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Evaluation of basal ganglia, brainstem raphe and ventricles in bipolar disorder by transcranial sonography

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ABSTRACT

Transcranial brain sonography (TCS) has become a reliable and sensitive diagnostic tool in the evaluation of extrapyramidal movement disorders. Alterations of brainstem raphe (BR) have been depicted by TCS in major depression but not in bipolar disorder. The aim of our study was to evaluate BR echogenicity depending on the different conditions of bipolar patients. Echogenicities of dopaminergic basal ganglia structures were assessed for the first time in bipolar disorder. Thirty-six patients with bipolar I disorder (14 depressed, 8 manic, 14 euthymic) were compared to 35 healthy controls. Echogenicities were investigated according to the examination protocol for extrapyramidal disorders using a Siemens Sonoline® Elegra system. The sonography examiner was blinded for clinical rating scores. Six patients (16.7%) showed hyperechogenicity of the substantia nigra. The raphe was hypoechogenic in 13 (36.1%) of the patients. No significant differences were seen between the subgroups. Compared to the control group, frequency of altered echogenicities did not reach statistical significance. The width of third ventricle was significantly larger in the patient group (3.8± −2.1 mm vs. 2.7±1.2 mm). Depressed bipolar patients with reduced BR echogenicity showed significantly higher scores on the Hamilton Depression Rating Scale as well as the Montgomery-Åsberg Depression Rating Scale. In contrast to unipolar depression, sonographic findings of bipolar patients may generally indicate structural integrity of mesencephalic raphe structures. If bipolar disorder coexists with hypoechogenic raphe structure, depressive symptoms are more severe.

1. Introduction

Transcranial sonography (TCS) depicts the echogenicity (intensity of reflected ultrasound waves) in different parenchymal regions of the brain. TCS has become a reliable and sensitive diagnostic tool in the evaluation of extrapyramidal movement disorders, especially in the differentiation of parkinsonian syndromes (Walter et al., 2003; Berg et al., 2008). Hyperechogenicity of the substantia nigra is a highly characteristic finding for idiopathic Parkinson's disease (Becker et al., 1995b; Walter et al., 2003; Berg et al., 2008). It is assumed that this echo signal alteration is based on increased amounts of iron, bound to proteins other than ferritin (Berg et al., 2002). Furthermore, alterations of brainstem raphe (BR) have been observed by TCS in major depression and in depressed patients with Parkinson's disease (Becker et al., 1995a, 2001; Berg et al., 1999; Walter et al., 2007b, c).

Bipolar affective disorders are characterized by recurrent episodes of depression as well as mania or hypomania (American Psychiatric Association, 2000). In histological studies, subtle structural deficits in the dorsal raphe with a regional reduction in the synthesis of noradrenalin have been described in patients with bipolar disorder (Baumann and Bogerts, 2001). The mesencephalic brainstem region is one of the few regions that can be investigated well by means of TCS (Berg et al., 2008).

Up to now, there is only one TCS study evaluating BR alterations in patients with bipolar affective disorders, revealing normal or even increased echogenicity of BR, irrespective of the existing disease conditions (Becker et al., 1995a). This observation led to the assumption that reduced echogenicity of BR may be specific to unipolar depression (Becker et al., 1995a).

The aim of our study was to evaluate BR echogenicity depending on the different conditions of bipolar I disorder patients. We hypothesized that hypoechogenic BR would be detected more frequently in

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the depressive subgroup compared to the other patient subgroups. Thus, frequency of hypoechogenic brainstem raphe in patients with bipolar disorder with current depressive episode is compared to findings in patients with bipolar disorder in remission, as well as with current manic episode. In addition, the echogenicity of the substantia nigra (SN) was assessed for the first time in bipolar affective disorder. This is of particular interest since additional SN alterations have been described recently as a frequent finding in patients with depressive symptoms (Walter et al., 2007b). Thus, a second hypothesis was that alterations of dopaminergic basal ganglia would be detected more frequently in the patient group than in the control group. Furthermore, recent studies postulate a dopaminergic dysfunction in the pathophysiology of bipolar affective disorders (Berk et al., 2007).

In the present study, a complete sonographic evaluation, determining echogenicities of serotonergic brainstem raphe nuclei as well as of dopaminergic basal ganglia, is performed for the first time in this disease entity.

2. Methods

2.1. Subjects

The sample consisted of 40 inpatients or outpatients with unequivocal diagnosis of bipolar I disorder. Patients were consecutively recruited from the Department of Psychiatry of the Ruhr University Bochum. Initially, we aimed to have 15 patients in each group of bipolar depression, mania and euthymia. Group membership determined using the Mini-International Neuropsychiatric Interview for DSM-IV (American Psychiatric Association, 2000) diagnosis of a current manic, depressed or remitted episode.

Four patients (9.7%) were excluded due to an inadequate temporal bone window for ultrasound examination. Further exclusion criteria were organic psychiatric disorders or recent concomitant neurological disorders (5 patients). Table 1 shows the demographic and clinical data of 36 bipolar I disorder patients who were included in the study. All patients received optimal medical treatment including antidepressant or antimanic medication or mood stabilizers (Table 2).

Initially, a control group of 15 healthy volunteers was created. These 15 persons underwent specific tests for depressive symptoms (HAM-D, MADRS and BDI) as well as for manic syndromes (see Section 2.2). To improve statistical analysis, the control group was expanded with 20 further healthy persons from a pre-existing group of healthy persons who form the reference group of our sonography laboratory.

Thus, 35 healthy volunteers without any neurological or psychiatric disorders in personal or family history served as an age-matched control group. They were recruited from the hospital staff, the medical student body as well as from the circle of their friends and family. Their demographic data are also shown in Table 1. All subjects gave written informed consent after the study was fully explained to them.

In accordance to the Helsinki Declaration of 1975, the study was approved by the local university ethics committee of the Ruhr University Bochum, Germany.

2.2. Clinical assessment

Clinical interviews and ratings were performed by a consultant in psychiatry or by a trained and experienced interviewer. Diagnosis of bipolar I disorder was confirmed using the structured Mini-International Neuropsychiatric Interview (MINI) for DSM-IV diagnosis (Sheehan et al., 1998). We excluded patients with diagnosis of mixed episode or rapid cycling. In addition, we collected data about previous episodes, the number and symptoms of episodes, age of onset of psychiatric disorder, age of first diagnosis of bipolar disorder, hospitalization rate and comorbidity. Moreover, pharmacological treatment and other therapeutic intervention were recorded.

Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Scale (MADRS) and self-ratings with Beck's Depression Inventory (BDI) (Beck et al., 1961; Hamilton, 1967; Montgomery and Åsberg, 1979). Severity of manic symptoms was evaluated using the Young Mania Rating (YMRS) and the Self-Report Manic Inventory (SRMI) (Young et al., 1978; Krüger et al., 1997). Severity of symptoms was defined on the YMRS with cutoff scores of >=16 for mild mania and on the HAM-D with >=16 points for mild depression. Euthymia was not explicitly defined by any symptom cutoffs. The overall severity of the psychiatric disorder was quantified using the Clinical Global Impression score (CGI) and Global Assessment of Functioning Scale (GAF).

In the control group, scores on the HAM-D and the BDI were obtained in all 35 healthy volunteers. Specific tests for manic

Table 1
Demographic and clinical variables of bipolar I disorder patients and healthy controls.

Variables	Bipolar depressive		Bipolar manic		Bipolar euthymic		Healthy controls		*H*	*d.f.*	*P*
	(*n* = 14)		(*n* = 8)		(*n* = 14)		(*n* = 35)				
	Mean (S.D.)		Mean (S.D.)		Mean (S.D.)		Mean (S.D.)				
Age [y]	40.4 (14.2)		48.1 (17.6)		44.9 (11.2)		37.4 (11.2)		5.44	3	0.14
Age at onset of psychiatric disease [y]	29.4 (7.9)		22.1 (11.5)		31.4 (9.7)		–		4.58	2	0.10
Age [y] at diagnosis of bipolar disorder	35.4 (10.3)		31.1 (16.3)		35.5 (9.0)		–		0.86	2	0.65
Hospitalizations [n]	6.9 (7.5)		6.5 (2.5)		4.9 (4.0)		–		2.12	2	0.35
Manic episodes [n]	7.6 (9.1)		8.0 (6.2)		10.9 (7.0)		–		2.29	2	0.32
Depressive episodes [n]	17.5 (26.5)		15.6 (12.7)		14.6 (16.5)		–		0.43	2	0.81
Total episodes [n]	24.1 (34.9)		23.6 (13.9)		25.4 (22.1)		–		1.34	2	0.51
BDI	37.2 (12.5)		14.1 (6.0)		10.1 (8.6)		3.8 (4.1)		19.74	3	<0.01
SRMI	13.3 (8.6)		17.6 (11.4)		8.4 (8.3)		1.7[a] (2.9)[a]		19.57	3	<0.01
HAM-D	21.8 (3.8)		10.1 (4.2)		7.6 (5.7)		1.9 (1.7)		38.25	3	<0.01
MADRS	29.2 (6.7)		8.5 (5.4)		8.4 (6.1)		1.5[a] (1.8)[a]		37.29	3	<0.01
YMRS	3.9 (3.9)		22.8 (4.8)		6.7 (5.3)		0.4[a] (0.7)[a]		31.13	3	<0.01
GAF	49.3 (9.4)		40.0 (14.1)		68.6 (15.0)		85.0[a] (0.0)[a]		36.74	3	<0.01
CGI	4.7 (0.7)		5.3 (1.3)		2.4 (1.3)		1.0[a] (0.0)[a]		38.8	3	<0.01
	N	%	*N*	%	*n*	%	*N*	%	χ^2	*d.f*	*P*
Sex (f/m)	7/7	50/50	3/5	38/63	6/8	43/57	19/16	54/46	1.01	3	0.80

H = Kruskal–Wallis-test; *d.f.* = degrees of freedom; BDI = Beck-Depression-Inventory; MSS = Mania-Self-Rating Scale; HAMD = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; SRMI = Self-Report Manic Inventory; GAF = Global Assessment of Functioning Scale; CGI = Clinical Global Impression Scale.

[a] Performed only in 15 of the 35 controls.