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Comparison of transcranial sonography-magnetic resonance fusion imaging in Wilson's and early-onset Parkinson's diseases

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ABSTRACT

Introduction: Wilson's disease (WD) is a hereditary disorder caused by *ATP7B* mutations resulting in systemic copper accumulation. WD may manifest as early-adulthood parkinsonism; and atypical cases may be difficult to distinguish from early-onset Parkinson's disease (EO-PD), a neurodegenerative disorder with onset ≤40 years of age. The aim of our study was to compare transcranial sonography (TCS) −magnetic resonance fusion imaging in WD and EO-PD and examine whether TCS can provide clinically useful information.

Methods: We examined 22 WD, 16 EO-PD, and 24 healthy control subjects. We measured echogenicity and determined presence of MRI signal changes in T2-weighted images in the substantia nigra (SN) and lentiform nucleus (NL). TCS with the capability of magnetic resonance fusion and Virtual Navigator was used. The echogenicity indices of SN and NL were processed using digital image analysis to eliminate subjective evaluation errors.

Results: Mean SN echogenicity index in EO-PD (39.8 ± 5.9 [SD]) was higher compared to WD (28.0 ± 4.6, $p < 0.0001$) and control subjects (28.8 ± 4.9, $p < 0.0001$). Mean NL echogenicity index was higher in WD (117.5 ± 37.0) compared to EO-PD (61.6 ± 5.4, $p < 0.0001$) and control subjects (54.9 ± 11.2, $p < 0.0001$). The SN hyperechogenicity had sensitivity 93.8%, and specificity 90.9%, while the NL hyperechogenicity had sensitivity 95.5% and specificity 93.8% for differentiation of WD and EO-PD. NL hyperechogenicity was more pronounced in WD subjects with putaminal MRI T2 hyperintensity ($p < 0.05$) but was also present in subjects without MRI abnormality.

Conclusions: There are distinct TCS findings in WD and EO-PD complementary to MRI that can be utilized as highly sensitive and specific biomarkers of these disorders.

1. Introduction

Wilson's disease (WD) is a hereditary disorder caused by *ATP7B* mutations resulting in copper accumulation in liver and brain. Timely diagnosis is essential since patients have a good prognosis if the treatment is provided in the early stage [1]. Diagnosis of

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neurological WD is straightforward in the majority of cases when typical biochemical abnormalities are present [2]. However, the diagnosis may be difficult in atypical cases that do not fulfill all the clinical and laboratory criteria [3]. Moreover, genetic confirmation may be difficult since *ATP7B* gene is large and more than 500 mutations were described [1], some of them with questionable pathogenicity [4].

According to guidelines, every patient with young adulthood-onset movement disorder should undergo screening for WD. WD may manifest with parkinsonism, either isolated or in combination with other symptoms such as dystonia, kinetic tremor or ataxia. In early-onset Parkinson's disease (EO-PD), parkinsonism is frequently accompanied by psychiatric symptoms and dystonia [5]. Therefore, the importance of the differential diagnosis between EO-PD and WD may arise, particularly in cases with atypical symptoms and/or inconclusive results of biochemical examinations.

Transcranial sonography (TCS) is a validated tool in the diagnosis of an early stage of PD [6] as well as in the differential diagnosis of PD and atypical parkinsonian syndromes [6,7] and dopa-responsive dystonia [8]. Typical findings in PD consist particularly of the hyperechogenicity and enlarged echogenic size of substantia nigra (SN) [6,9,10]. In the neurological form of WD, the echogenicity of SN is variable, while the hyperechogenicity of the lentiform nucleus (NL) has been consistent across studies [11–15]. It is unclear how echogenicity changes in WD interrelate to MRI abnormalities that typically consist of hyperintensity of basal ganglia, brainstem, and thalamus in T2-weighted (T2w) images [16].

Considering these different findings in EO-PD and WD patients, TCS could be a time-saving, low-cost, screening examination of these disorders. Potential drawbacks of TCS are limited anatomical clarity and dependence on examiner's subjective evaluation of hyperechogenicity. These obstacles are partially overcome by using Virtual Navigator for fusion of TCS and MRI which helps in precise identification of brain structures [17] and recently validated method of digital image analysis which reduces the sonographer's bias in the assessment of hyperechogenicity [18].

The aim of the study was to compare the echogenicity changes in SN and NL in EO-PD and WD in relation to MRI results and assess the utility of TCS as a screening examination in early-onset parkinsonism.

2. Methods

2.1. Patients

In WD patients, inclusion criterion was neurological WD with diagnosis established according to Leipzig criteria [19]. In EO-PD patients, inclusion criteria were diagnosis in accordance with the UK Parkinson's Disease Society Brain Bank criteria [20], and age at onset $\leq$ 40 years. For both groups, exclusion criteria were presence of deep brain stimulation (DBS) electrodes and insufficient temporal bone window for TCS examination. Out of 37 neurological WD patients from our database, 15 were not reachable or disagreed to participate. Out of 59 EO-PD patients from our database 21 were excluded because of DBS, 21 disagreed to participate and one was excluded due to insufficient temporal bone window. Twenty-two WD and 16 EO-PD patients participated in the study. The control group consisted of 24 healthy subjects with no neuropsychiatric disorder. All subjects signed informed consent and the study was approved by the Ethical Committee of General Teaching Hospital in Prague.

Information about initial clinical symptoms, abnormal serum ceruloplasmin concentration, urine copper excretion, liver copper concentration, and the presence of K-F ring at the time of diagnosis was retrieved from medical records.

Twenty WD patients were on a stable medication while two were *de novo* treatment naïve patients at the time of examination (Table 1). Fifteen PD patients were on a stable antiparkinsonian medication while one was treatment naïve. All PD patients were tested for *PARK2* mutations; heterozygous pathogenic mutation was found in one. Neurological impairment was assessed by the Unified Wilson's Disease Rating Scale (UWDRS) [21] in WD and by the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III) in EO-PD group respectively. Patients were examined on their usual symptomatic therapy. “Joint parkinsonism subscore” was calculated from items present jointly in both scales in order to compare the severity of parkinsonism in WD and EO-PD groups. This subscore consists of UPDRS-III except items 24, 30 and 31.

2.2. Magnetic resonance imaging

MRI was performed using 1.5 T whole body Philips Achieva system in EO-PD and WD patients. Standard spin echo T1w (resolution = $1.2 \times 1.2 \times 3$ mm^3, TE = 15 ms, TR = 500 ms) and T2w (resolution = $0.5 \times 0.5 \times 2$ mm^3, TE = 233 ms, TR = 2250 ms) sequences covering the whole brain were employed to quantify brain damage and generate anatomical images for TCS fusion. An experienced neuroradiologist blinded to the diagnosis quantified the MRI pathology. Degree of atrophy was graded as absent (0 points) mild (1 point) or severe (2 points) in three locations: 1) cerebellum and brainstem, 2) basal ganglia and subcortical region and 3) cortex. At that, presence of T2 hyperintensities in the caudate nucleus, putamen, globus pallidus, thalamus, mesencephalon, pons and T2 hypointensities in the NL, SN, and dentate nucleus were scored by 1 point each. The total sum of atrophy and signal changes build the composite MRI severity score (maximum 15 points) [22].

2.3. Transcranial sonography

The ultrasound system MyLab Twice (Esaote S.p.A., Genova, Italy) was equipped with the Virtual Navigation (MedCom GmbH, Darmstadt, Germany), which allows real-time image fusion of TCS and MRI images. The ultrasound scanner with a Reusable Tracking Bracket (CIVCO, Kalona, IA, USA) and sensor mount were used. The Virtual Navigator technology was implemented using an electromagnetic tracking system, composed of a transmitter and a small receiver, mounted on the ultrasound probe. SN was imaged in the axial mesencephalic plane (Fig. 1A) while NL and caudate nucleus (CN) were imaged in the axial thalamic plane (Fig. 1B) using the Fusion Imaging technique.

Following parameters were used: penetration depth of 16 cm, penetration high, dynamic range 7 (50 dB), frequency 1–4 MHz, enhancement 3, density 2, view 9, persistence 7, dynamic compression 0, gain 36%, grey map 0, S-view off, 2 focuses in 5 and 10 cm, mechanical index 0.9, tissue indices TIs 1.0, TIB 1.0 and TIC 2.1.

The butterfly-shaped structure of the mesencephalic brainstem and the region of SN in mesencephalic section and CN and LN in the thalamic section were depicted and images were saved in 8-bit grayscale DICOM format for offline analysis. Predefined elliptical ROIs were manually placed in the region of contralateral CN and LN and ipsilateral SN (Supplementary Figure). The echogenicity indices were calculated separately for SN, CN and LN from both right and left temporal bone windows using the B-Mode Assist software for digital image analysis [18,23]; the higher value of both measurements was used for analysis.

Standard visual assessment of SN and LN echogenicity [24] was also performed and results were compared with those obtained by digital image analysis. The mean SN echogenic area from both sides

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