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Childhood trauma dependent anxious depression sensitizes HPA axis function

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ABSTRACT

Anxious depression is a common subtype of major depressive disorder (MDD) and is associated with greater severity and poorer outcome. Alterations of the hypothalamic-pituitary-adrenal (HPA) axis, especially of the glucocorticoid receptor (GR) function, are often observed in MDD, but evidence lacks for anxious depression. Childhood adversity is known to influence both the HPA axis and risk of MDD. Therefore, we investigated GR-function in anxious depression dependent on childhood adversity.

We enrolled 144 depressed in-patients (49.3% females). Anxious depression was defined using the Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor score ≥7. Blood draws were performed at 6 pm before and 3 h after 1.5 mg dexamethasone ingestion for measurement of cortisol, ACTH and blood count to assess GR-function and the immune system. In a subgroup of n = 60 FKBP5 mRNA controlled for *FKBP5* genotype was measured before and after dexamethasone. Childhood adversity was evaluated using the Childhood Trauma Questionnaire (CTQ).

We identified 78 patients (54.2%) with anxious depression who showed a greater severity and worse outcome. These patients were more often exposed to sexual abuse (30% vs. 16%/p = 0.04) and emotional neglect (76% vs. 58%/p = 0.02) than patients with non-anxious depression. Anxious depressed patients showed an enhanced GR-induced FKBP5 mRNA expression (F = 5.128; p = 0.03) and reduced cortisol levels, partly dependent on sexual abuse (F = 7.730; p = 0.006). Additionally, the GR-induced leukocyte response was enhanced in patients with sexual abuse (F = 7.176; p = 0.008).

Anxious depression in dependence of childhood trauma is associated with heightened sensitivity of the HPA axis and the immune system which should be considered for treatment algorithms and targets.

1. Introduction

Anxious depression is a common subtype of major depression with a reported proportion ranging between 45–55%. It has been associated with an increased severity (Fava et al., 2004), worse response to treatment (Domschke et al., 2010; Fava et al., 2008), increased suicidality (Tollefson et al., 1994) and increased functional impairment (Joffe et al., 1993). Despite the huge burden and severe consequences DSM-5 does not recognize anxious depression as a diagnostic subtype, but it provides the option to add the specifier "anxious distress". Moreover, the definition of anxious depression is not uniform, some studies use a syndrome-based approach demanding a comorbid anxiety disorder to major depression, others use a dimensional approach with high levels of anxiety symptoms accompanying major depression.

The variety of definitions clearly hampered the investigation of the underlying biological mechanisms of this depression subtype. Recently neurobiological studies suggested that an increased immune dysregulation is associated with anxious depression (Gaspersz et al., 2018).

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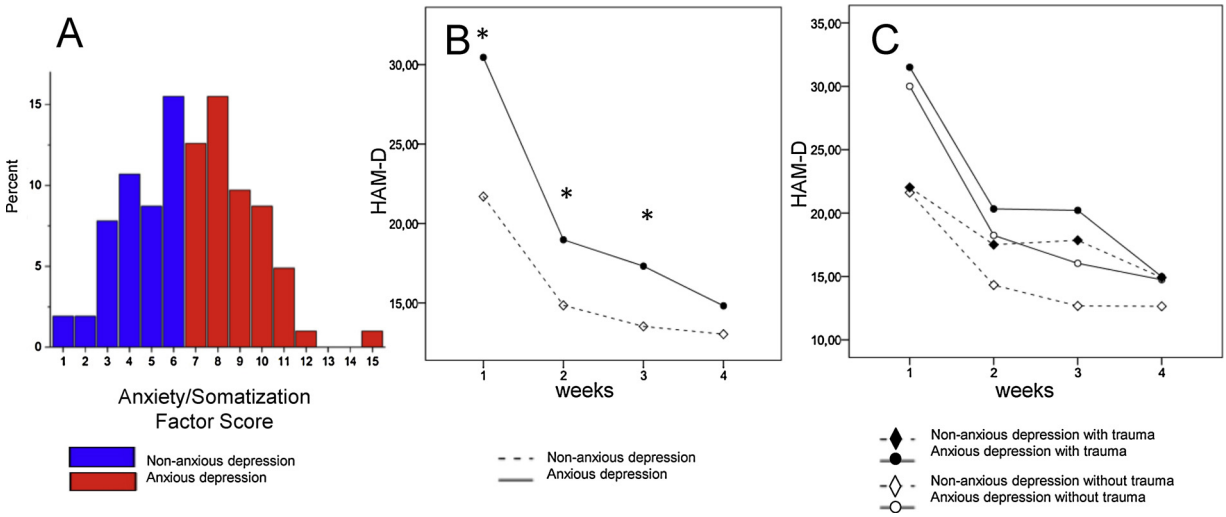

Fig. 1. A) Distribution of HAM-D Anxiety/Somatization Factor Score that defined anxious depression (threshold > = 7). Accordingly, 78 patients were categorized as anxious depressed, 66 patients had non-anxious depression. B) Hamilton Depression Rating Scale (HAM-D) scores over 4 weeks of hospitalization plotted against anxious depression and non-anxious depression. A repeated measures GLM adjusted for age and sex showed a significant main effect of the patient status ($F = 10.946$, $df = 1$; $p < 0.001$); * $p < 0.05$ posthoc analysis HAMD anxious vs. non-anxious depression C) HAM-D scores over 4 weeks of treatment plotted against depression type and childhood trauma status. Using a repeated measures GLM the combination depression type / childhood trauma showed a significant interaction ($F = 4.560$; $p < 0.001$) and main effect ($F = 8.304$; $p < 0.001$) on HAM-D scores over the entire course of 4 weeks.

Within the Netherlands Study of Depression and Anxiety (NESDA), anxious depression was not associated with basal, but with higher lipopolysaccharide(LPS)-stimulated levels of inflammatory markers (Gaspersz et al., 2017). Interestingly, studies investigating the hypothalamic-pituitary-adrenal (HPA) axis in patients with anxious depression did also find significant effects only when using challenge tests. A study applying a CRH challenge in 14 anxious depressed and 11 non-anxious depressed patients revealed an attenuated ACTH response associated with anxious depression (Meller et al., 1995). Another study using a dexamethasone suppression test observed a higher proportion of non-suppression in anxious depressed patients than in non-anxious depressed patients (Rao et al., 1989). However, a major limitation of these studies is the low sample size. More recently, genes of the HPA axis have been associated with the course of anxious depression (Binder et al., 2010). While hyperactivity of the HPA axis has robustly been observed in patients with major depression (de Kloet et al., 2005; Holsboer, 2000), it is not yet clear how the HPA axis is altered in the anxious subtype of major depression. The hyperactivity of the HPA axis in depression is supposed to be caused by a reduced sensitivity of the glucocorticoid receptor (GR) leading to an impaired negative feedback mechanism, which was revealed by GR-challenge tests like the dexamethasone-suppression test (DST) and the dexamethasone-corticotropin releasing hormone (CRH) test (Leistner and Menke, 2018).

The impact of childhood trauma has repeatedly been associated not only with an increased vulnerability for stress-related psychiatric disorders but also with distinct alterations of the HPA axis function and the immune system (Nusslock and Miller, 2016). For example, cerebrospinal fluid corticotropin releasing hormone (CRH) levels, as well as plasma cortisol and ACTH levels correlate with childhood trauma more than with current depression (Carpenter et al., 2004; Heim et al., 2000). Evidence from animal models indicates that the hyperactivity of the HPA axis associated with early life stress is moderated by a hyperactive CRH receptor 1 system (Plotsky et al., 2005). Early trauma has also been associated with an increased number of traumatic experiences across the lifespan and increases the vulnerability for later development of a post-traumatic stress disorder (Yehuda et al., 2001) that is associated with an increased negative feedback inhibition of the HPA axis and an increased sensitivity of the GR (Yehuda et al., 2015). However, the actual biological pathways through which childhood trauma effects the HPA axis and the immune system still remain unclear.

The objective of the present study was to investigate the function of the HPA axis as well as immune function in anxious and non-anxious depressed patients dependent on childhood trauma. As a measure of the HPA axis function we used our recently modified DST (mDST) analyzing cortisol, ACTH and *FKBP5* gene expression profiles as well as immune function (leukocyte response) 3 h after dexamethasone has been ingested. We could show that this approach may serve as an additional indicator of alterations in GR sensitivity in depression and other stress-related psychiatric disorders (Menke et al., 2014, 2012). Additionally, in contrast to the DST and the dex-CRH test, the mDST was not significantly influenced by plasma dexamethasone concentrations (Menke et al., 2016). Anxious depression was defined using the Hamilton Rating Scale for Depression (HAMD) anxiety / somatization factor score as applied in STAR*D (Fava et al., 2008), and the level of childhood trauma was assessed with the childhood trauma questionnaire (CTQ).

2. Methods

2.1. Recruitment of patients

We recruited 144 patients (mean age = 45.90 ± 15.13 SD, 49.3% females) suffering from a depressive episode who were admitted as inpatients to the Department of Psychiatry, Psychosomatics and Psychotherapy of the University Hospital of Wuerzburg, Germany. All individuals were of Caucasian origin. Patients were included 2–5 days after admission. The patients were treated with antidepressant medications according to doctor's choice and within a naturalistic setting. Severity of depressive symptoms was assessed at admission and then weekly by trained raters using the 21-item Hamilton Depression Rating Scale (HAMD). Patients were eligible when they fulfilled the criteria for at least a moderate depressive episode (HAMD ≥ 14). Response was defined as a HAMD reduction ≥50% and remission as HAMD < 10 after 4 weeks of treatment (Ising et al., 2009). Adverse events in childhood were assessed with the childhood trauma questionnaire (CTQ). The questionnaire comprises 5 subscales for sexual, physical and emotional abuse as well as emotional and physical neglect. According to Häuser et al. childhood trauma was acknowledged with mild/moderate severity (Hauser et al., 2011). Patients with severe general or neurological medical conditions were excluded. Blood was drawn to