Differentiation of Parkinson’s disease and Parkinsonism predominant multiple system atrophy in early disease stages by means of objective measurement in Susceptibility Weighted Imaging

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Research

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Abstract

Background

We have established radiological protocol and made morphological measurement of the lentiform nucleus (LN) and the signal intensity which we used to discriminate parkinsonism predominant multiple system atrophy (MSA-P) from Parkinson's disease (PD). But we don’t know whether it works especially in early stage of MSA-P. This case-control study aimed to investigate whether the new measurement of the morphological and intensity changes in susceptibility weighted imaging (SWI) of the LN could discriminate MSA-P from PD in their early stage and controls.

Methods

We retrospectively enrolled patients with MSA-P, PD, and sex- and age-matched controls between January 2015 and July 2020 at the Movement Disorder Center who underwent brain MR scanning with SWI sequence. Two specialists at the center reviewed the medical records and made the final diagnosis, and two experienced neuroradiologists performed MRI image analysis based on a defined radiological protocol to conduct the region of interest (ROI) based morphological measurements of the LN and the signal intensity.

Results

A total of 17 patients with MSA-P, 17 patients with PD within 2 years of the disease duration and 17 controls were enrolled in this study. We found that patients with MSA-P had significant decreased size in the short line (SL, cSL), and the ratio of the SL and the long line (SLLr, cSLLr) compared with the patients with PD and with the controls (P < 0.05). Combining these four indexes, this finding had a sensitivity of 58.8% and a specificity of 100% to distinguish MSA-P from PD.

Conclusions

As compared to PD and control subjects, the MSA-P patients are characterized by narrowing morphology of the posterior region of LN. The quantitative morphological change is a possible potential marker to differentiate MSA-P from PD in the early stage.

Background

Multiple-system atrophy (MSA) is a fatal neurodegenerative disease with autonomic failure, parkinsonian and/or cerebellar features which is classified as the parkinsonian subtype (MSA-P) and the cerebellar subtype (MSA-C). MSA-P and Parkinson's disease (PD) have similar clinical presentations such as rigidity, bradykinesia and response to levodopa which made it challenging in clinical practice to make differential
diagnosis in early stage (within 2–3 years of disease duration). It's very important to discriminate MSA-P from PD in early stage so as to tell prognosis in term of disability, response to therapy and survival accurately.

Conventional MRI has been used extensively to distinguish MSA-P and PD. Hyperintense rim of lateral putaminal margin and hypointensity of posterolateral putamen on routine FLAIR and/or T2 imaging have assisted the physicians in the differential diagnosis of MSA-P and PD[1]. But these are subjective, not found in all MSA-P patients and have low sensitivity especially in early stage[2]. Hypointense putaminal signal changes on T2* or susceptibility weighted imaging (SWI) are relatively specific for MSA-P[3, 4]. But these changes are also subjective. Recently there are several reports about signal intensity changes of the lentiform nucleus (LN) semi-quantitatively[5]. In Hwang’s study[6], quantitative measurement of the putaminal width were made, but the selection of the representative section was subjective. In our previous work we established radiological protocol and made morphological measurement of the LN and the signal intensity which we used to discriminate MSA-P from PD with specificity of 63.2% and sensitivity of 94.7%[7]. But we don’t know whether it works especially in early stage of MSA-P. This present study was aimed to investigate the new measurement of the morphological and intensity changes to discriminate MSA-P from PD and controls within 2 years of the disease duration.

Methods

Ethical approval and subjects description

This study was approved by the ethics committee at Qilu Hospital of Shandong University (Qingdao) and performed in accordance with the Helsinki Declaration of the world medical association. Participants were consecutively recruited at Movement Disorder Center of Neurology between Jan 2015 and July 2020 whose brain scanning including SWI sequence, as part of our previous study[7]. Clinical diagnoses of MSA-P and PD were made according to established criteria[8,9] by two clinicians (CP Zhao and JY Zhang) with movement disorders professional experience for more than 10 years. The disease duration was defined from the occurrence of the motor symptoms. We aimed to figure out the image difference of MSA-P and PD in relative early stage when it is difficult to differentiate clinically, we grouped patients with cut-off point of 2 years’ disease duration at the time of performing MR according to previous study[10]. In the light of the consensus guidelines in 2008[8], our MSA-P patients were with clinical probable MSA-P and regularly followed in our clinics. As a control group (CG), we selected the previously retrieved patients from Picture and Communication System (PACS) with same methods and exclusion criteria of our previous study except that we also included the subjects scanned on 1.5T MR. At last, 17 patients with MSA-P (14 on 3.0T, 3 on 1.5T MR), 17 age-sex and MR model matched PD with disease duration no more than 2 years and 17 CG were enrolled in this study.

Scanning model and parameters
The axial scans were set parallel to the intercommissural line. Scanning parameters on 3.0T MR scanner (Ingenia scanner, Philips Medical Systems, Netherlands) were as follows: slice thickness = 2 mm; TR = 20 ms; TE = 27 ms; flip angle 15°; FOV=220 mm; number of signal acquisitions 1; and matrix size 284 × 230. Scanning parameters on 1.5T MR (Achiva, scanner, Philips Medical Systems, Netherlands) were as follows: slice thickness = 2mm; TE=10 ms; TR= shortest; flip angle 10°; FOV=230 mm; number of signal acquisitions 1; and voxel size = 1mm× 1mm × 0.6mm.

Region of interest and morphometric index extraction

In the PACS system, the longest horizontal line (LL), the short line (SL), the calculated ratio of SL/LL (SLLr), and the area, the mean signal intensity (SIm_LN) and the standard deviation of the signal intensity (SIsd_LN) of the manually sketched boundary area of the LN were recorded by two experienced radiologists (QG Ren and XM Nan) in the magnitude image axis plane according to our previous study[7]. Those above indexes of both sides were recorded, the uniformity of these two radiologists measurement results were estimated by the mean value of both sides, moreover, the uniformity of the smaller side of SL by these two radiologists were also estimated. The cerebrospinal uid signal intensity of the 4th ventricle was also measured as SIm_CSF and SIsd_CSF. Then, the SIm_LN of each side was normalized to SIm_CSF with a signal intensity of 200 (nSIm) according to previous study[5]. Then, we calculated the mean measured value of each side by these two radiologists separately. According to our previous experience, the MSA-P patients are characterized by narrowing morphology and the inhomogeneous signal intensity of the posterior region of LN. So we chose the smaller SL side as corrected SL (cSL) and calculated the corrected ratio (cSLLr) by LL with the same side of cSL. as shown in Fig 1. We also chose the bigger SIsd_LN side as corrected cSIsd_LN,. Given all the other above indexes we calculated the mean values of the left and the right for the following statistical analysis.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 22.0, Chicago, Illinois) was used for statistical analysis. Continuous variables were expressed as the mean ± SD. One way analysis of variance (ANOVA) with post-hoc multiple comparisons conducted by Least Significant Difference (LSD) was used for groups and subgroups comparison when variables conformed to the normal distribution by Shapiro-Wilk test, otherwise nonparametric test (Kruskal-Wallis or Mann-Whitney U) was used. All statistical significance was defined as P value <.05. Receiver operating characteristic (ROC) curves were plotted to assess the value of the significant different index in differentiating MSA-P from PD and health controls, in which cutoff values were determined by using Youden's index . Kappa analysis was used to assess the uniformity of the smaller side of SL by the radiologists and Intraclass correlation coefficient (ICC) was to assess the uniformity of the mean values of the left and the right measured data by them.

Results

Demographic characteristics
The clinical and demographic characteristics of the subjects are summarized in Table 1. No significant age and sex differences were found in the three groups ($P > 0.3$), and there was no difference in disease duration between PD and MSA-P patients ($P < 0.05$).

**Uniformity of twice measurement results/ Intraobserver Variability**

Consistency of left and right short line differences between two radiologists was assessed by the Kappa value. Definitions of levels of agreement on the basis of kappa values were as follows: $k < 0.3$ indicated slight agreement; $k = 0.3–0.7$, moderate agreement; $k > 0.7$ meant good agreement. The kappa values in MSA-P were good agreement and were the best among the three groups as shown in Table 2.

**Comparison of the SL, LL, SLLr, Area, Slm, Slsd, nSlm among the three groups**

There were no statistical significances in LL, Slm_LN, Slsd_LN, Slm_CSF, Slsd_CSF and nSlm among the three groups ($P > 0.05$). We found significant decreases in SL, cSL, SLLr, cSLLr in the MSA-P group compared with the PD and control groups ($P < 0.05$), and a significant increase in cSlsd_LN in the MSA-P group compared with the PD ($P < 0.05$); there were significant decreases in Area in the MSA-P group compared to the control group ($P < 0.05$), but no significant difference was found between the MSA-P and PD groups ($P > 0.05$). All the results are shown in Fig 2 and Table 3.

**The ROC curve analysis**

The area under the curve (AUC) of cSL was the highest among the four indexes which had statistical difference for differentiating MSA-P from PD and also for MSA-P from CG. The AUC was 0.784 for MSA-P vs PD and 0.772 for MSA-P vs CG, the sensitivity and specificity were 64.7% and 82.4% respectively for MSA-P vs PD, and 88.2% and 64.7% respectively for MSA-P vs CG. When combining the four indexes, the results were better than a single index. The AUCs was were 0.824 for MSA-P vs PD and 0.889 for MSA-P vs CG, and the respective sensitivity and specificity were 58.8% and 100% respectively for MSA-P vs PD, and 94.1% and 82.4% respectively for MSA-P vs CG. The results were as shown in Fig 3.

**Discussion**

Our previous study showed that measurable morphology and signal changes of the lentiform nucleus (LN) can help to distinguish MSA-P from PD with a sensitivity of 94.7% and a specificity of 63.2% based on susceptibility weighted imaging. In this study, we further verified the feasibility of this measurement in the early disease duration. The major finding were as follows: first, using measurable morphology changes of LN can also to distinguish MSA-P from PD in their early stage with extremely high specificity and moderate sensitivity; second, diameter indexes were better than signal indexes for distinguish MSA-P from PD; third, using the smaller SL of the both sides can improve the sensitivity and specificity than using the mean value of two sides.

Studies on differential diagnosis between MSA-P and PD based on neuroimaging have shown encouraging findings in recent years. Regional apparent diffusion coefficients of middle cerebellar
peduncles completely differentiated MSA-P patients from Parkinson's disease patients with mean disease duration of 4.9 years [11]. Also by machine learning approach based on volumetry enabled accurate classification of subjects with early-stage parkinsonism of about 5.0 years' mean disease duration [12]. Proton magnetic resonance spectroscopy in the basal ganglia of MSA-P with mean disease duration of 3.4 years was also different from healthy controls [13]. Although the MSA-P subjects in these research were at Hoehn and Yahr stage \( \leq 3 \) and thought as early stage, as we know, there is great difference between the progression rate and prognosis of PD and MSA-P. More than 50% of MSA patients require walking aids within 3 years after the onset of motor symptoms, 60% require a wheelchair after 5 years [14]. That means most of MSA patients are at H &Y stage \( \geq 3 \) within 3 years but PD patients are still at the stage when patients have good levodopa response and have no balance problem. Within 2 years of disease duration it’s very difficult to differentiate MSA-P and PD from clinical manifestation. There were other research papers use 2 years as early stage to compare MSA-P and PD [15, 16]. We aimed to compare the SWI of MSA-P and PD within 2 years to evaluate the usefulness of SWI for differential diagnosis. Using our measurement protocol the specificity for MSA-P distinguishing from PD can achieve as high as 100%, although the sensitivity is relatively low.

Clinically-available 3T conventional MRI contributes little to differentiate PD from atypical parkinsonian disorders. The pathologic alterations of parkinsonism show abnormal brain iron deposition, and therefore SWI which is sensitive to iron concentration has been applied to find iron-related lesions for the diagnosis and differentiation of PD in recent decades [17]. Lentiform nucleus includes putamen and globus pallidus anatomically, Wang et al found that MSA-P subjects with mean disease duration of 2.3 years had significantly higher iron deposition in the putamen compared with those with PD, but not in globus pallidus [18]. The Signal intensity of the bilateral posterior, dominant side of the posterior, mean values of the bilateral anterior and posterior halves of the putamen on SWI differed significantly between MSA-P and PD, but there were much diversity in the course of the disease between two groups [4]. The mean SWI signal intensity of the putamen was significantly lower for MSA-P with disease duration of about 1.3 years than for PD with similar disease duration and controls, the ROI was selected in the posterior small region of the putamen [5]. In our present study we enrolled the subjects within 2 years of disease course and found out that the signal intensity changes of the whole LN posterior position were not obvious enough to distinguish MSA-P from PD in their early stage. Although the cSIsd_LN significantly increased in the MSA-P group compared with the PD, this index could not distinguish MSA-P from controls. We thought that the signal intensity changes of the whole LN posterior position were not good markers for early differential diagnoses of MSA-P, maybe only the posterior-dorsal part of the putamen signal intensity was helpful.

There were limited previous studies about morphology changes in MSA-P, such as, based on different brain structure volumes and machine learning algorithm [14], subjective putamen atrophy [19], striatal volumes-of-interest (VOIs) 123 I-FP-CIT uptake and support-vector-machine analysis [20]. These studies all considered the morphology change in MSA-P was useful marker for differential diagnosis with PD. In this present research we found that the diameter indexes were better than signal indexes for distinguish MSA-P from PD in the early stage. MSA is typically presenting with relatively more symmetrical
parkinsonism than PD [8]. It's interesting in our results, there was relatively asymmetrical of the measurement of the morphological changes especially the index of SL. Using the smaller side of SL (cSL) can improve the sensitivity and specificity other than using the mean value of two sides. The AUC of cSLr was increased from 0.737 to 0.784 compared to SLr.

Several limitations in our primary and exploratory study should be noted: (a) the sample size is relatively small because of the low prevalence of MSA and the fact that this was a single-center study, b) the retrospective study did not relate morphological and signal changes to the patient's clinical scales, such as the Unified Multiple System Atrophy Rating Scale (UMSARS) and the motor and activities of daily living (ADL) scale. Larger and more randomized samples are needed in the future.

**Conclusions**

In spite of these limitations, we further verified the feasibility of this objective measurement in the early disease duration based on our previous work. We found that the MSA-P patients were characterized by narrowing the posterior region of the LN compared with the PD and control groups, which might be helpful for physicians to differentiate MSA-P from PD in the early stage.

**Abbreviations**

SWI: susceptibility weighted imaging; LN: lentiform nucleus; MSA: multiple system atrophy; MSA-P: multiple system atrophy parkinsonian subtype; MSA-C: multiple system atrophy cerebellar subtype; PD: Parkinson's disease; CG: control group; PACS: Picture and Communication System; LL: longest horizontal line; SL: short line; SLLr: the ratio of SL/LL; Slm_LN: mean signal intensity of lentiform nucleus; SIsd_LN: standard deviation of signal intensity of lentiform nucleus; nSlm: normalized Slm_LN; cSL: corrected SL; cSLLr: corrected SLLr; ANOVA: One way analysis of variance; LSD: Least Significant Difference; ROC: Receiver operating characteristic; ICC: Intraclass correlation coefficient; AUC: area under the curve; VOIs: volumes-of-interest; UMSARS: Unified Multiple System Atrophy Rating Scale; ADL: activities of daily living.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the ethics committee at Qilu Hospital of Shandong University (Qingdao) and performed in accordance with the Helsinki Declaration of the world medical association.

**Consent for publication**

Not applicable.

**Availability of data and material**
Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Qingguo Ren\(^1\) made the measurements and finished the statistical analysis, draft and submitted the manuscript; Cuiping Zhao\(^3\) made the study concept, MSA-P and PD diagnose and revised the manuscript; Yihua Wang\(^2\) revised the manuscript; Jianyuan Zhang\(^3\) made the MSA-P and PD diagnose; Xiaomin Nan\(^1\) made the measurements and collected the controls data, Xiangshui Meng\(^1\) made the interpretation of the results, and revised the manuscript. Qingguo Ren and Yihua Wang are equal as first authors, Xiangshui Meng and Cuiping Zhao are equal as corresponding authors in this manuscript.

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Tables

Table 1. the demographic characteristic of MSA-P, PD and CG

|                      | MSA-P          | PD             | CG             | $P$  |
|----------------------|----------------|----------------|----------------|------|
| Age (years, mean±SD, range) | 58.76±8.16±50-83 | 60.65±8.65±48-83 | 58.94±8.37±50-83 | > 0.3 |
| Gender (Male/Female)  | 10/7           | 10/7           | 10/7           | 1.000 |
| Disease duration (months, mean±SD, range) | 18.35±7.57±3-24 | 18.47±7.92±4-24 | NA            | 0.906 |

Table 2. the kappa value and ICC of two radiologists’ measurement

|            | cSL side | SL  | LL  | SLLr | Area  | SIm   | Slsd  | nSIm  |
|------------|----------|-----|-----|------|-------|-------|-------|-------|
| PD         | 0.410    | 0.448 | 0.617 | 0.418 | 0.054 | 0.598 | 0.830 | 0.605 |
| MSA-P      | 0.778    | 0.755 | 0.834 | 0.706 | 0.781 | 0.883 | 0.951 | 0.849 |
| HC         | 0.242    | 0.716 | 0.327 | 0.734 | 0.698 | 0.850 | 0.826 | 0.855 |

Note: the cSL side consistency was assessed by Kappa analysis, the others by . Intraclass correlation coefficient (ICC).

Table 3. Comparison of morphological and signal measurement among different group (mean ± standard deviation)
|             | MSA-P      | PD         | CG          | P        |
|-------------|------------|------------|-------------|----------|
|             | *  | #  | &   |        |
| cSL (mm)    | 4.73±2.17 | 6.86±1.95 | 7.01±2.34   | 0.006    |
| SL (mm)     | 5.66±2.20 | 7.50±2.03 | 7.49±2.30   | 0.018    |
| LL (mm)     | 15.72±2.51| 16.40±1.73| 16.95±1.69  | 0.502    |
| cSLLr       | 0.30±0.11 | 0.41±0.10 | 0.41±0.12   | 0.005    |
| SLLr        | 0.36±0.11 | 0.45±0.11 | 0.44±0.12   | 0.013    |
| Area (mm²)  | 159.65±48.47| 179.75±35.68| 196.79±47.89| 0.193    |
| Slm_LN      | 734.07±446.85| 785.15±440.02| 915.83±502.24| 0.593    |
| Slsd_LN     | 157.90±100.74| 91.94±59.89 | 134.85±98.25 | 0.060    |
| cSlsd_LN    | 184.10±118.18| 101.10±66.48| 147.86±105.39| 0.040    |
| Slm_CSF     | 1041.76±168.89| 1118.68±97.41| 1127.44±108.12| 0.153    |
| Slsd_CSF    | 51.89±26.69 | 51.07±27.42| 59.19±37.76 | 0.904    |
| nSlm        | 139.05±78.71| 141.43±78.63| 166.18±94.86| 0.770    |

Note. * : MSA-P vs PD, # : MSA-P vs CG, & : PD vs CG, Significant P-values <0.05 are highlighted in bold..