Journal of Affective Disorders 151 (2013) 605–610

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Depression with psychotic features is influenced by the polymorphism of the serotonin transporter gene

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ARTICLE INFO

Article history:
Received 28 June 2012
Received in revised form
3 July 2013
Accepted 6 July 2013
Available online 12 August 2013

Keywords:
Major depression
Psychotic features
Psychopathology
Serotonin transporter gene

ABSTRACT

Introduction: Current diagnostic classifications regard psychotic symptoms during depressive episodes as indicators of depression severity. However, growing evidence suggests that depression with psychotic symptoms (MDP) may represent a distinct subtype of depression. In the course of the search for discriminating factors we tested the hypothesis that the serotonin transporter gene (5-HTTLPR) may interact with the manifestation of psychotic symptoms in acute depression.
Methods: 112 inpatients (61 female) with a depressive episode (16 bipolar, 86 unipolar) at admission were genotyped for 5-HTTLPR variants. Psychotic symptoms und general psychopathology were evaluated comprehensively using the Manual of the Association for Methodology and Documentation in Psychiatry (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie, 1981). For statistical analysis a chi-square test and a logistic regression model was used.
Results: 16 (14.3%) out of 112 patients were currently presenting with psychotic symptoms. The primary finding of our study was the higher prevalence of the s-allele of the 5-HTTLPR within the group of MDP patients (Pearson $\chi^2=7.87$; df=2; $p<0.03$). Secondly, in a logistic regression model, 5-HTTLPR was found to significantly contribute to the diagnosis of MDP ($\chi^2=6.5$; df=1; $p=0.01$). This effect was even more pronounced upon comparing only severely depressed patients with MDP patients. From a psychopathological perspective, MDP patients showed higher AMDP hostility and apathy scores but equal AMDP depression scores.
Discussion: This is the first study to show an influence of 5-HTTLPR on psychotic symptoms in acutely depressed patients.
Limitations: The lack of a control group and the relatively small sample size limits the present study's findings, thus replication in a larger sample is necessary.

1. Introduction

Increasing evidence suggests that major depression with psychotic symptoms (MDP) represents a distinct subtype of depression. In current diagnostic manuals, the presence of psychotic symptoms is regarded as an indicator of the severity of depressive symptoms (American Psychiatric Association, 1994). However, recent epidemiological data suggest that there is also a subgroup of mildly to moderately depressed patients who demonstrate psychotic symptoms, while most severely depressed patients do not develop psychotic symptoms in the course of their disease (Maj et al., 2007; Ohayon and Schatzberg, 2002). MDP differs from non-psychotic major depression in terms of neurobiological, epidemiological and psychopathological features. It shows a higher rate of dysregulation of the hypothalamus–pituitary–adrenocortical (HPA) system (Bond et al., 1986; Nelson and Davis, 1997; Posener et al., 2000), altered cerebral dopaminergic activity (Meyers et al., 1999) and specific differences have been described for the ventricle-to-brain ratio (Targum et al., 1983). Psychotic depressive syndromes are also characterized by higher rates of relapse and hospitalization, more courses of treatment refractory, and overall longer episodes than is the case in non-psychotic syndromes (Baethge et al., 2005; O'Neal et al., 2000).

Furthermore, a longstanding discussion as to whether there might be a diagnostic and pathophysiological overlap between MDP and Bipolar Disorder is ongoing: Patients with

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http://dx.doi.org/10.1016/j.jad.2013.07.005

MDP have been shown to display a higher risk of developing (hypo)mania than non-psychotic patients (Maj et al., 2007; Tohen et al., 2012).

From a psychopathological perspective, patients with MDP have been found to display more anxiety, less illness-related insight, a higher incidence of guilt feelings, more ruminative and referential ideas, and stronger agitation than their non-delusional depressed counterparts (Baethge et al., 2005).

The unique biological, epidemiological and psychopathological profile of MDP thus far indicated within the research has lead to a surge of interest within the field regarding the potential role of certain genetic entities in MDP. A promising candidate gene here may be the polymorphism within the promotor region of the serotonin transporter gene.

The gene coding for the serotonin transporter (5-HTT) has been located on chromosome 17q11.2 (Lesch et al., 1994). A polymorphic region (5-HTTLPR) has been identified upstream of the transcription starting point. It generally consists of either 14 or 16 repeated elements generating a long (l) or a short (s) allele. The short allele is associated with lower gene expression activity in vitro (Heils et al., 1996; Lesch et al., 1996) and in vivo, at least in non-smokers (Heinz et al., 2000; Kobiella et al., 2011). Meta-analytical research has reported a significant association between the s-allele and bipolar disorder (Lasky-Su et al., 2005). Somewhat similarly, three meta-analytical studies reported an association between the s-allele and unipolar depression (Furlong et al., 1998; López-León et al., 2008; Lotrich and Pollock, 2004). However, it is notable that two other studies concluded there to be no association (Anguelova et al., 2003; Willis-Owen et al., 2005). This may be explained by the heterogeneity of inclusion criteria for the analyses (Cohen-Woods et al., 2013).

Literature on the influence of 5-HTTLPR on psychotic symptoms in affective disorders is controversial; Table 1 shows the relevant results from studies using varying methodologies with samples of patients of central European origin. However, the mostly retrospective and medical record-based operationalization of psychotic symptoms may confound these partially contradicting findings, as has previously been discussed by others (Mihalopoulos et al., 2000; Seemüller et al., 2011).

For these reasons, we utilized a cross-sectional methodological design in this study that reflects a thorough evaluation of current psychopathology in MDP in order to adequately test the hypothesis whether the s-allele of the 5-HTTLPR genotype presents more frequently in MDP patients. Secondly, we aimed to investigate whether 5-HTTLPR significantly contributes to the occurrence of the diagnosis of MDP and whether the psychopathological profile of MDP patients is different from that of non-delusional depressed patients.

2. Methods

2.1. Sample characteristics

Of the 148 depressed patients that took part in phase II of the German Algorithm Project (GAP-2) (Bauer et al., 2009), 112 inpatients of central European origin (61 females, 51 males) gave their informed written consent for genetic analysis. The German Algorithm Project was conducted between 1990 and 2006 to test and implement an algorithm-guided, pharmacological treatment of depression. In GAP-1 (Adli et al., 2002), the feasibility and effectiveness of the treatment regime was tested in an open design. GAP-2 was a prospective, randomized controlled study that compared a standardized stepwise treatment regime (SSTR) to treatment as usual (TAU) at the then Department of Psychiatry of the Freie Universität Berlin. The institution's local ethical committee approved the study. Patients with a depressive syndrome consecutively hospitalized between June 1, 1997, and May 31, 2000, were screened for study eligibility by means of a clinical interview. Patients with an ICD-10 diagnosis of a major depressive episode with or without psychotic features and bipolar depression were invited to participate. Diagnoses were confirmed with the Composite International Diagnostic Interview, a fully structured diagnostic interview for the assessment of mental disorders, which provides current diagnoses in line with the approved ICD-10 criteria. (WHO, 1993). Exclusion criteria included organic mental disorders, schizoaffective disorders, alcohol or substance dependence, substance-related affective disorders, and ongoing prophylactic medication with a mood stabilizer (i.e., lithium, valproate or carbamazepine) that could not be discontinued (where the decision was made by the treating physician).

2.2. Clinical assessment

In case of pharmacological pretreatment, medication was tapered off before commencing the GAP-2 protocol. 38 patients (33.9%) had no psychopharmacological medication at admission, 34 (30.4%) had one, 30 (26.8%) had two, and 10 patients (8.9%) had more than two psychoactive drugs that had to be tapered off. Upon admission to the hospital, all subjects underwent a comprehensive psychopathological interview conducted by the treating physician using the Manual of the Association for Methodology and Documentation in Psychiatry (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie, 1981). The AMDP is a documentation system used for structured anamnestic data and psychopathology based on classical symptoms, as described by Jaspers (1946) and compiled by the German–Swiss–Austrian Association for Methodology and Documentation in Psychiatry

Table 1
5- HTTLPR and psychotic symptoms in affective disorders: research overview.

Authors	**Sample**	**Design**	**Evaluation of psychotic symptoms**	**Main Results**
Seretti et al. (1999a)	67 MDD 65 BP	Cross-sectional current psychopathology	HDRS	s-Allele associated with psychic anxiety but not with “delusional items”
Seretti et al. (1999b)	80 MDD BP 160	Retrospective lifetime	OPCRIT	No association
Seretti et al. (1999c)	SCH 162 MDD 83 BP 152	Retrospective lifetime	OPCRIT	No association
Ho et al. (2000)	139 MDD 131 BP	Retrospective lifetime	SADS -L	s-Allele associated with psychosis
Ospina-Duque et al. (2000)	103 BP I 112 Controls	Retrospective lifetime	DIGS	s-allele associated with psychosis
Serretti et al. (2002)	SCH 259 MDD 667 BP 789 66	Retrospective lifetime	OPCRIT	No association
Mendlewicz et al. (2004)	539 MDD 572 BP	Retrospective lifetime	SADS -L	No association
De Pradier et al. (2010)	137 BP	Retrospective lifetime	DIGS	s-Allele associated with psychosis

MDD: major depressive disorder; BP: bipolar disorder; SCH: schizophrenia; HDRS: Hamilton Rating Scale for Depression; OPCRIT: the operational criteria checklist for psychotic and affective illness; SADS-L: Schedule for Affective Disorders and Schizophrenia—Lifetime version; DIGS: Diagnostic Interview for Genetic Studies.