Alzheimer's disease, the most common cause of dementia in later life, is genetically heterogeneous. Mutations in three genes encoding the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) are responsible for autosomal dominant early onset cases. A few families have been described in which PSEN1 mutations, usually exon 9 deletions, cause progressive dementia associated with spastic paraparesis. We present a family in which another PSEN1 mutation causes disease that begins with spastic paraparesis and is associated with dementia that is not of the Alzheimer type.

The index case first presented at the age of 54 with lower back pain and gait difficulties; he was unable to squat unaided and walked with caution. He complained of a memory deficit that he attributed to the Algerian war, 34 years ago. On examination, he had brisk reflexes in all four limbs and normal muscle tone. Blood cell counts, CSF glucose and protein levels, electromyography, and nerve conduction velocity were unremarkable. A lumbar CT scan and cervicothoracic MRI showed no signs of spinal compression. Brain MRI showed mild cortical atrophy.

One year later, the patient had a bilateral extensor plantar reflex, with clonus of the patella and proximal muscle weakness in the lower limbs. There was no sign of cerebellar ataxia, and sensory modalities of the trunk and limbs were not affected. A second brain MRI showed mild cortico-subcortical atrophy. He was referred to our clinic at the age of 55 with the diagnosis of spastic paraparesis. He could not walk for more than one mile and complained of frequent falls. Gait was markedly spastic, but muscle tone at rest was normal. In addition to the pyramidal syndrome, there was gaze evoked nystagmus, saccadic ocular pursuit, and marked orthostatic hypotension. Dementia was evident, with a Mini Mental Status Examination (MMSE) score of 18/30 with deficits in visuospatial organisation and memory but no signs specific for Alzheimer's disease. Somatosensory evoked potentials and VLCFA (very long chain fatty acids) dosage were normal.

At the age of 57, the neurological examination was stable. The patient had a single generalised tonic-clonic seizure when he was 58, a brain CT scan showed global atrophy, and EEG was normal. Examination at the age of 60 showed additional signs: fasciculations of the tongue, facial hypomimia, and cramps during the night. There was gestural apraxia without dressing apraxia and a sustained nasopalpebral reflex. A detailed neuropsychological examination was performed, showing decreased global efficiency, with an MMSE score of 14/30 (temporospatial subscore 2/10). There was a deficit in long term memory, without impairment of recognition capacity, but no short term anterograde memory with no alteration of retrograde memory. There was no aphasia, ideomotor apraxia, or agnosia. Only visuospatial abilities were affected. Finally, neither anosognosia nor frontal behaviour was evident.

At the age of 61, he was able to walk with a walker and was able to dress and to wash himself. He still had cramps and orthostatic hypotension. Spastic paraparesis was a prominent feature with increased reflexes, except in the ankles, spasticity at rest and when walking, muscle weakness in the lower limbs, and urinary urgency. Ocular pursuit was saccadic with nystagmus and upward gaze ophthalmoplegia. Impaired vibration sense was noted in the ankles. Distal rest and postural tremor was observed but no cerebellar syndrome. Some visuospatial abilities were present, including oppositional hypertonia (gegenhalten) and gait apraxia, but surprisingly no anosognosia.

The family history was compatible with autosomal dominant dementia. His sister, who died at the age of 63, and his maternal grandmother (no information about age at death was available) became demented. His mother, who also had difficulty in walking, died at the age of 70 with dementia.

Sequence analysis of the entire coding region of the PSEN1 gene, as previously described, showed a Pro264Leu PSEN1 mutation in the proband. No DNA was available from affected relatives. Cosegregation of this P264L mutation with Alzheimer's disease was established in several families. Thierry Frebourg's laboratory has not found this mutation in a population of 50 controls and it results in a drastic substitution of a conserved residue present in dp5 (Drosophila) and SEL 12 (C elegans).

Several families with a similar association of progressive dementia and spastic paraplegia caused by PSEN1 mutations have already been described. They are characterised by the presence of large "cotton wool" plaques on neuropsychological examination. The clinical features were similar to the case described here, with the appearance of spastic paraplegia between 20 and 55 years, a few years before or after dementia. However, spastic paraplegia that remained isolated for up to 10 years or isolated dementia were observed in members of the family. Interestingly, dementia in our patient was not typical of Alzheimer's disease, since the cognitive impairment was less severe, as expected according to the young age and long disease duration. There was only impairment of visuospatial abilities and long term memory deficits (with respect of recognition) in the absence of other mnemonic, instrumental, or executive dysfunctions. Deletions of exon 9 in the PSEN1 gene have been found in three pedigrees. Surprisingly, the P264L mutation found in our family has been described in several families with Alzheimer's disease, but never in association with spastic paraplegia. It seems unlikely, however, that this association resulted from random association in four family members. Alternatively, two gene defects, the P264L PSEN1 mutation and another mutation responsible for spastic paraplegia, might segregate in the family. However, the SPG3 locus for autosomal dominant spastic paraplegia also located on chromosome 14 is not genetically linked to the PSEN1 gene and is associated with an early onset.
(2 to 15 years), in contrast to this family. Our results strongly suggest that the association of dementia and spastic paraparesis is not restricted to specific PSEN1 mutations, but may also represent variable phenotypic expression of more common mutations usually causing typical Alzheimer's disease. It is interesting that the P264L mutation can result in dementia that is not typical of Alzheimer's disease.

Authors' affiliations
M-L Jacquemont, A Brice, A Durr, Département de Génétique Médicale, Cytogénétique et Embryologie, Hôpital de la Salpêtrière, Paris, France
D Campion, T Frebourg, INSERM EPI 9906, Faculté de Médecine et de Pharmacie, Institut Fédératif de Recherches Multidisciplinaires sur les Peptides, Rouen, France
V Hahn, C Tallaksen, A Brice, A Durr, Fédération de Neurologie, Hôpital de la Salpêtrière, Paris, France
C Tallaksen, A Brice, A Durr, INSERM U289, Hôpital de la Salpêtrière, Paris, France

Correspondence to: Dr A Durr, Département de Génétique Médicale, Cytogénétique et Embryologie, Hôpital de la Salpêtrière, Paris, France; durr@ccr.jussieu.fr

REFERENCES

www.jmedgenet.com
Spastic paraparesis and atypical dementia caused by PSEN1 mutation (P264L), responsible for Alzheimer's disease

M-L Jacquemont, D Campion, V Hahn, C Tallaksen, T Frebourg, A Brice and A Durr

doi: 10.1136/jmg.39.2.e2

Updated information and services can be found at:
http://jmg.bmj.com/content/39/2/e2

These include:

References
This article cites 10 articles, 1 of which you can access for free at:
http://jmg.bmj.com/content/39/2/e2#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Dementia (34)
- Memory disorders (psychiatry) (67)
- Clinical diagnostic tests (356)
- Epilepsy and seizures (197)
- Eye Diseases (298)
- Molecular genetics (1254)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/