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Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer

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Summary Breast cancer is the most common cancer among females. Approximately 30% of cancer patients develop depression or depressive adaptation disorder within 5 years post diagnosis. Low grade inflammation and subsequent changes in neurotransmitter levels could be the pathophysiological link. In the current study we investigated the association of neurotransmitter precursor amino acids with a diagnosis of depression or state anxiety in 154 subjects suffering from breast cancer (BCA^+), depression (DPR^+), both or neither. Sociodemographic parameters, severity of depressive symptoms, and state anxiety (ANX) were recorded. Neopterin, kynurenine/tryptophan and phenylalanine/tyrosine were analysed by HPLC or ELISA. Significantly higher serum neopterin values were found in DPR^+ patients ($p = 0.034$) and in ANX^+ subjects ($p = 0.008$), as a marker of Th1-related inflammation. The phenylalanine/tyrosine ratio (index of the catecholamine pathway) was associated with the factors ''breast cancer'' and ''depression'' and their interaction (all $p < 0.001$); it was highest in the DPR^+BCA^+ group. The kynurenine/tryptophan ratio (index of the serotonin pathway) was significantly associated with the factors ''breast cancer'' and ''state anxiety'' and their interaction ($p < 0.001$, $p = 0.026$, $p = 0.02$, respectively); it was highest in the ANX^+BCA^+ group. In BCA^+ patients kynurenine/tryptophan ratios correlated with severity of state anxiety ($r = 0.226$, $p = 0.048$, uncorrected) and phenylalanine/tyrosine ratios with severity of depressive symptoms ($r = 0.376$, $p < 0.05$, corrected). In conclusion, levels of neurotransmitter precursor amino acids correlate

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with mental health, an effect which was much more pronounced in BCA^+ patients than in BCA^- subjects. Aside from identifying underlying pathophysiological mechanisms, these results could be the basis for future treatment studies: in BCA^+ patients with depression the use of serotonin-noradrenaline reuptake inhibitors might be recommended while in those with predominant anxiety selective serotonin reuptake inhibitors might be the treatment of choice.

1. Introduction

Breast cancer is the most common cancer among females, with an annual global incidence of more than 1.6 million cases (IARC, 2012; Suppli et al., 2014), of which an estimated number of 30% develop depression or depressive adaptation disorder within 5 years post diagnosis (Mitchell et al., 2011). A complex interplay of demographic factors such as age and living alone, psychosocial and disease related distress, as well as immunological aspects may play a role (Bower et al., 2002; Standish et al., 2008; Suppli et al., 2014). Regarding the underlying pathophysiological mechanisms of this association, immune dysregulation seems to be an important factor, since it can lead to an increased risk of breast cancer and is also found in a subset of patients with depression (Maes, 1999; Raison et al., 2006). The clinical correlation of certain autoimmune disorders such as thyroiditis or multiple sclerosis with an increased risk of breast cancer (Jiskra et al., 2004; Nielsen et al., 2006) and depression (Jackson, 1998; Siegert and Abernethy, 2005) underscores the importance of immunological factors in this respect.

Several immunological mechanisms might link chronic somatic disease such as breast cancer and psychological distress. One possibility is that inflammatory stimuli can influence the neurotransmitter pathways known to be important in the pathogenesis of depression (Dantzer et al., 2008; Sperner-Unterweger et al., 2014). Specifically, the serotonin pathway can be influenced by cytokines which enhance the activity of indoleamine 2,3-dioxygenase (IDO) or stress hormones which can activate tryptophan 2,3-dioxygenase (TDO) (Oxenkrug, 2010). Both enzymes are involved in the breakdown of tryptophan (TRP) to kynurenine (KYN) (Capuron et al., 2003). The resulting TRP depletion results in lower levels of serotonin (5-HT) which could in turn increase the risk for depressive symptoms (Myint, 2012) (Fig. 1). Additionally, breakdown of KYN to kynurenic and quinolinic acid generates two potentially neuroactive substances (Dantzer et al., 2011). Elevated KYN/TRP concentrations have also been described to mediate anxiety (Lapin, 1996). KYN/TRP is considered a marker of IDO and TDO activity (Fig. 1) (Widner et al., 2002). In addition to influencing the serotonergic neurotransmitter pathway, inflammatory stimuli can also affect the catecholamine synthesis via the enzyme co-factor, tetrahydrobiopterin (BH4). Cytokines may reduce the availability of BH4 which is necessary for the conversion of phenylalanine (PHE) to tyrosine (TYR) by phenylalanine hydroxylase (PAH) (Sperner-Unterweger et al., 2014). Tyrosine hydroxylase which converts TYR into L-3,4-dihydroxyphenylalanine (Levodopa) is also dependent on BH4. PHE/TYR ratio is used as an estimate of PAH activity (Fig. 1). Notably, also tryptophan hydroxylase which converts TRP to 5-HT is dependent on BH4 (Haroon et al., 2012). BH4 is synthesized from guanosine triphosphate, this reaction being upregulated upon stimulation with interferon gamma (IFN-γ) in various cells, only in macrophages and dendritic cells neopterin is formed instead (Sucher et al., 2010). Neopterin can thus be used as a marker of Th1-related inflammation (Sucher et al., 2010). To what extent the peripheral levels of neurotransmitter precursor amino acids influence and/or mirror the central situation is still under investigation (Raison et al., 2010; Schwarcz et al., 2012).

On the other hand, tumor induced activation of IDO or TDO can lead to formation of KYN and downstream products with subsequent inhibition of the antitumor immune responses leading to a poor prognosis (Opitz et al., 2011). Plasma KYN/TRP reflects TRP breakdown which includes the activities of IDO and/or TDO which may indirectly reflect the antitumor capability of the body (Platten et al., 2012). Dietary restriction of PHE and TYR has been shown to decrease tumor spreading (Abdallah et al., 1987). Elevated neopterin concentrations are found in various malignancies, among them breast cancer, and are often associated with a poor outcome (Sucher et al., 2010). Neopterin seems to also be an indicator of oxidative stress in humans which plays a role in carcinogenesis (Uberall et al., 1994), because IFN-γ activates human macrophage antimicrobial oxidative metabolism (Nathan et al., 1983).

To improve our understanding of the complex pathophysiology behind the interaction of breast cancer and psychological distress we investigated changes in neopterin as well as KYN/TRP and PHE/TYR.

2. Methods

2.1. Ethics statement

The study was approved by the ethics committee of Medical University Innsbruck, Austria. Written, informed consent was obtained from all participants prior to inclusion in the study.

2.2. Participants

225 patients were included in the study of which 154 were included in the final analysis. The cohort originated from two separate study populations: The patients with breast cancer were recruited from an ongoing study at the Department of Gynaecology and Obstetrics (Oberguggenberger et al., 2014), the control patients with depression as well as healthy subjects were recruited from a study at the Department of Psychiatry at the Medical University Innsbruck. Patients were excluded for the following reasons: