Discussion

Kernig's sign is the most common and, apart from nuchal rigidity, the only quantifiable sign of meningeal irritation.[3] Kernig's sign is sometimes interpreted as positive when the knee cannot be extended beyond 135°.[4] We considered Kernig's sign as positive in accordance with the opinion of its inventor (ie, if ''Kernig's angle'' was <180°).[1] It is known that Kernig himself let patients sit upright in order to elicit the sign later named after him and interpreted the test as positive if this resulted in immediate insuperable knee flexion.[1] Nevertheless, Kernig's original method was not used in this study, but the passive knee extension after initial hip and knee flexion to a right angle was carried out. This technique allows a more precise testing of Kernig's sign and is appropriated worldwide.[4 5]

The present study confirms the results of Thorner's forgotten paper from 1948.[2] In addition to Thorner, who only noted attenuation of Kernig's sign by concomitant hemiparesis without performing any quantification, the quantitative evaluation of Kernig's sign was carried out in the present study. This revealed that the ''Kernig's angle'' was in direct proportion to the degree of paresis: the more pronounced the paresis, the larger Kernig's angle (ie, the less pronounced Kernig's sign). Moreover, the present study showed that a quantitative analysis of Kernig's sign may be quite a differentiated clinical test, which allows more detailed evaluation of motor deficits than the Glasgow Coma Scale or the FOUR score. For instance, in patient Nos 1, 11 and 14, who had unilateral pyramidal signs without clear evidence of paresis, Kernig's sign was slightly less prominent on the affected side than on the non-affected side (135° vs 120°, 130° vs 120°, and 110° vs 100°, respectively) (table 1). In patient Nos 3–6 with hemiplegia, Kernig's sign was diagnosed exclusively on the non-paretic side, suggesting that a strictly unilateral Kernig's sign should point to a hemiplegia or a leg plegia. In patient Nos 2 (Medical Research Council (MRC) score 3) and 8 (MRC score 2) with pronounced paresis, Kernig's sign was only minimally positive on the paretic side showing an angle of 160° and 170°, respectively, which, according to Kernig, corresponded to a weak degree of contracture (>150°).[1] We found no correlation between the degree of Kernig's sign and the level of consciousness, whereas patients with deep areflexic coma were not included in our study because of absent meningeal signs.

Although the clinical relevance of an asymmetric Kernig's sign is limited to patients with coma or altered mental status, in intracranial haemorrhage, meningoencephalitide, etc, its diagnostic value should not be underestimated. An asymmetric Kernig's sign is certainly of purely phenomenological interest in completely conscious patients with meningeal irritation and paresis because hemiparesis in these patients can be better scored on a motor scale such as the MRC score. However, unilateral attenuation of Kernig's sign can be applied in everyday clinical practice of critical care neurology as a reliable indicator of hemiparesis.

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doi: 10.1136/jnnp.2007.127837

Competing interests: None.

References

1 **Kernig W**. Ueber die Beugekontraktur im Kniegelenk bei Meningitis. *Ztschr f Klin Med* 1907;**64**:19–69.
2 **Thorner MW**. Modification of meningeal signs by concomitant hemiparesis. *Arch Neurol Psychiatr* 1948;**59**:485–95.
3 **Levy M**, Wong E, Fried D. Diseases mimic meningitis. Analysis of 650 lumbar punctures. *Clin Pediatr (Phila)* 1990;**29**:254–5, 258–61.
4 **Campbell WW**. *DeJong's the neurologic examination*, 6th edn. Philadelphia: Lippincott, Williams & Wilkins, 2005:617–20.
5 **Triumfov AV**. *Local diagnosis in neurological diseases*, 15th edn. Moskau: MED press-inform, 2007:242–3.

Ataxic variant of Alzheimer's disease caused by Pro117Ala *PSEN1* mutation

Presenilin 1 (PSEN1) mutations account for the majority of cases of autosomal dominant early onset Alzheimer's disease (ADEOAD).[1 2] The *PSEN1* gene encodes for a 467 amino acid transmembrane protein which functions as a subunit of the γ-secretase complex that cleaves amyloid precursor protein to generate the Aβ amyloid peptide. More than 160 different mutations have been reported (www.molgen.ua.ac.be/ADMutations) with a great diversity of phenotypes: very early age of onset, early myoclonus seizures, parkinsonism, spastic paraplegia associated with ''cotton wool plaques'' or rare frontotemporal variant of AD. Ataxia has been rarely described during the course of ADEOAD caused by *PSEN1* mutations. Ataxia and psychiatric signs were recently reported as initial symptoms associated with a *PSEN1* Ser170Phe mutation.[3] We report three patients from the same family with early prominent severe ataxia associated with dementia caused by a novel *PSEN1* mutation.

Case report

Patient III2

A 35-year-old woman (fig 1) was seen for writing and balance difficulties, with memory complaints. All three symptoms occurred contemporaneously 1 year previously. Examination showed severe ataxia with instability, marked dysarthria and dysmetria with intention tremor, brisk reflexes and rare myoclonus. Neuropsychological assessment, including Mini Mental Scale (score 22/30), Grober and Buschke Learning Test (GBVLT) (delayed total recall 5/16), Digits Backwards (3), Backward Spatial Span (3), Trail Making Test Task A (time 104 s) and B (= 191 s), Rey–Osterrieth Complex Figure Copy (18/36) and 2 min category fluency task (n = 13 animals) yielded abnormal performances. Cerebral MRI revealed mild cortical atrophy. CSF examination, including 14.3.3 protein analysis, was normal. CSF amyloid β (Aβ) levels were not investigated. EEG detected sporadic bilateral generalised spikes and waves that were asymptomatic. Spinocerebellar ataxias types 1, 2, 3, 6, 7 and 17, and dentato-rubro-pallido-luysian atrophy were excluded. Sequence analysis of the prion protein gene was normal. Two years later the patient was completely dependent, with worsening of balance difficulties and falls twice per month. Cognitive state had deteriorated, with severe GBVLT immediate recall impairment (2/16), severe visuocontructive deficit (Rey figure copy 6/36) and reduced verbal fluency (six animals in 2 min).

A second MRI showed a diffuse cerebral atrophy, and Tc-99m HMPAO SPECT found hypoperfusion in the associated parietal area without cerebellar hypoperfusion.

Patient II2

At age 29 years, the father of patient III2 (fig 1) had developed cerebellar signs with head tremor associated with upper limb extremities intention tremor, dysarthria and gait difficulties. Examination at age 32 years displayed cerebellar signs with dysmetria, gait ataxia and left Babinski sign. EEG, CSF study and fractionated gas encephalography were normal. Examination at age 35 years demonstrated severe axial and four limb ataxia, dysarthria and pyramidal signs with hyperreflexia and lower limb spasticity. Impairment of short term and long term memory was noted but no neuropsychological test was performed. Cerebral tomodensitometry was normal. Patient status worsened rapidly and he died a few months later. Autopsy was not done.

Patient I1

Patient II2's mother complained of gait instability from the age of 24 years (fig 1). Examination revealed gait ataxia and balance impairment with wide based gait, four limb dysmetria and dysarthria. Subsequently, memory deterioration appeared as well as pyramidal signs. Cerebellar signs and cognitive impairment progressively worsened and the patient was then lost to follow up. She died at age 35 years.

Genomic DNA was isolated from blood lymphocytes of patient III2 and her mother II1 after informed consent was obtained. The entire coding sequence and the exon/intron boundaries of the *PSEN1* gene were sequenced, as previously described.[4] To ensure that mutations detected in patients were not common polymorphisms, we determined that they were absent in 50 control DNA samples.

One novel *PSEN1* mutation was found in patient III2. She was heterozygous for the c349 C>G pPro117Ala mutation in exon 5 and for the known polymorphism c953 A>G pGlu318Gly in exon 9. No *PSEN1* mutation was found in II1. This was consistent with the

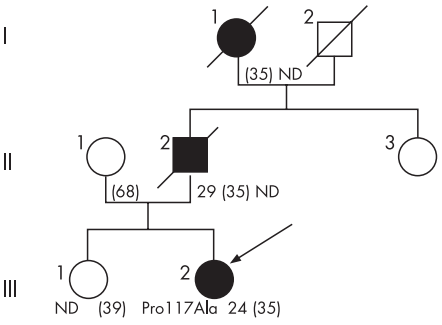

Figure 1 Family pedigree. Squares = males; circles = females; filled symbols = affected subjects; diagonal line = deceased subject; arrow = proband. ND, sequencing not done. Age of onset, current age or age at death (in parentheses) are indicated.

inheritance of both the mutation and polymorphism of patient III2 from her father.

Discussion

We have reported three patients from the same family affected with early progressive ataxia and dementia, associated with a new *PSEN1* mutation. *PSEN1* mutations account for 50–60% of ADEOAD.[4–6] Cerebellar signs, that occurred 1–7 years after the onset of cognitive deterioration, were previously reported with the following *PSEN1* mutations: Met139Val,[7] Glu280Ala,[8] Leu166Pro,[9] Tyr256Ser[10] and Leu282Val.[11] Our description seems similar to the predominant cerebellar ataxia associated with psychiatric symptoms recently reported in a 28-year-old-man carrying a *PSEN1* Ser170Phe mutation.[3] Of note, the phenotype was homogeneous in our family with early onset before 35 years and death between 35 and 40 years. This severity can be correlated with the Pro117Ala genotype because other substitutions of proline in position 117 (Pro117Leu, Pro117Arg, Pro117Ser) have been described previously as responsible for severe ADEOAD. However, no cerebellar sign was associated with these mutations. The original phenotype in the present family is due to the Pro117Leu mutation because the associated Glu318Gly substitution in exon 9 is a non-causative polymorphism.[12]

Whether ataxia is correlated with cerebellar pathology was not demonstrated in the present case in the absence of a neuropathological study. Cerebellar changes such as Aβ deposition in the molecular and inner granular layers and amyloid angiopathy have been reported in a series of 48 *PSEN1* linked ADEOAD but none had cerebellar ataxia.[8] Conversely, severe cerebellar degeneration was reported in patients who presented with cerebellar signs during the course of AD due to an Ile143Thr mutation.[13] Moreover, abundant diffuse amyloid deposits in the molecular layer, plaques in Purkinje cells and inner granular layers and severe loss of Purkinje cell dendrites were demonstrated in an ataxic case with a *PSEN1* Ser170Phe mutation.[3]

In conclusion, the present study demonstrates that *PSEN1* linked ADEOAD has to be considered, even when ataxia precedes dementia, the Pro117Ala mutation being responsible for a predominant precocious ataxia. Correlations between the functional consequences of this novel mutation on the Aβ species and this ataxic variant of AD are still not understood.

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doi: 10.1136/jnnp.2007.123026

Competing interests: None.

References

1 **Sherrington R**, Rogaev EI, Liang Y, *et al.* Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995;**375**:754–60.
2 **Rogaev EI**, Sherrington R, Rogaeva EA, *et al.* Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995;**376**:775–8.
3 **Piccini A**, Zanusso G, Borghi R, *et al.* Association of a presenilin 1 S170F mutation with a novel Alzheimer disease molecular phenotype. *Arch Neurol* 2007;**64**:738–45.
4 **Raux G**, Guyant-Marechal L, Martin C, *et al.* Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. *J Med Genet* 2005;**42**:793–5.
5 **Hutton M**, Busfield F, Wragg M, *et al.* Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. *Neuroreport* 1996;**7**:801–5.
6 **Arango D**, Cruts M, Torres O, *et al.* Systematic genetic study of Alzheimer disease in Latin America: mutation frequencies of the amyloid beta precursor protein and presenilin genes in Colombia. *Am J Med Genet* 2001;**103**:138–43.
7 **Finckh U**, Muller-Thomsen T, Mann U, *et al.* High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes. *Am J Hum Genet* 2000;**66**:110–17.
8 **Mann DM**, Pickering-Brown SM, Takeuchi A, *et al.* Amyloid angiopathy and variability in amyloid beta deposition is determined by mutation position in presenilin-1-linked Alzheimer's disease. *Am J Pathol* 2001;**158**:2165–75.
9 **Moehlmann T**, Winkler E, Xia X, *et al.* Presenilin-1 mutations of leucine 166 equally affect the generation of the Notch and APP intracellular domains independent of their effect on Abeta 42 production. *Proc Natl Acad Sci U S A* 2002;**99**:8025–30.
10 **Miklossy J**, Taddei K, Suva D, *et al.* Two novel presenilin-1 mutations (Y256S and Q222H) are associated with early-onset Alzheimer's disease. *Neurobiol Aging* 2003;**24**:655–62.
11 **Dermaut B**, Kumar-Singh S, De Jonghe C, *et al.* Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's disease due to a novel presenilin 1 mutation. *Brain* 2001;**124**:2383–92.
12 **Mattila KM**, Forsell C, Pirttila T, *et al.* The Glu318Gly mutation of the presenilin-1 gene does not necessarily cause Alzheimer's disease. *Ann Neurol* 1998;**44**:965–7.
13 **Martin JJ**, Gheuens J, Bruyland M, *et al.* Early-onset Alzheimer's disease in 2 large Belgian families. *Neurology* 1991;**41**:62–8.

Patients characteristics with cholinesterase inhibitor resistant hallucinations in dementia with Lewy bodies

Cholinesterase inhibitors (ChEIs) are effective in treating visual hallucinations (VH) in dementia with Lewy bodies (DLB). Nonetheless, approximately 35% of patients treated with rivastigmine showed no significant improvement according to the psychosis subscores of the Neuropsychiatry Inventory (NPI).[1] We conducted an observational study in our memory clinic and we report the characteristics of patients who showed resistant hallucinations (RH) to ChEIs.

Methods

We carried out an observational study of outpatients with DLB with hallucinations treated with ChEIs over 4 years. Probable DLB was diagnosed according to the second consensus criteria, and the severity of dementia was assessed using the Mini-Mental State Examination (MMSE) score. We excluded patients who required concomitant medications other than ChEIs that influence hallucinations or if they were treated with antipsychotics. Episodes of delirium were determined using clinical assessment (DSM-IV), and a standard biological screening was performed when hallucinations appeared. Patients with concomitant cerebrovascular pathology were excluded.

The consultant initiated ChEIs in accordance with the criteria of the first double blind placebo controlled trial in DLB with rivastigmine.[1] Rivastigmine was chosen preferentially, and donepezil or galantamine was proposed when rivastigmine was not tolerated or when a single daily dose was desirable. The dose of ChEIs was titrated monthly to the maximum tolerated dose. The minimal daily efficient dose of rivastigmine (6 mg), donepezil (5 mg) or galantamine (16 mg) was the threshold under which patients were excluded. Patients were followed for 6 months.

Different modalities of hallucinations were assessed at baseline and during the follow-up period and were quantified using the global hallucinations subscore of the NPI (HS-NPI) scored on 12 points. Efficacy of ChEIs was evaluated as the number of patients whose HS-NPI score improved by at least 30% from baseline. Patients who fell below the threshold level of improvement were classified as RH patients.

Results

Thirty-six DLB patients (18 females/18 males) were included. Mean age was 65.9 (9.1) years. Mean MMSE score was 24.7 (4.2). Baseline severity of dementia was mild (MMSE $\geq$18) in 33 patients and moderate (10$<$ MMSE $<$18) in three patients. Hallucinations appeared, on average, 2.2 (1.4) years after the onset of the disease. The mean HS-NPI was 7.1 (3.1). Twenty-two patients were treated with rivastigmine, nine with donepezil and five with galantamine; none had stopped ChEIs treatment. The mean decrease in HS-NPI was 3.5, and was significant (7.2 (3.1) vs 3.7 (3.2); $U = -4.9$, $p<0.0001$). Nine patients (24%) had RH (22% with rivastigmine, 22% with donepezil and 40% with galantamine). The characteristics of the two groups are described in table 1. We performed a logistic regression analysis to clarify which factors had independent prognostic value in RH. When we entered severity of dementia, HS-NPI baseline score, type of hallucinations, delusion, depressive symptoms and type of ChEIs into the model, delusion (odd ratio 0.29, 95% CI 0.001 to 0.64) predicted resistance of ChEIs on VH. Non-visual hallucinations and depressive symptoms were more frequent in patients with RH, but this was not significant.

Discussion

The frequency of patients with RH was 24%, in agreement with the literature data. This observational study has proposed that delusions are associated with RH. Various biological abnormalities have been described between patients with hallucinations and those with