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Short Communication

Substantia Nigra Hyperechogenicity in Parkinson's Disease and Related Disorders: A Follow-up Study

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Summary

Background: Previous studies have shown that the hyperechogenic area of the substantia nigra (SN) does not change over the disease course in patients with Parkinson's disease (PD). However, longitudinal changes in SN echogenicity in patients with atypical parkinsonian syndrome (APS) remain unclear. We evaluated the change in SN hyperechogenic area over time in patients with PD and those with APS, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

Methods: A total of 22 patients with parkinsonism (14 PD, aged 71.0 ± 8.3 years; 8 APS (6 PSP and 2 MSA), aged 69.9 ± 9.6 years) who underwent transcranial sonography twice (≥6 months apart) were included in this study. Patients with insufficient temporal bone windows were excluded.

Results: The mean interval between examinations was 24.7 ± 15.3 months. No differences were detected in the hyperechogenic SN area between the first and second examinations (all patients, 0.17 ± 0.09 cm^2 vs. 0.17 ± 0.08 cm^2, p = 0.67; PD, 0.20 ± 0.08 cm^2 vs. 0.20 ± 0.08 cm^2, p = 0.45; APS, 0.11 ± 0.06 cm^2 vs. 0.12 ± 0.06 cm^2, p = 0.37, respectively). In both groups, there were no correlations between the hyperechogenic SN area and disease duration or severity.

Conclusion: The hyperechogenic SN area did not change over the disease course in PD or APS patients.

Key Words: Parkinson's disease, atypical parkinsonian syndrome, substantia nigra hyperechogenicity, transcranial sonography

Introduction

Hyperechogenicity of the substantia nigra (SN) on transcranial sonography (TCS) is a common finding in patients with Parkinson's disease (PD), with a prevalence of 68-99%[1)]. SN hyperechogenicity can also be detected in atypical parkinsonian syndrome (APS), including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). The prevalence of SN hyperechogenicity is 0-25% in patients with MSA and 0-41% in patients with PSP[1)]. Several previous studies in patients with PD showed that the size of the hypere-

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Table 1 Background characteristics of the patients.

	Total	PD	APS	p value*
Age (y)	70.6 ± 8.6	71.0 ± 8.3	69.9 ± 9.6	0.780
Sex (male/female)	13/9	11/3	2/6	0.026
Disease duration (y)	7.14 ± 3.2	7.5 ± 3.8	6.5 ± 1.6	0.40
Hoehn and Yahr stage				0.017
Stage 2	7	6	1	
Stage 3	5	5	0	
Stage 4	8	3	5	
Stage 5	2	0	2	
Cardiac MIBG scintigraphy				
H/M ratio (Early)	2.2 ± 0.5	1.9 ± 0.4	2.7 ± 0.3	< 0.0001
H/M ratio (Delayed)	2.1 ± 0.8	1.6 ± 0.5	2.7 ± 0.7	0.001

PD = Parkinson's disease
APS = atypical parkinsonian syndrome
*P value = PD vs. APS

chogenic area did not change over 3-10 years of follow-up[2,3]. However, in patients with APS, it is unclear whether the hyperechogenic SN area changes over the disease course. We evaluated the changes in the hyperechogenic area of the SN in patients with PD and those with APS over a mean interval of two years.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Dokkyo Medical University. The subjects provided written informed consent.

Subjects

From April 2009 to May 2017, patients with PD or APS who underwent successful TCS examinations twice at least 6 months apart were enrolled in this study. A total of 22 patients with parkinsonism (14 PD and 8 APS; 1 MSA-C; 1 MSA-P; 5 PSP-Richardson syndrome (PSP-RS); and 1 PSP-parkinsonism (PSP-P)) were included. Diagnoses of PD, MSA, and PSP were made based on the UK PD Society Brain Bank Clinical Diagnostic Criteria[4], the second consensus statement on the diagnosis of MSA[5], and the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria, respectively[6,7].

Transcranial sonography

We used a conventional transcranial Doppler sonography apparatus with a 2.5 MHz transducer (LOGIQ 7; GE Healthcare, Tokyo, Japan) to scan the midbrain through the bilateral temporal bone windows (6-8 cm). The dynamic range was set at 50-60 dB. We manually drew a border around the hyperechogenic region of the SN and then calculated its area. When bilateral hyperechogenic areas in the SN were observed, the larger area was used for analysis[8]. We compared the size of the hyperechogenic SN area between the first and second assessments.

Statistical analyses

To compare continuous variables, the Mann-Whitney U test or an unpaired t test was used as appropriate. The chi-square test or Fisher's exact test was applied to compare categorical variables between two groups. To compare the hyperechogenic area of the SN between the first and second measurements, a paired t test was used. Correlation between hyperechogenic SN area and disease duration or disease severity were analyzed using Spearman's rank correlation coefficients.

Results

The clinical characteristics of the patients with PD and those with APS are shown in Table 1. There were no differences in mean age or disease duration between the two groups. However, the APS group contained a higher proportion of female patients and had greater disease severity as measured by the Hoehn

Table 2 Comparison of the hyperechogenic SN area between the two examinations for each patient.

No.	Diagnosis	SN area at first exam (cm^2)	SN area at second exam (cm^2)	p value	Interval (months)
1	PD	0.11	0.17		8
2	PD	0.14	0.13		32
3	PD	0.27	0.26		12
4	PD	0.37	0.32		33
5	PD	0.27	0.26		29
6	PD	0.28	0.28		19
7	PD	0.20	0.16		42
8	PD	0.09	0.04		14
9	PD	0.20	0.23		35
10	PD	0.20	0.20		54
11	PD	0.08	0.07		32
12	PD	0.18	0.24		9
13	PD	0.30	0.21		7
14	PD	0.20	0.20		12
PD Mean		0.20 ± 0.08	0.20 ± 0.08	p = 0.45	24.1 ± 14.6
15	MSA-C	0.08	0.08		55
16	MSA-P	0.12	0.14		31
17	PSP-P	0.26	0.24		12
18	PSP-RS	0.07	0.08		27
19	PSP-RS	0.07	0.09		16
20	PSP-RS	0.08	0.06		47
21	PSP-RS	0.09	0.12		8
22	PSP-RS	0.11	0.12		10
APS Mean		0.11 ± 0.06	0.12 ± 0.06	p = 0.37	25.8 ± 17.7

APS = atypical parkinsonian syndrome, PSP-RS = progressive supranuclear palsy–Richardson syndrome, PSP-P = progressive supranuclear palsy–parkinsonism, PD = Parkinson's disease, SN = substantia nigra, exam = examination

and Yahr (HY) stages. The heart-to-mediastinum ratios of cardiac ^{123}I-MIBG uptake were significantly lower in the patients with PD than in those with APS (early phase: 1.9 ± 0.4 vs. 2.7 ± 0.3, $p < 0.001$; delayed phase: 1.6 ± 0.5 vs. 2.7 ± 0.7, $p = 0.001$, respectively). The mean interval between the TCS examinations was 24.7 ± 15.3 months. No differences were detected between the first and second examinations in the SN hyperechogenic areas (all patients, 0.17 ± 0.09 cm^2 vs. 0.17 ± 0.08 cm^2, $p = 0.67$; PD, 0.20 ± 0.08 cm^2 vs. 0.20 ± 0.08 cm^2, $p=0.45$; APS, 0.11 ± 0.06 cm^2 vs. 0.12 ± 0.06 cm^2, $p =0.37$, respectively; each patient's data are shown in Table 2). No correlations were detected between SN area and disease duration or disease severity (Table 3).

Discussion

Our study showed that the hyperechogenic area of the SN did not change over an average interval of two years in patients with PD, in agreement with previous studies[2,3]. Additionally, we demonstrated the novel finding that the hyperechogenic area of the SN did not change in patients with APS. To the best of our knowledge, no longitudinal studies have evaluated the hyperechogenic area of the SN over time in patients with APS.

The causes of SN hyperechogenicity are only partly understood; however, several pathophysiological changes, including increases in tissue iron and calcium content, protein aggregation, and glial activation with increases in focal heavy metal deposits, have been implicated[1]. Mutational analyses have identified some gene mutations related to SN hyperechogenicity in PD patients, including Ile63Thr, Asp544Glu and Arg793His mutations. In cell studies, the functional relevance of Ile63Thr and Asp544Glu has been shown[9]. Furthermore, in asymptomatic and symptomatic *Parkin* muta-

Table 3 Correlation of hyperechogenic SN area at the first examination with hyperechogenic SN area at the second examination, disease duration and disease severity.

PD			
SN at first exam	SN at second exam	Disease duration	Disease severity
1.000	0.829*	0.089	0.176
APS			
SN at first exam	SN at second exam	Disease duration	Disease severity
1.000	0.817*	0.172	-0.243

*$p < 0.05$, *Spearman's rank correlation.*
PD = Parkinson's disease
APS = atypical parkinsonian syndrome
SN = substantia nigra
exam = examination

tion carriers, hyperechogenic SN areas were found to be enlarged[10]. As in a previous report[2], the SN hyperechogenic area was not associated with disease duration or disease severity in the present study. Taken together, the evidence indicates that SN hyperechogenicity may indicate vulnerability changes in the nigrostriatal system reflecting genetic factors[9], but more studies are needed to clarify this association.

The study of isolated REM sleep behavior disorder (iRBD), which is considered the possibility of a prodromal condition of neurodegeneration[11], may be instructive in considering the implications of change in SN hyperechogenicity. Miyamoto et al.[12] reported that SN hyperechogenicity was more common in patients with iRBD (37.3-41.2%) than in controls (9.5-10.7%); however, there was no correlation between SN hyperechogenicity and striatal 6-[18F] fluoro-meta-tyrosine uptake in iRBD patients. Another longstanding study including 20 iRBD patients with a mean follow-up duration of 12.1 ± 2.6 years showed a positive SN hyperechogenicity ratio of 35.3%[13]. Overall, SN hyperechogenic changes may be a static marker that emerges in the prodromal phase of neurodegenerative disorders and does not change with subsequent neurodegeneration.

On the other hand, the pathogenesis of SN hyperechogenic changes in APS has not been extensively studied. Although a normoechogenic SN is a typical finding in patients with PSP[14], some patients with PSP showed hyperechogenic changes in the SN, and the prevalence of the finding may vary according to the clinical subtype of PSP. Ebentheuer et al.[15] reported that patients with PSP-P showed a higher rate of SN hyperechogenicity than those with PSP-RS (85.7% vs. 3.7%). Alster et al.[16] reported that hyperechogenic changes in the SN were observed in 14% of patients with PSP-RS and 73% of patients with PSP-P. Similarly, in our study, one patient with PSP-P showed a larger hyperechogenic area in the SN than the five patients with PSP-RS. Although the pathology explaining this difference is unclear, histopathological differences that include the isoform composition and distribution of insoluble tau neurofibrillary tangles may account for the difference in TCS findings between the two subgroups of PSP.

Our study has some limitations. First, our findings are preliminary, as the sizes of the MSA and PSP groups were small, which could have impacted the overall findings. This may be related to the fact that APS has a much lower prevalence and faster disease progression than PD. Another reason for the small sample size is that the bone windows are narrower in Asians than Caucasians, resulting in a lower successful SN observation rate[9]. Notably, in a study from Japan, 50% of female patients over 70 years old and 70% of female patients over 75 years old could not be evaluated for SN echogenicity[17]. In our institution, the mesencephalon detection ratios with TCS were 56.5% in APS and 52.5% in PD. Second, the follow-up interval was not as long compared to that in a previous study among patients with PD only[2,3]. This also seems to be related to the more rapid disease progression in patients with APS.

Conclusion

We showed that the hyperechogenic area of the SN did not change over a mean interval of two years in patients with PD and APS. Our findings support the notion that SN hyperechogenicity could be a static marker for nigrostriatal vulnerability rather than a progression marker among patients with PD-related disorders, including MSA and PSP.

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Author contributions

Conceptualization, H.F., J.H., Y.W., H.S., A.N., H.T., K.O., K.H. and K.S.; methodology, H.F., J.H., A.N., H.T., and K.S.; formal analysis, H.F. and K.S.; data curation, H.F., J.H., Y.W., H.S., K.O., and K.S.; writing—original draft preparation, H.F.; writing—review and editing, K.H. and K.S.; visualization, K.H. and K.S.; supervision, K.S.; project administration, K.H. and K.S. All authors have read and approved the published version of the manuscript.

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Disclosure of relationships and activities

None declared.

Data availability

The data used in this study are available from the corresponding author upon request.

Conflict of interest

The authors declare that they have no potential conflicts of interest related to this article.

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