Loss of swallow tail sign on susceptibility-weighted imaging in dementia with Lewy bodies

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Contributors

GR and GL had full access to the data set of this study and take responsibility for the integrity of data and the accuracy of data analysis. All authors made substantial contributions to the intellectual content of the paper.

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ABSTRACT

We assessed nigral dorsolateral hyperintensity (swallow tail sign) at susceptibility-weighted imaging (SWI) using 3T-MRI in 15 dementia with Lewy bodies (DLB), 11 Alzheimer's dementia (AD), 8 frontotemporal dementia (FTD) patients and 10 subjects with subjective memory complaint (SMC). More DLB patients lacked nigral hyperintesity ($p < 0.05$). Sensitivity, specificity, and accuracy of DLB diagnosis were respectively 80%, 64%, and 73% vs AD, 80%, 75%, and 78% vs FTD, 80%, 90%, and 84% vs SMC. Considering bilateral loss, sensitivity decreased (53%) but specificity increased (82-100%). Swallow tail sign loss, especially if bilateral, can be useful for DLB diagnosis.

Introduction

The diagnosis of dementia with Lewy bodies (DLB) may be challenging. Alzheimer's dementia (AD) is the most frequent misdiagnosis [1]. The availability of accurate diagnostic tools is crucial. The new revised DLB diagnostic criteria include the use of imaging biomarkers, e.g. reduced dopamine uptake in basal ganglia demonstrated by SPECT/PET or abnormal ^{123}iodine-MIBG myocardial scintigraphy [2]. As for MRI, susceptibility-weighted imaging (SWI) is a technique with increasing clinical applications. It allows enhancing the contrast of substances with different magnetic susceptibility to the surrounding tissue background (e.g. iron, calcium). SWI using high field MRI scanners (at least 3 Tesla) can detect a dorsolateral hyperintense signal area (also called "swallow tail" sign) in the substantia nigra (SN) of healthy controls [3]. It corresponds to the nigrosome-1, the largest among five clusters of dopaminergic cells in the SN pars compacta and where there is the maximal dopaminergic neuronal loss (90%) in Parkinson's disease (PD) patients [4]. Recent studies have demonstrated that dorsolateral hyperintense signal area lacks in PD patients, and may distinguish them from healthy controls with high sensitivity and specificity [5,6]. Most DLB patients have SN degeneration as in PD. The aim of the present study was to investigate the utility of SWI for detection of the swallow-tail sign to differentiate DLB from other degenerative dementias.

Methods

We consecutively recruited 15 DLB patients, 12 AD patients, 10 frontotemporal dementia (FTD) patients and 10 subjects with subjective memory complaint (SMC) at the Department of Clinical Research in Neurology, Pia Fondazione di Culto e Religione "Card. G. Panico", Tricase, Italy from September 2015 to August 2016. Patients fulfilled the appropriate diagnostic criteria [7-9]. All subjects were studied in a 3 Tesla system (Ingenia®, Philips Medical System) and a 32-channel head coil. Acquisition protocol included axial SWI sequences (TR = 31, TE = 7.2, Flip angle = 17, Voxel size = 0.80x0.81x1.60, Scan duration = 3 minutes). SMC subjects had no MRI abnormalities.

SN was cranio-caudally sampled obtaining five axial sections and displayed by MPR reconstruction starting from an oblique plane, parallel to the corpus callosum. Two neuroradiologists (DG and RDB), blinded to the clinical conditions and to each other's decisions, examined SWI images to classify the subjects according to the presence or loss of the dorsolateral nigral hyperintensity. A third rater (GR) resolved the discordances.

Radiological DLB diagnosis requested the uni- or bilateral loss of nigral hyperintensity.

We followed up all the subjects for at least one year to confirm diagnosis.

Statistical analyses were performed using SPSS 24.0. The differences in demographic and clinical data were evaluated by $\chi 2$ test for categorical variables and Kruskal-Wallis test followed by Mann-Whitney U test for continuous variables. Agreement was tested using Cohen's k statistics. The difference in the distribution of the nigral hyperintensity among the groups was tested by logistic regression models using the age at the MRI as covariate. $P < 0.05$ was considered significant. The ability to identify DLB was assessed using the clinical diagnosis as gold standard. Sensitivity, specificity, and accuracy were calculated.

The procedures used followed the Helsinki Declaration regarding international clinical research involving human beings. The local Human Ethics Committee approved the study and all subjects gave their written informed consent to the study.

Results

Two scans (one AD and one FTD) were excluded due to motion artifacts. One FTD patient interrupted MRI scan before SWI acquisition for claustrophobia. Finally, we studied 15 DLB patients (all DLB probable), 11 AD patients (all AD probable), eight FTD patients (seven behavior variants and one primary progressive aphasia) and 10 SMC subjects. Age slightly differed among the groups, while sex did not. The patients did not differ in disease duration and MMSE scores (**Table 1**). Raters agreement was 86% (kappa = 0.71, $p < 0.0001$). Twelve out of 15 DLB patients lacked nigral hyperintesity unilaterally or bilaterally, unlike the other groups (AD: 4/11; FTD: 2/8;

SMC: 1/10; $p < 0.05$. **Table 1; Figure 1**). Sensitivity, specificity, and accuracy values are reported in **Table 1**.

After one-year follow-up, all diagnoses were confirmed. However, one AD patient, who had only mild parkinsonian symptoms at the time of MRI scan, reported a worsening of the parkinsonism and the appearance of visual hallucinations after a major surgery (7 years after dementia onset). Due to the late occurrence of these symptoms, we confirmed the diagnosis of AD, but considering a mixed type, with concomitant Lewy body (LB) disease [8]. Accordingly, if we use as gold standard the possible presence of LB pathology, including this patient in the LB group, the sensitivity, specificity, and accuracy of SWI increase respectively to 81%, 70%, and 77% vs AD, 81%, 75%, and 79% vs FTD, and 81%, 90%, and 85% vs SMC, (considering only the bilateral loss: 56%, 90%, and 69% vs AD, 56%, 88%, and 67% vs FTD, and 56%, 100%, and 73% vs SMC).

Discussion

In this study we evaluated the dorsolateral nigral hyperintensity using 3T SWI, disclosing a loss of this sign in the majority of the DLB patients, differently from the patients with AD and FTD and SMC. In the pairwise post-hoc analyses DLB patients significantly differed from other groups except for FTD, although the prevalence of the swallow tail sign loss was clearly higher in the DLB patients compared with FTD patients. The lack of significance was probably due to the smaller number and age of patients with FTD lowering statistical power. The assessment of dorsolateral nigral hyperintensity was able to identify DLB with good diagnostic accuracy, with a sensitivity of 80% and a specificity ranging from 64% (vs AD) to 90% (vs SMC). If we considered only the bilateral loss, sensitivity decreased to 53% but specificity increased, ranging from 82% (vs AD) to 100% (vs SMC). Currently, there are only few data on the evaluation of swallow-tail sign in DLB, reported by two recent retrospective studies [10,11]. A first study on DLB, AD and mild cognitive impairment subjects performed both a visual evaluation of SWI images reporting as abnormal not only a loss but also a hypointensity of the nigrosome-1 of 50% or greater and a semi-quantitative

analysis using a contrast ratio between signal of nigrosome-1 and of midbrain tegmentum [10]. Interestingly, the authors reported a sensitivity and specificity of about 90% for both approaches, slightly better than DaT-SPECT. However, these approaches, although very accurate, are less simple than identifying an absence or presence of nigral hyperintensity and hence probably more difficult to apply in clinical practice [11]. The second study, which also included some FTD patients, evaluated an heterogeneous sample merging the MRI exams from four different scanners (1.5 or 3 Tesla), probably determining the low agreement (kappa=0.4) and results [11]. They reported an overall sensitivity of 63%, specificity of 79%, and accuracy of 76%, better using 3T SWI and thinner slices. They did not evaluate bilateral loss separately [11]. Our data, using a single 3T scanner and a fixed SWI protocol, show as the evaluation of the swallow-tail sign is reliable and has an accuracy to diagnose DLB similar to that reported by the second previous work [11], although the specificity clearly increased in the case of bilateral loss.

Limit of our and previous studies is the lack of pathological diagnosis, as the clinical diagnosis is yet suboptimal [1]. The low sample size and the quite long disease duration of DLB and AD patients should be considered other limitations of this study. Future studies will have to evaluate the swallow tail sign in patients with early-stage disease. Furthermore they will need to include more patients, especially with FTD. A minor limit could be the use of SMC subjects as controls. However, the possibility of a subclinical disease was very low. Finally, the slight difference in the age of the subjects could be a further limit, although recent data have suggested that age-related increase in iron concentration does not affect the visibility of swallow tail sign [12]. However, age of DLB and AD patients did not differ and we performed the statistical analyses using the age as covariate.

In conclusion, the assessment of the dorsolateral nigral hyperintensity could be a reliable and noninvasive biomarker of SN degeneration, useful for the clinical diagnosis of DLB, although the accuracy seems to be suboptimal. Remarkably, the bilateral loss increased the diagnostic specificity

up to more than 80% and could be considered a good imaging biomarker of DLB in patients with dementia.

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Table 1. Demographic, clinical and MRI characteristics of subjects at the time of the scan.

	DLB (n=15)	AD (n=11)	FTD (n=8)	SMC (n=10)	p Value
Sex (M/F)	8/7	4/6	3/5	5/5	NS[A]
Age	76 ± 7	74 ± 8	64 ± 12	67 ± 9	<0,05[B1]
Age at onset	71 ± 7	69 ± 8	61 ± 13	/	NS[B]
Disease duration	5 ± 3	5 ± 3	3 ± 2	/	NS[B]
MMSE	17 ± 6	13 ± 5	19 ± 6	28 ± 2	<0,001[B2]
Parkinsonism (UPDRS part III)	15/15 (27±8)	1/11 (13)	1/8 (15)	/	/
Visual hallucinations	15/15	0/11	0/8	/	/
Fluctuating cognition*	14/15	0/11	0/8	/	/
REM sleep behavior disorder[#]	11/15	0/11	0/8	/	/
Severe neuroleptic sensitivity[**]	0/15 (NA:6)	0/11 (NA:7)	0/8 (NA:4)	/	/
Loss of dorsolateral nigral hyperintensity					
Unilateral + bilateral	12/15 (80%)	4/11 (36%)	2/8 (25%)	1/10 (10%)	<0,05[C3]
Unilateral	4/15 (27%)	2/11 (18%)	1/8 (12.5%)	1/10 (10%)	
Bilateral	8/15 (53%)	2/11 (18%)	1/8 (12.5%)	0/10 (0%)	

Diagnostic accuracy values for the loss of the dorsolateral nigral hyperintensity, using DLB clinical diagnosis as the gold standard				
Uni- or bilateral loss	**DLB vs AD**	**DLB vs FTD**	**DLB vs SMC**	**DLB vs non-DLB**
Sensitivity	80%	80%	80%	80%
Specificity	64%	75%	90%	76%
PPV	75%	86%	92%	63%
NPV	70%	67%	75%	88%
Accuracy	73%	78%	84%	77%
Bilateral loss	**DLB vs AD**	**DLB vs FTD**	**DLB vs SMC**	**DLB vs non-DLB**

Sensitivity	53%	53%	53%	53%
Specificity	82%	88%	100%	90%
PPV	80%	89%	100%	73%
NPV	56%	50%	59%	79%
Accuracy	65%	65%	72%	77%

PET and SPECT data were available only for few patients and are not reported in details.
DLB = dementia with Lewy bodies; AD = Alzheimer's dementia; FTD = frontotemporal dementia; SMC = subjective memory complaint; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; NS = not significant.
*anamnestic. #anamnestic, no polysomnography. **NA = not applicable because never treated with neuroleptics.
A = Chi-square Test. B = Kruskal-Wallis Test. C = logistic regression using age as covariate.
1 = post-hoc Mann-Whitney U test: DLB vs FTD $p < 0.05$, DLB vs SMC $p < 0.05$
2 = post-hoc Mann-Whitney U test: DLB vs SMC $p < 0.001$, AD vs SMC $p < 0.001$, FTD vs SMC $p < 0.01$
3 = post-hoc logistic regression: DLB vs AD $p < 0.05$, DLB vs FTD NS, DLB vs SMC $p = 0.005$, DLB vs non-DLB $p = 0.004$

Figure legend

Figure 1. Examples of normal bilateral dorsolateral nigral hyperintensity (A: AD patient), unilateral loss (B: DLB patient) and bilateral loss (C: DLB patient). The arrows indicate the visible dorsolateral nigral hyperintensities.