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Serum biomarkers predictive of depressive episodes in panic disorder

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ABSTRACT

Panic disorder with or without comorbid agoraphobia (PD/PDA) has been linked to an increased risk to develop subsequent depressive episodes, yet the underlying pathophysiology of these disorders remains poorly understood. We aimed to identify a biomarker panel predictive for the development of a depressive disorder (major depressive disorder and/or dysthymia) within a 2-year-follow-up period. Blood serum concentrations of 165 analytes were evaluated in 120 PD/PDA patients without depressive disorder baseline diagnosis (6-month-recency) in the Netherlands Study of Depression and Anxiety (NESDA). We assessed the predictive performance of serum biomarkers, clinical, and self-report variables using receiver operating characteristics curves (ROC) and the area under the ROC curve (AUC). False-discovery-rate corrected logistic regression model selection of serum analytes and covariates identified an optimal predictive panel comprised of tetranectin and creatine kinase MB along with patient gender and scores from the Inventory of Depressive Symptomatology (IDS) rating scale. Combined, an AUC of 0.87 was reached for identifying the PD/PDA patients who developed a depressive disorder within 2 years ($n = 44$). The addition of biomarkers represented a significant ($p = 0.010$) improvement over using gender and IDS alone as predictors (AUC = 0.78). For the first time, we report on a combination of biological serum markers, clinical variables and self-report inventories that can detect PD/PDA patients at increased risk of developing subsequent depressive disorders with good predictive performance in a naturalistic cohort design. After an independent validation our proposed biomarkers could prove useful in the detection of at-risk PD/PDA patients, allowing for early therapeutic interventions and improving clinical outcome.

1. Introduction

The core features of panic disorder (PD) are unexpected recurrent panic attacks that lead to distressing thoughts about future attacks, physical harm and maladaptive behaviors to prevent them (American-Psychiatric-Association, 2013). The characteristic lack of objective triggers or cues distinguishes PD from panic attacks that occur in the context of other psychiatric disorders. A panic attack is defined as rapid intense peak of fear accompanied by considerable impairment due to associated somatic (e.g. accelerated heart rate, excessive sweating) and cognitive symptoms (e.g. fear of dying or losing control). The lifetime prevalence for PD is 4.2% (12-month prevalence 2.7%) (Kessler et al., 2005b) with an average age of onset in the mid-twenties (Kessler et al., 2005a). Over a third of first-onset PD patients make treatment contact within one year of disease onset, more than in any other anxiety disorder (Wang et al., 2005). Not surprisingly, PD has been listed as the anxiety spectrum disorder with the highest disease burden (Wittchen et al., 2011).

Patients with PD or panic attacks in general have a greater risk of developing various comorbid psychiatric disorders (Baillie and Rapee, 2005; Batelaan et al., 2012; Goodwin and Hamilton, 2001; Reed and Wittchen, 1998), and suffer increased chronicity rates and symptom severity (Batelaan et al., 2012; Goodwin et al., 2004b). While agoraphobia has been shown to be the most common comorbid anxiety disorder of PD, major depressive disorder (MDD) is the most common comorbid affective disorder (Weissman et al., 1997). Recurrent panic attacks increase the risk of dysthymia and brief episodes of depression (Asselmann et al., 2014; Baldwin, 1998). Both, longitudinal (Goodwin et al., 2004a) and cross-

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sectional (Goodwin and Gotlib, 2004) studies suggest an increased risk of depressive disorders in patients suffering from panic attacks with up to 50–65% of PD patients being diagnosed with depression during their disease course. A lifetime history of panic attacks as well as recently experienced panic attacks independently increase the susceptibility to depressive disorders (Baillie and Rapee, 2005). Interestingly, panic attacks and PD have been shown to typically precede MDD (Kessler et al., 1998; Starcevic et al., 1993), while depressive episodes increase the risk of future panic attacks but not of a subsequent PD diagnosis (Kessler et al., 1998). Depressive disorders succeeding a PD diagnosis have been associated with an earlier onset and an increased number of treatment attempts and hospital visits earlier in life (Grunhaus et al., 1994). Furthermore, comorbid depression in PD increases self-rated disease severity and disability and decreases psychosocial functioning (Lecrubier and Ustun, 1998; Reich et al., 1993).

Previous studies have already examined the impact of environmental, temperamental and clinical variables as risk factors for the subsequent development of a depressive episode in PD. A past history of depression and traumatic events (Ball et al., 1994) has been shown to increase the chance of developing a depressive disorder in PD patients (Servant et al., 1991). Panic attack severity positively correlates with PD and depressive episode incidence rates (Asselmann et al., 2014). Molecular mechanisms involved in the onset of depressive symptoms in PD patients have as yet not been extensively studied. Prospective studies of non-depressed individuals on the other hand have identified putative depression risk markers in genetic studies (Zimmermann et al., 2011) and blood analyses (Guintivano et al., 2014; Khandaker et al., 2014; Wium-Andersen et al., 2013). Additionally, we have previously shown that serum analyte readouts could help to detect social anxiety disorder (SAD) patients who subsequently develop a depressive episode (Gottschalk et al., 2015). However, as of yet, no biomarkers have been established predicting the onset of a depressive disorder in patients affected by PD.

Here, we analyzed serum from patients diagnosed with PD or PD with agoraphobia (PD/PDA; note that in DSM-IV a PD diagnosis always included the specifier with or without agoraphobia) without a comorbid depressive disorder to identify molecular biomarkers that – combined with clinical indicators – can help to predict the onset of depressive episodes within a 2-year follow-up period. Patients were enrolled in the Netherlands Study of Depression and Anxiety (NESDA). Multiplexed immunoassays were used to determine concentrations of 165 analytes in serum collected during the clinical assessment at baseline. Initially 67 patients diagnosed with PD/PDA and no other comorbid anxiety disorder were investigated. Subsequently we also included PD/PA patients with comorbid anxiety disorder diagnoses (n = 53; total n = 120). Optimized predictive panels comprised of sociodemographic variables, self-report inventories and serum analytes were established for both approaches. Predictive performances of the selected patient variables and serum biomarkers were assessed individually and in combination in order to compare their potential clinical utility.

2. Subjects and methods

2.1. Sample

Data from NESDA, a longitudinal naturalistic cohort study were used (Penninx et al., 2008). The NESDA study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Antwerp University Hospital. At baseline 2981 persons aged 18–65 years were included, 2329 (78%) of which had a lifetime or current anxiety or depressive disorder and 652 (22%) healthy controls. Recruitment was performed from the community (n = 564; 19%), primary care (n = 1610; 54%) and specialized mental health care (n = 807; 27%). Collection of the baseline data set ran between September 2004 and February 2007 at clinical sites in Amsterdam, Groningen and Leiden. Local ethic boards gave approval for all participating sites and written informed consent was collected of each participant. The following exclusion criteria were used: non-fluency in Dutch or a clinical diagnosis of other major psychiatric disorders than anxiety and depressive disorders, such as e.g. psychotic disorder, bipolar disorder, severe addictive disorder, obsessive compulsive disorder. The assessment of baseline data took place in a 4 h interview, covering primary clinical psychopathology, psychiatric characteristics, physical and psychosocial testing, medication use, sociodemographics and an overnight fasting blood draw. Serum samples were stored at −80 °C (Penninx et al., 2008). A response rate of 87.1% was archived for the 2-year follow-up assessment.

For a subset of NESDA individuals (n = 1840) blood analyte abundance was analyzed. Inclusion criteria for the multiplexed immunoassay serum analysis were participation in the 2-year follow-up and a sufficient amount of available serum (1 mL). For the presented study only patients with a baseline diagnosis of PD or PDA during the 6 months prior to sampling were investigated. In order to classify patient subgroups with or without subsequent first onset or recurrence of a depressive episode, we excluded individuals with a comorbid depressive disorder diagnosis during the 6 months prior to baseline assessment. The final analysis included 120 patients with a PD/PDA diagnosis, 53 of which had a comorbid anxiety disorder diagnosis (SAD or generalized anxiety disorder (GAD)).

2.2. Clinical characteristics

The Composite International Diagnostic Interview (CIDI) lifetime version 2.1 (World-Health-Organization, 1997) was conducted by specially trained clinical research staff to establish diagnoses of anxiety disorders (PD, PDA, SAD and GAD) and depressive disorders (MDD and dysthymia). At the 2-year follow-up assessment, the presence of the above mentioned DSM-IV classified anxiety and/or depressive disorders between the baseline assessment and follow-up was re-evaluated applying CIDI. The CIDI was chosen due to its proven sensitivity for anxiety and depressive disorders (Wittchen, 1994; Wittchen et al., 1989), test-retest (Wacker et al., 2006) and inter-rater (Wittchen et al., 1991) reliability. The Beck Anxiety Inventory (Beck et al., 1988) and the Fear Questionnaire (Marks and Mathews, 1979) were used as a clinical scale for anxiety and fear symptoms respectively. The Inventory of Depressive Symptomatology (Rush et al., 1996) was used as a clinical scale for depressive symptoms. Presence of chronic non-psychiatric diseases (cardiac diseases, cancers, respiratory diseases, diabetes) was established via self-reported medical history. Self-reported usage of psychotherapeutic services (psychiatrist- or psychologist-mediated) was assessed for the 6 months prior to the baseline interview. Medication use was assessed based on regular drug use (>50% of days) in the month prior to the interview, and classification was based on the World Health Organization Anatomical Therapeutic Chemical system. For the current analysis we included selective serotonin reuptake inhibitors (SSRI; N06AB), serotonin-norepinephrine reuptake inhibitors (SNRI; N06AX16, N06AX21), tricyclic antidepressants (TCA; N06AA), anxiolytics including benzodiazepines (ANX; N03AE, N05BA, N05CD, N05CF). Non-psychiatric drug variables included cardiovascular medication (C01-05 and C07-09; cardiac therapy, anti-hypertensives, diuretics, vaso-dilators and protectors, beta blockers, calcium channel blockers, renin-