single unaffected subject performed poorly on the story recall test, a test which is vulnerable to attention problems.

MRI

MRI was performed on 11 at-risk subjects. Abnormalities in all five affected cases consisted of multiple white-matter lesions that were bright on T₂-weighted scans and hypointense on T₁-weighted scans (white-matter hyperintensities, WMHs). There was no evidence of haemorrhage. The WMHs were distributed throughout the cerebral white matter. The area around the occipital pole of the lateral ventricles was affected particularly. Where scans were more severely abnormal, the lesions were confluent throughout the frontal and occipitoparietal white matter. In two subjects there was clear-cut lacunar infarction of the cerebral deep white matter. The corpus callosum was affected by punched-out lesions on T₁-weighted scans and atrophy.

Results of MRI in advanced cases are also shown for comparison: Two MRI scans obtained from Case V in 1991 and 1998, also cases W from the Worster-Drought pedigree and case 2B from the second pedigree. These show a dramatic, confluent white-matter hyperintensity involving the periventricular areas of the occipital and frontal lobes. There are lesions in the corpus callosum and lacunar infarcts.

Three of the MRI scans from the unaffected group were completely normal. In two unaffected subjects (aged >50 years) a few small peripheral cerebral white-matter hyperintensities were noted on T₂-weighted images and were considered to be within the normal range for the subjects' ages. In one subject (aged >50 years), WMHs were present to a degree out of keeping with the subject's age. They did not involve the corpus callosum. This subject was neurologically and neuropsychologically normal and had a history of hypertension. On balance, the WMHs were thought to be due to hypertension rather than FBD.

Discussion

The study has extended the Worster-Drought pedigree (Fig. 1), by incorporating a family published as having

Table 1 Results of neuropsychology in early-affected and control groups

	NART	VIQ	PIQ	RMT words	RMT faces	Visual design recall		Story recall		Paired associate learning trial 2
						Immediate	Delayed	Immediate	Delayed	
Early-affected cases										
1	110	101	118	–	–	–	–	–	–	–
2	117	104	111	–	–	–	●●	–	●	●●
3	110	118	140	●	–	–	●	●	●	–
4	124	129	125	●	●●	●●	●●	●●	●●	●●
5	120	104	129	–	–	–	–	–	●	●
Unaffected family										
Control	127	120	139	–	–	–	–	–	–	–
Control	108	89	111	–	–	–	–	●●	●●	–
Control	112	103	121	–	–	–	–	–	–	–
Control	115	106	116	–	–	–	–	–	–	–
Control	117	121	140	–	–	–	–	–	–	–
Control	116	119	118	–	–	–	–	–	–	–
Control	118	104	122	–	–	–	–	–	–	–

●● = definitely abnormal finding (<10th percentile of age-matched normal distribution); ● = abnormal finding in context with overall performance (10th–25th percentile of age-matched normal distribution). Tests of naming, frontal lobe function, general intelligence and perceptual tasks are not included as they were normal in all subjects tested.

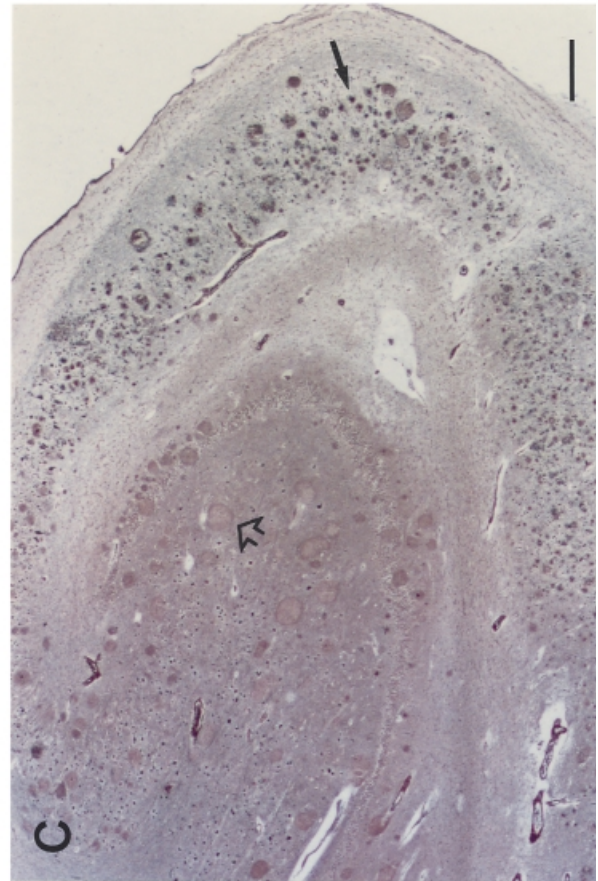
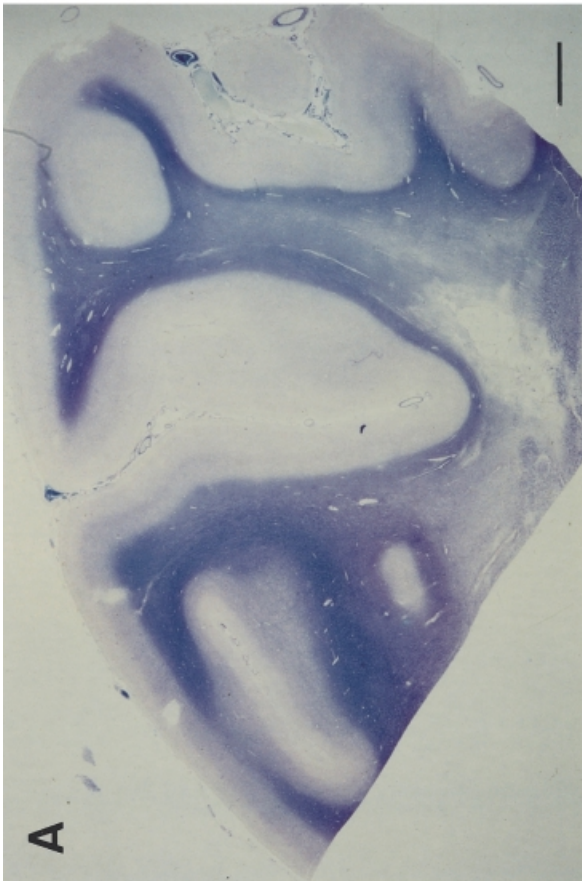
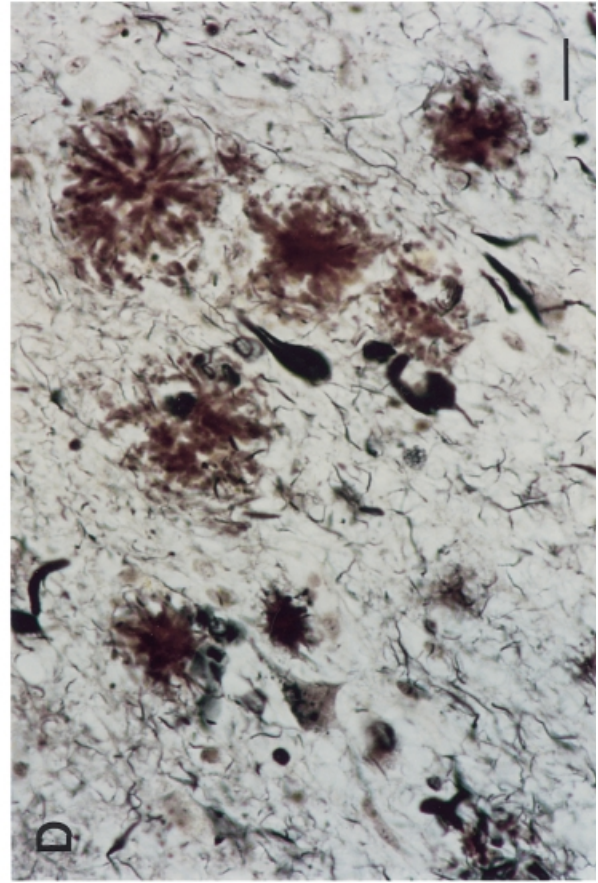
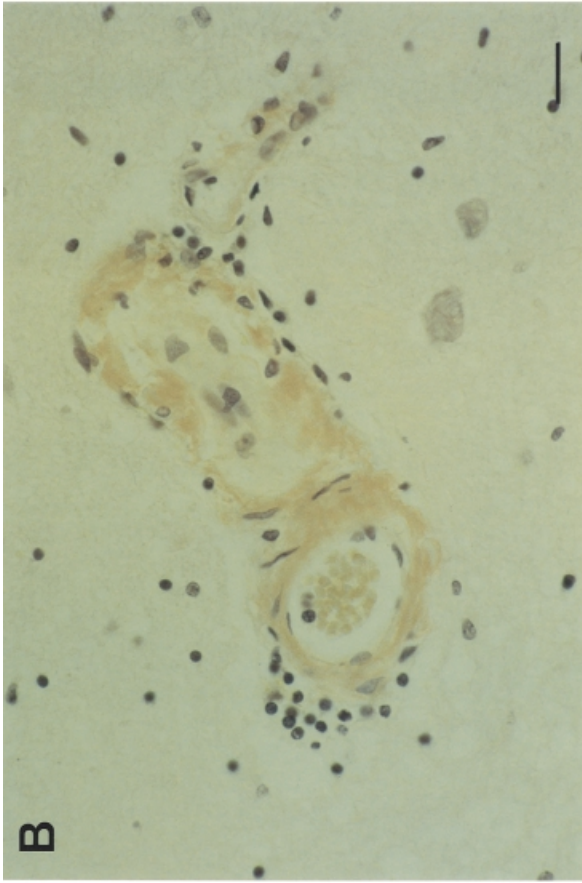
familial cerebellar ataxia. A second family with an identical condition has been described, but no common ancestor has been found with the large pedigree. The characteristic MRI abnormality at an early stage of the disease consists of multiple WMHs in the cerebral white matter. These are widespread but involve particularly the white matter around the frontal and occipital horns of the lateral ventricles. Infarction and atrophy of the corpus callosum was also seen. Isolated memory loss is the most consistent neuropsychological finding at an early stage. As the disease progresses, spastic paraplegia and cerebellar ataxia are very common findings. Any of these three signs may be dominant at presentation. Brainstem signs and stroke-like episodes are seen occasionally. Headaches, personality change, psychological problems and sleep disturbance occur early on. Uncommon clinical findings include myoclonic or generalized tonic–clonic seizures and clinically significant intracerebral haemorrhage. All five subjects from the at-risk group who were thought to be affected had abnormal MRI images. This was corroborated by neurological signs in three and abnormal memory in four. One subject was said to be affected solely by an MRI abnormality similar to those of the other four affected subjects.

The second pedigree relates to the same disease as the Worster-Drought pedigree. The clinical features of the two cases from the new family presented are strikingly similar to those observed in the larger family. The neuropathological findings in Case 3 were also strikingly similar to those in all cases autopsied in the Worster-Drought pedigree. These included severe amyloid angiopathy, often with perivascular plaques involving all areas of the central nervous system, hippocampal amyloid plaques with characteristic morphological appearances, and hippocampal neurofibrillary tangles. The involvement of the cerebellum was also

prominent and characteristic. The hippocampus and cerebellum were pathologically the most severely affected areas. In these two anatomical regions, in addition to the spinal cord, there was a high level of expression of *BRI* compared with other brain regions (Vidal *et al.*, 1999). An important question remains whether the ABri seen in these areas was produced locally or of vascular origin, as this may have implications for treatment strategies.

Both the vascular and plaque amyloid, as in a previously reported case from the original Worster-Drought family, was found to be negative on Aβ and PrP immunohistochemistry (Ghisso *et al.*, 1995). Although in FBD a population of the hippocampal amyloid plaques is non-neuritic (Plant *et al.*, 1990), in a recent study of three cases with FBD, including the current cases, it was possible to demonstrate by using a panel of phosphorylation-dependent and -independent anti-tau antibodies that many of the hippocampal amyloid plaques, similar to the neuritic plaques of Alzheimer’s disease, are associated with abnormal, dystrophic neurites, and that the neurofibrillary tangles are immunohistochemically similar to those found in Alzheimer’s disease. It was also shown by electron microscopic examination of hippocampal neurofibrillary tangles in one case studied ultrastructurally that these tangles are composed of paired helical filaments in FBD (Revesz *et al.*, 1999). The finding in this study of a close association of neuronal cytoskeletal abnormalities with amyloid plaques supports the notion that the recently identified amyloidogenic peptide, ABri (Vidal *et al.*, 1999), is neurotoxic and is of primary importance in the initiation of neurodegeneration in FBD.

Memory loss was a consistent finding in the early cases. In FBD the white-matter lesions are not severe enough to explain the memory deficits satisfactorily. Also, there were no frontal or executive abnormalities such as might be



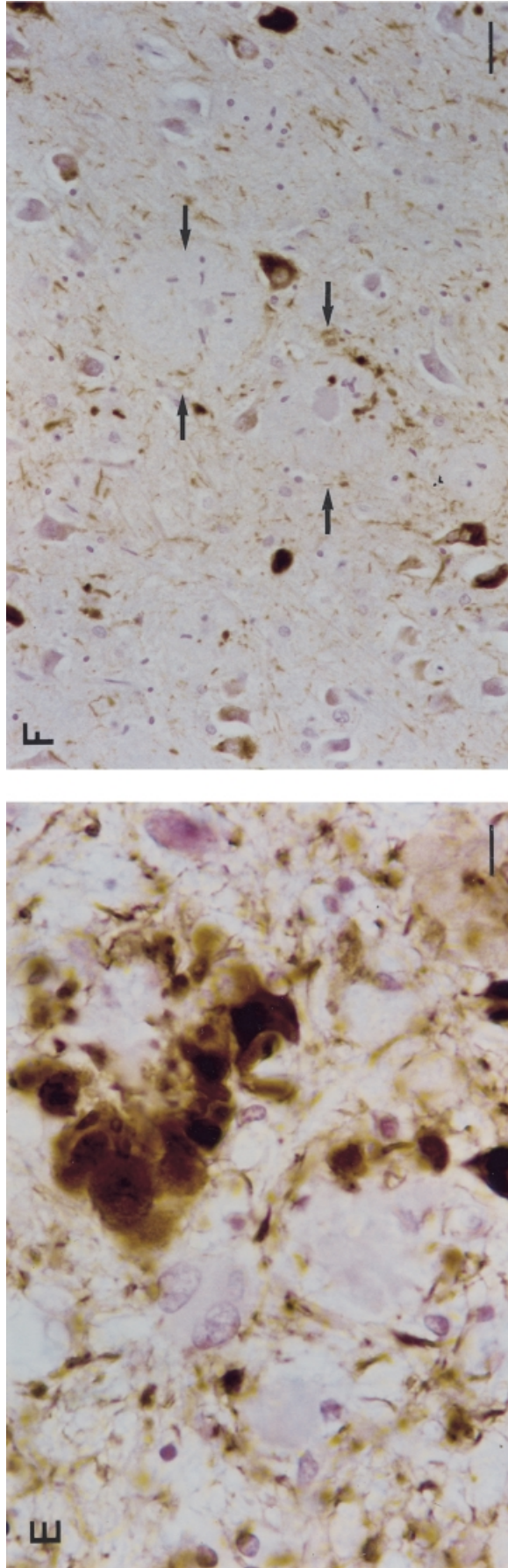


Fig. 6 (A) Photomicrograph showing myelin pallor and lacunar infarct. Luxol fast blue–cresyl violet. Scale bar = 2.5 mm. (B) Example of severe amyloid angiopathy in a small cortical artery. Congo red preparation. Scale bar = 33 μ m. (C) All regions of the hippocampus show numerous argyrophilic amyloid plaques. Open arrow points to a large plaque in CA4; filled arrow points to a small amyloid plaque in CA1. Bielschowsky's silver impregnation. Scale bar = 0.5 mm. (D) Photomicrograph showing argyrophilic neurofibrillary tangles, neuropil threads and small amyloid plaques in CA1. Bielschowsky's silver impregnation. Scale bar = 20 μ m. (E) Distended, tau-positive neurites are seen around some of the small plaques in CA1. AT180 immunohistochemistry. Scale bar = 10 μ m. (F) Example of a large amyloid plaque devoid of neurites in CA4 (upper two arrows) and another with an associated tau-positive neuritic component (lower two arrows). AT180 immunohistochemistry. Scale bar = 45 μ m (Case 2B).

expected if the white-matter disease was contributing to the neuropsychological findings. Therefore, it is likely that memory loss results largely from the loss of hippocampal neurons.

At autopsy there are areas of axonal loss, gliosis and partial demyelination in the deep white matter, the abnormality being most severe in the parietal and occipital lobes. This leads to increased water content in the area involved and hence a high signal level on T₂-weighted scans. The corpus callosum was severely affected at autopsy and on imaging. It is likely that the pathology is a result of partial infarction or chronic hypoperfusion caused by amyloid angiopathy in small vessels penetrating to the deep white matter. In FBD the corpus callosum and occipital lobe white matter appear to be affected early, and this may represent a selective vulnerability of the microvasculature of these areas. The corpus callosum has a blood supply consisting of short arterioles (length <8 mm, diameter <100 µm) originating from three separate arteries. This tends to make the corpus callosum resistant to large-vessel vascular disease, as atherosclerosis is regional and affects arteries rather than arterioles. Blood vessels of the size of those supplying the corpus callosum are characteristically obliterated by amyloid in FBD.

In HCHWA-D and HCHWA-I, the phenotype is determined largely by clinically significant intracerebral haemorrhage (Haan *et al.*, 1990). The rarity of significant haemorrhage in FBD probably relates to differences in vessel pathology. In HCHWA-D, fresh haemorrhage is often seen in the meninges, and the meningocortical arteries are affected by amyloid-beta deposits, leading to aneurysmal dilatation of the vessel wall, thinning and fibrinoid necrosis. Although similar aneurysmal changes and fibrinoid necrosis are seen in FBD, these are less severe and the vessels affected are not usually more than 150 µm in diameter.

Very few known causes of dementia could be confused with FBD, with its clinical picture of progressive dementia, spasticity and ataxia in the fifth or sixth decade, a dominant family history and WMH on MRI. To date, however, affected members of these two pedigrees have rarely been given a consistent diagnosis in life. The following diagnoses may be offered in FBD: Gerstmann-Sträussler-Scheinker syndrome; primary progressive multiple sclerosis; spinocerebellar ataxia with cognitive impairment; atypical early-onset Alzheimer's disease; OPCA (olivo-ponto-cerebellar atrophy) and Binswanger's disease due to hypertension; and CADASIL (cerebral autosomal dominant syndrome with stroke-like episodes). A genetic test, consisting of a polymerase chain reaction and restriction fragment digestion, allows simple and accurate diagnosis (Vidal *et al.*, 1999) in these families. However, phenotypic variants resulting from different mutations of the same gene may be identified in future.

FBD should be classified with other inherited single-gene disorders that are characterized by a severe cerebral amyloid angiopathy. This list includes HCHWA-D (APP, amyloid precursor protein), HCHWA-I (cystatin-c), oculoleptomeningeal amyloidosis (transthyretin) and the Danish

familial amyloid angiopathy known as hereditary ophthalmoto-encephalica (Stromgren, 1981; Plant and Esiri, 1997; Vidal *et al.*, 2000). Amyloid deposition and neurofibrillary tangles may also be seen with premature stop codon mutation in the *Prp* gene. Compared with FBD, the two most similar conditions pathologically are some cases of familial Alzheimer's disease (Corsellis and Brierley, 1954; Crook *et al.*, 1998) and hereditary ophthalmoto-encephalica.

Deposition of ABri is the first step along an 'amyloid cascade' that leads to neurofibrillary tangle formation and neurodegeneration. FBD may be used as a model that could shed light on the origin of Alzheimer's disease by probing the mechanism by which amyloid deposition leads to cytoskeleton dysfunction and neurodegeneration (Hardy *et al.*, 1998). In this regard, FBD appears to be strikingly similar to the presenilin-1 exon 9 deletion, in which the phenotype includes a predominant spastic paraparesis and pathologically there are large 'cotton wool' amyloid plaques (Crook *et al.*, 1998). Any uncharacterized familial amyloid angiopathies should be screened for mutations in the *BRI* gene.

Acknowledgments

This work was supported, in part, by NIH grants AG10953, AG05891 and AG08721.

References

- Corsellis JAN, Brierley JB. An unusual type of presenile dementia. *Brain* 1954; 77: 571-87.
- Coughlan AK. The Adult Memory and Information-Processing Battery (AMIPB). Leeds (UK): Psychology Department, St James University Hospital; 1985.
- Crook R, Verkkoniemi A, Perez-Tur J, Mehta N, Baker M, Houlden H, et al. A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. *Nat Med* 1998; 4: 452-5.
- Doshi RB, Revesz T, Harwood G, Plant G. Familial cerebral amyloid angiopathy (British type) with non-neuritic plaque formation is not restricted to a single family [abstract]. *Neuropathol Appl Neurobiol* 1996; 22: 163-3.
- Ghiso J, Plant GT, Revesz T, Wisniewski T, Frangione B. Familial cerebral amyloid angiopathy (British type) with nonneuritic amyloid plaque formation may be due to a novel amyloid protein [letter]. *J Neurol Sci* 1995; 129: 74-5.
- Griffiths RA, Mortimer TF, Oppenheimer DR, Spalding JM. Congophilic angiopathy of the brain: a clinical and pathological report on two siblings. *J Neurol Neurosurg Psychiatry* 45; 1982: 396-408.
- Haan J, Algra PR, Roos RA. Hereditary cerebral hemorrhage with amyloidosis-Dutch type. *Arch Neurol* 1990; 47: 649-53.
- Hardy J, Duff K, Hardy KG, Perez-Tur J, Hutton M. Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau. *Nat Neurosci*; 1998; 1: 355-8.

Kim SH, Wang R, Gordon DJ, Bass J, Steiner DF, Lynn DG, et al. Furin mediates enhanced production of fibrillogenic ABri peptides in familial British dementia. *Nat Neurosci* 1999; 2: 984–8.

Love S, Duchon LW. Familial cerebellar ataxia with cerebrovascular amyloid. *J Neurol Neurosurg Psychiatry* 1982; 45: 271–3.

McKenna P, Warrington EK. Graded Naming Test. Windsor (UK): NFER-Nelson; 1983.

McMenemey WH. Discussion. In: Wolstenholme GEW, O'Connor M, editors. Alzheimer's disease and related conditions: a CIBA Foundation Symposium. London: J. and A. Churchill; 1970. p. 132–3.

Nelson HE. A modified card sorting test sensitive to frontal lobe defects. *Cortex* 1976; 12: 313–24.

Nelson HE, Willison J. National Adult Reading Test (NART); 1992.

Plant GT, Esiri MM. The familial cerebral amyloid angiopathies. In: Esiri MM, Morris JH, editors. The neuropathology of dementia. Cambridge: Cambridge University Press; 1997. p. 260–76.

Plant GT, Revesz T, Barnard RO, Harding AE, Gautier-Smith PC. Familial cerebral amyloid angiopathy with nonneuritic amyloid plaque formation. *Brain* 1990; 113: 721–47.

Raven JC. Advanced Progressive Matrices. London: H. K. Lewis; 1960.

Revesz T, Holton JL, Doshi B, Anderton BH, Scaravilli F, Plant GT. Cytoskeletal pathology in familial cerebral amyloid angiopathy (British type) with non-neuritic amyloid plaque formation. *Acta Neuropathol (Berl)* 1999; 97: 170–6.

Stromgren E. Heredopathia ophthalmo-oto-encephalica. In: Vinken

PJ, Bruyn GW, editors. Handbook of clinical neurology, Vol. 42. Amsterdam: North-Holland; 1981. p. 150–2.

Vidal R, Frangione B, Rostagno A, Mead S, Revesz T, Plant G, et al. A stop codon in the BRI gene associated with familial British dementia. *Nature* 1999; 399: 776–81.

Vidal R, Revesz T, Rostagno A, Kim E, Holton JL et al. A decamer duplication in the 3' region of the BR1 gene originates a new amyloid peptide that is associated with dementia in a Danish kindred. *Proc Natl Acad Sci USA* 2000; 97: in press.

Warrington EK. Recognition Memory Test Manual. Windsor (UK): NFER-Nelson; 1984.

Warrington EK, James M. The Visual Object and Space Perception Battery. Bury St Edmunds (UK): Thames Valley Test Company; 1991.

Warrington EK. The Camden Memory Tests. The Paired Associate Learning Test. Hove (UK): Psychology Press; 1996.

Wechsler DA. The Wechsler Adult Intelligence Scale—Revised. San Antonio (TX): Psychological Corporation; 1986.

Worster-Drought C, Hill TR, McMenemey WH. Familial presenile dementia with spastic paralysis. *J Neurol Psychopathol*; 1933; 14: 27–34.

Worster-Drought C, Greenfield JG, McMenemey WH. A form of familial presenile dementia with spastic paralysis. *Brain* 1940; 63: 237–53.

Received July 7, 1999. Revised November 4, 1999.
Accepted November 30, 1999

Appendix

Early-affected cases from the Worster-Drought pedigree (Fig. 1)

Case 1

A history of sleep disturbance, headaches and mild depression. General and neurological examination was normal.

Case 2

History of memory loss, brief episodes of sudden onset expressive dysphasia, dysarthria. There were vascular risk factors. Limb examination showed a mild degree of increase in resting tone of the legs. Power was normal. Reflexes were brisk in the lower limb, more so on the left, with bilateral adductor reflexes and non-sustained clonus at the ankle. The right plantar was downgoing but the left equivocal. Co-ordination testing was abnormal, with mild past-pointing, dysidiadochokinesia and heel–shin ataxia worse on the left.

Case 3

History of intermittent dull frontal headaches. General examination was normal. Limb examination showed slightly increased tone in both legs. Power was normal. Limb reflexes were brisker in the legs than the arms. Both plantars were flexor. He was unable

to tandem-walk, and there was evidence of mild symmetrical cerebellar ataxia.

Case 4

History of progressive memory loss. No evidence of spasticity or ataxia.

Case 5

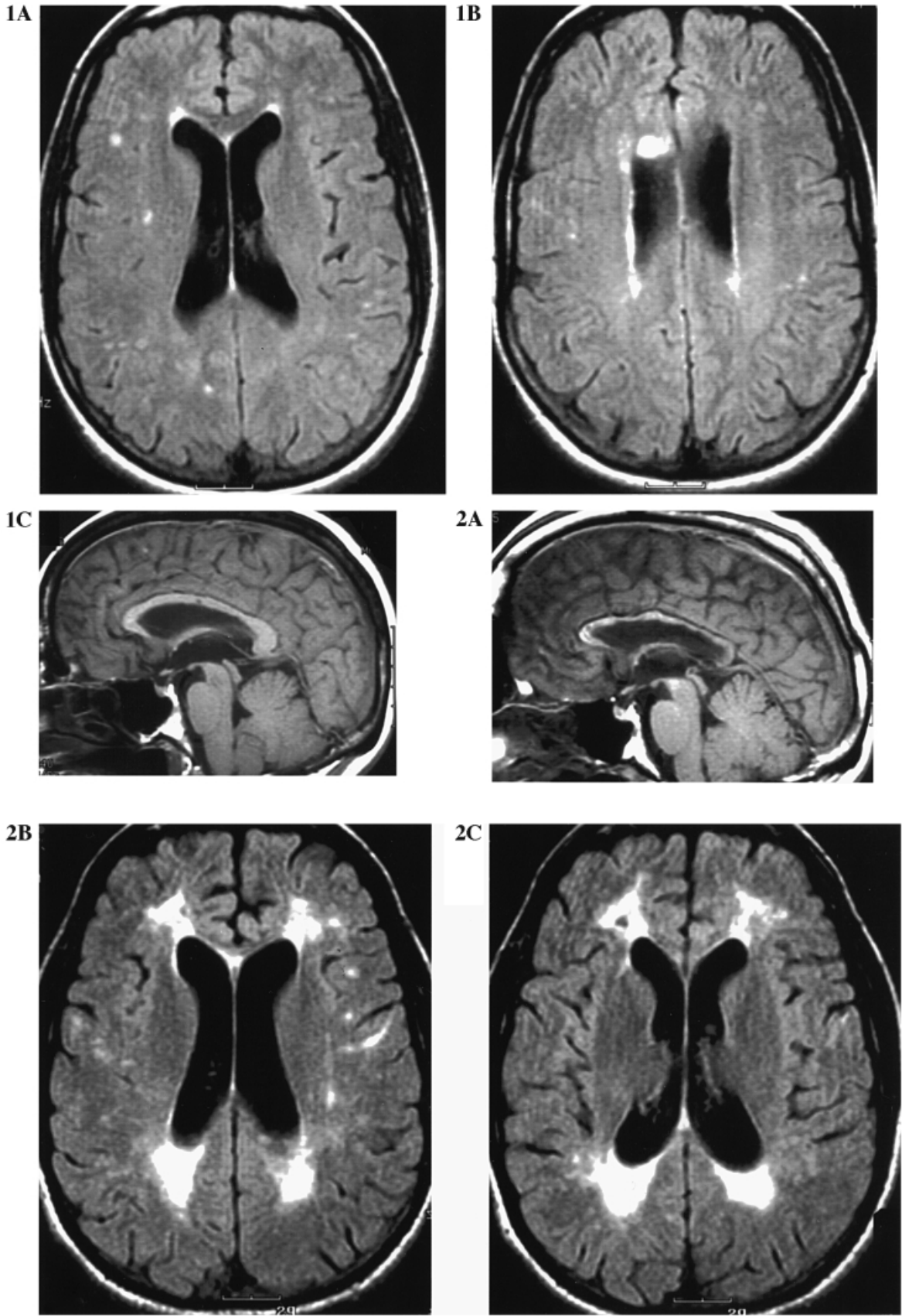
History of gradually worsening muscular aches. General examination was normal. Limb examination showed increased tone of the lower limbs of a spastic type but no catch. Power was normal. Reflexes were slightly brisk and were symmetrical, with downgoing plantars. Co-ordination and sensation were normal.

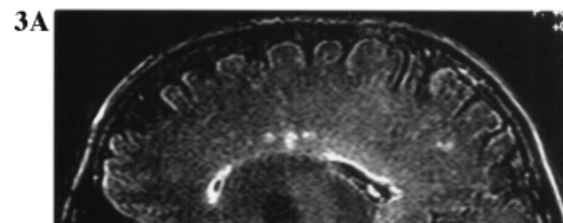
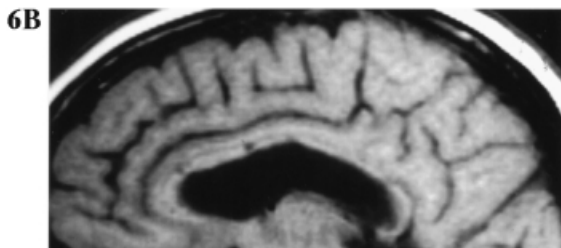
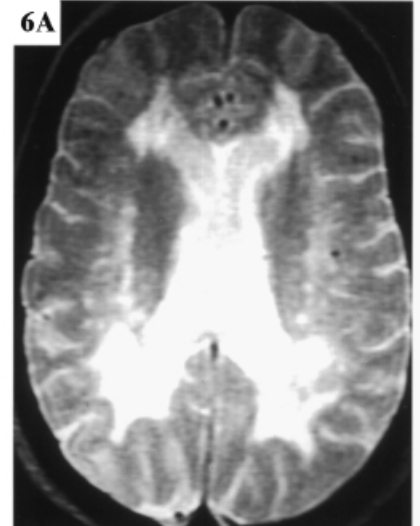
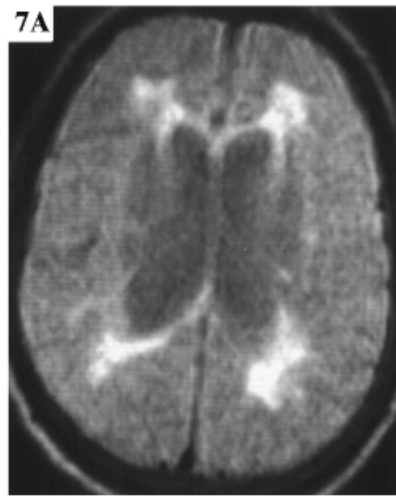
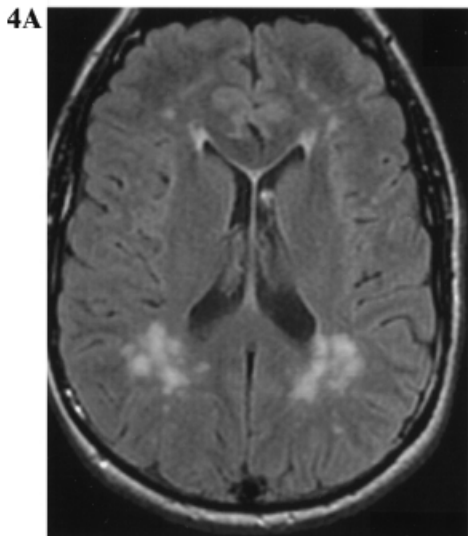
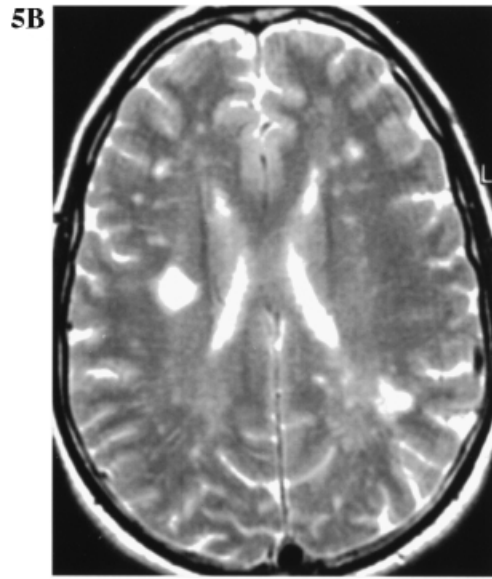
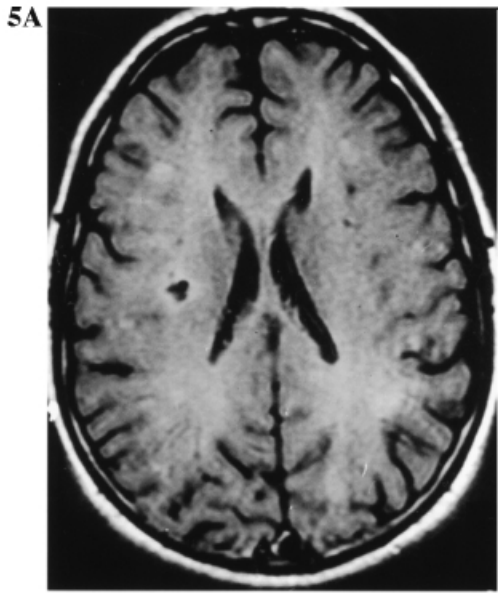
Historical affected cases from the Worster-Drought pedigree (Fig. 1)

Only the newly identified historical cases and additional history are included here. See paper by Plant and colleagues (Plant *et al.*, 1990) for details of other cases that have not been updated.

Case A

It is not known if either of this married couple suffered from FBD. They married in the late 18th century and had 11 children.





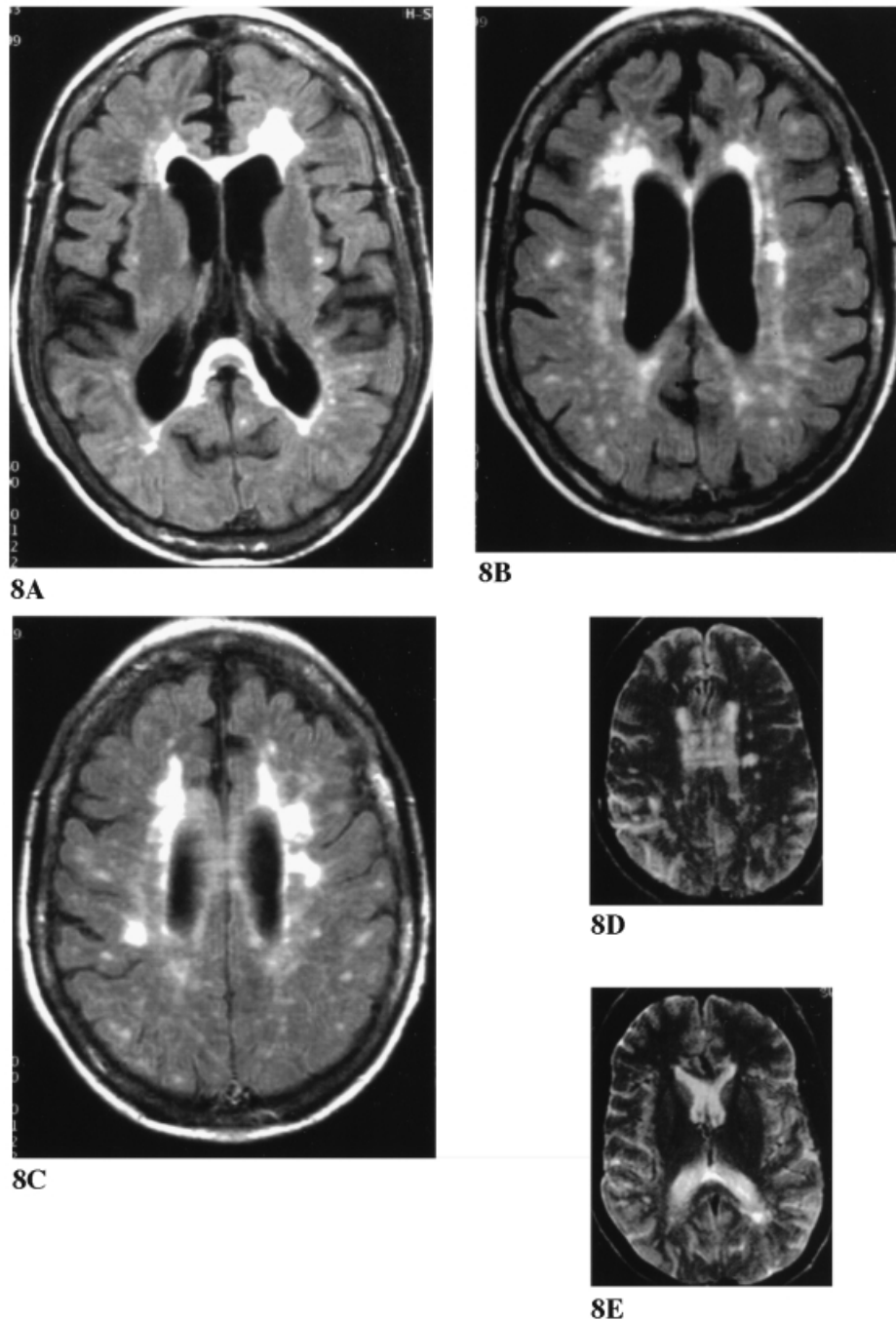


Fig. A1 MRIs 1–5 correspond to the early-affected cases 1–5. **Case 1:** (A) FLAIR MRI showing small scattered WMHs and a rim of hyperintensity around the frontal horn of the lateral ventricles; (B) FLAIR MRI showing a large corpus callosum WMH; (C) T₁-weighted MRI showing small infarcts of the anterior corpus callosum. **Case 2:** (A) FLAIR MRI showing multiple WMHs of the corpus callosum and lacunar infarction of the frontal lobe white matter; (B) FLAIR MRI showing confluent WMH around the frontal and occipital horns; (C) T₁-weighted MRI showing a severely atrophic corpus callosum. **Case 3** (A) FLAIR MRI showing multiple WMHs adjacent to the corpus callosum. **Case 4** (A) FLAIR MRI showing confluent WMH around the occipital pole of the lateral ventricles, a rim of hyperintensity around the frontal horn and lacunar infarction. **Case 5** (A and B) T₁- and T₂-weighted MRIs showing lacunar infarction of deep white matter. MRIs 6–8 correspond to the patients indicated. Patient W: (6A and 6B) T₂-weighted MRIs showing severe WMH throughout the deep cerebral white-matter and lacunar infarction. Patient 2B: (7A) FLAIR MRI showing frontal and occipital WMH signal. Patient V: (8A–8C) FLAIR MRIs showing periventricular WMH signal and corpus callosum lesions; (8D and 8E) T₂-weighted MRIs from the same patient (V) obtained 7 years earlier.

Identification of the second and 11th children as the ancestors of the whole pedigree was possible because they possessed a rare surname.

Case B

The earliest known case of FBD, born in 1808. She was a laundress and the wife of a plumber and journeyman. She died aged 55 years in 1862 in the Union Workhouse, Battersea. Death certificate stated 'paralysis'. She had 10 children (seven girls, two boys, one unknown). Names and birthdates are known for the children, but only two are known to have had FBD. Worster-Drought stated that at least one other daughter died of the same illness but the details are not known.

Case C

This woman died at home. The cause of death was 'paralysis and exhaustion from bed sores'.

Case D

Died in 1896 aged 60 years. His death certificate stated 'cerebral disease five years'.

Case E

Died aged 52 years of 'disseminated sclerosis'; paralysis was apparently the predominant clinical feature.

Case F

This woman was admitted to Banstead Asylum in 1908, aged 50 years. Presenile dementia was the reason for admission. She died a year later aged 51 years and had an autopsy on-site (the first known examination of the brain post-mortem in FBD). The brain parenchyma was commented on as being particularly pale. The cause of death was a 'fresh haematoma of the Dura Mater'.

Case G

Information from Worster-Drought states that she became ill aged 48 years. She died at home in south London of 'disseminated sclerosis and coma'.

Case H

Little was known of this woman, who died of FBD aged 50 years. It appears that paralysis was the predominant feature in her case as her cause of death appears as 'primary lateral sclerosis (2 years), paraplegia (4 months)'.

Case I

Died in 1929 aged 59 years after an illness lasting 10 years. During his life he was said to have a brain tumour.

Case J

Died aged 53 years. It appears that psychiatric problems were a feature additional to paralysis in this case as the cause of death was paralysis agitans and mental derangement.

Case K

Died aged 50 years. Death certificate stated 'complications of epilepsy'. A post-mortem was performed in Durham but the results have been destroyed. No descendants.

Case L

History has been obtained from a living nephew. Her symptoms began in her 40s with a tremor, unsteadiness and cognitive decline. Gradually progressive until she died aged 60 years in 1963. No children.

Case M

Little is known of this woman who died aged 78 years from generalized arteriosclerosis and parkinsonism. It is possible, but unlikely, that she had FBD as she lived 8 years longer than the oldest age of death in known cases. She has no descendants.

Case N

Became unwell from age 60 years onwards. Her illness was characterized by memory loss and ataxia. Memory loss was the first symptom. When walking she appeared off-balance 'as if she had been drinking'. She had to hold onto furniture to get around inside the house. She fell over in her garden and fractured her femur, and her illness became much worse after hospital admission. The psychiatric problems became more severe; she would repeat the same word over again. She was offered electroconvulsive therapy at one stage but it is not known if this treatment was administered. She died after a stroke and bronchopneumonia, aged 70 years. Arteriosclerosis and parkinsonism are also given on the death certificate but the evidence for these is not known. She had one daughter who does not have FBD at the age of 70 years.

Case O

Admitted to Atkinson-Morley hospital in 1963 aged 53 years with sudden deterioration and said to have had a 'brain hemorrhage'. On discharge she was impaired but able to walk. There was a gradual deterioration from then onwards, with balance problems, agoraphobia, memory loss and continued headaches. She died aged 60 years.

Case P

Died in 1954 aged 54 years. He was diagnosed as having disseminated sclerosis as an inpatient at Dulwich Hospital at his death but is known to have visited the Ministry of Pensions Hospital in Newcastle during his illness. He had one son.

Case Q

Died in 1963 aged 64 years. On his death certificate was 'Progressive Cerebral Atrophy'. He was treated at St Bartholomew's Hospital and attended the Three Counties Hospital. His illness started 10 years before his death and involved him losing his balance. He had one son, who is unaffected.

Case R

Male. Born 1910. Died aged 54 years. Paralysis began at age 48 years. Prior to this he became depressed and withdrawn and he became irritable. He was admitted acutely to a psychiatric hospital on many occasions. Descendants give a clear history of generalized tonic-clonic seizures once he had clearly become affected by the condition.

Case S

History obtained from her husband's second wife. Long illness characterized by loss of balance, reduced mobility, then became unable to walk; loss of speech, reading, and loss of memory. Gradually progressive illness of >10 years. Died aged 65 years in 1971; her death certificate stated 'Ia. myocardial failure. Ib. disseminated sclerosis'. No children.

Case T

Clinical information in the original 1982 case report was limited as the authors had access only to the patient's records and the family were not interviewed. At age 49 years she developed a slight unsteadiness of gait. This gradually progressed and she began to fall over when walking and to drop objects. Early in the disease a symmetrical cerebellar ataxia and nystagmus on lateral gaze was found on neurological examination. She could not walk without a stick by her early fifties and later required a wheelchair. Aged 56 years she had a small stroke with pain down one half of the body and a weak left leg. On examination shortly afterwards, she had left ankle clonus and a left extensor plantar. Although the original case report states that memory loss was not a feature until the last 6 months of her illness, her children noticed a personality change much earlier in the illness with occasional euphoria. Late in her illness she was admitted to a nursing home as she became progressively more overweight and incapacitated with incontinence of urine. At this stage she had slurred speech and would repeat things, with clear-cut impairment of short-term memory. She died aged 59 years of septicaemia resulting from a urinary tract infection.

Case U

This man died suddenly aged 48 years. An autopsy demonstrated a ruptured berry aneurysm but the brain was not examined in detail. History obtained from the two sons of this man indicates that he had a progressive neurological impairment prior to the sudden event. This consisted of personality change, memory loss, loss of mobility and an abnormal gait. On this evidence it seems likely that he did indeed have FBD.

Case V

The patient was examined at age 66 years. A history of her illness was obtained from two of her daughters. She left school at age 17 years and worked as a bank teller and later as a manager of a bookshop. Throughout her life she suffered occasional headaches. Her first symptom was dizziness. Shortly afterwards she developed an 'off-balance' gait. Irritability also became a problem. At age 57–58 years she was asked to leave her work because of a combination of slurred speech on the telephone and temperament. At this stage she held onto furniture to help get around the house. She began to complain of muscle stiffness. Clear evidence of mental impairment was apparent at age 62 years, when she was unable to name common plants in her garden; however, she would still follow recent events in the news. Her mobility and ability to self-care then gradually declined. There was no history of sudden deterioration consistent with ischaemic stroke or haemorrhage. Aged 65 years she was admitted to a nursing home, unable to transfer from bed to wheelchair, incontinent of urine, and unable to feed herself.

On examination she was a frail, thin lady. Sense of smell was normal. She had broken pursuit eye movements and diplopia, though this was difficult to ascertain. Acuity, pupils and fundoscopy were normal. Facial movement and sensation were normal. She had a slurring dysarthria and mild problems with swallowing liquids. She had no tremor at rest. There was moderate spasticity of arms and legs. Power was lost in a pyramidal pattern, slightly more so on the right than the left, legs more than arms. Hip flexion was graded 3/5 on the right, 4-/5 on the left. All limb reflexes were pathologically brisk, although there was no ankle clonus and abdominal reflexes were absent. Past-pointing and dysidiadochokinesia was marked and symmetrical. Joint position sense was intact in the toes.

Neuropsychological testing revealed a premorbid level of functioning at a high average intelligence, but on WAIS-R the verbal IQ was 80 and performance IQ was 65, reflecting a marked degree of intellectual deterioration, more evident in non-verbal tasks. Her memory tasks for both verbal and visual material were very impaired. She was disorientated in time but orientated for place and person. Visual perception was also impaired.

Case W

See case V2 in the paper by Plant and colleagues (Plant *et al.*, 1990).

*Case reports from the second pedigree**Case 2A*

Case 2A was an engineer who presented at the age of 51 years. He gave a history of memory loss that had led to him becoming confused in his work. There had also been some fluctuations in his mood and he had become increasingly withdrawn and apathetic. A diagnosis of depression was made. The following year he was admitted for neurological investigation, by which time he had become aware of impaired balance and difficulty dressing himself. His speech had become less fluent. On examination he was found to have increased tendon reflexes and extensor plantars with cerebellar signs in the upper limbs but no gait ataxia. Neuropsychological testing revealed a premorbid level of functioning in the high average range (IQ 112) but his overall score on six subtests of the WAIS (Wisconsin Adult Intelligence Scale) was much lower than this, giving an IQ of 85. Memory was relatively well preserved and he was able to name a group of

famous faces, but perceptual skills were markedly abnormal as he was able to name only three of 10 objects from unusual views and he was unable to count groups of scattered dots accurately. There was a motor dyspraxia affecting the left upper limb.

A CT brain scan was abnormal, showing extensive white-matter low attenuation compatible with white-matter ischaemic change. CSF was examined and this was normal apart from a slightly elevated protein level of 0.95 g/l. EEG showed frequent bursts of slow activity over both hemispheres.

He continued to be cared for at home, attending a day centre, until the age of 55 years, when he deteriorated to the extent that his wife found it difficult to look after him. He was behaving aggressively and had become incontinent of urine. He was found to be disorientated in time and place. He showed emotional lability and was dysphasic. He had increased tone in all four limbs and his gait was ataxic and spastic. When he was admitted he repeatedly attempted to leave the ward. There is otherwise scant information in the notes; 3 days later he suddenly became breathless and died within a few hours. At autopsy, myocardial infarction was found to be the cause of death. The brain was macroscopically normal but a detailed examination was not carried out.

Case 2B

The brother of case 2A presented aged 51 years with an 18-month history of progressive unsteadiness and a 6-month history of slurred speech. He had experienced episodes of rotational vertigo related to extension and flexion of his neck. On examination he was found to have gait ataxia, a cerebellar type of dysarthria, gaze-evoked nystagmus on horizontal versions gaze and impaired (saccadic)

pursuit eye movements. There was no evidence of hypertension or generalized vascular disease. There were no upper motor neuron signs. Neuropsychological testing revealed a premorbid level of functioning in the high average range (IQ 112), but on WAIS his verbal IQ was 96 and performance IQ was 103, reflecting a mild degree of intellectual deterioration. Verbal memory was weak but visual memory was within normal limits for his age.

A CT scan showed extensive white-matter low-signal abnormalities consistent with white-matter ischaemic change. Spinal fluid was normal.

Six months later he was readmitted because of a deterioration in the above problems and, in addition, he had developed intermittent diplopia and occasional choking when drinking. CT showed no significant change and EEG was within normal limits. A few years later the cerebellar signs in the eyes and limbs were considerably more marked but there was still no evidence of significant cognitive impairment or spasticity. He had an MRI scan which again showed marked white-matter ischaemic change and some evidence of cortical atrophy. Vision deteriorated abruptly in his left eye (the cause of this has not been well established); visually evoked potentials were normal. By 1989 he had been wheelchair-bound for 1 year. During that year definite impairment of memory had become apparent; his vision was blurred and he no longer watched television. On examination, the cerebellar signs were more marked still and he had developed increased tone in all four limbs; all tendon reflexes were exaggerated, as was the jaw-jerk, and plantar responses were extensor. In the last year of his life he was incontinent of urine, unable to speak and totally dependent. He died suddenly in 1992 at the age of 61 years. Cause of death was cerebral haemorrhage (see pathological description in main paper).

See Fig. A1 for MRIs of some of the patients described in this appendix.