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Influence of education on cognitive performance and dopamine transporter binding in dementia with Lewy bodies

Guillaume Lamotte[a,b,*], Rémy Morello[c], Adrien Lebasnier[d], Denis Agostini[d], Gérard Bouvard[d], Vincent De La Sayette[a,e], Gilles L. Defer[a,f]

[a] *Department of Neurology, University Hospital of Caen, Avenue Cote de Nacre, 14033 Caen, France*
[b] *Department of Neurology, MedStar Georgetown University Hospital, Washington, DC, USA*
[c] *Department of Statistics and Clinical Research, University Hospital of Caen, France*
[d] *Department of Nuclear Medicine, University Hospital of Caen, EA 4650, France*
[e] *Unité INSERM U1077, Neuropsychologie et neuroanatomie fonctionnelle de la mémoire humaine, Université de Caen Basse, Normandie, France*
[f] *Unité INSERM U919, Sérine protéase et physiopathologie de l'Unité Neurovasculaire, GIP Cycéron, Université Caen Basse, Normandie, France*

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ABSTRACT

Objectives: Dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) are the two most common forms of dementia. These two diseases share some clinical and pathological similarities, yet the loss of dopaminergic neurons confirmed by 123-I-Ioflupane Single Photon Emission Computed Tomography (SPECT) is a suggestive feature of DLB. Current evidence suggests that higher education has a protective effect on the risk of developing clinical AD. However, how education influences cognitive performance and the presynaptic dopamine transporter marker in DLB is unknown.
Materials and methods: We reviewed 56 consecutive patients with DLB who underwent a 123-I-Ioflupane SPECT from January 2009 to August 2013 at the University Hospital of Caen. We collected clinical and neuropsychological data from medical files and 123-I-Ioflupane SPECT data for all patients.
Results: There was no correlation between education and global cognitive performance in patients with DLB. However, there was a positive correlation between education and tests exploring visuoconstructive functions (Rey complex figure copy and recall) and verbal retrieval strategies (Grober and Buschke free recall test). There was also a positive correlation between education and dopamine transporter binding. Higher educated patients had higher binding in the striatum, putamen and caudate nucleus ($p = 0.001$ for each regions of interest). Dopamine transporter binding in the striatum, putamen and caudate nucleus was lower in the subgroup of patients with REM sleep behavior disorder, but was not associated with other DLB symptoms.
Conclusion: Higher education may have a protective effect on visuoconstructive performance and verbal retrieval strategies and may influence dopaminergic nigrostriatal neurodegeneration in patients with DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is characterized by progressive dementia and core clinical features including fluctuating cognition, visual hallucinations, and spontaneous parkinsonism [1]. Aside from the rare familial variants, the cause of DLB is unknown and most of the cases are thought to result from a complex interaction between genetic and environmental factors [2]. Current evidence suggests that higher education has a protective effect on the risk of developing clinical Alzheimer's disease (AD) [3]. There is an overlap, both clinically and pathologically, between DLB and AD [2]. However, the influence of education on cognitive performance in DLB is unknown and no significant association was found between the level of education and the risk of DLB in a recent case-control study [4]. The cognitive features in DLB include a dysexecutive syndrome, visuospatial impairment, behavioral symptoms, and memory impairment, which is usually less prominent than in AD [1]. The dorsolateral frontostriatal circuit plays a key role in planning, attention and memory recall, as well as connects the frontal cortex with the striatum and the dopaminer-

* Corresponding author at: Department of Neurology, University Hospital of Caen, CHU de Caen Basse Normandie, Avenue Cote de Nacre, Basse Normandie, 14033 Caen, France.
E-mail address: guillaumelamotte14@gmail.com (G. Lamotte).

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gic system [5]. 123-I-Ioflupane Single Photon Emission Computed Tomography (SPECT) is a reliable and reproducible tool used to evaluate the striatal presynaptic dopaminergic innervation [6], and low dopamine transporter protein (DAT) binding is a suggestive feature of DLB [1]. To date, the manner in which education influences dopamine neurotransmission in DLB is unknown.

Therefore, the aim of this study was to identify if the education level, defined by years of school after first grade, influences cognitive performance and DAT binding assessed with 123-I-Ioflupane SPECT in DLB patients. Primary evaluation criteria were the Mini-Mental-Status-Examination (MMSE) score and the DAT binding in the striatum, caudate nucleus and putamen. Secondary evaluation criteria were the scores on tests exploring executive, memory and instrumental functions when available. We also investigated if DAT binding correlated with motor and non-motor symptoms in DLB.

2. Materials and methods

2.1. Patients

We retrospectively reviewed 56 consecutive patients with a diagnosis of probable DLB according to the international diagnostic criteria [1]. All patients underwent a 123-I-Ioflupane SPECT from January 2009 to August 2013. Examinations were performed as part of routine clinical patient assessments at the Department of Nuclear Medicine of the University Hospital of Caen (France) outside of a research purpose to aid patient management. Due to the retrospective analysis of the data, no informed patient consent was required by the local ethics committee and no radiographic and pathologic images were used in this manuscript. Patients were recruited from the Departments of Neurology and Gerontology, and all patients were originally diagnosed by a movement disorder specialist or by a gerontologist with an expertise in memory disorders. The following were criteria for patient exclusion: symptoms suggestive of a diagnosis other than probable DLB, significant vascular pathology as shown with magnetic resonance imaging (MRI) or computed tomography (CT), persistent severe psychiatric illness, normal pressure hydrocephalus, and the use of any medication known or suspected to interact with DAT binding [7].

We collected clinical and neuropsychological data from medical files for all patients. The score on the MMSE was used to assess global cognitive status and was the primary evaluation criterion. Executive functions were evaluated using the Trail Making Test-A time, the category and phonemic fluency tests, and the Grober and Buschke free recall total score. Memory functions were evaluated using the Grober and Buschke free and cued recall total scores and the Rey complex figure delayed recall score. Instrumental functions were evaluated using praxis tests and the Rey complex figure copy score. Severity of the parkinsonian syndrome was assessed with the Hoehn and Yahr (H&Y) scale, while cognitive fluctuation, REM sleep behavior disorder (RBD) and hallucinations were assessed as present or absent based on history and interview of patients and relatives. Education level was defined by years of school completed after first grade.

2.2. SPECT scanning

For all patients, 123-I-Ioflupane SPECT was performed according to the same protocol, which was in line with the latest recommendations [7]. Thyroidal uptake of free radioiodine was blocked using lugol solution. 150 MBq of the DAT radioligand 123-I-Ioflupane were administered intravenously to the patient, then SPECT imaging was performed using a gamma camera (Ecam, Siemens Medical Solution) fitted with a LEHR collimator. Images were acquired in a 128 × 128 matrix and reconstructed using a filtered back-projection method. For the semiquantitative analysis, the regions-of-interest (ROI) were defined on single-slice views around the striatum, the caudate nucleus, and the putamen. For the striatum (putamen and caudate nucleus), the surrounding white matter and the cerebrospinal fluid were not included in the ROI. The occipital cortex (background ROI) was defined as the reference region on the basis of its low DAT concentration and low 123-I-Ioflupane binding. Specific binding was defined by: [(mean counts of the striatal/putamen/caudate nucleus ROI – mean counts of the background ROI)/(mean counts of the background ROI)]. In order to account for the possibility that asymmetry in DAT binding between the right and left side could impact the results, we analyzed the lowest (most affected), highest (least affected), and mean DAT binding values of each right-left ROI pair. The result of the SPECT DAT scan was used as a supportive criterion in the diagnosis, however patients with normal 123-I-Ioflupane SPECT (n = 4) were not excluded if the criteria of probable DLB were otherwise met. Because DAT binding is influenced by age [8], DAT-binding analyses were corrected for age. To control for age, we used a partial correlation model with age as a control variable. We also performed a supplementary analysis to control for the physiologic decline of DAT binding with age.

Table 1
Demographic and clinical data of the 56 patients with DLB.

Age at diagnosis, mean ± SD (y)	74.2 ± 6.9
Sex (M/F)	31/25
Education level, mean ± SD (y)	8.6 ± 2.7
Duration of the disease, mean ± SD (mo)	50.3 ± 30.3
Subjective symptoms before scan, mean ± SD (mo)	21 ± 21.2
H&Y, mean ± SD	2.4 ± 1
L-Dopa-equivalent dose, mean ± SD, (N)	147.2 ± 224.7 (20)
MMSE, mean ± SD	20.4 ± 4.9
Motor phenotype	
Akinetic-rigid, N (%)	37 (66.1)
Tremor dominant, N (%)	2 (3.6)
Akinetic-rigid and tremor, N (%)	13 (23.2)
No PD core motor symptoms, N (%)	4 (7.1)
Visual hallucination, N (%)	34 (60.7)
Fluctuation, N (%)	47 (83.9)
RBD, N (%)	29 (51.8)

Education level was defined by the number of year of school after first grade; H&Y. Hoehn and Yahr scale; mo: months; MMSE. Mini Mental State Examination; RBD: Rapid eye movement sleep Behavior Disorders; y: years.

2.3. Statistical analysis

Quantitative variables were described using means and standard deviations (SD). Qualitative variables were described using numbers and percentages. The relationship between two quantitative variables was assessed using the Pearson correlation coefficient. The assumption of homogeneity of variance was tested using Levene's test of equality of variances. All tests were two-tailed and their levels of significance (p) were defined as $p < 0.05$. IBM®-SPSS® 20.0 for Windows was the statistical software used. Bivariate and multivariate analyses were performed in order to account for potential confounding factors.

3. Results

Mean age at diagnosis was 74.2 ± 6.9, mean MMSE was 20.4 ± 4.9, and mean education level was 8.6 ± 2.7 (range 6–16). Mean follow-up time was 50.3 ± 30.3 months after the onset of symptoms (Table 1). Levodopa was used in 20 patients with a mean dose of 147.2 ± 224.7 milligrams (L-Dopa-equivalent dose) and cholinesterase inhibitors were used in 35 patients (63% of patients).