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 Tyr256Ser¹⁰ 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 A β 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 A β 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

- 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.
- 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.
- Picini A, Zanuso 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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 A β 24 production. *Proc Natl Acad Sci U S A* 2002;**99**:8025–30.
- Miklosy 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.
- 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.
- Mattila KM, Forsell C, Pirttilä T, *et al.* The Glu318Gly mutation of the presenilin-1 gene does not necessarily cause Alzheimer's disease. *Ann Neurol* 1998;**44**:965–7.
- Martin JJ, Gheuens J, Bruylant 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 (odds 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

Table 1 Clinical characteristics of patients with dementia with Lewy bodies, with cholinesterase inhibitor resistant hallucinations (RH patients) compared with patients with dementia with Lewy bodies whose hallucinations improved with cholinesterase inhibitors (improved patients)

	RH patients (n = 9)	Improved patients (n = 27)
Age	66.6 (8.5)	65.2 (8.6)
Sex (M/F)	3/6	15/12
Severity of dementia (mild/moderate)	7/2	26/1
Duration of DLB	2.7 (2.1)	2.0 (1.1)
Hallucinations baseline subscore NPI	8.6 (3.0)	6.6 (3.1)
Type of hallucinations		
Visual	4 (44)	23 (85)
Non-visual	5 (56)	4 (15)
Delusion	7 (78)	2 (7)
Depressive symptoms	8 (89)	13 (48)
Nightmares	6 (67)	24 (89)
Sleep apnoea	0 (0)	5 (18)
Extrapyramidal signs	6 (67)	21 (78)
MRI hyperintensities	4 (44)	6 (22)
Type of ChEIs		
Rivastigmine	5 (55)	17 (63)
Donepezil	2 (22.5)	7 (26)
Galantamine	2 (22.5)	3 (11)
Maximal dosage	7 (78)	13 (49)

ChEIs, cholinesterase inhibitors; DLB, dementia with Lewy bodies; NPI, Neuropsychiatry Inventory. Results are shown as number of patients (%).

delusions. This may explain the variable response to ChEIs. Muscarinic M1 receptors² are only increased in patients with delusions whereas M4 receptors are only increased in patients with VH.³ Moreover, plaques and tangles staging are associated with VH and not with delusions.⁴

The data, although limited by the open label design of the study and the small number of patients, need to be confirmed in double blind studies using behavioural scales with subscores to assess each psychotic symptom. Hallucinations associated with delusions might require different treatment than isolated VH.

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doi: 10.1136/jnnp.2007.119446

Funding: This work was supported by grant EA 2691.

Competing interests: None.

References

- 1 **McKeith I**, Del Ser T, Spano P, *et al*. Efficacy of rivastigmine in dementia with Lewy bodies: a randomized, double-blind, placebo-controlled international study. *Lancet* 2000;**356**:2031–6.
- 2 **Ballard CG**, Piggott M, Johnson M, *et al*. Delusion associated with elevated muscarinic binding in dementia with Lewy bodies. *Ann Neurol* 2000;**48**:868–76.
- 3 **Teaktong T**, Piggott MA, McKeith IG, *et al*. Muscarinic M2 and M4 receptors in anterior cingulate cortex: relation to neuropsychiatric symptoms in dementia with Lewy bodies. *Behav Brain Res* 2005;**20**:299–305.
- 4 **Ballard CG**, Jacoby R, Del Ser T, *et al*. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with Lewy bodies. *Am J Psychiatry* 2004;**161**:843–849.

BOOK REVIEW

Paediatric neurology: principles and practice, 4th edition

Edited by Kenneth F Swaiman, Stephen Ashwal, Donna M Ferriero. Philadelphia: Elsevier, 2007, pp 1177. ISBN 139780323033657

Published at the end of last year, this two volume set is the fourth edition of a highly respected American textbook of paediatric neurology. In the current edition, the editors have updated and supplemented previous editions. In particular, a new co-editor Dr Ferriero brings additional neonatal expertise to the text. These books are weighty in every sense, comprising a total of 2672 pages, and logically divided into 16 sections which cover all areas of paediatric neurology, beginning with clinical evaluation and diagnostic testing, through to all aspects of developmental and acquired neurological disorders. Recent advances in basic science and genetics are reflected throughout the text—for example, there are now chapters on neurogenetics and on the neurophysiology and genetics of epilepsy. Less mainstream aspects are also covered in some detail—for example, there are sections on the effects of systemic disease on the nervous system and on the neurobehavioural disorders and their psychopharmacology. The second volume finishes with a useful section on the overall care of children with neurological disorders, including new chapters on ethical issues and the role of the internet and its resources. Each chapter is well referenced (up to 2004) and the index is excellent.

Despite this being an American textbook, it is highly applicable to UK practice both for experienced clinicians and those in training. Areas of potential diversity such as statutory procedures in non-accidental injury or ethical

judgements are dealt with in a broad manner. A few eponymous terms are absent—for example, Pickwickian syndrome is now just one aetiological factor in sleep apnoea and Ondine's curse is simply referred to as congenital central alveolar hypoventilation. Overall, this book admirably fulfils its aims in giving a comprehensive clinical overview of the subject, presented alongside the relevant science. It can be strongly recommended to any clinician involved in the care of children with developmental and neurological disorders.

L J Carr

CORRECTIONS

doi: 10.1136/jnnp.2006.102731corr1

M P J Garssen, R van Koningsveld, P A van Doorn. Treatment of Guillain-Barré syndrome with mycophenolate mofetil: a pilot study. *J Neurol Neurosurg Psychiatry* 2007;**78**:1012–3. The authorship of this paper was incorrectly assigned to just three authors. The paper was actually authored by the entire Dutch GBS study group: MPJ Garssen, R van Koningsveld and PA van Doorn (writing group), ISJ Merkies, M Scheltens-de Boer, Erasmus Medisch Centrum, Rotterdam; JA van Leusden, Medisch Centrum Alkmaar, Alkmaar; IN van Schaik, Academisch Medisch Centrum, Amsterdam; WHJP Linssen, Sint Lucas Andreas Ziekenhuis, Amsterdam; F Visscher and AM Boon, Stichting Oosterscheldeziekenhuizen, Goes; CG Faber, Academisch Ziekenhuis Maastricht, Maastricht; J Meulstee and MJJ Prick, Nijmeegs Interkonnektioneel Ziekenhuis Canisius-Wilhelmina, Nijmegen; LH van den Berg and H Franssen, Universitair Medisch Centrum Utrecht, Utrecht; JAP Hiel, Sint Joseph Ziekenhuis, Veldhoven, The Netherlands; PYK van den Bergh and CJM Sindic, Clinique Universitaire St. Luc, Brussels, Belgium.

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doi: 10.1136/jnnp.2004.052654corr1

M C Obonsawin, S Jefferis, R Lowe, *et al*. A model of personality change after traumatic brain injury and the development of the Brain Injury Personality Scales (*J Neurol Neurosurg Psychiatry* 2007;**78**:1239–47). In figure 3 of this paper, panels A and B should be on the left hand side, and panels C and D on the right hand side. In addition, the lines for "Social engagement" and "Emotional engagement" on all panels should be in black.

doi: 10.1136/jnnp.2006.103739corr1

J Ludwig, P Remien, C Guballa, *et al*. Effects of subthalamic nucleus stimulation and levodopa on the autonomic nervous system in Parkinson's disease (*J Neurol Neurosurg Psychiatry* 2007;**78**:742–5). In figure 1, panels B, D and F, the symbols for "before levodopa" and "after levodopa" should be interchanged—that is, the triangles should be named "before levodopa" and the squares "after levodopa".