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Transcranial sonography of brainstem structures in panic disorder

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ABSTRACT

Panic disorder has been associated with altered serotonin metabolism in the brainstem raphe. The aim of study was to evaluate the BR echogenicity on transcranial sonography (TCS) in panic disorder. A total of 96 healthy volunteers were enrolled in the "derivation" cohort, and 26 healthy volunteers and 26 panic disorder patients were enrolled in the "validation" cohort. TCS echogenicity of brainstem raphe and substantia nigra was assessed on anonymized images visually and by means of digitized image analysis. Significantly reduced brainstem raphe echogenicity was detected more frequently in panic disorder patients than in controls using both visual (68% vs. 31%) and digitized image analysis (52% vs. 12%). The optimal cut-off value of digitized brainstem raphe echogenicity indicated the diagnosis of panic disorder with a sensitivity of 64% and a specificity of 73%, and corresponded to the 30th percentile in the derivation cohort. Reduced brainstem raphe echogenicity was associated with shorter treatment duration, and, by trend, lower severity of anxiety. No relationship was found between echogenicity of brainstem raphe or substantia nigra and age, gender, severity of panic disorder, or severity of depression. Patients with panic disorder exhibit changes of brainstem raphe on TCS suggesting an alteration of the central serotonergic system.

1. Introduction

Panic disorder is an anxiety disorder characterized by recurrent unexpected panic attacks accompanied by somatic and psychological symptoms. It may also include behavioral changes and ongoing worry about the implications or concern about having other attacks, and about one in three people with panic disorder develops agoraphobia (American Psychiatric Association, 2000). Substantial comorbidity between panic disorder and other anxiety disorders or major depression has been described (Kessler et al., 2003).

The monoamine neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) plays an important role in the pathophysiology of anxiety and panic attacks (Bell and Nutt, 1998; Baldwin et al., 2005). Panic disorder is associated with reduced availability of the postsynaptic inhibitory serotonergic receptor, the serotonin-1A (5-HT1A) subtype, which is also known to play a key role in depression. The areas with the most significant reductions are brainstem raphe (BR), amygdala, orbitofrontal cortex, and anterior lateral temporal cortex (Nash et al., 2008). Positron emission tomography (PET) studies have shown lower 5-HT1A binding in anterior cingulate, posterior cingulate, and BR in patients with panic disorder (Neumeister et al., 2004).

Transcranial sonography (TCS) is a non-invasive diagnostic method that displays tissue echogenicity of the brain through the intact skull. It allows one to differentiate brain structures, for example, brainstem, substantia nigra (SN), red nucleus, BR, thalamus and ventricular system (Walter et al., 2007a). TCS demonstrates reduced echogenicity of BR in patients with major depressive disorder, obsessive–compulsive disorder, but also in Parkinson's, Huntington's or Wilson's diseases with depression (Becker et al., 1995; Berg et al., 1999; Walter et al., 2005, 2007b; Mijajlovic, 2010; Krogias et al., 2011b; Mavrogiorgou et al., 2013). It has been

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suggested that reduced BR echogenicity might reflect an alteration of the central serotonergic system (Becker et al., 2001; Walter et al., 2007c).

In view of the previously reported similarities of BR 5-HT receptor alteration in major depressive and panic disorders, we hypothesized that BR alteration might also be detected by TCS in patients with panic disorder. In major depressive disorder, an increased frequency of abnormal SN hyperechogenicity has also been found; a TCS finding thought to reflect an alteration of the nigrostriatal dopaminergic system (Walter et al., 2007b). We therefore compared the echogenicity of BR and SN in patients with panic disorder and healthy controls using visual evaluation and a novel digitized image analysis tool.

2. Methods

2.1. Patients and control subjects

One-hundred healthy volunteers were examined as members of the derivation cohort in the neurosonological laboratory during 1 month for the evaluation of normal values for BR and SN for visual measurements and digitized image analysis. Healthy controls were recruited from the University Hospital Volunteer Database. Only volunteers with the BDI-score 0–13 and the BAI-score of 0–16 points were included. Two months later, 26 out of 33 screened patients with panic disorder and 26 age- and sex-matched healthy volunteers were examined as members of the validation cohort.

We enrolled patients with panic disorder who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for panic disorder, with or without agoraphobia, using the Mini-International Neuropsychiatric Interview (MINI) version 5.0.0 (American Psychiatric Association, 2000; Sheehan et al., 1998). Exclusion criteria for both the derivation and the validation cohort included the presence of any other current Axis I psychiatric disorder using the MINI, the history of any other psychiatric disorder, and current or past serious medical or neurological disorders.

Participants who exhibited low quality of the TCS B-mode image due to insufficient temporal bone windows, as tested by digitized image analysis, were excluded from the study (4 healthy volunteers and 1 panic disorder patient). The image quality was evaluated using the developed B-mode Assist System as an integral part of digitized image analysis (Blahuta et al., 2013; Skoloudík et al., 2014). Images with a mean value of brightness intensity $I \geq 25$ in all 5×5 mm pixels were considered to be of low quality.

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (revised in 2004 and 2008). The study was approved by the Ethics Committee of University Hospital Ostrava, Czech Republic. All patients provided written informed consent.

2.2. Clinical examination and psychological tests

Patients with panic disorder and healthy volunteers were subjected to MINI version 5.0.0 to assess DSM-IV-TR Axis I disorders, physical and neurological examination, and completed the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). In patients with panic disorder, clinical severity of their symptoms was assessed using the Panic Disorder Severity Scale (PDSS). Clinical Global Impression (CGI), Hamilton Anxiety Scale (HAMA), 17-item Hamilton Depression Scale (HAMD-17), Sheehan Disability Scale (SDS), Dissociative Experiences Scale (DES), and Somatoform Dissociation Questionnaire (SDQ-20) were performed in all patients. Age, sex, education level, tobacco use, alcohol consumption, duration of panic disease, type, dose and duration of treatment, number of antidepressants used, presence and duration of agoraphobia, and hand preference (right- or left-handedness) were collected for statistical analysis.

2.3. TCS

The BR and SN were imaged in all participants from both the right and the left temporal bone windows in the axial mesencephalic plane using the ultrasound system MyLab Twice (Esaote S.p. A., Genova, Italy) with a 2.5-MHz phased-array transducer (PA240). The examination was performed through a temporal bone window with the following standard parameters (Skoloudík et al., 2014): penetration depth of 16 cm, penetration high, dynamic range 7 (50 dB), frequency 1–4 MHz, enhancement 3, density 2, view 9, persistence 7, dynamic compression 0, gain 26%, gray map 0, S view off, 2 focuses in 5 and 10 cm, mechanical index 0.9, tissue indices TIs 1.0, TIB 1.0 and TIC 2.1.

The butterfly-shaped structure of the mesencephalic brainstem and the region of BR and SN were depicted as clearly as possible from the transversal plane (Fig. 1) using slow craniocaudal probe motion. One image of BR and SN, and one video (lasting for at least 5 s) were obtained and saved from both the right and the left temporal bone windows. Personal data and examination times were deleted and all acquired anonymized images and videos were encoded with a unique key. All examinations were performed by a single sonographer (MJ) who was blinded to the diagnoses.

2.4. Visual manual measurement and digital image analysis

Semiquantitative visual evaluation of BR was performed and BR was evaluated as normal or disrupted. Echogenicity of BR was rated as reduced when its structure was interrupted or not detectable, i.e. isoechogenic with the adjacent brain tissue (Walter et al., 2007a; Berg et al., 2006, 2008). Isoechogenic BR with the adjacent brain tissue was evaluated separately. Manual SN echogenic size measurements were performed on axial mesencephalic scans automatically after zooming and freezing of the image. Manual encircling of the outer circumference of the ipsilateral echogenic SN area was performed to evaluate the echogenic area of SN (Berg et al., 2008). For all subsequent processing steps of the digital analysis and measurement, images without SN or BR area

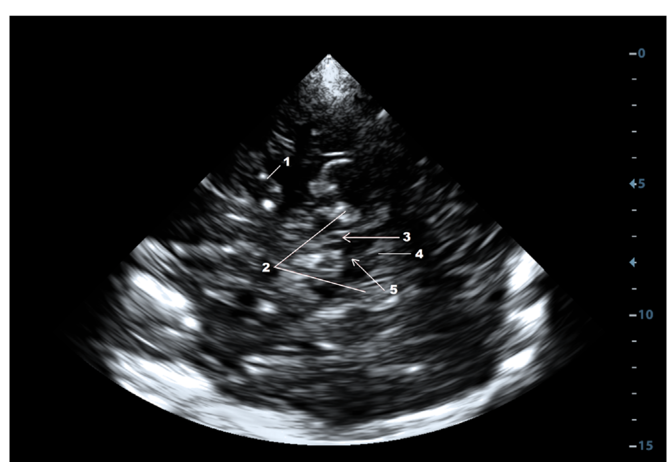

Fig. 1. Transcranial sonography: brainstem with substantia nigra and brainstem raphe imaged from transtemporal approach, axial mecencephalic plane. 1 – Middle cerebral artery, 2 – perimesencephalic cisterns, 3 – substantia nigra, 4 – fourth ventricle, and 5 – brainstem raphe.