PostScript

LETTER

A case with a 120 base pair insertional mutation in the prion protein gene: the first case in Japan

Familial prion diseases are associated with underlying mutations in the prion protein gene located on the short arm of human chromosome 20.[1] The normal and wild type of the prion protein gene encodes the cellular prion protein, PrP^{C}, and it is thought that there is a post-translational modification to a disease related form, protease resistant PrP^{Sc}. PrP^{Sc} and PrP^{C} have the same amino acid sequence, but PrP^{Sc} is richer in β sheets. PrP^{Sc} is distinguished from PrP^{C} in that it is protease resistant and associated with infectivity. It is known that PrP^{Sc} deposition is associated with the pathological changes of spongiform degeneration, neuronal loss, and astrocytic gliosis. Underlying mutations are point mutations and octapeptide repeat (24 bp repeat) insertional mutations. In healthy people, the repeat is designated R1-R2-R2-R3-R4, where only R1 is a nonapeptide and the others are octapeptides, between codon 51 and 91.[2] Prion disease families with mutations of one, two, four, five, six, seven, eight, or nine extra octapeptide repeat insertions have been reported.

We report a case with a 120 bp insertional mutation in the prion protein gene. To our knowledge, this is the first such case studied in Japan. The patient, a 45 year old woman, showed signs of dementia and cerebellar atrophy at the onset. In the next 4 years, her motor function did not become worse, though her higher brain function was deteriorating gradually. Cases with the same mutant protein have been reported in an American family, an American family of Ukrainian origin, and a German family.[2–4] The clinical features of this case are very similar to those of the reported cases, but there are subtle differences in the DNA sequence of the octapeptide repeat region.

Case report

A 45 year old woman had shown difficulty in calculation as an initial symptom, and exhibited some difficulty in her job because of memory deficits. She showed psychomotor retardation and became housebound; her full activity gradually declined and her need for support for daily living activities became gradually greater.

She had graduated from junior college at 20 years of age, worked as a childminder until the age of 26 years, and had married at 24 years. She had begun to help in her mother's business at 43 years of age. She has a medical history of hypertension, and no history of neurosurgery or tissue grafting. There is no known family history of neurodegenerative disease.

When admitted to our hospital at 45 years of age, she was cooperative and well nourished. On examination, she was disorientated in time and place, showed memory impairment for recent events, and had difficulty in concentration and calculation. Her Mini Mental State Examination (MMSE) score was 21, and her verbal IQ from the Wechsler Adult Intelligence Scale - Revised was 70. Evaluation of cranial nerve function was normal. Muscle tonus and reflexes were physiological and symmetric. She showed mild cerebellar ataxia in the left upper and lower limbs, but could walk by herself. Routine biochemical and haematological investigations were almost normal except for mild anaemia, and her thyroid function was also normal. Brain magnetic resonance imaging (MRI) showed mild atrophy in cerebral cortex and cerebellar vermis, but there was no evidence of hyperintensity of grey matter in T2 weighted images. Single photon emission computed tomography (SPECT) showed general hypoperfusion in cerebral cortex. Electroencephalogram (EEG) showed a 9~10 Hz, 20~40 μV diffuse wave pattern, but no paroxysmal discharge. Cerebrospinal fluid 14-3-3 was not examined.

The DNA analysis revealed that she had a 120 bp insertional mutation in the prion protein gene, and that the codon 129 polymorphism was Met/Met. The patient's children have not been tested for the insertion, because we could not obtain informed consent.

Two years later, when the patient was aged 47 years, her neurological signs showed no remarkable change, and brain MRI revealed mild cerebral and cerebellar atrophy. SPECT and EEG showed no remarkable change. At 49 years of age, MMSE score was 13, where disorientation and attention deficit were apparent, but she showed little deterioration in cerebellar ataxia and could walk by herself.

Discussion

Our research involved a patient with slowly progressive dementia and five extra octapeptide repeat insertions in the human prion protein gene. At 45 years of age, she exhibited disorientation, difficulty in concentration, and cerebellar ataxia. Over the next 4 years, she showed no marked deterioration in cerebellar ataxia, but mild deterioration in orientation, attention, and memorisation.

The clinical features of published cases with insertions of five extra octapeptide repeats are shown in table 1. The average age at onset in those cases, 44 years (range 26 to 61), is relatively young, and cases with long duration of illness have been observed. Goldfarb *et al* reported that the long extra octapeptide repeat was associated with early age at onset and long duration of the illness.[2] In the same family, there is little variation in symptoms at the onset and in clinical course. Common clinical features in reported cases are progressive dementia, progressive cognitive impairment, personality change, cerebel-

Table 1 Clinical features and the octapeptide repeat pattern of published cases with five extra octapeptide repeats insertion including this case

Reference	Sex/age at onset	Duration of illness	Clinical features	The octapeptide repeat pattern (normal: R1-R2-R2-R3-R4)
This report	F/45	4 years, alive at 49 years	Progressive dementia, disorientation, cerebellar signs	R1-R2-R2a-R2-R2-R3g-R2-R2-R3-R4
Goldfarb *et al*[2]	M/31	15 years	Progressive dementia, abnormal behavior, cerebellar signs, tremor, rigidity, myoclonus. EEG: diffuse slowing	R1-R2-R2-R3-R2-R3g-R2-R2-R3-R4
	M/45	5 years	Progressive dementia, mood change, disorientation, cerebellar signs, tremor, hyper-reflexia	
Cochran *et al*[3]	M/42	7 years	Cognitive impairment, cerebellar ataxia,	R1-R2-R2-R3-R2-R2-R2-R2-R3-R4
	M/44	7 years, alive at 52 years	Cognitive impairment, personality change, spasticity	
	F/26	12 years, alive at 38 years	Poor socialisation, cerebellar ataxia, personality change	
Skworc *et al*[4]	F/51	2 years	Cerebellar ataxia, spasticity, progressive dementia, cognitive impairment, mutism	R1-R2-R2-R3g-R3g-R3g-R2-R2-R3-R4
	F/61	8 years	Long-standing personality disorders, cerebellar ataxia, spasticity, progressive dementia	
	F/52	4 months	Rapidly progressive dementia, spasticity, myoclonus. EEG: periodic complexes	

lar ataxia, and spasticity. With regard to the symptomatic change in time course, patients often showed mental disorder at an early stage, which remained stable for several years, followed by rapid deterioration ending to death. In almost all of the cases, brain MRI showed cerebral and cerebellar atrophy, but no specific findings. EEG showed a diffuse slowing, and in few cases periodic synchronous discharges.

The expanded octapeptide repeat regions of this case and published cases with 120 bp insertion mutations are shown in table 1.[2–4] In our case, the repeat is designated R1-R2-R2a-R2-R2-R3g-R2-R2-R3-R4, and this DNA sequence is different from other sequences in the reported cases. The clinical features in this case are progressive dementia, disorientation, and cerebellar signs. The patient's motor function has shown no marked decline in 4 years, but her higher brain function has become gradually worse. In this case, no other members of this family show similar symptoms. Genetic testing for prion disease should be considered as a differential diagnosis in unusual cases of impaired mental disorder.

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References

1 **Knight RSG**, Will RG. Prion diseases. *J Neurol Neurosurg Psychiatry* 2004;**75**(suppl 1):i36–42.
2 **Goldfarb LG**, Brown P, McCombie WR, *et al.* Transmissible familial Creutzfeldt-Jakob disease associated with five, seven, and eight extra octapeptide coding repeats in the PRNP gene. *Proc Natl Acad Sci USA* 1991;**88**:10926–30.
3 **Cochran EJ**, Bennet DA, Cervenakova L, *et al.* Familial Creutzfeldt-Jakob disease with a five-repeat octapeptide insert mutation. *Neurology* 1996;**47**:727–33.
4 **Skworc KH**, Windl O, Schulz-Schaeffer WJ, *et al.* Familial Creutzfeldt-Jakob disease with a novel 120-bp insertion in the prion protein gene. *Ann Neurol* 1999;**46**:693–700.

BOOK REVIEW

The self in neuroscience and psychiatry

Edited by Tilo Kircher, Anthony David. Published by Cambridge University Press, Cambridge, 2003, pp 466, £30.00 (paperback). ISBN 0-521-53350-3

This is a thought provoking book. Tilo Kircher and Anthony David have persuaded 22 authors to write on aspects of the self. The title might be ''The self and schizophrenia'' for this is the central focus. In his chapter Parnas makes this explicit:

> ''The most fundamental level of selfhood that appears to be affected in early schizophrenia is the automatic pre-reflective articulation of the first person perspective'' (page 217)

and quotes Bleuler:

> ''Ganz intakt ist dennoch das Ich nirgends''

''The I is, however, never completely intact'' to this effect. The proposal is that by attacking the self as a concept and dealing with its scientific and philosophical implications one can arrive at a more fundamental understanding of the nature of schizophrenia than Bleuler's concept that it is a disorder of association. However, the implications are wider than this.

To be sure there are some disagreements and differences in emphasis between the contributors. Thus Berrios and Marková in a characteristically thorough historical survey conclude that the self is ''fundamentally a western construct'' to be explained by means other than neurobiology. Bentall writes:

> ''To many hard-nosed biological scientists, the self might seem an almost metaphysical concept'' (page 301)

and quotes Baumeister:

> ''Providing a satisfactory definition of the self has proven fiendishly difficult. It is what you mean when you say ''I''. Most people use ''I'' and ''self'' many times each day, and so most people have a secure understanding of what the self is – but articulating that understanding is not easy''.

Phillips writes:

> ''Sartre and Heidegger come to mind as philosophers who reject the notion that there is anything like a human nature or natural self-development …'' (page 320)

These quotations provide a background of cautious scepticism but there is much in this volume to convince the reader that addressing the problem of the self and its relationship to the phenomena of psychosis takes one into the core problem of the neural basis of psychotic symptoms and indeed the nature of human consciousness.

For example, there is the question of the relationship between the self and the central executive—a key concept in ''cognitive psychology''. Blakemore and Frith (chapter 19) outline the theory that auditory hallucinations and delusions of control arise because of a failure in the mechanism by which the predicted consequences of self-produced actions are derived from an internal ''forward'' model that predicts and cancels the sensory consequences of self-produced actions. This widely discussed model has a nice wiring diagram (figure 19.1) according to which a patient lacks awareness of initiating an action or thought or of its predicted consequences. However, as Zahavi argues on pp 67–68 there is a problem. The account is based on the assumption that the ''mineness'' of experience comes about as the result of high order representation, and that such meta-representational accounts of conscious experience are flawed in that they depend on an infinite regress—that is, they require the invocation of an ''homunculus'' whose function in turn needs to be accounted for by a further homunculus at a higher level. Similar criticisms apply to theory of mind formulations discussed by Kai Vogeley in chapter 17. A more parsimonious account of the differences between cortical function in other primates, mammals, and humans is required.

Where then is the neural basis of the self? According to Markowitsch (chapter 9) it is located in the right pre-frontal and anterior temporal cortex on the basis of evidence relating to the hemispheric encoding and retrieval asymmetry (HERA) hypothesis of episodic memory, according to which left pre-frontal cortex is engaged in recording episodic memories while right pre-frontal cortex is relevant to retrieval. Keenan *et al* (chapter 8) agree on the basis of studies that implicate right hemisphere/pre-frontal cortex in self-recognition and self-face recognition as well as episodic memory. These chapters therefore introduce the topic of cerebral asymmetry; but do not tell us why it is relevant.

I missed reference to what I have called the Broca-Annett axiom—the concept that cerebral asymmetry is the characteristic that defines the human brain.[1 2] This is the notion that at some point in hominid evolution the brain lateralised and that this innovation was critical to the evolution of language. On page 198 of this volume Panksepp refers to the problems of animal models of schizophrenia:

> ''Not only is it risky to infer mental processes simply from the study of behavioural responses, but some of the key symptoms of schizophrenia (eg thought disorder) may be impossible to model in creatures of modest cortical endowment''.

If, as Panksepp also suspects may be the case, the disease is specific to the human capacity for language, the problem is deeper than this. Miskolczy[3] considered that schizophrenia was a disease of *Homo sapiens*-specific cerebral cortex; the Broca-Annett axiom is a lead to the nature of its anatomical basis. Gallup *et al* (page 147) place the problem of self-awareness in the context of primate evolution by considering the point in the primate lineage at which evidence of self-recognition emerges in mirror experiments. They equate this point with the development of the capacity for a ''theory of mind and appreciation of the existence of others'' and relate this capacity to ''enlargement of the frontal lobes and vulnerability to the phenomena of psychosis''. However, theory of mind interpretations of mirror recognition have been contested.[4] Susceptibility to schizophrenia may be more precisely related to