VISUAL ANALYSIS OF NIGROSOME-1 IN THE DIFFERENTIAL DIAGNOSIS OF PARKINSON'S DISEASE AND ESSENTIAL TREMOR

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Differentiation between Parkinson's disease, especially in its early stages, and essential tremor, which is a phenotypically similar movement disorder, still remains an unsolved challenge for neurology. The aim of this study was to assess the diagnostic significance of nigrosome imaging (nigrosomes are dopaminergic neuron clusters in the substantia nigra of the midbrain) using 3T high-resolution SW-MRI. The study was conducted in 20 patients with Parkinson's disease and 10 patients with essential tremor. Visual analysis of the acquired nigrosome-1 images was performed using a 4-point ordinal rating scale. Differences in sex, age and duration of the disease were calculated using the Fisher exact test and the Mann–Whitney U test. The diagnostic value of the method was assessed using Pearson's chi-squared test. Nigrosome-1 was bilaterally or unilaterally absent in 70% of parkinsonian patients. Less specific changes to the substantia nigra (SN) were observed in two more parkinsonian patients (10%), whose nigrosome-1 appeared reduced in size. By contrast, nigrosome-1 was bilaterally intact in all patients (100%) with essential tremor ($p < 0.001$). Our preliminary findings demonstrate the high potential of noninvasive nigrosome-1 imaging in the differential diagnosis of Parkinson's disease and essential tremor.

Keywords: Parkinson's disease, essential tremor, nigrosome-1, magnetic resonance imaging, SWI

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Center of Neurology (Protocol № 2–5/20 dated March 18, 2020). Informed consent was obtained from all study participants.

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ВИЗУАЛЬНЫЙ АНАЛИЗ НИГРОСОМЫ-1 В ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКЕ БОЛЕЗНИ ПАРКИНСОНА И ЭССЕНЦИАЛЬНОГО ТРЕМОРА

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Дифференциальная диагностика болезни Паркинсона и фенотипически схожего двигательного расстройства — эссенциального тремора, особенно в дебюте заболевания, остается одной из нерешенных задач современной неврологии. Целью исследования было оценить диагностическую значимость визуализации нигросом — кластеров дофаминергических нейронов в черной субстанции (ЧС) среднего мозга, выявляемых при использовании SWI-режима высокоразрешающей магнитно-резонансной томографии (3 Тесла), у 20 пациентов с болезнью Паркинсона и у 10 пациентов с эссенциальным тремором. Визуальный анализ изображений нигросомы-1 проводили с использованием четырехчленной порядковой шкалы. Различия по гендерному, возрастному составу и продолжительности заболевания рассчитывали с помощью точного критерия Фишера, U-критерия Манна–Уитни. Для расчета диагностической ценности данной методики использовали критерий χ^2 Пирсона. У пациентов с болезнью Паркинсона в 70% случаев наблюдали одно- или двустороннее исчезновение нигросомы-1. Еще у двух пациентов с болезнью Паркинсона (10%) выявили менее специфичные изменения черной субстанции — уменьшение объема нигросомы-1. Напротив, у всех пациентов с эссенциальным тремором (100%) нигросома-1 оставалась сохранной с двух сторон ($p < 0,001$). Полученные предварительные результаты демонстрируют высокий потенциал методики визуального анализа нигросомы-1 в дифференциальной диагностике болезни Паркинсона и эссенциального тремора.

Ключевые слова: болезнь Паркинсона, эссенциальный тремор, нигросома-1, магнитно-резонансная томография, SWI-режим

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Parkinson's disease (PD) and essential tremor (ET) are common movement disorders that predominantly affect the elderly [1, 2]. Both diagnoses are clinical and rely on the sum of their typical neurological manifestations. According to the criteria for PD published by the International Parkinson and Movement Disorder Society in 2015, bradykinesia combined with resting tremor and/or rigidity in the presence of supportive criteria and the absence of absolute exclusion criteria indicates clinically definite or clinically probable PD [3]. Importantly, apart from motor manifestations, the clinical picture of PD can include non-motor symptoms that predate motor impairment and progress gradually as the disease advances [4].

According to the updated criteria proposed by the International Parkinson and Movement Disorder Society in 2017, ET is defined as "an isolated tremor syndrome of bilateral upper limb action tremor with at least 3 years' duration, with or without tremor in other locations" [5]. In practice, patients with ET often present with additional neurological symptoms that go beyond the definition of ET, including resting tremor, impaired tandem gait, etc. Such cases are classified as ET plus. Besides motor

manifestations, many patients with ET have various non-motor symptoms [2] that usually do not have any particular clinical significance but complicate differentiation between ET and PD.

Radionuclide imaging, e.g. positron-emission tomography (PET), single photon emission computed tomography (SPECT) and transcranial sonography (TCS), can be used to differentiate between ET and PD by assessing damage to the substantia nigra (SN), the primary target of neurodegeneration in PD, which remains intact in ET [6, 7]. However, radionuclide imaging has objective limitations impeding its exploitation in clinical neurological practice.

The use of magnetic resonance imaging (MRI) for diagnosing PD and differentiating it from nondegenerative forms of parkinsonism became possible with the spread of high-field MR scanners and the introduction of additional MRI sequences into the standard MRI protocol.

Dopaminergic neurons of SN are arranged into cell clusters called nigrosomes [8]. Nigrosome-1, the largest of 5 known nigrosomes, appears on high-resolution susceptibility weighted images (SWI) as an oval slightly hyperintense region in the dorsal SN. Nigrosome-1 divides SN into 2 parts, bearing resemblance to a swallow tail, hence its name “the swallow tail sign” [9]. Recent research has shown that location of the hyperintense nigrosome-1 region in the surrounding hypointense SN structures can be quite variable and does not always fit the “swallow tail” profile [10]. Patients with PD demonstrate a loss of dorsolateral nigral hyperintensity due to the involvement of nigrosome-1 in neurodegeneration [9, 11]. In ET, structural and functional changes have been reported in the cerebellum and the brain stem (predominantly in the locus coeruleus) [12]. Despite the lack of consistency between the results of pathomorphological studies and the understudied pathogenesis of ET, so far there has been no reliable evidence about the presence of pronounced SN degeneration in patients with ET comparable to that in patients with PD. Consequently, attempts have been made to determine the diagnostic significance of visual assessment of nigrosome-1 images in discriminating between PD and ET. The method has demonstrated high sensitivity and high specificity; besides, it does not require image post-processing and therefore is effective and suitable for clinical practice [13, 14].

To our knowledge, there are no publications analyzing the described neuroimaging pattern of SN changes in the Russian cohort of patients with movement disorders. The aim of this study was to assess the biomarker role of dorsolateral nigral hyperintensity loss in differentiating between PD and ET, which is a phenotypically similar disorder.

METHODS

Participants

Participants were recruited from in- and outpatients undergoing treatment at the Research Center of Neurology from January to October 2020. The study included 20 patients with tremor-dominant/mixed types of PD (group 1) and 10 patients with ET (group 2). The diagnosis was made based on the current criteria for each of these disorders. PD staging was done using the functional Hoehn–Yahr scale: 40% of the patients had stage 1 (n = 8), 30% had stage 2 (n = 6), and 30% had stage 3 (n = 6). The patients gave informed consent to participate in the study and have their personal data processed.

The following exclusion criteria were applied: the past history of other neurologic/psychiatric disorders; psychoactive substance abuse; alcohol abuse; intake of tremorogenic drugs; tremor-inducing metabolic disorders; structural damage to the brain (neoplasms, infarction, brain injury sequelae); MRI artifacts precluding the analysis of MR images; age under 18 and above 80 years.

MRI protocol and analysis of MR images

MRI protocol

All MR images were acquired using a 3T Siemens MAGNETOM Verio scanner equipped with an 8-channel head coil. SWI sequences were acquired to assess nigrosome-1 appearance (TR = 27 ms, TE = 20 ms, slice thickness = 1.5 mm, dist. factor = 20%, FoV = 172 × 230 mm^2, scan time = 2 min 59 s). Besides, T2, T1 MPR, T2 FLAIR and DWI images were acquired to exclude other causes of parkinsonism. The axial plane was parallel to the line connecting the anterior and posterior commissures across all brain structures.

Qualitative analysis of acquired images

On the acquired SW images, nigrosome-1appeared as an oval slightly hyperintense region in the hypointense area of the dorsal midbrain (SN). Visual analysis of the images was performed using the following 4-point ordinal scale: 0 points — the norm (nigrosome-1 is visualized bilaterally); 1 point — the image has no diagnostic value (nigrosome-1 is poorly visualized on one or both sides or is diminished in size, i.e. partially lost); 2 points — abnormality (nigrosome-1 is absent unilaterally); 3 points — abnormality (nigrosome-1 is absent bilaterally). For illustrative purposes, MR images of 4 patients with different nigrosome-1 appearance are provided in Fig. 1. Qualitative analysis was conducted by 2 radiologists who had no access to the patients’ medical records and were working independently. If their conclusions were conflicting, preference was given to the opinion of the more experienced radiologists.

Statistical analysis

The results of the study are presented below as medians and lower and upper quartiles (Med, lq, uq). Demographic characteristics of the patients (age, sex, duration of the disease) were compared using the Fisher exact test and the Mann–Whitney U-test. Nigrosome-1 scores were compared between the groups using Pearson’s chi squared test. In all statistical tests, the significance threshold was assumed to be $p < 0.05$. The data were analyzed in StatTech v1.1.0, SPSS Statistics.

RESULTS

Demographic characteristics

The PD and ET groups did not differ significantly in terms of sex and age (p = 0.246, p = 0.082, respectively). The duration of the disease was significantly longer in the patients with ET than in those with PD ($p < 0.003$). The analysis of associations between the disease and sex was performed using Fisher’s exact test; the associations between age and disease duration were tested using the Mann–Whitney U test. Demographic characteristics of the patients are provided in Table.

Neuroimaging data

Nigrosome-1 was clearly visible bilaterally in all patients with ET (n = 10), so all patients from group 2 scored 0 points on the rating scale (100%).

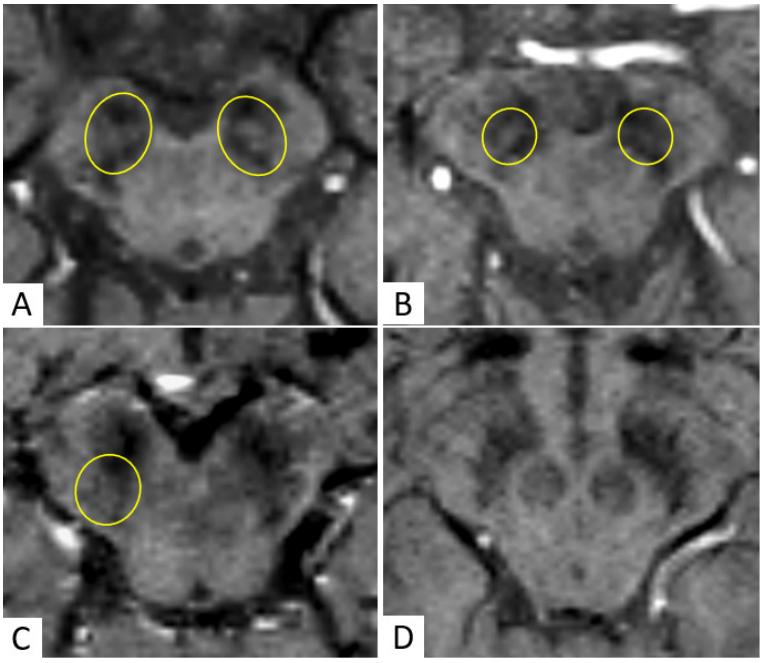

Fig. 1. Susceptibility-weighted MR images in the axial plane; slices pass through the cerebral peduncles. The substantia nigra is hypointense on SWI sequences, whereas nigrosomes-1 (*yellow circles*) are hyperintense. The figure shows different patterns of nigrosome-1 appearance in patients with PD (**A** — 0 points, **B** — 1 point (nigrosome-1 is reduced in volume on the *left*), **C** — 2 points, **D** — 3 points)

However, it was absent in 70% of patients with PD (n = 14); the ratio of unilateral and bilateral loss of dorsolateral nigral intensity was 1 : 1. Accordingly, 7 patients with PD scored 2 points (35%) and 7 other patients with PD scored 3 points (35%).

Nigrosome-1 was intact (0 points) in 4 patients with PD (20%); 2 more patients with PD (10%) scored 1 point: their MRI scans showed a reduction in nigrosome-1 size on one side, which was interpreted as having no diagnostic value. Comparison of the PD and ET groups demonstrated a significant difference in the results expressed as percentage ($p < 0.001$, Pearson's χ^2).

Thus, the study demonstrates a high diagnostic value of non-invasive visual nigrosome-1 assessment in differentiating between PD and ET: the sensitivity and specificity of the method were 70% and 100%, respectively. The results are provided in Fig. 2.

DISCUSSION

Oftentimes, discrimination between early-stage PD and phenotypically similar disorders poses a certain difficulty to a neurologist. The aim of this study was to assess the diagnostic significance of non-invasive nigrosome-1 assessment in differentiating PD from ET.

It has been over 20 years since heterogeneity of the SN pars compacta (i.e. identification of nigrosomes and the nigral matrix by immunohistochemical staining) was discovered and the staging of nigrosome damage due to PD-related neurodegeneration was pathomorphologically confirmed [8, 15]. Non-invasive imaging of nigrosome-1 became possible with the spread of high-field MR scanners and the introduction of SWI sequences into the standard brain MRI protocol [9, 16]. SWI is a technique that utilizes 3D pulse MRI sequences sensitive to magnetic field inhomogeneities. It is based on the following phenomenon: iron, calcium and deoxyhemoglobin can enhance a local magnetic field and induce a positive phase shift, in comparison with the surrounding cerebral tissues. Tissues containing these paramagnetic agents appear on SW images as regions of hypointense MR signal [17, 18].

In healthy subjects, SN appears on MR images as a hypointense midbrain region dorsally divided into 2 segments by an oval hypointense area. Histopathological studies have confirmed that this dorsolateral nigral hyperintensity corresponds to nigrosome-1 and that signal enhancement may be associated with low iron content in this region in comparison with the surrounding SN [19].

Nigrosome-1 is not visualized in patients with PD. Apart from the loss of dopaminergic neurons, this may be associated with iron accumulation occurring in parallel [20, 21]. The loss of dorsolateral nigral hyperintensity is currently regarded as one of the most promising biomarkers of PD. For example, a recent meta-analysis reports that the diagnostic accuracy of nigrosome-1 imaging for the differentiation between patients with idiopathic PD and healthy individuals demonstrates high sensitivity and high specificity [22].

Table. Demographic characteristics of the patients

Characteristic	Categories / units of measurement	Disease		p
		PD	ET	
Sex, abs. (%)	Women	11 (55)	8 (80)	0.246
	Men	9 (45)	2 (20)	
Age, Me [Q_1–Q_3]	Full years	60 [52.25–66.5]	73.5 [58.5–77.25]	0.082
Disease duration, Me [Q_1–Q_3]	Full years	3 [2–6.5]	10 [8.5–15.75]	0.003

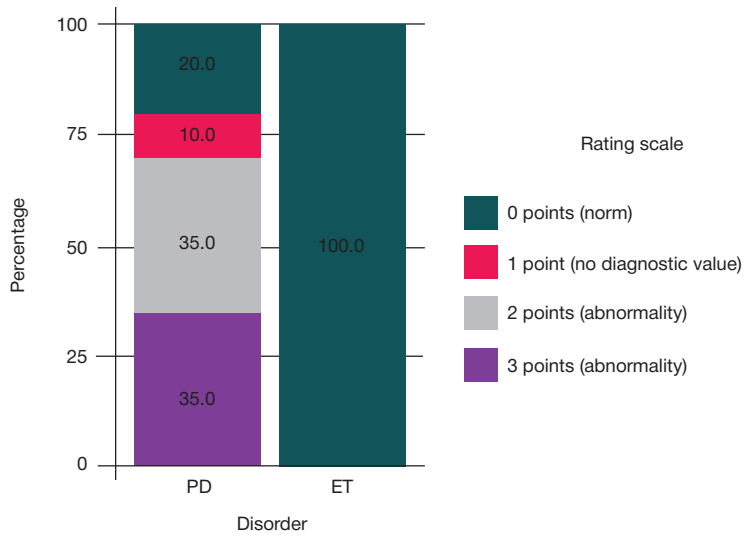

Fig. 2. Results of non-invasive nigrosome-1 assessment in patients with PD and ET

The diagnostic value of this neuroimaging marker in differentiating between PD and ET was assessed in two studies published in 2019. Jin L. et al. analyzed MR images of 68 patients with PD, 25 patients with ET and 34 control subjects. The method demonstrated high sensitivity (79.4%) and high specificity (92.0%) [13]. M. S. Perez Akly et al. studied dorsolateral nigral hyperintensity in 16 patients with PD and 16 patients with ET. The results were comparable to the results of the study by Jin L. et al. According to one of 2 involved radiologists, the sensitivity and specificity of the method were 93.75% and 87.5%, respectively. The second radiologist reported 93.75% sensitivity and 75% specificity [14]. Thus, the method was shown to be effective in differentiating between PD and ET by 2 independent research teams.

Our study also confirms the diagnostic value of noninvasive nigrosome-1 imaging. In contrast with ET patients, the absence of dorsolateral nigral hyperintensity in SN was observed in the majority of our PD patients. The sensitivity and specificity of the method tested on the small cohort of patients were 70% and 100%, respectively.

Artifacts from motion and metal dental implants were a significant limitation of our study. From initially examined 39 patients (26 patients with PD, 13 patients with ET), only 30 whose MR images were suitable for the analysis were included in the study. To reduce the number of artifacts from motion, the patient's head can be stabilized with sand sacks or foam pillow support, and mild medical sedation can be applied [16].

CONCLUSIONS

Our findings supported by the results of foreign studies lead us to conclude that noninvasive neuroimaging has a potential to become a useful tool in the differential diagnosis of diseases accompanied by tremor and other movement disorders, including differentiation between PD and ET, especially in the early stages of the disease.

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