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ORIGINAL PAPER

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Prominent behavioural and psychiatric symptoms in early-onset Alzheimer's disease in a sib pair with the presenilin-1 gene R269G mutation

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Abstract Two siblings with the R269G mutation in the presenilin-1 gene causing early-onset Alzheimer's disease are presented, only the second family with this mutation to be reported. Behavioural and psychiatric symptoms were prominent in both cases, as well as cognitive decline. Other reports of presenilin-1 gene mutations associated with behavioural and psychiatric symptoms are reviewed. The distribution of such mutations throughout the presenilin-1 gene argues against specific genotype-phenotype correlations, and suggests a role for other genetic and/or epigenetic factors in the pathogenesis of behavioural and psychiatric features in early-onset Alzheimer's disease associated with presenilin-1 gene mutations.

Key words Alzheimer's disease · dementia · presenilin-1 gene mutation

Introduction

Behavioural and psychiatric symptoms are well-recognised features of sporadic Alzheimer's disease (AD) [4, 12] that may necessitate specific treatment [1, 17]. However, whether behavioural and psychiatric symptoms are features of early-onset AD (EOAD) associated with mutations in the gene encoding the protein presenilin-1 (PSEN-1), the commonest genetic cause of AD, is not clear. Although many (> 100) such deterministic mutations have been reported (see molgen-www.uia.ac.be/Admutations), the clinical details provided are often brief, although occasional pedigrees and individual cases with prominent behavioural and psychiatric symptoms, with or without cognitive features, have been presented [7, 9–11, 15, 16, 19].

To our knowledge, only one previous family with the PSEN-1 R269G mutation has been reported, but clinical details were sparse [14]. We report a sib pair with the PSEN-1 R269G mutation in which behavioural and psychiatric symptoms were prominent.

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Case reports

Case 1

At the age of 49 years, this man presented to a psychiatrist with a major depressive disorder of moderate severity with marked somatic symptoms. This occurred in the context of job redundancy and the recent death of his mother in her eighties from Alzheimer's disease (reported age at onset 79 years). There was no previous history of psychiatric disorder. The patient did not respond to dothiepin or fluoxetine and was, therefore, treated with a course of electroconvulsive therapy (ECT) with partial remission of symptoms. One year into his illness, obsessional features (especially related to monetary matters) became apparent, and his treatment was switched to clomipramine. Testing of orientation, concentration and memory at this time was normal. Six months later, however, at the age of 50 years, he had declined: although still able to manage most aspects of self-care, and able to discuss accurately subjects of personal interest (such as football), there were episodes of agitation with physical aggression towards other family members. He now performed poorly on brief cognitive testing, during which he seemed very anxious: he was incapable of simple tests of concentration, and could not register three objects for immediate recall. There appeared to be word-finding difficulties and impairments in visuospatial function.

Structural brain imaging with CT scan was normal. A

subsequent MRI showed some mild, non-specific cortical atrophy but no hippocampal atrophy. An EEG showed bilateral moderate excess of slow wave activity, a non-specific finding. Perfusion brain imaging (^{99m}Tc-HMPAO-SPECT), $2^1/_2$ years after symptom onset, showed some hypoperfusion of the posterior parietal cortex, but was normal elsewhere, and was not thought diagnostic of patterns recognised in dementia syndromes. CSF examination was normal.

He continued to decline, needing increasing help with self-care. Episodes of weepiness replaced the previous outbursts of aggression. Speech output was largely incomprehensible. Myoclonus was observed, particularly at night. He then developed episodes in which he would appear to talk to people who were not present. These were thought to represent auditory hallucinations and were treated with risperidone. A repeat EEG showed no new change. Three years into his illness, his younger sister (case 2) was reported to be developing similar problems, at which point blood was sent for DNA analysis. This showed a C to G nucleotide transversion in exon 8 of the PSEN-1 gene, resulting in an arginine to glycine substitution at amino acid 269 (R269G), a mutation previously reported to be deterministic for early-onset Alzheimer's disease [14]. Four years into his illness, tonic-clonic seizures developed and he was commenced on sodium valproate.

Case 2

This lady presented to her general practitioner at the age of 49 with "confusion" which had caused her to give up work. She could not locate her usual bus stop, and could no longer operate the cash till at her place of work. There was no prior history of psychiatric disorder. She was diagnosed with "stress" and treated with thioridazine. At age 50, when first seen in hospital, she was unable to give a coherent history of her difficulties. She had lost interest in eating and had lost a significant amount of weight. She developed "following behaviour", for example, accompanying her husband when he went to the toilet. She was noted to be restless, neglected her personal hygiene, had a poor appetite, and would put on inappropriate items of clothing. She scored 8/30 on the MMSE, with disorientation in time and place, impaired 5-min recall (0/3), naming problems with circumlocutions and paraphasias, apraxia and visuospatial difficulties. There were no abnormal neurological signs. Premorbid IQ could not be established as she could not grasp the requirements of the National Adult Reading Test (NART) [13]. Using the Middlesex Elderly Assessment of Mental State (MEAMS) [6], she failed all 12 subtests, with evidence of receptive problems apparent. Her severe general cognitive impairments precluded further testing.

In the family history, she was the youngest of three siblings. Her eldest brother suffered from post-traumatic epilepsy since childhood, but had no behavioural or cognitive problems. Her other brother, 31 months her senior, had behavioural disturbance and cognitive dysfunction (case 1).

Structural imaging (CT, MRI) showed global atrophy but no focal lesion. EEG showed excess slow wave activity. CSF analysis was normal aside from a moderately elevated protein (0.9 g/l). In the light of her brother's behavioural and cognitive problems, blood was sent for DNA analysis; it showed the same R269G mutation in the PSEN-1 gene.

In hospital she became agitated, and made attempts to leave. She was treated with haloperidol. Myoclonus and tonic-clonic seizures emerged later, the latter requiring treatment with anti-epileptic medications. She was discharged to a nursing home, but has had occasional hospital admissions because of uncontrolled seizures.

Discussion

Age at onset of disease in both these siblings was 49 years. One presented with a depressive illness, followed by obsessional features and auditory hallucinations. Both had agitation early in the disease course which, following the categories of the Cohen-Mansfield Agitation Inventory [2], would be classified as physically aggressive behaviour (case 1) and physically non-aggressive behaviour (case 2). Both developed cognitive decline, seizures and myoclonus, and were found to have the same mutation in the PSEN-1 gene. Whether the mother was similarly affected, or suffered from sporadic AD, is not clear; her age of onset was around 30 years later than her children. Most PSEN-1 mutations have a pedigree-specific age at onset (i. e. are fully penetrant), but there are occasional reports of non-penetrance (I143F) [18] and of disease onset more than 30 years apart in family members carrying the same mutation (M139V) and identical apolipoprotein E genotype [8].

The underlying diagnosis of EOAD was delayed in case 1, due to the behavioural and psychiatric features without obvious cognitive impairment at presentation, and the non-specific investigation findings. In a subsequent retrospective audit of SPECT scans at this institution [3], three out of five observers adjudged the SPECT scan of case 1 to be normal when it was viewed blind to any clinical information, and all five adjudged it to be normal when viewed with knowledge of the clinical history at presentation.

In the only other report of a family with the R269G PSEN-1 mutation [14], age of onset in the proband was 47. The clinical picture was memory loss, dysfluent speech and seizures, although a history of previous alcohol abuse complicated the assessment. The proband's father and uncle had died with dementia at the ages of 52 and 54, respectively, but no other clinical details were available.

A further mutation at codon 269 of the PSEN-1 gene, R269H, has also been reported in a single case [8, 9]. Age at disease onset was 47 years, disease duration was 9

years, and the history was marked by visual and auditory hallucinations and myoclonus, but there was no report of seizures or extrapyramidal features [9]. Compared to sporadic AD cases, the R269H mutation was shown to be associated with increased deposition of amyloid β-peptide (Aβ), as were other familial EOAD cases examined, and there was also a faster rate of neurofibrillary tangle (NFT) formation and accelerated neuronal loss, also seen in familial EOAD cases with the mutations M139V, I143F, G209V, and E280A [8].

Behavioural and psychiatric symptoms were prominent in our patients. Although such symptoms are well-recognised features of AD [1, 4, 12, 17], they have been reported only infrequently in EOAD with PSEN-1 mutations. As mentioned, the R269H index case had visual and auditory hallucinations [9]. Depression and psychosis (visual hallucinations) occurred in two members of a British pedigree with the L250S mutation, which, like R269G and R269H, also affects exon 8 of the PSEN-1 gene [10]. Prominent frontotemporal features, including depressed mood, personality change, aggression, defective judgement, stereotyped behaviour, emotional unconcern, and neglect of personal hygiene, occurred in three members of French kindred shown to have the L113P mutation [16]. In this context, it is of note that, in our case 1, current autobiographical events of particular personal interest, such as football matches, were largely preserved, a feature reminiscent of the selective memory functioning ("remembers what s/he wants to remember") seen in frontotemporal dementia. Two members of an Italian kindred with the L392P mutation, affecting exon 11, had early and prominent bipolar affective symptoms [19]. In a patient with very early onset AD (age 33) due to a G206V mutation in exon 7, anxiety, depression and post-traumatic stress disorder were noted at presentation [7]. Behavioural features such as paranoid thinking, ritualistic behaviour, and anxiety were prominent in three members of a Spanish kindred with the V89L mutation in exon 4 [15]. Anxiety and depression were also noted in one patient with the M139V mutation in exon 5 [11], although similar symptoms were not mentioned in other cases with the same mutation [5].

The various PSEN-1 mutations in which the reported clinical phenotype has included prominent behavioural and psychiatric features are spread throughout the PSEN-1 gene and, hence, do not suggest a particular phenotype-genotype correlation. Therefore, it seems likely that other genetic and/or epigenetic factors must contribute to the development of behavioural and psychiatric symptoms in EOAD associated with PSEN-1 mutations, as previously noted for clinical [5, 11] and neuropathological [8] features. However, systematic studies of behavioural and psychiatric symptoms in patients with PSEN-1 mutations will be required to answer this question definitively.

References

1. Ballard CG, O'Brien J, James I, Swann A (2001) Dementia: management of behavioural and psychological symptoms. OUP, Oxford
2. Cohen-Mansfield J, Billig N (1986) Agitated behaviors in the elderly. I. A conceptual review. J Am Geriatr Soc 34:711–721
3. Doran M, Vinjamuri S, Collins J, Parker D, Larner AJ (2003) SPECT perfusion imaging in the differential diagnosis of presenile dementia: a retrospective regional audit. J Neurol Neurosurg Psychiatry 74:1177
4. Folstein MF, Bylsma FW (1994) Noncognitive symptoms of Alzheimer disease. In: Terry RD, Katzman R, Bick KL (eds) Alzheimer disease. Raven Press, New York, pp. 27–40
5. Fox NC, Kennedy AM, Harvey RJ et al. (1997) Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene. Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. Brain 120:491–501
6. Golding E (1989) The Middlesex Elderly Assessment of Mental State. Bury St Edmunds, Thames Valley Test Company
7. Goldman JS, Reed B, Gearhart R, Kramer JH, Miller BL (2002) Very early-onset familial Alzheimer's disease: a novel presenilin 1 mutation. Int J Geriatr Psychiatry 17:649–651
8. Gómez-Isla T, Growdon WB, McNamara MJ et al. (1999) The impact of different presenilin 1 and presenilin 2 mutations on amyloid deposition, neurofibrillary changes and neuronal loss in the familial Alzheimer's disease brain: evidence for other phenotype-modifying factors. Brain 122:1709–1719
9. Gómez-Isla T, Wasco W, Pettingell WP et al. (1997) A novel presenilin-1 mutation: increased β-amyloid and neurofibrillary changes. Ann Neurol 41:809–813
10. Harvey RJ, Ellison D, Hardy J et al. (1998) Chromosome 14 familial Alzheimer's disease: the clinical and neuropathological characteristics of a family with a leucine serine (L250S) substitution at codon 250 of the presenilin 1 gene. J Neurol Neurosurg Psychiatry 64:44–49
11. Larner AJ, du Plessis DG (2003) Early-onset Alzheimer's disease with presenilin-1 M139V mutation: clinical, neuropsychological and neuropathological study. Eur J Neurol 10:319–323
12. Mirea A, Cummings J (2000) Neuropsychiatric aspects of dementia. In: O'Brien J, Ames D, Burns A (eds) Dementia (2nd edn). Arnold, London, pp. 61–79
13. Nelson HE, Willison J (1991) The National Adult Reading Test (2nd edn) NFER-Nelson, Windsor, UK
14. Perez-Tur J, Croxton R, Wright K et al. (1996) A further presenilin 1 mutation in the exon 8 cluster in familial Alzheimer's disease. Neurodegeneration 5:207–212
15. Queralt R, Ezquerra M, Lleó A et al. (2002) A novel mutation (V89L) in the presenilin-1 gene in a family with early onset Alzheimer's disease and marked behavioural disturbances. J Neurol Neurosurg Psychiatry 72:266–269
16. Raux G, Gantier R, Thomas-Anterion C et al. (2000) Dementia with prominent frontotemporal features associated with the L113P presenilin 1 mutation. Neurology 55:1577–1578
17. Robert P (2002) Understanding and managing behavioural symptoms in Alzheimer's disease and related dementias: focus on rivastigmine. Curr Med Res Opin 18:156–171
18. Rossor MN, Fox NC, Beck J, Campbell TC, Collinge J (1996) Incomplete penetrance of familial Alzheimer's disease in a pedigree with a novel presenilin-1 gene mutation. Lancet 347:1560
19. Tedde A, Forleo P, Nacmias B et al. (2000) A presenilin-1 mutation (Leu392Pro) in a familial AD kindred with psychiatric symptoms at onset. Neurology 55:1590–1591

Prominent behavioural and psychiatric features have now been reported in two siblings with MI39V EOAD (Rippon GA, Crook R, Baker M, et al. (2003) Presenilin 1 muation in an African American family presenting with atypical Alzheimer dementia. Arch Neurol 60: 884–888)