The predictive value of transcranial sonography in clinically diagnosed patients with early stage Parkinson’s disease: Comparison with DAT PET scans

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HIGHLIGHTS

• SN-TCS and DAT PET results were compared in early stage PD patients.  
• SN-TCS had moderate sensitivity and specificity.  
• SN-TCS had high positive predictive value.  
• SN-TCS would not be used as a diagnostic tool for early stage PD patients.  
• Positive SN-TCS will reduce an added presynaptic neuronimaging scan.

ARTICLE INFO

Article history:  
Received 2 April 2014  
Received in revised form 18 August 2014  
Accepted 30 August 2014  
Available online 10 September 2014

Keywords:  
Parkinson’s disease  
Substantia nigra  
Transcranial sonography  
Dopamine Transporter Positron Emission Tomography  
Computed Tomography Imaging

ABSTRACT

Early and correct diagnosis of Parkinson’s disease (PD) is critical for patient counseling and therapeutic management. The diagnostic accuracy of transcranial sonography of substantia nigra (SN-TCS) for early stage PD patients remains controversial. Dopamine transporter (DAT) imaging is sensitive to detect presynaptic dopamine neuronal dysfunction, and has been studied as a diagnostic tool for degenerative Parkinsonism. To investigate the predictive value of SN-TCS for the DAT PET scans in clinically diagnosed early stage PD patients, we performed the SN-TCS and DAT Positron Emission Computed Tomography (PET) imaging examinations on 53 patients. Using the DAT PET results as clinical gold standard, the sensitivity and specificity of TCS was 68.75% and 40% respectively. The positive predictive value (PPV) of an abnormal TCS for an abnormal PET scan was 91.67%. However, the negative predictive value (NPV) for a normal PET scan was only 11.76%. The false negative rate was 31.25%. In 35 patients, the result of the SN-TCD was in accordance with the result of the DAT PET scan (Kappa = 0.042, P > 0.05). The consistency between SN-TCS and PET scans was poor. We conclude that SN-TCS would not be used as a diagnostic tool for early stage PD patients. Negative result of TCS could not exclude the diagnosis of PD. Further tests like DAT-PET is needed for validation. On the other hand, positive SN-TCS will reduce the added diagnostic value of a presynaptic neuronimaging scan.

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1. Introduction

Parkinson’s disease (PD), the second most common neurodegenerative disorder, is characterized by loss of dopamine neurons in the substantia nigra (SN) and the subsequent deficiency in striatal dopaminergic system [1]. The diagnosis of PD still depends on clinical criteria, and the misdiagnosis is as high as 25% of cases as confirmed by anatomic-pathologic studies [2]. Early and correct diagnosis of PD is critical for patient counseling and therapeutic...
management. Selected neuroimaging studies have an ancillary role in confirming the diagnosis.

Transcranial sonography (TCS) of the SN has emerged as a promising, non-invasive tool to diagnose idiopathic PD. It has been reported that SN hyperechogenicity may be present in about 90% of idiopathic PD patients [3]. TCS has been recommended for the early diagnosis of PD and in the detection of subjects at risk for PD by EFNS/MDS-ES (Level A) [4]. But a recent prospective cohort study by Bouwmans et al. [5] showed the opposite founding. Therefore, the diagnostic accuracy of TCS for early stage PD patients remains controversial.

In vivo molecular imaging studies using positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) have led significant advances in the knowledge of the neurobiology and pathophysiology of PD. Dopamine transporter (DAT) imaging is sensitive to detect presynaptic dopamine neuronal dysfunction, and has been studied as a diagnostic tool for degenerative parkinsonism [4]. The implementation of DAT scans as a diagnostic tool in PD was approved in Europe in 2000, and the US FDA approved its clinical use in 2011. Normal DAT PET can be used to exclude underlying true nigrostriatal dysfunction [6]. In this study, using the DAT PET results as clinical gold standard, we assessed the diagnostic accuracy of SN-TCS on 53 patients diagnosed as PD based on clinical features in their early stages. We calculated the predictive value of the SN-TCD for the results of the DAT PET scans. We also assessed diagnostic consistency between SN-TCD and DAT PET scan.

2. Methods

2.1. Participants

We recruited in this study consecutive patients from the outpatient clinic of our hospital with definite PD based on the United Kingdom PD brain bank criteria [7]. Hoehn and Yahr (H–Y) stages <3 both on their on and off states. All the patients had structural MRI to exclude symptomatic causes of parkinsonism. Patients with atypical parkinsonian syndromes such as progressive supranuclear palsy, multiple system atrophy or corticobasal degeneration were excluded.

We initially studied 57 patients, of whom we had to exclude 4 (7%) with inconclusive SN-TCS because of an inappropriate temporal bone window (i.e. insufficient to acquire a 2-dimensional image of the intracranial structures). This percentage of inconclusive results is within the normal range [8,9]. All the remaining 53 patients then underwent DAT PET examination. SN-TCS and DAT PET examinations were performed independently by physicians blinded to the results of the other. The flowchart of categorization of subjects was presented as Fig. 1.

All subjects read and signed an informed consent prior to participation in the study. This investigation was approved by the Institutional Review Board of Capital University of Medical Science, Beijing Tiantan Hospital, Beijing, China.

![Flowchart of categorization of subjects.](image-url)
2.2. Procedures

2.2.1. Clinical assessments

Information regarding demographics, medical and family history, disease course, and treatment were collected during an interview. All subjects underwent a thorough neurologic examination and comprehensive motor testing. The severity of parkinsonian symptoms was assessed by subscale III of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) [10] and disease stage was estimated using the H–Y Scale.

2.2.2. SN-TCS

For TCS examination, the same one color-coded, phased array ultrasound system equipped with a 2.5 MHz transducer was used (PHILIPS IU22). The transducer was placed over the transtemporal bone window with a penetration depth of 14–16 cm and a dynamic range of 50 dB. The SN was identified within the butterfly-shaped structure of the mesencephalic brainstem as clearly as possible, scanning from both temporal bone windows, and quantified by encircling and measuring the area of hyperechogenic signals in the SN region as previously described [8]. All subjects were reassessed by a second ultrasound physician, who was blinded to the results of the first physician, to determine the reproducibility of the measurement. Both sonographers were blinded for the PET results and the clinical diagnoses. Kappa coefficient value of the interobserver agreement was 0.74 (95% confidence interval: 0.67, 0.83).

Planimetric quantification of the areas of increased echogenicity was done on both sides of the SN independently. In accordance with previously reported cut-off values, areas of echogenicity < 0.20 cm² were classified as normal (SN−) and areas of echogenicity ≥ 0.20 cm² were classified as hyperechogenic (SN+) [8]. For qualitative assessment, SN echogenicity of each individual was classified according to the more affected side.

2.2.3. DAT PET

In this study, we used DAT scan with 11C-CFT (11C-labeled 2β-carbomethoxy-3β-(4-fluorophenyl) tropane, PET Center of No. 1 Hospital affiliated to General Hospital of the Chinese People’s Liberation Army). Medication, (amantadine, levodopa, selegiline, pramipexole, piribedil, etc.) which could interfere with the radio-tracer, was stopped at least 5 half-life times before the PET was made. PET scans were performed in a quiet and dimly lit room. Images were collected after intravenous injection of 185–370 MBq of 11C-CFT 40 min and continued 25–35 min to get tomography through computer reconstruction. Since no DAT distributes in cerebellum (CB), the CB was used as the reference area for region of interest (ROI) analysis. According to ROI and the same CT image, three most clear images were selected to outline the ROI of bilateral caudate nucleus, bilateral putamen and cerebellum. Software was used to get the average data. The average ROI was used to get (ROI-CB)/CB as 11C-CFT uptake index of these areas. The index was further compared to that of healthy control to confirm the normality of tracer uptake. PET with asymmetrical low 11C-CFT uptake was considered as positive result. The scans were analyzed by a nuclear medicine specialist who was blinded for the clinical diagnosis and the SN-TCS results. PET and TCS images of our four distinctive patients were showed in Fig. 2 (A and C show PET with asymmetrical low 11C-CFT uptake. A and B show hyperechogenicity in the butterfly-shaped structure of the mesencephalic brainstem).

2.3. Statistic analysis

The diagnostic accuracy of SN-TCS was determined by comparing their results to the surrogate gold standard: DAT PET scans. Diagnostic accuracy is defined as the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Finally, we used Kappa test to compare the consistency of the two examinations. SPSS (SPSS 16.0) was used for statistical analysis. P values of less than 0.05 were considered statistically significant.

3. Results

3.1. Descriptives

The mean age of the 53 patients was 56.79 ± 9.37 years, and the majority (35/53) was male. The mean course of the disease
was 3.42 ± 3.34 years, and the mean Hoehn and Yahr score was 1.71 ± 0.69. The average UPDRS III score was 23.32 ± 12.24.

3.2. Accuracy of SN-TCS in clinically diagnosed PD patients

For the complete overview of the results of the SN-TCS, DAT PET in each subgroup of patients, see Fig. 1.

In the 53 subjects (18 women, 35 men) whose mesencephalic brainstem was adequately displayed by TCS, 36 subjects (67.92%) had a distinctly hyperechoic SN, with an echogenic signal exceeding 0.20 cm² on one or both sides. Of the 36 patients, 33 (91.67%) had an abnormal DAT PET. 17 of the 53 patients had normal SN echogenicity, while only 2 had a normal PET. Taking PET results as the gold standard, the sensitivity of SN hyperechogenicity was 68.75% (33/48), and the specificity was 40% (2/5).

3.3. Predictive value of SN-TCS for the results of the DAT PET scans

To estimate the predictive values of SN echogenicity for the early-diagnosed PD patients, all the 53 patients were included in the analysis. In 35 patients (66.04%), the result of the SN-TCS was in accordance with the result of the DAT PET scan. The PPV of a positive SN-TCS for an abnormal PET was high: 91.67% (33/36). However, the NPV of a negative SN-TCS for a normal PET was only 11.76% (2/17). The false negative rate of SN-TCS for the DAT imaging result was 31.25% (15/48).

3.4. The consistency of TCS and DAT PET

TCS and PET were both positive in 33 patients (62.26%), while 2 patients (3.77%) got a double negative results. Namely, in 35 patients, the result of the SN-TCD was in accordance with the result of the DAT PET scan (Kappa test, Kappa = 0.042, P > 0.05). So the consistency was poor (see Table 1).

4. Discussion

Substantia nigra (SN) hyperechogenicity in PD was first described by means of transcranial sonography (TCS) more than 15 years ago [11], and this finding has been confirmed by many groups worldwide [9,12–14]. The results of previous studies suggest that SN-TCS is valid for the diagnosis and differential diagnosis of idiopathic PD and differentiate between in the early stages [15,16]. As far as we know, the present study is the first to investigate the predictive value of SN-TCS with DAT PET as gold standard in clinically diagnosed early stage PD in a group of Asians.

In this prospective blinded study we show that SN-TCS may be not sensitive enough to diagnosis PD at early stage. In present study, only 67.92% of patients with PD diagnoses according to the UK Brain Bank criteria were SN-TCS positive. When compared with the DAT PET scan, the sensitivity of SN-TCS was only 68.75%, and negative predictive value was only 11.76%. In the remaining 17 SN negative patients, majority (88.23%) showed a positive DAT PET scan. The false negative rate of SN-TCS for the DAT imaging result was 31.25%. Nearly one-third patients might be misdiagnosed. There are several explanations for our lower sensitivity rate.

Firstly, unlike previous studies, we chose DAT PET scan as gold standard instead of the clinical diagnosis after follow-up. In routine clinical practice, there is a tendency toward overdiagnosis of non-PD patients [17]. Clinical overdiagnosis of PD is found in 15–47% [18,19] of cases in the community and in hospital studies, where postmortem confirmation of non-PD diagnoses occurred in 10–24% [20,21]. Since the follow-up diagnosis is made according to clinical criteria, clinical diagnosis should not be selected as gold standard to evaluate the SN-TCS. On the other hand, patients with suspected PD can be identified early and accurately using DAT imaging [22,23]. The advantage of the higher sensitivity and specificity of DAT imaging is that true presynaptic dysfunction within striatal dopaminergic system can be identified. Since presynaptic dopamine PET was abnormal in all kinds of degenerative parkinsonism, it should not be selected as gold standard for differential diagnosis between PD and atypical parkinsonism. Thus, the design of present study did not enroll the cases with progressive supranuclear palsy, multiple system atrophy or corticobasal degeneration. PET can provide higher resolution and better physical quantitative capacity than SPECT. Taken together, we chose DAT PET scan as surrogate golden standard instead of the clinical diagnosis after follow-up. This is, of course, not as good as post-mortem neuropathological analysis, but the best possible alternative at present.

Secondly, stability of SN hyperechogenicity of PD patients during the disease course is still a controversy. Several reports have suggested that there is an association of echosignal extension and disease severity [24,25]. While the study of Berg et al. [26] indicated that SN echointensity to be stable during follow-up. The patients in our study were in the early stages of their disease. Whether this is also the case in early-stage patients remains unclear.

Thirdly, sensitivity of TCS is uncertain across different race populations and varied between PD subtypes [27,28]. Huang et al. [28] have found there were Racial–ethnic differences in hyper-SN in Asians and Caucasians. Schweitzer [27] sonographically investigated 16 PD patients in whom the rate of progression had been determined by serial 18-fluorodopa PET over a follow-up period of 65.7–26.7 months. They found a significant negative correlation between the right-to-left averaged SN echogenic size and the rate of disease progression in the caudate nucleus and in the putamen. The subgroup with smaller SN echogenic sizes showed later disease onset and faster disease progression. Huang et al. [28] found that, in Asian population, enlarged hyperechogenicity of SN is a common finding in late-onset form of PD, but not in early-onset form of PD whose disease onset age <50 years. It may suggest that a differing influence of factors determining SN echogenicity may account for different pathogenic subgroups of idiopathic PD. Because the subjects in our study included both subtypes, the specificity in our study which was higher than that of early-onset form (50%), but lower than that of late-onset form (85%) [27] is reasonable.

Finally, the quality of the ultrasound system and the TCS technique itself all are non-trivial variable. One needs considerable personal expertise to perform and interpret a TCS correctly. Although the ultrasound physicians in this study were specialized and blinded to the clinical diagnosis, it is still difficult to avoid subjective error when identify the SN hyperechoic area.

The positive predictive value (PPV) of SN-TCS against DAT PET in our study was as high as 91.67%, which confirmed previous studies [15,29]. A positive SN-TCS is a good predictor in diagnosing parkinsonism with nigrostriatal degeneration. This indicates that if SN-TCS is abnormal in patients with clinical diagnosis PD, the clinician can be confident of presynaptic dysfunction within striatal dopaminergic system. For clinical practice, this would imply that

| Table 1: Predictive value of SN-TCS for the results of the DAT-PET scan. |
|----------------|----------------|----------------|----------------|----------------|
|                | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Kappa | P value |
| TCS            | 68.75          | 40             | 91.67                      | 11.76                     | 0.042 | 0.690   |
a positive SN-TCS in a patient with an early-stage, recently diagnosed PD, would reduce the added diagnostic value of a presynaptic PET/SPECT.

This research has limitations. Actually, although we chose DAT-PET, with high sensitivity and specificity, it still cannot replace histopathological data. In addition, only 53 patients were included in this study, research with greater number of participants is required in further studies to support our hypothesis.

5. Conclusion

To sum up, the moderate sensitivity and specificity, low NPV of an abnormal TCS for PD in our study suggest that TCS would not be used as a diagnostic tool for early stage PD patients. Negative results of TCS could not exclude the diagnosis of PD. Further tests like DAT-PET is needed for validation. On the other hand, compared with DAT PET, TCS is a quick, non-invasive, generally available, and low-cost procedure. The high positive predictive value indicates that in those hospitals where TCS is a routine examination for patients with suspected parkinsonian disorders, positive SN-TCS will reduce the added diagnostic value of a presynaptic PET or SPECT scan.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors wish to thank all patients, who took part in the study. This study was supported by the Scientific Research Common Program of Beijing Municipal Commission of Education (No. KZ201210025028), the Beijing municipal science and technology plan (No. Z11110005880000) and High Level Technical Talent Training Program in Beijing Healthcare System (No. 2011-3-022). These funding agencies did not participate in design or analysis, manuscript preparation, or approval of this study.

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