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ORIGINAL PAPER

Brainstem raphe lesion in patients with major depressive disorder and in patients with suicidal ideation recorded on transcranial sonography

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Abstract Recent transcranial sonography (TCS) studies showed that disruption of echogenic midbrain line, corresponding to basal limbic system and raphe nuclei (RN) within, might represent functional marker for the development of depression. Major depressive disorder (MDD) is one of the most common psychiatric disorders associated with suicidal ideation. We initiated this study to assess the usefulness of TCS recording in a group of MDD patients and in MDD patients who also reported suicidal ideation, on the assumption that TCS might serve as a screening method for differentiating patients at risk of suicide. Altogether 71 subjects: 17 patients with MDD, 14 patients with MDD who also reported suicidal ideation and 40 healthy controls, were studied using TCS by two independent physicians. Reduced raphe echogenicity was found in 8 of 17 (47%) of the patients with MDD but only in 6 of 40 (15%) controls. In patients with suicidal ideations that finding was even more pronounced (12 of 14, 86%) with the highest frequency of completely not visible TCS RN finding (10 of 14, 72%). Data showed that altered echogenicity of the RN is frequent in patients with suicidal ideation. Normal RN echogenicity in MDD patients was associated with less severe depressive symptoms and rarely with the presence of suicidal ideations. As far as we know, these are the first ever obtained results which show that TCS might help differentiating MDD patients with suicidal risk or eventually predict good disease recovery based on the findings of RN hypo- or normoechogenicity.

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Introduction

Numerous evidence from neuroimaging, biochemical and animal studies implicates basal limbic system involment in the pathogenesis of the mood disorders. Depletion of monoamine serotonin and dopamine system is a frequent finding in the depressive state and deficient levels of serotonin are associated with suicide and depression [11]. Histopathological studies also found linkage between the morphological alteration of the dorsal raphe nucleus (RN) as a major brain serotonin source and the major depressive disorder (MDD) or suicide ideations [3]. Structural and functional imaging studies with magnetic resonance imaging (MRI), computer tomography (CT) and single photon emission tomography (SPECT) of MDD have shown a spectrum of abnormal findings [15]. Although there are reports of MRI signal alteration of RN, a characteristic neuroimaging pattern of abnormality has not yet been found [6, 20–23]. Recently, transcranial sonography (TCS) findings of hyperechogenic finding of the substantia nigra (SN) have been found to have a diagnostic value in patients with idiopathic Parkinson's disease (PD) [8, 12].

Also, recent TCS studies showed that disruption of echogenic midbrain line corresponding to basal limbic system and RN within might represent as the functional marker for the development of MDD [5]. Furthermore, it appears that such RN depletion on TCS is frequent in

depressive states irrespective of diagnostic category [5, 25]. Also, MDD is the most common psychiatric disorder associated with suicidal ideation [14]. Still, there is lack of evidence that, in patients with suicidal ideation, TCS might record same RN alteration. Therefore, we initiated this study to assess usefulness of TCS recording in a group of MDD patients and in MDD patients who reported suicidal ideation, on the assumption that TCS might serve as a screening method for differentiating patients at the risk of suicide.

Patients and methods

Altogether 71 subjects: 17 patients with MDD (mean age 48.0 ± 5.9), 14 patients with MDD who also reported suicidal ideation (mean age 51.3 ± 9.4) and 40 healthy controls (mean age 50.6 ± 7.2), were studied using TCS. All the patients were treated at the University Hospital "Sestre milosrdnice" in the Department of Psychiatry and the Department of Neurology, Zagreb, Croatia. Informed consent was obtained before entering the study. Approval for the study was granted by the Local Ethics Committee. The psychiatric diagnosis of MDD was made according to the diagnostic criteria of DSM-IV [1]. Severity of the disease was measured according to Hamilton depression rating scale (HDRS) and clinical global impression scale (CGI) [17, 18]. Present suicidal ideation in MDD patients was obtained by HDRS (item 3). The mini mental state examination (MMSE) was administered to rule out dementia syndromes [16]. Each subject underwent a semi-structured psychiatric interview as well as a complete neurological examination. None of the subjects with MDD had any comorbid psychiatric or somatic illness or reported alcohol dependence. All the patients received appropriate medication if needed, choice or duration of which was independent of inclusion criteria. Table 1 shows patients demographic data obtained at the same day TCS was performed.

Control group consisted of subjects without the history of any form of neurodegenerative or psychiatric disorders. Only patients with temporal acoustic bone windows that enabled the identification of structures within the mesencephalic brainstem were included.

Transcranial sonography

TCS was performed freehandedly with ultrasound system (Alpha 10; Aloka, Tokyo, Japan) equipped with 2.5 MHz transducer. The measurement was done two times by two independent physicians (M.B., A. L.-H.) blinded on the results of the other. The insonation was done throughout both temporal "bone window" on intact skull. Penetration depth was 14 cm and gain image was adopted individually. The echogenicity of the pontomesencephalic nuclei raphe was rated semiquantitatively on a three-point scale with red nucleus as a reference point: 1, RN not visible; 2, slighty echogenic/interrupted RN; 3, normal RN echogenicity [5]. RN echogenicity was regarded as reduced only if the findings of both physicians agreed. Additionally, SN area in each patient was analysed by standardised protocol; mesencephalic echogenicity in the area of SN was displayed, manually marked, measured two times and mean value was calculated and presented in square centimeters. In accordance with the previous studies (including our own performed at the present ultrasound system), as a cut-off values of SN areas of echogenicity $\leq$0.19 cm^2 were classified as normal and areas of echogenicity $\geq$0.20 cm^2 on both sides were classified as hyperechogenic [4, 10, 12].

Statistical analyses

The normal distribution of data was assessed for all measures and for each group by Kolmogorov–Smirnov test. Because normal distribution for all measures was not confirmed, patients with MDD or MDD with suicidal ideation and healthy control subjects were compared by age, CGI, HDRS, duration of illness, MMSE and number of

Table 1 Clinical data of the subjects at the same day the TCS was performed

	MDD patients $N = 17$	MDD patients with suicidal ideation $N = 14$	Controls $N = 40$	Kruskal–Waliss
Age, years, mean ± SD (mean rank)	48.00 ± 5.93 (26.54)	51.30 ± 9.42 (35.88)	50.22 ± 7.03 (20.50)	1.899
CGI, mean ± SD (mean rank)	4.14 ± 1.23 (48.43)	6.17 ± 1.19 (58.83)	1.35 ± 0.48 (20.67)	51.047*
Duration, months, mean ± SD	29.77 ± 28.12	67.07 (±53.49)	0	
HDRS, mean ± SD (mean rank)	23.68 ± 5.22 (50.38)	34.71 ± 8.77 (61.36)	4.85 ± 2.86 (20.50)	53.027*
MMSE, mean ± SD (mean rank)	27.65 ± 1.27 (33.74)	27.93 ± 1.54 (37.75)	27.82 ± 1.63 (36.35)	0.329
Number of depressive episodes (mean ± SD)	2.47 ± 1.64	3.86 ± 1.79	0	

HDRS hamilton depression rating scale, *MMSE* mini mental state examination, *CGI* clinical global impression scale

* $p < 0.001$

depressive episodes by Kruskal–Wallis nonparametric analysis of variance. The correlation between the number of episodes of depression, duration of depression and intensity of MDD symptoms based on HDRS or CGI, MMSE, age and ehogenicity was analysed using Spearman's rank correlation. Chi-square test was used to measure difference between ehogenicity between MDD, MDD with suicidal ideation and healthy control group. p Value of <0.01 was considered to denote the presence of a statistically significant difference. Statistic was done with SPSS software (SPSS for Windows 11.0, SPSS, Chicago, IL, USA).

Results

Results showed significantly lower RN echogenicity in patients with MDD and MDD patients with suicidal ideation compared to control group (Table 2, Chi-square test = 47.99, $p < 0.01$). Reduced raphe echogenicity was found in 8 of 17 (47%) of the patients with MDD but only in 6 of 40 (15%) controls. In patients with suicidal ideations that finding was even more pronounced (12 of 14, 86%), with the highest frequency of completely not visible TCS RN finding (10 of 14, 72%) (Figs. 1 and 2).

Table 2 TCS finding of MDD patients, patients with suicidal ideation and controls

	NR not visible *N* (%)	Slighty echogenic NR *N* (%)	Normal NR echogenicity *N* (%)
MDD patients $N = 17$	0	8 (47)	9 (53)
MDD patients with suicidal ideation $N = 14$	10 (72)	2 (14)	2 (14)
Controls $N = 40$	6 (15)	0	34 (85)

Chi-square test = 47.99, $p < 0.01$

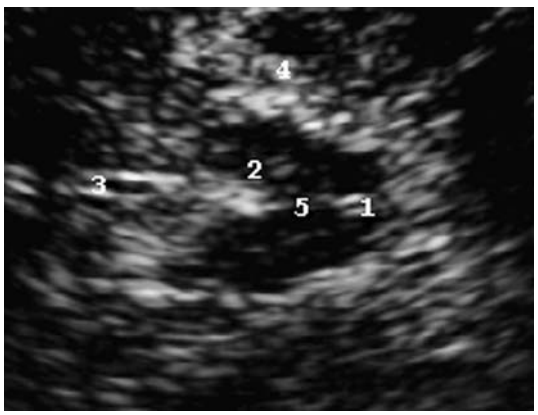

Fig. 1 Normal TCS findings in healthy adult. Butterfly-shaped mesencephalon of low echogenicity surrounded by hyperechogenic basal cisterns (*4*). In medial line RN (*5*) and (*1*) aqueducts are shown. Nucleus ruber (*2*), third ventricle (*3*)

We found significant negative correlation between raphe echogenicity and the number of depressive episodes ($r = -0.440$, $p = 0.013$), as well as the severity of the disease measured according to HDRS ($r = -0.560$, $p < 0.001$) and CGI ($r = -0.411$, $p < 0.001$) and TCS findings. Also, sonographic findings showed significantly negative correlation with the duration of the illness ($r = -0.482$, $p = 0.009$). However, no correlation was found between the age of patients and TCS findings ($r = 0.148$, $p = 0.532$) (Fig. 3).

Bilateral SN hyperechogenicity exceeding 0.20 cm^2 was found in 5 (29%) MDD patients, in 4 (28%) MDD patients with suicidal ideation and in 4 (10%) controls (Fig. 4).

We also found significant inter-observer reliability for the detection of RN echogenicity ($\kappa = 0.80$) just as for the detection of SN sizes ($\kappa = 0.85$).

Discussion

Our results showed that altered echogenicity of the mesencephalic midline, which corresponds to the RN is frequent in patients with MDD. Such finding is rare in healthy subjects; however, in patients with suicidal ideation that finding was even more pronounced. On the other hand, normal RN echogenicity in MDD patients was associated with less severe depressive symptoms and rarely with the presence of suicidal ideations. These results are first to show that TCS might help differentiating MDD patients with suicidal risk or eventually predict good disease recovery based on the findings of RN hypo- or normoechogenicity. In addition, it appears that reduced RN echogenicity is a marker of severity and chronicity of the disease in MDD patients.

These data are in line with previous reports which showed that the alteration of RN echogenicity is much more frequent in depressed patients [5, 7]. The same occurs also in PD depressed patients and it represents stable liability to depressive state rather than a category of depression [8, 25].

Anatomically, echogenic midline in mesencephalon corresponds to accumulation of several pathways and nuclei of rostral brainstem. It includes ascending and descending fibre tracts of the medial forebrain bundle, dorsal longitudinal fascicle, mammilotegmental tract and fasciculus retroflexus. The echogenic midline also includes dorsal RN as well as tracts connecting numerous brainstem and other cerebellar nuclei (e.g., interpeduncular nuclei, central superior nucleus) with diencephalic and telencephalic brain areas. Its projection reaches virtually all brain areas and is the major monoamine serotonin brain source [13].

In this study, observed frequency of RN disruption (15%) or SN hyperechogenicity (10%) in healthy subjects, closely

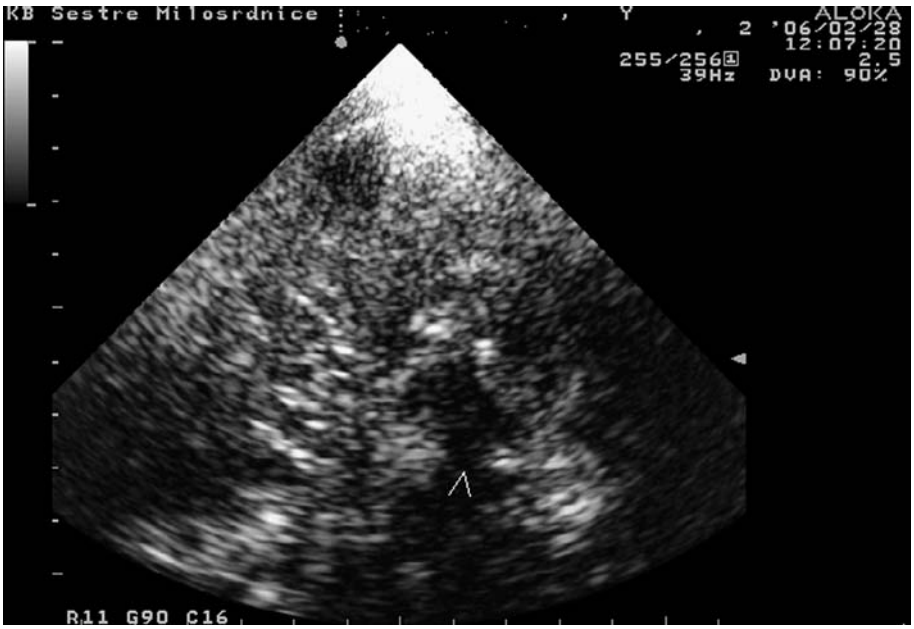

Fig. 2 *Arrow* shows raphe lesion in 35-year-old female patient with MDD who also reported suicidal ideation

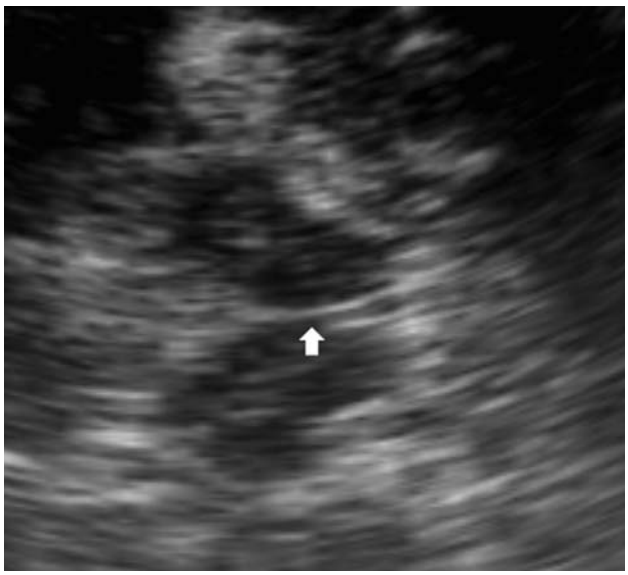

Fig. 3 *Arrow* shows normal echogenicity of RN in 43-year-old male patient with MDD but without suicidal ideations

corresponds to previous reports [6, 9]. Both of these findings might indicate a pre-existing vulnerability factor for the development of depressive states or PD. In addition, a sonographic finding of SN hyperechogenicity appears to be associated with an impairment of the nigrostriatal system that may be disclosed by neuroleptics [10]. Furthermore, increased frequency of SN hyperechogenicity in MDD group might reflect epidemiological findings of increased risk of MDD subjects to develop PD [19, 24]. Normal echogenicity of RN was found in nine patients with MDD without suicidal ideation. Interestingly, all patients with normoechoic RN had lower HDRS and CGI score. Such finding might be due to serotonergic compensatory mechanism as reported in postmortem depressed suicides. Also, that finding is in line with the reports of increased numbers of serotonin neurons and more neuronal tryptophan hydroxylase-2 expression in the RN of depressed suicides [2]. Therefore, we speculate that normoechoic finding of RN in MDD patients might be a predictive sign of a good disease recovery. The cause of such alteration remains unclear. The change of acoustic impedance, which is recorded on TCS, can be the result of microstructual changes of cytoarchitecture with gliosis and/or mineral deposits. On the other hand, disruption of fibre tract integrity might result in hypoechogenic finding of RN [6]. However, further correlations with pathohistological studies are needed to disclose true nature of RN midline hypoechogenicity.

It is still unclear if the brainstem RN alteration leads to depression or is a result of long standing depression. Reduced RN echogenicity just as an increased hyperechogenicity of SN in PD appears to be just one of the factors in the development of MDD or PD, because not all patients with PD or depression exhibit these features. Also, a combination of both these findings appears to be associated with PD patients with depressive disorder, prior to the onset of PD [24].

Major limitation for this approach is a need for adequate temporal bone window and approximately 10% of individuals end as not suitable for this approach. The tissue brightness or echogenicity of different structures within the ultrasound image is also influenced by the system parameters set by each investigator, resulting in a certain subjectivity which is a general problem in diagnostic ultrasound. Also, limitation of our study is a relatively small sample of patients and lack of follow-up recording.

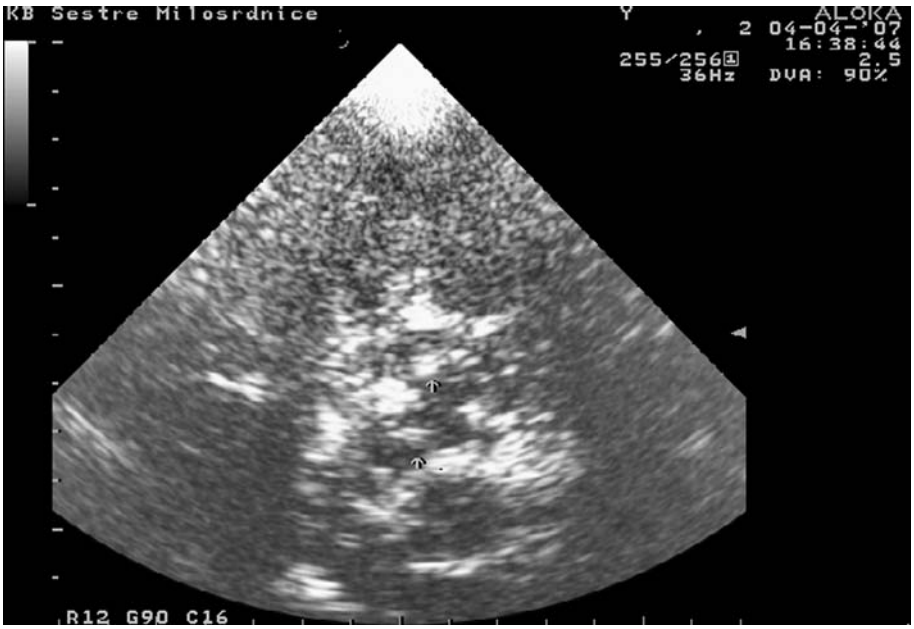

Fig. 4 TCS finding of bilateral SN hyperechogenicity

Although caution in data presentation is advisable due to these limitations, our results suggest that TCS might be a novel neuroimaging method for screening suicidal patients within the group of the depressed one. Furthermore, it appears that undisrupted finding of RN in MDD patients might predict good disease recovery. Recent studies have proofed that novel high resolution MRI techniques can provide superior anatomical detail and alterations of RN, however, availability and price of such approaches might emphasis the value of alternative neuroimaging techniques such as TCS.

Conclusion

In conclusion, TCS is an easy bedside method of two-dimensional black and white brain imaging with spatial resolution lower than other imaging modalities, but with the ability to display echogenic changes in brain parenchyma and basal ganglia. Due to fine resolution, portability, lack of invasiveness and low cost, assuming appropriate temporal bone window, TCS may serve as a practical and sufficiently sensitive neuroimaging tool in depressive mood disorders. Further efforts with better controlled design and follow-up assessment are needed to validate this approach.

References

1. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Press, Washington DC
2. Bach-Mizrachi H, Underwood MD, Tin A, Ellis SP, Mann JJ, Arango V (2008) Elevated expression of tryptophan hydroxylase-2 mRNA at the neuronal level in the dorsal and median raphe nuclei of depressed suicides. Mol Psychiatry 13:507–513
3. Ball W, Whybrow PC (1993) Biology of depression and mania. Curr Opin Psychiatry 6:27–34
4. Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K (1995) Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. Neurology 45:182–184
5. Becker G, Becker T, Struck M, Lindner A, Burzer K, Retz W, Bogdahn U, Beckmann H (1995) Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. Biol Psychiatry 38:180–184
6. Becker G, Berg D, Lesch KP, Becker T (2001) Basal limbic system alteration in major depression: a hypothesis supported by transcranial sonography and MRI findings. Int J Neuropsychopharmacol 4:21–31
7. Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, Lindner A, Reichmann H, Riederer P, Beckmann H, Reiners K (1997) Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. J Neurol Neurosurg Psychiatry 63:590–596
8. Berg D, Supprian T, Hofmann E, Zeiler B, Jäger A, Lange KW, Reiners K, Becker T, Becker G (1999) Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. J Neurol 246:1186–1193
9. Berg D, Siefker C, Ruprecht-Dörfler P, Becker G (2001) Relationship of substantia nigra echogenicity and motor function in elderly subjects. Neurology 56:13–17
10. Berg D, Jabs B, Merschdorf U, Beckmann H, Becker G (2001) Echogenicity of substantia nigra determined by transcranial ultrasound correlates with severity of parkinsonian symptoms induced by neuroleptic therapy. Biol Psychiatry 50:463–467
11. Boldrini M, Underwood MD, Mann JJ, Arango V (2005) More tryptophan hydroxylase in the brainstem dorsal raphe nucleus in depressed suicides. Brain Res 1041:19–28
12. Budisic M, Trkanjec Z, Bosnjak J, Lovrencic-Huzjan A, Vukovic V, Demarin V (2008) Distinguishing Parkinson's disease and

essential tremor with transcranial sonography. Acta Neurol Scand 119:17–21
13. Carpenter MB, Sutin J (1993) Human Neuroantomy. Williams and Wilkins, Baltimore
14. Cooper-Patrick L, Crum RM, Ford DE (1994) Identifying suicidal ideation in general medical patients. JAMA 272:1757–1762
15. D'haenen H (2001) Imaging the serotonergic system in depression. Eur Arch Psychiatry Clin Neurosci 251:75–80
16. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
17. Guy W (1976) Clinical global impression. ECDEU assessment manual for psychopharmacology (revised). National Institute of Mental Health, Rockville
18. Hamilton M (1967) Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296
19. Hoeppner J, Prudente-Morrissey L, Herpertz SC, Benecke R, Walter U (2009) Substantia nigra hyperechogenicity in depressive subjects relates to motor asymmetry and impaired word fluency. Eur Arch Psychiatry Clin Neurosci 259:92–97
20. Kanner AM (2004) Structural MRI changes of the brain in depression. Clin EEG Neurosci 35:46–52
21. Meisenzahl EM et al (2009) Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study. Eur Arch Psychiatry Clin Neurosci (Epub ahead of print)
22. Steele JD, Bastin ME, Wardlaw JM, Ebmeier KP (2005) Possible structural abnormality of the brainstem in unipolar depressive illness: a transcranial ultrasound and diffusion tensor magnetic resonance imaging study. J Neurol Neurosurg Psychiatry 76:1510–1515
23. Supprian T, Reiche W, Schmitz B, Grunwald I, Backens M, Hofmann E, Georg T, Falkai P, Reith W (2004) MRI of the brainstem in patients with major depression, bipolar affective disorder and normal controls. Psychiatry Res 131:269–276
24. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R (2007) Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 130:1799–1807
25. Walter U, Prudente-Morrissey L, Herpertz SC, Benecke R, Hoeppner J (2007) Relationship of brainstem raphe echogenicity and clinical findings in depressive states. Psychiatry Res 155:67–73