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Raphe nuclei echogenicity changes in major depression

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Abstract

Background: Major depression is a common disorder with great social and individual burdens. Transcranial sonography (TCS) is a useful and noninvasive measure for assessment of normal and impaired brain parenchyma. The brainstem raphe nuclei are in close association with dorsocaudal limbic system and plays an important role in depression. In this study we compared the echogenicity of the raphe nuclei in patients with major depressive disorder and the control group.

Methods: Thirty patients suffering from depression, diagnosed by a psychiatrist, and 30 cases of similar age and sex were entered into the case and control groups respectively. Semi-structural clinical conversation was done according to the DSM IV-TR in order to confirm the depression by the psychiatrist member of the group. Echogenicity of the brainstem raphe nuclei was assessed by a trained neurologist using TCS. To compare the mean echogenicity between the two groups independent sample t-test was used. In order to assess the strength of association between the disease and the echogenicity, odds ratio was also calculated.

Results: The echogenicity of the brainstem raphe nuclei was significantly decreased in depressed patients (36.7%) in comparison with the control group (10%) (p= 0.015, OR= 5.21).

Conclusion: Echogenicity of the brainstem raphe nuclei in patients with depression is significantly lower than normal population. To confirm the results, we recommend a meta analysis considering previous articles' results.

Keywords: Major depressive disorder, Transcranial sonography (TCS), Raphe nuclei echogenicity.

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Introduction

Major depression is a relatively common disorder that imposes a great burden on communications. Lifetime prevalence has been reported widely from 3% in Japan to 17% in United States (1, 2). Risk of depression increases in many neurological diseases such as stroke and Parkinson's disease (3). In 1989, transcranial sonography (TCS) was introduced as a device that can distinguish the normal and impaired brain parenchyma (4,5). TCS can easily detect the echogenicity of the brainstem raphe nuclei in midline of the midbrain (6).

For the first time, Becker and his colleagues in 1994 found decreased echogenicity of the brainstem raphe nuclei in TCS of depressed patients (7). There was no relationship between the severity of depression and decreased echogenicity. This finding was seen in unipolar depressed patients and not in bipolar patients (8,9). Similar findings were seen in depressed pa-

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tients with Parkinson disease or Wilson disease (9, 10). In contrast to the unipolar depressed patients, echogenicity of the brainstem raphe nuclei was normal in depressed multiple sclerosis patients (11).

In spite of the brain imaging studies investigating the morphologic changes of the raphe nuclei in depression presented previously, herein for the first time we designed this study to compare the echogenicity of the raphe nuclei in Iranian patients with major depressive disorder and the control group.

Methods

Ethical approval

This project has been approved by the ethics committee of Tehran University of Medical Sciences. The study was performed in Rasoul-e-Akram hospital from June to October 2012. Both the case and control groups were given information regarding the study prior to the clinical test and the written consent was also signed by all participants. The authors respected to the declaration of Helsinki.

Subjects

The sample size was calculated using comparison of means collected from two different populations (using expected means for equal groups) from previous similar studies. Thirty patients suffering from depression, diagnosed by a psychiatrist, and also 30 persons with similar age and sex were allocated to the case and control groups respectively. The psychiatrist member of the group accomplished semi structural clinical interview according to the DSM IV-TR to confirm depression. The exclusion criteria included presence of any organic, mental or neurologic problems. Moreover, based on another study we found that TCS in psychotic patients is different from non-psychotic depressed patients (8); therefore, depressed patients with psychotic features were not entered into the study. Patients with poor temporal bone window were also excluded.

Transcranial sonography

Transcranial sonograhy was done by a trained neurologist through the temporal bone window using a phased-array ultrasound system with a 2.5 MHz transducer (My Lab 30) and penetration depth of 14-16 cm. The examiner was blinded to the participants (depressed or normal). The echogenicity of the raphe nuclei was assessed using a semi-quantitative visual scale (normal echogenicity with continuous echogenic midline structures and hypoechogenicity with absent or dotted midline structures).

Statistical analysis

To analyze the data, SPSS version 18 (PASW) was used. Mean ± standard deviation (SD) and frequency percentages were representative of quantitative and qualitative variables respectively. To show the strength of association between the disease and the brainstem raphe nuclei echogenicity, odds ratio was calculated. Chi square test was performed to compare the frequency of decreased echogenicity among groups. A p-value of less than 0.05 was considered to show the statistical significant difference.

Results

In this study, a total of 60 cases in two equal groups were entered for analysis. Thirteen patients were male and seventeen patients were female in each group (male to female ratio was 13/17 in both groups). The mean age in depressed patients was 40± 1.03 years (the youngest patient was 22 years old the oldest one was 59 years old). The mean age in the control group was similar to the case group, with a similar standard deviation (ranged from 22 years to 61 years). In the depression group, 11 patients had decreased echogenicity of the brainstem raphe nuclei (36.7%) and 19 patients had normal raphe nuclei echogenicity (63.3%). In the control group three persons had decreased raphe nuclei echogenicity (10%) and 27 had normal echogenicity of the raphe nuclei (90%) (OR = 5.21, 95%

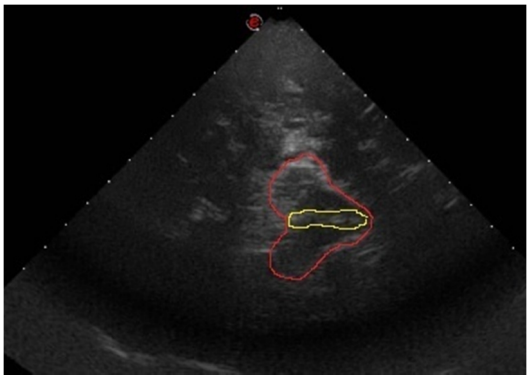

Fig. 1. TCS of a patient with normal raphe nuclei echogenicity (outline of the midbrain is delineated with red and the raphe echogenicity with yellow color)

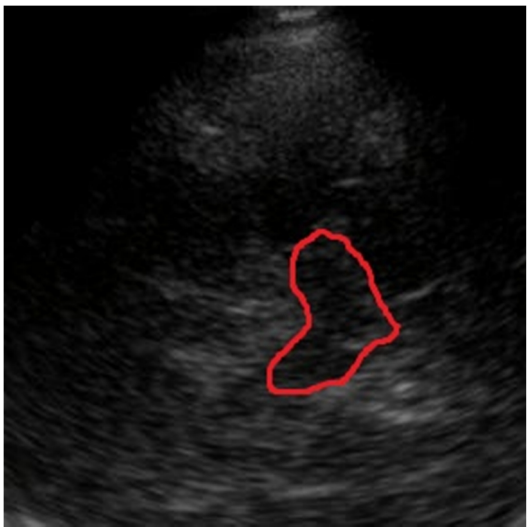

Fig. 2. TCS of a patient with depression showed severely decreased raphe nuclei echogenicity (the red line demonstrates outlines of midbrain, without hyperechogenicity of the raphe nuclei at the midline).

CI: 1.27 to 21.23) (Figs. 1 and 2).

Comparing the frequency of decreased echogenicity between the patients and the control group, the brainstem raphe nuclei echogenicity was significantly lower in patients with major depression. (Chi square test p value= 0.015)

Discussion

In our study, the echogenicity of the the brainstem raphe nuclei in patients with depression was significantly lower than the normal control population (36.7% of depressed patients versus 10% of the control group). In the Becker's study, hypoechogenicity of the brainstem raphe nuclei was seen in 50-70% of monopolar depressed patients (7). In another study by Walter's, echogenicity of the raphe nuclei was found decreased in unipolar depressed patients (53% in comparison with 9% in healthy individuals) (9). Walter showed that patients with decrease echogenicity of the raphe nuclei had better response to selective serotonin reuptake inhibitors (SSRIs) (12). In a recent study, the brainstem raphe nuclei echogenicity was lower in depressed patients with suicidal attempts in comparison with depressed patients without suicidal attempts (13). Decreased echogenicity of the raphe nuclei was also seen in other neurologic diseases accompanied by depression. Decreased brainstem raphe nuclei echogenicity was seen in 35-85% of depressed patients with Parkinson's disease (PD) versus 6-27% in non-depressed PD patients (9, 13, 14). In the Walter study on 21 patients with Wilson disease (with and without neurologic signs), the brainstem raphe nuclei echogenicity was low in 3 patients (10).

In contrast to the movement disorders (including Parkinson disease, Wilson disease and Huntington disease) with depression which showed hypoechogenicity of the brainstem raphe nuclei, in multiple sclerosis (MS) this finding has not been reported. In the Berg study on two groups of MS patients (with and without depression), there was no difference in the raphe nuclei echogenicity between the two groups (9).

By these findings, it seems that basal limbic system disorders cause depression and decreased echogenicity of the brainstem raphe nuclei, but disorders of basal limbic projections (subcortical regions in multiple sclerosis and stroke) with depression have normal echogenicity of the brainstem raphe nuclei (8).

The present findings based on morphological impairment of the nuclei reflect the molecular parenchymal involvement of brainstem in depression. The brainstem raphe nuclei are in close association with the dorsocaudal limbic system (15, 16).

The exact etiology of altered brainstem

raphe nuclei echogenicity is not clear. Its changes could be due to tissue impedance alteration secondary to shift in tissue cell density, alteration of interstitial matrix components, or change of fibre tracts. Brainstem raphe nuclei are the main source of serotoninergic transmitters which innervate prefrontal cortex. Decreased echogenicity of the brainstem raphe nuclei in major depression is compatible with alteration of these nuclei in brain MRI and patho-anatomic studies. In other words, decreased echogenicity of the brainstem raphe nuclei in TCS reflects decreased level of serotonin in major depressed patients. The better response of depressed patients with hypoechogenicity of the brainstem raphe nuclei to SSRIs supports this hypothesis too (17).

In previous studies, sampling has not been based on epidemiological methods (18), but in this study, sampling method was statistically defined. To increase the accuracy of this study, TCS of all patients was done by one experienced neurologist. The examiner was blinded to the patients' diagnoses and he did not have any conversation about mood status of patients. In previous studies it has been shown that there is no relationship between the severity of depression and the brainstem raphe nuclei echogenicity (7). We also didn't compare the patients according to the disease duration and its severeity. We recommend this to be considered in future studies with larger samples. To confirm the results, we also recommend meta analysis considering previous articles' results.

Conclusion

TCS is a noninvasive, low cost, easy accessible and without side effect diagnostic procedure for evaluation of the brain parenchyma in many neurologic diseases. It is also very helpful for assessment of the brainstem raphe nuclei echogenicity and can be a useful supplementary tool in patients with major depressive disorders. Decreased brainstem raphe nuclei echogenicity in major depression points to involvement of basal limbic system.

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