Brainstem nuclei changes in migraine detected by transcranial sonography

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Title:

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Conflict of interest

The authors declare that there is no conflict of interest.

Keywords: Migraine; Neuroimaging; Transcranial sonography, Basal ganglia alteration

Abstract

Objective

The aim of this study was to estimate the role of transcranial sonography in detecting basal ganglia changes as structural biomarkers in migraine.

Methods

Transcranial sonography was performed on Aloka prosound α-10. Semiquantitative and planimetric methods were applied when basal ganglia changes were detected.

Comparison between groups was performed by student t test and Spearman's correlation test.

Results

We analyzed 30 migraine patients and 30 age/ sex matched controls.

Substantia nigra hyperechogenicity was detected in 36.7% migraineurs and in 13.3% controls (t test, p=0.036888). Hyperechogenic substantia nigra was found in 70% aura patients and in 20% patients without aura (p= 0.007384). Mean substantia nigra echogenic size of all migraine patients was 0.16±0.07 cm^2 and 0.12±0.043 cm^2 in controls (t test, p=0.0011). Lentiform nucleus hyperechogenicity was seen in 50% migraine patients and 13.3% controls (t test, p= 0.002267). Mean lentiform nucleus echogenic size of all migrenous patients was 0.34±0.08 cm^2 and in controls 0.20±0.008 cm^2 (t test, p= 0.0021). Caudate nucleus hyperechogenicity was found in 26.7% migraine patients and in 6.6% controls (t test, p= 0.037667).

Mean frontal horn width in migraine patients was 8.73+/-1.76 mm and in controls 7.10+/-1,71 (t test, p=0.0006).

Substantia nigra hyperechogenicity correlated with disease duration (p= 0.05467) and third ventricle width (p= 0.02976).

No other differences between migraineurs and controls were found.

Conclusion

Althrough there are significant differences in transcranial findings between migraineurs and controls, the overall significance of those findings are still to be evaluated.

Introduction

Migraine is a common, widespread neurological disorder with pathophysiology that is still not fully understood. Over the past several years different imaging techniques have been used for detection of structural and functional abnormalities in migraine patients like functional magnetic resonance and it's variants, PET and SPECT. Those techniques can reveal brain regions responsible for onset and symptoms of migraine attack. They can also identify regional structural and functional brain abnormalities in migraineurs [1, 2].

Transcranial sonography (TCS) and analysis of brainstem nuclei is widely used method in movement disorders [3]. Till now TCS in migraine has been limited only to the blood flow analysis [4]. Recent studies revealed activation of basal ganglia neurons and changes in their volume and functional connectivity with different brain areas that affects and possible modulates nociceptive pathways [5, 6].

The goal of our study was to emphasize the role of transcranial sonography in detecting changes of basal ganglia as structural biomarkers in migraine.

Methods

We analyzed thirty patients who were referred to our outpatient clinic with diagnose of migraine. They underwent a TCS of brain parenchyma once at the neurosonology laboratory of our clinic. The informed consent was obtained from all participants.

TCS was performed on Aloka prosound α- 10 with 2-4 MHz transducer, dynamic range 45-55dB and the penetration depth of 14-16 cm. First we identified mesencephalon and performed analysis of substantia nigra (SN), raphe nuclei (NR) and red nucleus (RN). Estimation of SN echogenicity has been done in planimetric manner. For most ultrasound systems the size of SN smaller then 0.20 cm^2 is considered normal [7]. NR were estimated semiquantitatively on the three-point scale using RN as a reference point [8]. At the diencephalic plane we estimated the third, contralateral lateral ventricle, lentiform (NL) and caudate (NC) nuclei [picture 1]. Hyperechogenicity of those nuclei were measured in the same way like SN [9].

Comparison between groups was performed by unpaired student t test, chi- square test and Spearman's correlation test.

Results:

Clinical assessment. Thirty three patients were included in our study but three were immediately excluded because of inadequate temporal bone windows. We analyzed 3 males and 27 females, mean age 40.4+/- 11.7 years, average disease duration was 14.2+/-11.0 years with attack frequency of 3.4+/-2.8 per month. Ten patients (33.3%) have migraine aura and 14 (46.7%) have positive family history for migraine. We also analyzed 30 age/ sex matched controls (5 males, 25 female, mean age 38.8 +/- 9.9 years).

Transcranial sonology findings. SN hyperechogenicity was detected in 11/30 migraine patients (36.7%). Hyperechogenic SN was found in 7/10 (70%) aura patients and in 4/20 (20%) patients without aura (chi- square test, p= 0.007384). Mean SN echogenic size of all migraine patients was 0.16±0.07 cm². Aura patients had mean SN size 0.17±0.07 cm² and patients without aura 0.15±0.07 cm² (t test, p= 0.4550). In control group we found 4/30 (13.3%) hyperechogenic SN mean size 0.12±0.043 cm². Compared to migrenours we found significant difference in number (t test, p=0.036888) and size of hyperechogenicity (t test, p=0.0011). There was no difference in NR and RN between migrenours and controls. LN hyperechogenicity was seen in 15/30 (50%) migrenous and 4/30 (13.3%) in controls (t test, p= 0.002267). Mean LN echogenic size (when measured) of all migrenous patients was 0.34±0.08 cm² and in controls 0.20±0.008 cm² (t test, p= 0.0021). Thalamus hyperechogenicity was detected as dot-like in 2/30 (6.7%) migrenous patients and in 2/30 controls. Size of thalamus hyperechogenicity ranged from 0.28±0.11 cm ² in migrenours and 0.24±0.05 cm² in controls (t test, p= 0.6582). Caudate nucleus hyperechogenicity was found in 8/30 (26.7%) migraine patients and in 2/30 (6.6%) controls (t test, p= 0.037667) with no significant difference in hyperehogenic area size. Normal width of the third ventricle was found in all patients and controls (< 7 mm) with no difference between migrenous and controls. Normal width of the frontal horn of the lateral ventricles was found in all migraine patients and controls (< 15 mm). Mean frontal horn width in migraine patients was 8.73+/-1.76 mm and in controls 7.10+/-1.71 (t test, p=0.0006) [table]. We investigated correlation of SN echogenic sizes in migraine patients with age (largest size of each individual, Spearman correlation, n= 30, rho== 0.21234, p= 0.25995) and disease duration (n= 30, rho= -0.35521, p= 0.05407). We also found no correlation of SN echogenicity sizes in aura patients and age (n=10, rho= -0.04088, p= 0.215) and with disease duration (n=10, rho= -0.16051, p= 0.6578). Moreover, SN size of migraine patients with aura correlated with width of the third ventricle (n=10, rho=-0.68221, p= 0.02976). We found no correlation between SN echogenicity sizes in all migraine patients and widths of the third ventricle (n=30, rho= -0.08699, p= 0.6476), frontal horn of the lateral ventricle (n=30, rho= 0.0691, p= 0.71709). There

was no correlation of NL, NC and thalamus hyperechogenic areas sizes with patients age, disease duration or widths of third ventricle and anterior horn of lateral ventricle.

Limitation of the study is a relatively small sample.

Conclusion

Changes of basal ganglia especially SN hyperechogenicity are well known pathognomonic features of idiopathic Parkinson disease [10]. Similar TCS findings may represent overlapping of pathological mechanisms despite different clinical representation. Regarding SN we also have to consider involvement of red nucleus which is located closely to SN region. Regardless we have to consider that changes of the SN might correspond to an increased risk of iPD in migrenous patients. We found hyperechogenicity of SN in 13% of healthy controls that is insignificantly higher that in other studies. Hyperechogenicity of NL and NC may correspond to the pain pathway damage. We found correlation between SN hyperechogenic size and third ventricle width. Significance of those findings is still to be investigated.

There is a question whether the structural and functional changes of the brain represent the effect of migraine or do they predispose the higher vulnerability to the disease.

This technique can identify structural targets as biomarkers for sub-groups of patients with specific therapeutic and possible prophylactic measures. To our knowledge, a report of transcranial sonography basal ganglia changes in migraine has not been published previously. Usage of transcranial sonography can serve diagnostic and possible prognostic aid in identifying migraine sub-types.

Ethical approval: The study had been approved by the institutional research ethics committee and had been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and it's later amendments and are comparable ethical standards.

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↑↓ echogenicity (migraine)	↑↓ echogenicity (controls)	p
SN≥0.21 cm² N=11/30 (36.7%) mean= 0.16±0.07	N= 4/30 (13.3%) mean= 0.12±0.043	*p(N)= 0.036888 *p(mean)= 0.0011
NR (1-3) ↓NR (1,2) n= 4/30 (13.3%)	N= 3/30 (10%)	p(N)=0.687573
↑NL N= 15/30 (50%) mean= 0.34± 0.08	N= 4/30 (13.3%) mean= 0.20±0.008	*p(N)= 0.002267 *p(mean)= 0.0021
↑NC N= 8/30 (26.7%) mean=0.34±0.07	N= 2/30 (6.6%) mean= 0.24±0.042	*p(N)= 0.037667 p(mean)= 0.0956
↑N ruber N=1/30 (3.3%)	N= 1/30 (3.3%)	p(N)=1
↑thalamus N=2/30 (6.7%) mean= 0.28±0.11	N= 2/30 (6.7%) mean= 0.24±0.05	p(N)= 1 p(mean)= 0.6582
3th ventricle (mm) mean=4.07±1.26	mean=3.5± 1.07	p(mean)= 0.0657
Ant. horns of lat.ventricle (mm) mean=8.73±1.76	mean= 7.1±1.71	*p(mean)= 0.0006
↑↓ echogenicity (migraine with aura)	↑↓ echogenicity (migraine without aura)	p
SN≥0.21 cm² N= 7/ 10 (70%) mean= 0.17±0.07	N= 4/20 (20%) mean= 0.15±0.07	*p(N)= 0.007384 p(mean)= 0.4550

NR (1-3) ↓NR (1,2) N= 2/10 (20%)	N= 2/20 (10%)	p(N)= 0.447521
↑NL N=4/10 (40%) mean=0.38±0.05	N=11/20 (55%) mean=0.32±0.08	p(N)= 0.438578 p(mean)= 0.1669
↑NC N= 2/10 (20%) mean= 0.40±0.00	N= 6/20 (30%) mean= 0.32± 0.07	p(N)= 0.559305 p(mean)= 0.1951
↑N ruber N=0/10	N=1/20(5%)	p(N)= 0.472021
↑thalamus N= 1/10 (10%) mean= 0.36±0.00	N=1/20(5%) mean= 0.20± 0.00	p(N)= 0.604773
3th ventricle (mm) mean= 3.60±0.97	mean= 4.30±1.34	p(mean)= 0.1540
Ant. horns of lat.ventricle (mm) mean= 8.50± 2.22	mean= 8.85±1.53	p(mean)= 0.6619

Table 1**.** Sonographyc correlation of mesencephalic and diancephalic nuclei in migraineurs and controls and migraineurs with and without aura.

SN= substantia nigra; NR= raphe nuclei; NL= lentiform nuclus; NC= nucleus caudatus; ↑= hyperechogenicity; ↓= hypoechogenicity.

- p values< 0.05 considered statistically significant (student t test, chi-square test)

Fig 1. Mesencephalic and diencephalic plane. (a) Hyperechogenic substantia niga (thick arrow) and normal ehogenicity of raphe nuclei (arrowhead). (b) Normal finding: red nuclei (arrow), nuclei raphe (arrowhead). (c) Hyperehogenic lentiform nuclus (arrow), 3th and anterior ventricle enlargement (two sided arrows). (d) Normal finding.