doi: 10.53446/actamednicomedia.1219434

Acta Medica Nicomedia

Cilt: 6 Sayı: 2 Haziran 2023 / Vol: 6 Issue: 2 June 2023
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

INVESTIGATION OF SUBSTANTIA NIGRA HYPERECHOGENICITY BY TRANSCRANIAL SONOGRAPHY IN PATIENTS WITH ESSENTIAL TREMOR

ESANSİYEL TREMOR HASTALARINDA TRANSKRANİYAL SONOGRAFİ İLE SUBSTANTİA NİGRA HİPEREKOJENİTESİNİN ARAŞTIRILMASI

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ABSTRACT

Objective: Essential tremor (ET) is the most common movement disorder. ET diagnosis may precede future Parkinson's disease. Substantia nigra hyperechogenicity in transcranial sonography (TCS) is associated with Parkinson's disease. The underlying etiology of substantia nigra hyperechogenicity remains unclear. In this study, we aimed to investigate the significance of the substantia nigra hyperechogenicity in patients with essential tremor.

Methods: A total of 55 patients with ET and 60 matched controls underwent TCS. The hyperechogenic area was measured in the SN. Approximately ten years after their baseline TCS, all patients were inquired about their current condition, treatment, and medications to determine whether they had received a diagnosis of PD.

Results: A total of 15 subjects were excluded due to insufficient image acquisition. The echogenic area of the SN ranged from 0.01 to 0.86 cm^2 (mean 0.25±0.15) in the patient group and from 0.02 to 0.72 cm^2 (mean 0.15±0.16) in the control group. Patients with ET had a significantly larger echogenic area than controls (p=0.001). 47% (26/55) of the patients have hyperechogenic SN, whereas only 15 % (9/60) of healthy controls have hyperechogenicity in the substantia nigra. None of the patients reported having a change in their diagnoses of ET.

Conclusions: The results of this study show that SN hyperechogenicity is increased in patients with ET. Transcranial sonography may contribute to understanding the pathophysiology of ET.

Keywords: Essential tremor, parkinson's disease, substantia nigra hyperechogenicity, transcranial sonography

ÖZ

Amaç: Esansiyel tremor (ET) en sık görülen hareket bozukluğudur. ET ayrı bir hastalık olarak kabul edilse de, klinik takipte ET tanılı vakaların Parkinson Hastalığına (PH) ilerleyebildiği bilinmektedir. Transkraniyal sonografide (TKS) Substantia nigra (SN) hiperekojenitesi saptanması, PH ile ilişkili bulunmuştur. Ancak bu radyolojik bulgunun etiyolojisi ve klinik anlamı belirsizliğini korumaktadır. Biz de bu çalışmada esansiyel tremorlu hastalarda SN hiperekojenisitenin önemini araştırmayı amaçladık.

Yöntem: Bu çalışmada ET tanısı olan toplam 55 hastaya ve yaşları benzer 60 kontrole TKS uygulandı ve SN hipekojeniteleri ölçüldü. Başlangıç TKS'lerinden yaklaşık on yıl sonra, tüm hastalara tekrar ulaşıldı ve PD teşhisi alıp almadıkları, mevcut durumları, tedavileri ve ilaçları hakkında sorular soruldu.

Bulgular: Çalışmaya dahil edilen 115 hastadan 15'i yetersiz görüntü kalitesi nedeniyle çalışmadan dışlandı. SN'nin ekojenik alanı hasta grubunda 0,01 ile 0,86 cm^2 (ortalama 0,25±0,15), kontrol grubunda ise 0,02 ile 0,72 cm^2 (ortalama 0,15±0,16) arasında değişiyordu. ET'li hastalarda kontrollere göre anlamlı ölçüde daha büyük bir ekojenik alan ölçüldü (p=0,001). Hastaların %47'si (26/55) hiperekojenik SN'ye sahipken, sağlıklı kontrollerin sadece %15'i (9/60) substantia nigra'da hiperekojeniteye sahipti. Hastaların hiçbiri takipte ET tanılarında bir değişiklik olduğunu bildirmedi.

Sonuç: Bu çalışmanın sonuçları, ET'li hastalarda SN hiperekojenitesinin arttığını göstermektedir. Transkraniyal sonografi ET patofizyolojisini anlamaya katkı sağlayabilir.

Anahtar Kelimeler: Esansiyel tremor, parkinson hastalığı, substantia nigra hiperekojenitesi, transkraniyal sonografi

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Submitted/Başvuru: 06.01.2023 • **Accepted/Kabul:** 02.05.2023 • **Published Online/ Online Yayın:** 30.06.2023

Introduction

Essential tremor (ET) is the most common movement disorder in adults [1]. It is characterized by action tremor of the arms, which may progress in severity, spreading to the limbs or head and becoming disabling. There is still an ongoing debate on the pathology underlying the disease. Essential tremor has been proposed to be a neurodegenerative condition considering its insidious onset, progressive course, and association with an increased risk for Parkinson's disease (PD) and Alzheimer's disease. In addition, autopsy findings of loss of Purkinje cells in the cerebellum and Lewy bodies in the locus coeruleus supported the neurodegenerative nature of ET [2]. However, there have been claims that ET might be a disorder of a thalamocorticocerebellar network rather than a degenerative condition [3]. In addition, in some ET subgroups, a transformation from ET to PD has been reported [4]. The diagnosis of ET is based on a thorough patient history-taking and clinical examination, with particular attention given to differentiating from PD. However, due to the overlapping clinical features, it may be challenging to distinguish ET from PD, even for expert neurologists in movement disorders.

Currently, the differentiation between ET and PD may be possible by dopamine transporter imaging, which can demonstrate presynaptic neurodegeneration consistent with PD [2]. However, this imaging modality is expensive and only available at some facilities. Transcranial sonography (TCS) is a non-invasive and inexpensive tool used to assess the presence of hyperechogenicity of the substantia nigra, indicating a degenerative course in PD or alike, and recognized as an additional diagnostic tool in PD [5,6]. Previous studies showed significant hyperechogenicity in the area of SN in patients with PD compared with ET and healthy controls [7]. Hyperechogenic SN is defined if the calculated hyperechogenic SN area is greater than the determined cut-off value for SN echogenicity, which may differ from center to center [5]. Consistent with the guidelines, a cut-off value of 0.21 cm^2 for SN hyperechogenicity was determined in our center to differentiate PD from healthy controls [8]. In addition, several studies also assessed SN hyperechogenicity in ET patients and reported a wide range of incidences from 0% to 33% [7,9–14]. SN hyperechogenicity in ET was attributed to the close anatomical relation of the nucleus ruber to the SN, with a consideration of a linkage between ET and PD which is the increased risk of ET transforming to PD [7,14,15]. In addition, a recent longitudinal study suggested that increased substantia nigra hyperechogenicity may be a risk marker in determining the early Parkinson's signs in ET patients [16]. However, other studies found no difference in SN hyperechogenicity between ET and controls [7]. In order to address these gaps, we investigated ET patients with TCS for the evaluation of SN hyperechogenicity and, after 10 years, inquired into their clinical status about the risk for transformation to PD.

Methods

The present study involved fifty-five consecutive patients in a prospective design diagnosed with ET from June 2008 to 2010. In all patients, the diagnosis was based on the criteria of the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET)[17]. Informed consent was obtained from each patient. The study was approved by the institutional review board of Göztepe Training and Research Hospital.

Demographic data and clinical characteristics of the patients were recorded. A detailed family history was taken. The duration of the disease and age of disease onset was inquired. ET was classified as mild, moderate, or severe based on the WHIGET criteria.

All patients underwent transcranial sonography performed by the same experienced radiologist who was blinded to the diagnosis of the patients, using a 1-4 MHz transducer (Siemens Antares Medical System, Munich, Germany). The penetration depth was 16 cm, with a dynamic range between 40-60 dB. The transducer was placed on the preauricular region of the temporal bone in the axial plane so that the butterfly-shaped hypoechogenic midbrain could be visualized. After acquisition, the image of the midbrain was frozen, the mesencephalic tegmentum was marked and the echogenicity of the substantia nigra was depicted. The marked echogenic area was calculated in cm^2 automatically by the device. Images with insufficient acquisition were excluded. The results obtained from ET patients were analysed according to the disease duration and severity of ET and in comparison, with 60 age- and sex-matched healthy controls who had visited the neurology outpatient clinic for various reasons and who had been found to have no neurologic problem during the enrolment period.

In addition, patients were contacted via telephone calls about 10 years after their baseline TCS examinations for their current condition, treatment and medications and to determine whether they had received a diagnosis of PD. Those with increased SN values above the cut-off values of the present study and the cut-off values reported for PD patients [8] were particularly inquired with respect to transformation risk from ET to PD.

Statistical Analysis

Continuous variables were expressed as mean (±standard deviation) and categorical variables were expressed as number and percentages. as well as one-way analysis of variance for comparisons between groups, Tukey multiple comparison test for subgroup comparisons, independent t test for comparison of paired groups, chi-square test for comparison of qualitative data were used.

Sensitivity, specificity, positive predictive value, negative predictive value, LR were calculated in determining the cut-off points for SN+ (hyperechogenicity of substantia nigra), and the area under the ROC curve was calculated. The results were evaluated at the significance level of $p < 0.05$, at a 95% confidence interval.

Results

Of 55 patients with ET and of 60 controls, 10 and 5 subjects, respectively, were excluded due to insufficient image acquisition. Demographic and clinical characteristics of the patients are summarized in Table 1. The patient and control groups were similar in age and gender (p>0.05). The mean age of the patients was 55.2±15.2 the mean duration of the disease 10.5±10.3 years, and the mean age of onset 55.2 ±15.2 years. There was a male predominance (36/19).

Table 1. Clinical and demographic characteristics of the patients and the control group

		ET n:55	Control n:60
Age (years)		62.52±6.23	65.05±9.49
Sex	**Male**	36 (65.5%)	32 (53.3%)
	Female	19 (34.5%)	28 (46.7%)
Disease Duration (years)		10.47 ± 10.32	N/A
Family history of ET (n)		32 (58.1%)	N/A

Abbreviations: ET, essential tremor; n, number; N/A, not applicable

The estimated echogenic area of the SN ranged from 0.01 to 0.86 cm^2 (mean 0.25±0.15) in the patient group and from 0.02 to 0.72 cm^2 (mean 0.15±0.16) in the control group. Patients with ET had a significantly larger echogenic area than controls (p=0.001). Transcranial sonography findings are shown in Table 2. No significant corelation was found between the echogenic SN area and sex, age, family history, duration and age of the disease onset, and disease severity. Nearly half of the patients (26/55) have hyperechogenic SN whereas only 15 % (9/60) of healthy controls have hyperechogenic SN.

Table 2. Transcranial sonography findings of the ET patients and control group

	ET N:55	Control N:60	P value
MB (cm^2)	2.63±0.41	2.76±0.53	0.052
SN (cm^2)	0.25±0.15	0.15±0.16	**0.001**
SN/MB	0.10±0.07	0.05±0.06	**0.001**

Significant p-values are shown in bold. Abbreviations: MB, Midbrain; SN, Substantia nigra.

In ROC analyses, the area under the curve was 0.753 (Figure 1). A cut-off value of 0.13 cm^2 for the hyperechogenic SN area in ET represented a sensitivity of 78.3%, a specificity of 70.9%, a positive predictive value of 68.4% and a negative predictive value of 80.2%.

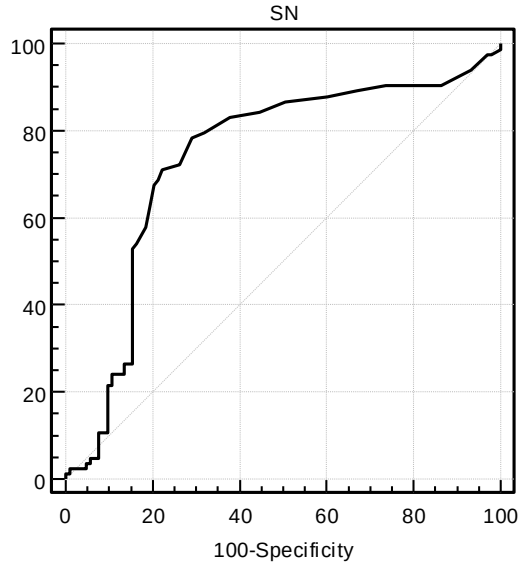

Figure 1. ROC curve of the cut-off value of hyperechogenic SN
Area Under Curve: 0.753±0.037 (0.683 – 0.815)

After a period of nearly ten years from baseline TCS evaluations, 20 patients were available to follow-up controls. Among them, 7 patients who had been considered to have hyperechogenic SN based on both the cut-off values of the present study and the cut-off values reported for PD patients. None of the responding patients reported having a change in their diagnoses of ET.

Discussion

In the present study, SN hyperechogenicity was seen significantly higher in ET patients than healthy controls. SN hyperechogenicity indicating the striatal degeneration suggests an association between ET and PD.

In a follow-up study, of 70 ET patients with baseline TCS findings 54 were examined after a mean of 6.16 years for a new-onset diagnosis of PD with clinical features and TCS. Strikingly seven of 18 patients (38.8%) who had SN hyperechogenicity developed PD on ET supporting the increased risk of PD development on ET[15]. Despite numerous investigation on the relation between ET and PD including epidemiologic, imaging, pathologic and genetic studies, the association has not been defined clearly [3,4,15]. Our data may create a base for investigating ET converting to PD. Further follow-up studies may be combined with multimodal assessment methods such as DAT SCAN or instrumented motion analysis.

Not surprisingly, similar to PD patients in the literature, SN echogenicity showed no correlation with the clinical features of the patients [5]. The exact reason underlying this echogenicity in SN remains unclear, but studies claim increased iron accumulation during the degenerative process of the disease, indicating the vulnerability of the region [6,18]. Thus, our results are important for showing a possible link between the ET and the radiological findings of sonographic evaluation of SN.

The limitation of the study may be the selection of the patients. The diagnosis of ET is made based on clinical features.

Conclusion

Our results demonstrate that SN hyperecogenicity is significantly increases in ET group compared to healthy controls. Although, the follow-up study did not support the relation between conversion of ET to PD in the patients with larger SN hyperecogenicity, undoubtful difference with healthy controls still prove the value of transcranial sonography studies in the diagnosis and as well as enlightening the mechanisms of ET.

Compliance with Ethical Standards

The study was approved by the institutional review board of Göztepe Training and Research Hospital (No:01.06.2009; 57/N2)

Conflict of Interest

All authors declare that they have no conflicts of interest.

Author Contribution

OOC: Design the study collect the data and wrote the manuscript; FC, IAC, SA, AO, EO, NI: Contributed to the scientific content, statistical analysis and manuscript writing. All authors read and approved the final version of the manuscript.

Financial Disclosure

There are no financial conflicts of interest to disclose.

References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord Off J Mov Disord Soc*. 2010;25(5):534-541. doi:10.1002/mds.22838
2. Louis ED, Huang CC, Dyke JP, Long Z, Dydak U. Neuroimaging Studies of Essential Tremor: How Well Do These Studies Support/Refute the Neurodegenerative Hypothesis? *Tremor Hyperkinetic Mov*. 2014;4(0):235. doi:10.5334/tohm.224
3. Rajput AH, Adler CH, Shill HA, Rajput A. Essential tremor is not a neurodegenerative disease. *Neurodegener Dis Manag*. 2012;2(3):259-268. doi:10.2217/nmt.12.23
4. Tarakad A, Jankovic J. Essential Tremor and Parkinson's Disease: Exploring the Relationship. *Tremor Hyperkinetic Mov*. 2019;8(0):589. doi:10.5334/tohm.441
5. Yilmaz R, Berg D. Transcranial B-Mode Sonography in Movement Disorders. In: *International Review of Neurobiology*. Vol 143. Elsevier; 2018:179-212. doi:10.1016/bs.irn.2018.10.008
6. Berg D, Siefker C, Becker G. Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. *J Neurol*. 2001;248(8):684-689. doi:10.1007/s004150170114
7. Stockner H, Sojer M, K KS, et al. Midbrain sonography in patients with essential tremor. *Mov Disord*. 2007;22(3):414-417. doi:10.1002/mds.21344
8. Walter U, Školoudík D. Transcranial sonography (TCS) of brain parenchyma in movement disorders: quality standards, diagnostic applications and novel technologies. *Ultraschall Med Stuttg Ger 1980*. 2014;35(4):322-331. doi:10.1055/s-0033-1356415
9. Budisic M, Trkanjec Z, Bosnjak J, Lovrencic-Huzjan A, Vukovic V, Demarin V. Distinguishing Parkinson's disease and essential tremor with transcranial sonography. *Acta Neurol Scand*. 2009;119(1):17-21. doi:10.1111/j.1600-0404.2008.01056.x
10. Chitsaz A, Mehrbod N, Saadatnia M, Fereidan-Esfahani M, Akbari M, Abtahi SH. Transcranial sonography on Parkinson's disease and essential tremor. *J Res Med Sci Off J Isfahan Univ Med Sci*. 2013;18(Suppl 1):S28-31.
11. Doepp F, Plotkin M, Siegel L, et al. Brain parenchyma sonography and 123I-FP-CIT SPECT in Parkinson's disease and essential tremor. *Mov Disord Off J Mov Disord Soc*. 2008;23(3):405-410. doi:10.1002/mds.21861
12. Kim JS, Oh YS, Kim YI, Koo JS, Yang DW, Lee KS. Transcranial sonography (TCS) in Parkinson's disease (PD) and essential tremor (ET) about putative premotor symptoms of PD. *Arch Gerontol Geriatr*. 2012;54(3):e436-e439. doi:10.1016/j.archger.2012.01.001
13. Luo WF, Zhang YC, Sheng YJ, Fang JC, Liu CF. Transcranial sonography on Parkinson's disease and essential tremor in a Chinese population. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2012;33(5):1005-1009. doi:10.1007/s10072-011-0876-x
14. Laučkaitė K, Rastenytė D, Šurkienė D, et al. Ultrasonographic (TCS) and clinical findings in overlapping phenotype of essential tremor and Parkinson's disease (ET-PD). *BMC Neurol*. 2014;14(1):54. doi:10.1186/1471-2377-14-54
15. Sprenger FS, Wurster I, Seppi K, et al. Substantia nigra hyperechogenicity and Parkinson's disease risk in patients with essential tremor: SN + and PD Risk In Patients With ET. *Mov Disord*. 2016;31(4):579-583. doi:10.1002/mds.26515
16. Cardaioli G, Ripandelli F, Paolini Paoletti F, et al. Substantia nigra hyperechogenicity in essential tremor and Parkinson's disease: a longitudinal study. *Eur J Neurol*. 2019;26(11):1370-1376. doi:10.1111/ene.13988
17. Louis ED, Ottman R, Ford B, et al. The Washington Heights-Inwood Genetic Study of Essential Tremor: methodologic issues in essential-tremor research. *Neuroepidemiology*. 1997;16(3):124-133. doi:10.1159/000109681
18. Zecca L, Berg D, Arzberger T, et al. In vivo detection of iron and neuromelanin by transcranial sonography: a new approach for early detection of substantia nigra damage. *Mov Disord Off J Mov Disord Soc*. 2005;20(10):1278-1285. doi:10.1002/mds.20550