



Transcranial ultrasound (TCS) in sarcoidosis - relation to fatigue, depression and anxiety

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Abstract

BACKGROUND: Up to date neuroimaging is known to complement clinical findings in the diagnostic work up mostly of parkinsonian syndromes. No investigation was performed to evaluate the transcranial ultrasound findings (TCS) in sarcoidosis. It is already recognized that impaired echogenicity of the mesencephalon structures can correlate with the impaired cognitive functions. In this study we wanted to elucidate the TCS findings and the relation with the sensation of fatigue, depressive feelings and anxiety in sarcoidosis patients.

METHODS: 40 biopsy positive sarcoidosis patients were enrolled in this study (28female/12male);mean age 48.5±12.15yrs.TCS was performed in the Neurology Clinic , Belgrade, Serbia, by an experienced neurologist. Prior to TCS patients were evaluated for fatigue, depression and anxiety using: Fatigue Assessment Scale, (FAS- mean total score 25.55±7.54), Beck Depression Inventory (BDI- mean 18.25±12.52), Hamilton Anxiety Scale (HAMA mean -16.15±7.79) and Hamilton Depression Scale (HAMD- mean 13.75± 7.79).Statistical analyses were done using Fisher's Exact Test and Discriminate Analysis with CCD ≥ 0.51. **RESULTS:**7/40pts had hyperechogenicity of substantia nigra (SN); and 25/40 had hyperechogenicity of nucleus rubber (NR). Fisher's Exact Test revealed significant hyperechogenicity of NR in patients with FAS≥22. (Fisher's value=0.042).Significant hyperechogenicity of NR was found in patients with BDI >10, (Fisher's value=0.017). HAMA anxiety score >17 also significantly coexisted with hyperechogenicity of NR (Fisher's value=0.041). Discriminate Analysis revealed significant discrimination of depressive pts. Patients with BDI≥10 (28/40pts) had chronic sarcoidosis, steroid therapy ≤10mg and FAS total score ≥22, and NR hyperechogenicity. (Lambda=0.643, Chi² =15.702, CCD=0.598, df=5, p<0.01).Reliability of discrimination 85%.Discriminant Analysis of HAMA showed that patients with HAMA score ≥17 (20/40 pts) were older, had FAS total score ≥22 and hyperechogenicity of NR (Lambda=0.738,Chi² =10.916, CCD=0.511, df=4, p<0.05) Reliability of discrimination 75%. Hypoechoicinity of SN was found in 33/40pts suggesting the restless leg syndrome in these patients. **CONCLUSION:** Further analyses are necessary in this field, possibly to reveal the role of other findings and other possible causes of fatigue in sarcoidosis.

Introduction

Transcranial sonography (TCS) in the B-mode has the ability to image, infratentorial and supratentorial brain structures. For this reason, it has potential use in the diagnosis and differential diagnosis of various pathologies.

Up to date neuroimaging is known to complement clinical findings in the diagnostic work up mostly of parkinsonian syndromes. However no investigation was performed to evaluate the transcranial ultrasound findings (TCS) in sarcoidosis.

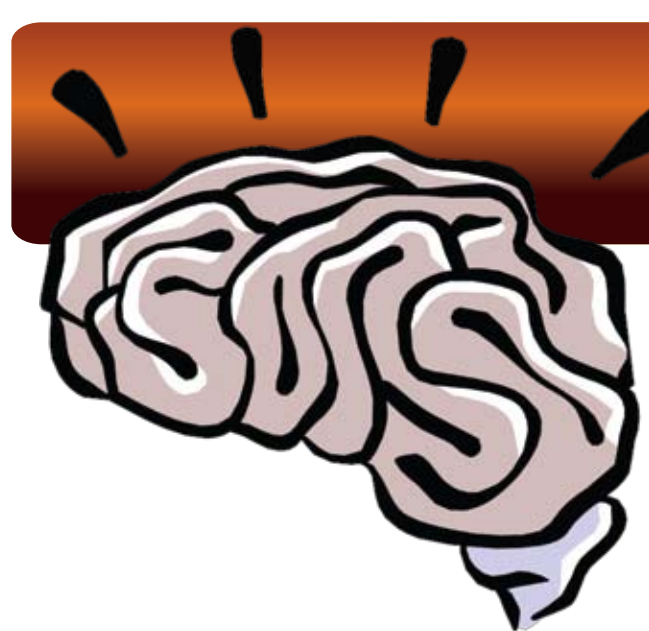
It is already recognized that impaired echogenicity of the mesencephalon structures can correlate with the impaired cognitive functions. In this study we wanted to elucidate the TCS findings and the correlation between the sensation of fatigue, depressive feelings and anxiety in sarcoidosis patients.



"Others have seen what is and asked why. I have seen what could be and asked why not".
- Pablo Picasso

Literature:

- M. Mijailovic. Transcranial Sonography in Depression In International review of Movement Disorders. 2010;Volume 90, 259-270 - Walter U, Hoepfner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 2007; 130: 1799-807. - Berg D. Transcranial brain parenchyma sonography in movement disorders: state of the art. Ultrasound in Med. & Biol., 2007;33:15-25 - Hoepfner J, Prudente-Morrissey L, Herpertz SC, Benecke R, Walter U. Substantia nigra hyperechogenicity in depressive subjects relates to motor asymmetry and impaired word fluency. Eur Arch Psychiatry Clin Neurosci 2009; 259: 92-97. - Friedman A, Frankel M, Flaumenhaft Y, Merenlender A et al. Programmed Acute Electrical Stimulation of Ventral Tegmental Area Alleviates Depressive-Like Behavior. Neuropsychopharmacology 2009; 34:1057-66 - Godau J, Wevers AK, Gaenslen A, Di Santo A, Liepelt I, Gasser T, Berg D. Sonographic abnormalities of brainstem structures in restless legs syndrome. Sleep Med 2008, 7:782-9. - Godau J, Sojer M. Transcranial Sonography in Restless Legs Syndrome. International Review of Neurobiology. Volume 90, 2010;199-215



Glossary

• The **substantia nigra – SN** ("black substance") is a brain structure located in the mesencephalon (midbrain) that plays an important role in reward, addiction, and movement; also starter function, motivation, drive.

• The **nucleus ruber – NR**

Functions: Motor coordination (above all shoulder and upper arm but also forearm and hand), arm movements during walking, crawling (baby); movement initiation, muscle tone, body posture; circadian rhythm, but '*Pessimistic*' bias: internal adaptation and preparation processes in order to act according to potential or certain unpleasant events.

• **Raphe**

Their main function is to release serotonin to the rest of the brain.

Purpose

The area of ventral tegmentum is very important in emotional responsiveness, the feeling of security, and motivation. This area can thus influence the cognitive impairments in humans.

The purpose of this study was to elucidate the interactions between depression, anxiety and fatigue with the mesencephalic structures i.e. substantia nigra (SN) nucleus ruber (NR) and brainstem raphe.

We used:

• Hamilton Depression Scale (HAMD) and Beck Depression Inventory (BDI), to evaluate the feeling of depression in our patients.

- For evaluation of the anxiety we used Hamilton Anxiety Scale, (HAMA) and
- For fatigue, Fatigue Assessment Scale (FAS).

We also evaluated the existing steroid therapy in the possible outlook of depression and anxiety.

Methods

In this study 40 biopsy positive sarcoidosis patients were analyzed (28 female / 12 male) mean age 48.0±12 years. Patients recruited for this study are the part of the major cohort of patients. They are all members of the Yugoslav Association of Sarcoidosis (YAS) that counts 1570 patients with different clinical forms of sarcoidosis. Patients voluntarily cooperated in completing the study questionnaires (HAMA, HAMD, BDI, and FAS) before performing transcranial ultrasound. Transcranial sonography was performed in the Clinic of Neurology, Clinical center Belgrade, by experienced neurologist.

Statistical analyses:

- between the groups without and with anxiety according to the HAMA score ≥17,
 - between the groups without and with depression HAMD score ≥17 & BDI score ≥10, and
 - between groups without and with fatigue FAS score ≥22
- were done using Fisher's Exact Test.

The Discriminant analyses were done in order to estimate the coexistence of TCS impairments with anxiety, depression and fatigue in the analyzed group. Canonical Discriminant Function Coefficient (CCD) was estimated as ≥ 0.051. Min. mistake α value was estimated as 0.05. Statistical analyses were done using SPSS version 18, Chicago, Illinois.

Normal findings in transcranial sonography

Photo: Mesencephalic brainstem of a healthy individual with normal, only slightly visible substantia nigra, and normal, highly echogenic brainstem raphe, which has the same echogenicity as the red nucleus



TCS images of corresponding midbrain axial sections in three subjects. The butterfly-shaped midbrain was encircled for better visualization (dotted line). Thick arrows indicate brainstem raphe; thin arrows: red nucleus; substantia nigra is encircled with full line.

Transcranial sonography (TCS)



Echogenicity of substantia nigra – (SN)

Normal 0.19cm²
0.19-0.24cm² moderate hyperechogenicity
Above 0.24cm² hyperechogenicity



Echogenicity of brainstem raphe:

Echogenicity of brainstem raphe is rated semi-quantitatively using the highly echogenic red nucleus or signal intensity of the basal cisterns as reference points. (Grade 1) Brainstem raphe echogenicity should be rated as reduced only if it appears interrupted (or not visible) at both sides of investigation. Hypoechoicinity grade 0 observed to be related to depression.



Hyperechogenicity of NR and SN

Echogenicity of red nucleus – (NR)

Normally, the red nucleus can only be discerned on TCS by dot-like echo signals at the lateral border of the red nucleus near the SN, and/or the medial border of the red nucleus near the brainstem midline raphe. In case of a signal increase ("hyperechogenicity"), the red nucleus shows high echogenicity at its whole anatomic extension. While reduced echogenicity of red nucleus has not been described as a pathological condition, its hyperechogenicity has been associated with restless legs syndrome (Godau et al., 2008).

Conclusion

TCS study revealed the possibility of ultrasound investigations of the ventral tegmentum structures in sarcoidosis.

- Depression, anxiety and fatigue frequently accompany sarcoidosis. Besides other possible reasons related to granulomatous inflammation, the cognitive impairments mentioned above might possibly interrelate with structural changes in these areas of the brain; correlation probably caused by the lack of adaptable forces generated in these areas, to carry on with disabling, chronic disease.
- The most interesting fact that comes out of this study is that the majority of our patients (33/40) showed hypoechoicinity of SN and hyperechogenicity of NR (25/40), the findings related to movement disorders i.e. restless legs syndrome.

This study is the very beginning, in the field of sarcoidosis and transcranial sonography. It is done in a small group of 40 volunteer patients and these are the first modest results.

Results

	N	Mean	SD
BDA Total score	40	18.25	12.52
FAS Total score	40	25.55	7.54
HAMA Total score	40	16.15	8.32
HAMD Total score	40	13.75	7.79
Age	40	48.00	12.20

Table 1.
Descriptive statistics: Total scores (FAS, BDI, HAMA, HAMD, age)

TCS	Substantia nigra (SN)	Nucleus ruber (NR)	Raphe
Hyperechogenicity	7/40	25/40	
Hypoechoicinity	33/40		29/40
Normal TCS		15/40	11/40

Table 2.
Transcranial ultrasound in our patients (40 pts)

TCS impaired	Patients with FAS ≥22 (29/40) pts 72.5%	Fisher's Exact Test
NR (right/left) (hyperechogenicity)	FAS ≥22 21/29 FAS <22 4/11	0.012
SN (right/left) (hyperechogenicity)	FAS ≥22 5/29 FAS <22 2/11	
Raphe (Hypoechoicinity)	FAS ≥22 21/29 FAS <22 8/11	

Table 3.
Patients with TCS impairments and FAS

TCS impaired	Patients with BDI ≥10 (28/40) pts 72.5%	Fisher's Exact Test
NR (right/left) (hyperechogenicity)	BDI ≥ 10 21/28 BDI < 10 4/12	0.017
SN (right/left) (hyperechogenicity)	BDI ≥10 5/28 BDI < 10 2/12	
Raphe (Hypoechoicinity)	BDI ≥10 18/28 BDI < 10 11/12	

Table 4.
Patients with TCS impairments and BDI

TCS impaired	Patients with HAMA ≥17 (20/40) pts 50%	Fisher's Exact Test
NR (right/left) (hyperechogenicity)	HAMA ≥17 17/20 HAMA < 17 8/20	0.041
SN (right/left) (hyperechogenicity)	HAMA ≥17 5/20 HAMA < 17 2/20	
Raphe (Hypoechoicinity)	HAMA ≥17 12/20 HAMA < 17 17/20	

Table 5.
Patients with TCS impairments and HAMA

No significant results of discriminant function were found considering HAMA and TCS impairments.

Discriminant Function for Beck Depression Inventory (BDI)

- Patients with:
- chronic sarcoidosis
 - Steroid therapy (10-5mg/daily)
 - FAS ≥22
 - Nucleus ruber TCS impairments (hyperechogenicity)

Classification:
85 % correctly classified.

(Lambda=0.643, Chi square =15.702, CCD=0.598, df=5, p<0.01)

Discriminant Function for Hamilton Anxiety Scale (HAMA)

- Patients with:
- FAS ≥22
 - Nucleus ruber and /or substantia nigra TCS impairments (hyperechogenicity)
 - older

Classification:
75 % correctly classified.

(Lambda=0.738, Chi square =10.916, CCD=0.511, df=4, p<0.05)