Neurology & Neurophysiology

Hu, et al., J Neurol Neurophysiol 2014, 5:5
http://dx.doi.org/10.4172/2155-9562.1000238

Research Article Open Access

CSF and Neuropsychological Correlates of Visual Hallucination in Dementia with Lewy Bodies

William T Hu*, **Manuel Hazim, Chadwick M Hales, James L Lah and Allan I Levey**

Department of Neurology, Emory University, Atlanta, USA

***Corresponding author:** William Hu, Department of Neurology, Emory University 615 Michael Street, 505F Atlanta, GA 30322, USA, Tel: 404-727-4174; E-mail: wthu@emory.edu

Received date: July 28, 2014, **Accepted date:** Oct 13, 2014, **Published date:** Oct 20, 2014

Abstract

Objective: To identify clinical features of dementia with Lewy bodies (DLB) least likely associated with Alzheimer's disease pathology, and to determine whether it is associated with a unique neuropsychological profile.

Methods: Clinical records of 98 patients given the diagnosis of DLB at a specialty cognitive and behavioral neurology clinic in a tertiary referral center were retrospectively reviewed for core, suggestive, and supportive features of DLB as well as demographic variables, cerebrospinal fluid (CSF) Alzheimer's biomarkers, and longitudinal neuropsychological analyses.

Results: Core, suggestive, and supportive features were common in this cohort, with 69% and 39% of patients assigned the diagnosis of probable DLB and possible DLB fulfilling consensus criteria for probable DLB. 26 of 98 clinically diagnosed DLB patients had CSF Alzheimer's biomarker analysis, and visual hallucination was the only feature not associated with CSF suggestive of Alzheimer's disease. 42 of 98 patients had longitudinal neuropsychological analyses, and patients with visual hallucinations had worse baseline executive functions but slower longitudinal decline in executive functions than patients without visual hallucinations.

Conclusion: Visual hallucination in clinically diagnosed DLB is associated with CSF biomarkers consistent with a non-AD disorder and a unique longitudinal neuropsychological profile. DLB patients with visual hallucinations can be considered a unique DLB endophenotype for future biomarker discovery and validation.

Keywords: Biomarker; Cerebrospinal fluid; Executive function; Parkinsonism

Introduction

The clinicopathologic entity of dementia with Lewy bodies (DLB) has been one of much controversy. Since Lewy bodies were first linked to dementia [1], the ante-mortem detection of Lewy pathology has been elusive [2-5]. Lewy pathology [6] - including Lewy bodies and Lewyneurites - can occur in cognitively healthy seniors, patients with Parkinson's disease with or without cognitive impairment, as well as patients with Alzheimer's disease (AD) with or without Parkinsonism [7]. The term Lewy body disease has been proposed to group those with diagnosed with dementia with Lewy bodies and those diagnosed with Parkinson's disease dementia (PDD)[8]. However, one must overlook the drastic diagnostic performance differences between DLB (low sensitivity, high specificity)[4,5] and PDD (high sensitivity, low specificity for cause of dementia)[9] to systematically merging the two patient cohorts in hopes of identifying phenotypic overlaps in Lewy body disease. The co-existence of AD pathology (anywhere from focal to diffuse) in both syndromes further complicates matters, especially when there is no consistent, evidence-based method to assign causality among concurrent pathologic changes. As such, the natural history of Lewy pathology remains difficult to interpret [10,11].

Unlike Lewy pathology, AD pathology is increasing detected in the ante-mortem phase through biomarkers from pre-symptomatic and symptomatic individuals [12]. Because AD remains the most common alternate finding in neuropathologic studies of clinically diagnosed DLB, we hypothesize that the introduction of AD biomarkers will significantly enhance the natural history studies of DLB. Here we describe a DLB case series from a tertiary referral center, explore potential clinical features most correlated with cerebrospinal fluid (CSF), and determine the cognitive profiles most correlated with these clinical features.

Methods

Records of all patients evaluated and followed at the Emory Clinic Cognitive & Behavioral Neurology Clinic between January 1st, 2010 and June 30th, 2014 were retrospectively reviewed by WTH and MH. All patients were evaluated by neurologists (William Hu, Chadwick Hales, James Lah, Allan Levey) experienced in the diagnosis and treatment of dementing disorders including DLB, AD, and frontotemporal dementia. Each patient with qualifying diagnosis was individually identified, including those with "Lewy body dementia", "dementia with Lewy bodies", "probable/possible dementia with Lewy bodies", "Lewy body disease", "diffuse Lewy body disease". Every patient had undergone blood work, neuropsychological testing, and brain imaging to rule out alternate causes of cognitive impairment. Records were reviewed for the presence of core, suggestive, and supportive features of DLB according consensus guidelines[13]. As part of new patient evaluation and follow-up, a form-based review of system was administered yearly to determine whether patients had

experienced visual, auditory, and tactile hallucinations; tremors, gait changes, and falls; sleep disturbance (including insomnia, sleep apnea, dream enactment behavior, restless leg syndrome); and systemic symptoms (constipation as part of the gastroenterologic review of systems). Clinician examination was reviewed for the presence of key parkinsonian features, including tremors (resting, action, postural), rigidity (at least one limb), bradykinesia, and gait instability (gait examination and pull test). As Parkinsonism can be common in neurodegenerative disorders, we elected to use 2 or more parkinsonian features as the presence of Parkinsonism. Demographic information including age at evaluation, disease duration, gender, and education was also recorded.

26 patients underwent CSF analysis, and CSF AD biomarkers - including amyloid-beta 1-42 (Aß42), total Tau (t-Tau), and Tau phosphorylated at threonine 181 (p-Tau181) - were measured in all subjects using a protocol modified from the Alzheimer's Disease Neuro-Imaging Initiative to optimize measurement precision as previously described[14].The ratio of CSF t-Tau/Aß42 was used to determine whether each DLB patient had CSF biomarkers consistent with AD (t-Tau/Aß42 ≥ 0.39) or not consistent with AD (t-Tau/Aß42 < 0.39) [15]. DLB patients with CSF analysis were then categorized as with or without positive CSF AD biomarkers.

Standardized neuropsychological analyses were performed in 96 out of 98 patients at baseline, and 190 out of 193 total patient-visits. Each patient underwent testing for memory (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] word list delayed recall raw score and percent retention) [16], executive function (Trail Making Test B [17,18], reverse digit span, letter-guided fluency [19]), language (Boston Naming Test, category fluency for animals) [19], and visuospatial function (CERAD praxis copying) [16]. All cognitive sub-test scores were converted to age-, gender-, education-, and race-adjusted Z-scores. A domain specific Z-score was then calculated based on the average of all Z-scores within that domain, and a composite Z-score was calculated by averaging the four domain specific Z-scores. Mini-Mental State Examination (MMSE) was administered from 2010 to 2012, and Montreal Cognitive Assessment (MoCA) was administered from 2012 to 2014.

Statistical Analysis

All statistical analyses were performed in SPSS 20 (Chicago, IL). At baseline, Chi-squared tests were used for categorical variables, and Student's T-test or analysis of variance was used for continuous variables. To determine if CSF AD biomarker profiles were associated with certain DLB features, Chi-squared test or Fisher's exact test was performed between those with CSF t-Tau/Aß42 ≥ 0.39 and those with CSF t-Tau/Aß42 < 0.39, with $p < 0.01$ as the threshold for significance to account for multiple comparisons. For longitudinal analysis, a linear mixed model was used to allow for within-subject correlation of repeated neuropsychological measures, and unique slopes and intercept for each subject. Time (in months) was entered as a repeated factor, and cognitive scores (memory/executive/language/visuo-spatial composite Z-scores) were entered as dependent variables. Time was treated as both a random and a fixed effect. Demographic variables (age, gender, education) were entered as fixed effects along with their interaction with time. For between-group longitudinal analysis using the linear mixed model, T-statistics were computed for the interaction term between time and the presence of visual hallucination. A significant difference in this interaction term was interpreted as a difference in slope (greater or slower decline over time) between those with and without visual hallucination. Statistical significance was set at $p < 0{\cdot}05$.

Results

98 patients were included in this study, including 80 given the diagnosis of probable DLB and 18 given the diagnosis of possible DLB. Patients given these two diagnoses were similar according to baseline demographics, clinical features, and cognitive testing results (Table 1), with the exception that resting tremor was more common in patients assigned the diagnosis of possible DLB.

	Probable DLB (n=80)	Possible DLB (n=18)
Male (%)	51 (64%)	9 (50%)
Age at evaluation, yr (SD)	71 (8.2)	72.9 (9.3)
Disease duration at evaluation, yr (SD)	2.59 (0.22)	2.19 (0.35)
Education, yr (SD)	15.0 (0.4)	14.4 (0.8)
Fulfilled McKeith criteria for probable DLB (%)*	55 (69%)	7 (39%)
Clinical features	46 (57%)	7 (39%)
Visual hallucination	51 (64%)	11 (61%)
Spontaneous parkinsonism	20 (25%)	10 (56%)
Resting tremors**	8 (10%)	1 (6%)
Action or postural tremors	42 (52%)	11 (61%)
Rigidity	34 (42%)	7 (39%)
Bradykinesia	60 (75%)	12 (67%)
Gait instability	21 (26%)	3 (17%)
Fluctuation	39 (49%)	4 (22%)
Dream enactment behavior	23 (29%)	5 (28%)
Sleep talking	47 (59%)	9 (50%)

Visuospatial difficulties	17 (21%)	5 (28%)
Constipation	9 (11%)	0
Orthostatic lightheadedness		
Cognitive Z-scores at baseline	-1.96 (0.18)	-1.84 (0.40)
Memory	-1.99 (0.13)	-2.01 (0.31)
Executive	-1.20 (0.12)	-1.37 (0.35)
Language	-2.77 (0.16)	-2.77 (0.45)
Visuospatial	-1.99 (0.12)	-2.00 (0.33)
Composite		

Table 1: Baseline demographics of the cohort. Patients were included in the current study if they were assigned a diagnosis of "probable DLB" or "possible DLB" by their treating neurologists. Patients carrying the diagnosis of probable DLB were more likely to fulfill the McKeith criteria for probable DLB than patients carrying the diagnosis of possible DLB (* p = 0.029), and were much less likely to have resting tremors (** p = 0.02).

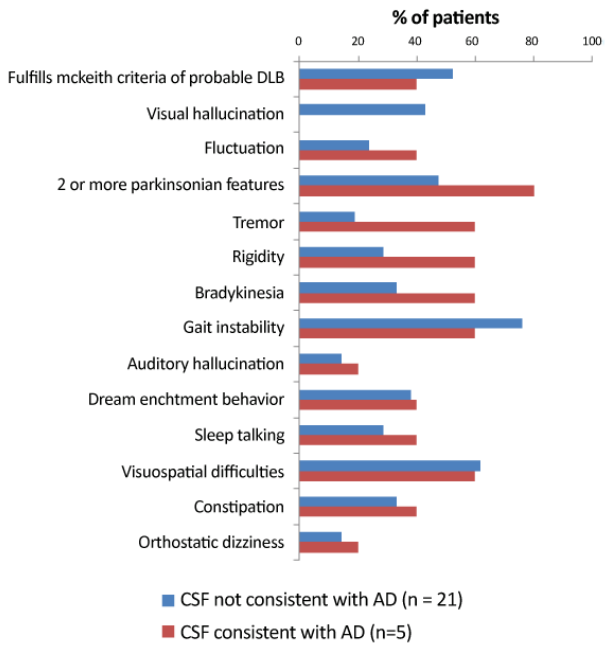

Figure 1: Prevalence of DLB-associated features according to CSF AD biomarker profile. 21 of 26 patients had CSF profiles consistent with a non-AD disorder, and 5 patients had CSF profiles consistent with AD.

Because there is currently no reliable ante-mortem biomarker for Lewy pathology in demented individuals, we set out to determine if the clinical diagnosis of DLB was associated with CSF AD biomarker profiles consistent with non-Alzheimer's disorders. Compared to patients who did not undergo CSF analysis, patients who underwent CSF analysis were younger (65.5 yr vs. 73.4 yr, p < 0.001) but otherwise similar in demographic factors, clinical features, and baseline neuropsychological performance. All 26 patients had CSF AD biomarker analysis, and two patients with CSF profiles consistent with a non-AD disorder had autopsy finding of diffuse Lewy body disease. When their clinical features and neuropsychological analyses were examined, DLB patients with CSF biomarkers consistent with a non-AD disorder (n=21) were more likely to have visual hallucination than those with CSF biomarkers consistent with AD (43% vs. 0%, p = 0.129, Figure 1). The two groups were otherwise similar in other clinical features and baseline performance on detailed cognitive testing (data not shown).

We next determined if there was a unique longitudinal cognitive profile associated with visual hallucination at baseline. Compared to patients who did not undergo follow-up (n=56), patients who underwent longitudinal follow-up (n=42) were less cognitively impaired (composite cognitive Z-score of -1.634 vs. -2.266, p < 0.001) and less likely to have visual hallucinations (43% vs. 62%, p = 0.067). However, since visual hallucination was still very common in those with longitudinal analysis, we performed mixed linear analysis to determine if visual hallucination was associated with worse baseline cognitive performance as well as worse longitudinal progression. Visual hallucination at baseline was not associated with different baseline or longitudinal differences in composite cognitive Z-scores (main effect for baseline: F=0.149, p=0.700; for longitudinal change: F=0.422, p=0.519). When each cognitive domain-specific Z-score was examined, visual hallucination was strongly associated with a unique baseline (F=5.238, p=0.024) and longitudinal (F=11.385, p=0.001) executive function profile. Compared to those without visual hallucinations, DLB patients with visual hallucinations had worse baseline executive function but slower longitudinal decline in executive function (Table 2, Figure 2). Given the possible floor effect (i.e., DLB patients with visual hallucinations have bottomed out on their executive function tests), a cohort of longitudinal followed healthy control seniors with normal cognition (n=38) were introduced to the model. Compared to the healthy control seniors, mixed linear analysis showed that DLB patients with hallucinations had a definite longitudinal decline in their executive functions (p=0.016) even though the group-level slope of decline is smaller than that for DLB patients without visual hallucinations.

Discussion

The longitudinal clinical correlate of Lewy pathology is poorly understood. Here we show that the visual hallucination is highly associated with CSF biomarkers consistent with a non-AD disorder among clinically diagnosed DLB patients. Consistent with prior reports, DLB patients with visual hallucinations had worse baseline

executive dysfunctions [20]. We further showed in a longitudinal cohort that DLB patients with visual hallucinations had slower longitudinal decline than DLB patients without visual hallucinations. We propose that visual hallucination in DLB is associated with a unique CSF and neuropsychological signature, and can be used to identify a DLB endophenotype for further biomarker discovery.

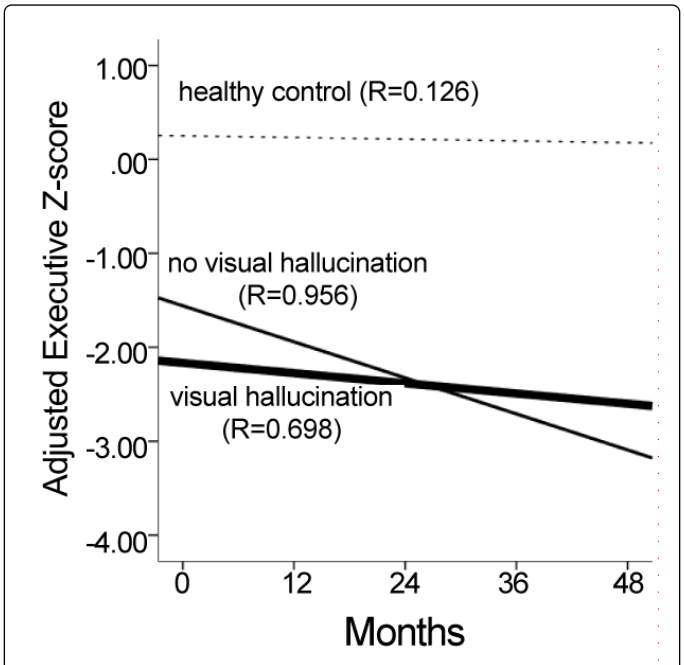

Figure 2: Adjusted longitudinal change in executive Z-scores of DLB patients with (n=18) and without (n=24) visual hallucinations as well as health seniors (n=38). Executive Z-scores were adjusted for age, gender, education, disease duration, and presence of 2 or more parkinsonian features.

Parameter	Estimate (95% confidence interval)	p-value
Intercept	-1.015 (-3.684, 1.654)	0.447
Age (yr)	-0.013 (-0.043, 0.018)	0.409
Male gender	0.661 (0.094, 1.228)	0.023
Education (yr)	0.005 (-0.073, 0.832)	0.897
Disease duration (yr)	-0.063 (-0.183, 0.056)	0.293
2 or more parkinsonian features	-0.262 (-0.585, 0.060)	0.110
Months	-0.003 (-0.016, 0.009)	0.606
Visual hallucination	-0.480 (-0.894, -0.066)	0.023
Visual hallucination x Months	0.021 (0.008, 0.034)	0.002

Table 2: Effect of visual hallucination on executive dysfunction in DLB. Mixed linear modeling of the relationship between visual hallucination and longitudinal decline in executive function adjusted for age, gender, education, disease duration, and the presence of 2 or more parkinsonian features (n=42 for the

The biological significance of pure Lewy pathology vs. mixed AD/Lewy pathology is unknown. Unlike one prior report examining 22 autopsy-confirmed cases of DLB[21], we did not find those with visual hallucinations to have worse visuospatial decline over time even though our DLB patients had quite impaired performance on visuospatial testing (Table 1). This may be due to differences in patient population as baseline visual hallucination was uncommon in the prior population and 63% of their DLB patients had intermediate or high probability AD on autopsy. Among our patients with CSF analysis, 19% had CSF biomarkers suggestive of AD and none of them had visual hallucinations. This is consistent with prior observation using cerebral amyloid imaging that a moderate proportion of clinically diagnosed DLB patients had AD pathology[22].We may hypothesize that these patients have mixed AD/Lewy pathology, although it is also possible that they have atypical Alzheimer's disease without any Lewy pathology. Alternatively, this proportion is in keeping with the proportion of healthy seniors with CSF biomarkers consistent with AD from large series such as the Alzheimer's DiseaseNeuro-imaging Initiative (ADNI) [15], and may represent incidental rather than pathologic findings. Future studies should compare the degree of cortical Lewy pathology between clinically diagnosed DLB patients with AD-like CSF and pathologically confirmed pure Lewy body disease to determine whether those with AD-like CSF had sufficient degree of diffuse cortical Lewy pathology to account for early features suggestive of Lewy pathology.

While this is a moderate series of DLB patients with CSF AD biomarkers and longitudinal analyses, our study has a number of limitations. In keeping with other retrospective reviews, our determination of the presence or absence of clinical features depended on detailed clinical notes. We primarily focused on features which were consistently documented as absent or present, but there were other features inconsistently captured (e.g., neuroleptic sensitivity)which could hold critical clinical significance. No patient had functional imaging in the diagnostic work-up for DLB [23], and dream enactment behavior was not always followed up with sleep study to document true REM behavior disorder. Only a portion of the baseline and longitudinal cohort had CSF analysis, and a larger number of CSF samples will be necessary to determine whether there are more subtle differences in clinical features between those with different AD biomarker profiles. Similarly, only a portion of the baseline population underwent longitudinal follow-up, and the omission of more severely affected patients from longitudinal analysis may bias our longitudinal analysis. Finally, only two cases had undergone autopsy, and the variability in clinical features (both baseline and longitudinal) can be heavily influenced by the distribution of Lewy pathology as well as other co-pathology including AD, inclusions immunoreactive to TAR DNA binding protein of ~43 kD., and microvascular lesions. Nevertheless, we propose that visual hallucination - one of the most prominent and distinguishing features of Lewy pathology - is not likely associated with AD-like CSF, and has a unique longitudinal executive function profile.

References

1. Okazaki H, Lipkin LE, Aronson SM (1961) Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. J NeuropatholExpNeurol 20: 237-244.
2. Kosaka K, Yoshimura M, Ikeda K, Budka H (1984) Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? ClinNeuropathol 3: 185-192.
3. Burkhardt CR, Filley CM, Kleinschmidt-DeMasters BK, de la Monte S, Norenberg MD, et al. (1988) Diffuse Lewy body disease and progressive dementia. S Neurology 38: 1520-1528.

4. Litvan I, MacIntyre A, Goetz CG, Wenning GK, Jellinger K, et al. (1998) Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol 55: 969-978.
5. Nelson PT, Jicha GA, Kryscio RJ, Abner EL, Schmitt FA, et al. (2010) Low sensitivity in clinical diagnoses of dementia with Lewy bodies. J Neurol 257: 359-366.
6. Dickson DW (2002) Dementia with Lewy bodies: neuropathology. See comment in PubMed Commons below J Geriatr Psychiatry Neurol 15: 210-216.
7. Schneider JA, Arvanitakis Z, Yu L, Boyle PA, Leurgans SE, et al. (2012) Cognitive impairment, decline and fluctuations in older community-dwelling subjects with Lewy bodies. Brain 135: 3005-3014.
8. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, et al. (2007) DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 68: 812-819.
9. Hughes AJ, Daniel SE, Blankson S, Lees AJ (1993) A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 50: 140-148.
10. Ballard CG, O'Brien JT, Swann AG, Thompson P, Neill D, et al. (2001) The natural history of psychosis and depression in dementia with Lewy bodies and Alzheimer's disease: persistence and new cases over 1 year of follow-up. J Clin Psychiatry 62: 46-49.
11. Ransmayr G (2000) Dementia with Lewy bodies: prevalence, clinical spectrum and natural history. J Neural TransmSuppl : 303-314.
12. Hu WT, Shaw LM, Trojanowski JQ (2013) Alzheimer's disease biomarkers: walk with deliberate haste, don't run blithely on? ActaNeuropathol 126: 625-629.
13. McKeith IG (2006) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis 9: 417-423.
14. Hu WT, Watts K, Grossman M, Glass J, Lah JJ, et al. (2013) Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLD-TDP. Neurology 81: 1945-1952.
15. Shaw LM, Vanderstichele H,Knapik-Czajka M, Clark CM, Aisen PS, et al. (2009). Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65 : 403-413.
16. Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A (1988) Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. See comment in PubMed Commons below Psychopharmacol Bull 24: 641-652.
17. Reitan RM (1955) The relation of the trail making test to organic brain damage. See comment in PubMed Commons below J Consult Psychol 19: 393-394.
18. Reitan RM (1958) Validity of the Trail Making test as an indicator of organic brain damage., in Percept Mot Skills 271-276.
19. Benton AL and Hamsher K (1976) Multilingual Aphasia Examination, ed. Iowa City: University of Iowa.
20. Cagnin A, Gnoato F, Jelcic N, Favaretto S, Zarantonello G, et al. (2013) Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. J NeurolNeurosurg Psychiatry 84: 505-510.
21. Hamilton JM, Salmon DP, Galasko D, Raman R, Emond J, et al. (2008) Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies. Neuropsychology 22: 729-737.
22. Foster ER, Campbell MC, Burack MA, Hartlein J, Flores HP, et al. (2010) Amyloid imaging of Lewy body-associated disorders. MovDisord 25: 2516-2523.
23. McKeith IJ O'Brien, Walker Z, Tatsch K,Booij J, Darcourt J, et al.(2007). Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol6: 305-313.