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Psychoneuroimmunology of alexithymia

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Content

Summary

Alexithymia represents a deficit in identifying and expressing emotions, paucity of fantasies, and an externally oriented cognitive style. Currently, numerous studies document that alexithymia and several mental and somatic disorders are significantly related. Several findings also indicate that this association might be caused by alexithymia related dysregulation of neuroendocrine and immune functions. Together these findings indicate that stressors related to alexithymia could underlie the process of neuroendocrine and immune dysregulation that likely may present a significant risk, sustaining and mediating pathogenesis of several disorders and particulary psychosomatic illnesses. In this context, it is also known that several proinflammatory cytokines may play a role in pain generation and that alexithymia is significantly associated with pain symptoms in several pain disorders.

Following these findings this study includes several new data developing current state of the art and showing some alexithymia specific changes in patients with neurological disorders. Main finding of this study shows that alexithymia and anxiety in their specific interactions are linked to increased levels of interleukine-8 (IL-8) in cerebrospinal fluid (CSF) in the group of patients with non-inflammatory neurological disorders (NIND). This finding suggests that IL-8 could have exceptional role in mediation of the relationship between psychopatological symptoms and inflammatory response.

Other main results of this study indicate that increased neuropathic pain in sciatica patients is associated with elevated levels of alexithymia, depression, anxiety and C-reactive protein (CRP). In this context, several proinflammatory cytokines including IL-8 have been suggested to play an important role in pathogenesis of the neuropathic pain and may link it to psychopatological symptoms.

In this context, future studies focused on disturbances of cytokine production in alexithymia and other psychopatological symptoms could provide new research directions and potentially useful clinical findings in specific groups of neurological patients.

Shrnutí

Alexithymie představuje poruchu identifikace a vyjadřování emocí a je navíc spojena s nedostatkem fantazie a externě orientovaným kognitivním stylem. V současnosti je mnoho studií, které popisují významný vztah alexithymie a různých psychických a somatických onemocnění. Některé nálezy poukazují na fakt, že tento vztah může být zprostředkován narušením neuroendokrinních a imunitních funkcí u alexithymických subjektů. Tyto poznatky navíc poukazují na to, že stresové podněty u alexithymických subjektů mohou vést k narušení neuroendokrinních a imunitních funkcí, co může představovat významný rizikový faktor v patogenezi různých, hlavně psychosomatických onemocnění. V této souvislosti je známo, že pro-zánětlivé cytokíny můžou hrát významnou roli při vzniku neuropatické bolesti, a že alexithymie je dávána do souvislosti se symptomy bolesti u některých poruch.

Vzhledem k těmto nálezům, tato studie přináší některé nové poznatky ve o alexithymii v případě specifické skupiny neurologických pacientů. Hlavní nález této studie ukazuje, že alexithymie a symptomy úzkosti v jejich specifickém vztahu souvisejí se zvýšenou hladinou interleukinu-8 (IL-8) v mozkomíšním moku (CSF) a to u skupiny pacientů s "nezánětlivými" neurologickými poruchami (NIND). Tyto nálezy take naznačují, že IL-8 může hrát výjimečnou roli zprostředkovávající vztah mezi psychopatologickými příznaky a procesy zánětu.

Další důležitý výsledek této studie představuje sledování, že neuropatická bolest u pacientů s radikulární bolestí je spojená se zvýšenou hladinou alexithymie, symptomů deprese a anxiety a take se zvýšenou hladinou C-reaktívniho proteinu (CRP) v séru. Vzhledem k těmto zjištěním jsou různé pro-zánětlivé cytokiny, včetně IL-8, dávány do souvislosti s patogenezí neuropatické bolesti a uvažuje se o tom, že mohou představovat pojítko mezi neuropatickou bolestí a psychopatologickými symptomy.

V tomto kontexte, další studie zaměřené na výzkum cytokinů u alexithymie a u dalších psychopatologických procesů mohou poskytnout nové výzkumné perspektivy a potenciálně užitečné klinické poznatky týkající se některých typů neurologických onemocnění

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1. Introduction

With an attempt to explain basic pathophysiological processes involved in the relationship between psychopathological symptoms and somatic health several theories have been developed. Nemiah and Sifneos in 1970s have observed that many patients with so-called „psychosomatic diseases" have deficits in capacity of symbolization of emotions, verbal behavior, fantasies, and dreams. It was proposed that these psychological features can cause numerous symptoms including physiological dysfunctions that may result into somatic illnesses. This conceptualisation has evolved into the concept of alexithymia that links the influence of emotions and personality on physical illness and health.

In this context, alexithymia could be defined as an inability to complete emotional experience, which means, that the person is not able to experience feelings, differentiate between various emotional feelings, verbalize emotional experiences, reflect and to some extent analyze feelings, or fantasize about them (Bermond et al., 1999 and 2006). Alexithymia is today clinically relevant and multidimensional construct (Kooiman et al., 2002; Ogrodniczuk et al., 2011) that reflects general deficit in the cognitive and affective processing of emotions (Taylor and Bagby, 2004; Bermond et al., 2010). Alexithymia is characterized by relative and absolute stability (Tolmunen et al., 2011) and is distributed normally in the general population (Bagby and Taylor, 1997). Alexithymia consists of both, trait and state components (Tolmunen et al, 2011) and the balance between those two components is variable among different subjects and situations (Lumley et al., 2007). The prevalence of alexithymia is amounted to be around 10-20% (Salminen et al., 1999; Moriguchi et al., 2007) in general population, with significantly higher prevalence in some clinical samples (Eizaguirre et al., 2004; Parling et al., 2010).

Several potential psychosocial, cultural and biological factors are discussed in etiology of alexithymia (Taylor and Bagby, 2004; Picardi et al., 2011). According to some authors alexithymic features can also be caused by neural dysfunctions, which might result in different emotional-physiological responses (Bermond et al., 2006). The prominent

fundamental neural structures involved in emotional functions with functional relevance for alexithymia is still discussed and likely include corpus callosum, anterior commissure, anterior cingulated cortex, prefrontal cortex, amygdale, and insular cortex. In spite of the fact that alexithymia was first studied in relationship to the psychosomatic illnesses (Taylor et al., 1999), recent research have largely studied and demonstrated significant association between alexithymia and various psychopathology states, particularly depression, dissociation or anxiety (Frewen et al., 2008a and 2008b; Tolmunen et al, 2010 and 2011). It is needed to mention that although alexithymia has been originally associated with propensity to do poorly in traditional dynamic psychotherapy (Sifneos, 1973) several recent studies have described positive effects of psychotherapy (Grabe et al., 2008).

In this context, some recent studies have documented that alexithymia is related to dysregulation of immune and neuroendocrine functions. Up to date it has been published 20 studies examining immune system functions and 10 studies examining neuroendocrine response in alexithymia. Majority of these studies have demonstrated increased levels of some inflammatory cytokines, decreased function of cellular immunity and hyperactivation of HPA axis in alexithymia. In spite of some limitation it could be summarised that stressors related to alexithymia could underlie the process of immune and neuroendocrine dysregulation that likely presents a significant risk factor in pathogenesis of several illnesses. Following recent findings this study is focused on some psychoneuroimmunological pathways examining the association alexithymia with immune dysregulation and neuropathic pain.

2. Hypotheses and aims of the study

2.1. Several recent findings indicate that various interactions between nervous and immune system are important in the pathophysiology of alexithymia (Todarello et al., 1997; Pedrosa et al., 2007; Guilbaud et al.,

2009). With the purpose to reexamine relationship of IL-8 with depressive and anxiety symptoms, and assess the relationship between IL-8 level and alexithymia we have performed clinical study of serum and cerebrospinal fluid levels in a group of neurological patients with non-inflammatory disorders who undergone cerebrospinal fluid assessment for diagnostic purposes.

2.2. Although several recent data document relationship between alexithymia and pain symptoms (Lumley et al., 2002; Hosoi et al., 2010), there are only few descriptive or cross-sectional studies that have examined relationship between alexithymia and LBP (Low Back Pain). In this context, it is known that alexithymia is related to increased serum levels of C-reactive protein (CRP) (de Berardis et al., 2008; Honkalampi et al., 2011) and that increased levels of CRP are likely associated with neural lesions in LBP patients with the sciatica pain (Stürmer et al., 2005). With respect to the current findings a purpose of this study is to examine a hypothesis whether there is a relationship between pain variables including neuropathic pain and alexithymia. Further purpose of this study is to examine a hypothesis whether there is a relationship between alexithymia and serum CRP levels and whether and

3. Methods

3.1. In order to examine the hypothesis, assessment of IL-8 level in CSF during rest conditions and other biochemical measures were performed. For biochemical assessment CSF was drawn from L4-5 or L3-4 interspace using a standard sterile preparation and a total of 8 – 10 ml of CSF was removed. In addition, psychometric measures (TAS-20, BDI-II, SAS) were performed in the selected group of 33 consecutive inpatients with non-inflammatory neurological disorders (NIND) that have been selected from the total group of 10 patients indicated for CSF examination.

3.2. With the purpose to examine the hypotheses, we have investigated a group of sciatica pain patients divided into three subgroups differentially associated with a level of neuropathic pain and with different presentations of pain duration, and focal neurological signs and performed an assessment of pain variables, neuropathic pain, levels of CRP in serum, depressive symptoms, anxiety symptoms, alexithymia, demographic and BMI data in the group of 66 consecutive LBP inpatients suffering from pain related to lower extremity involving radicular pain symptoms (sciatica pain). The patients had diagnosis of L4, L5 or S1 radiculopathy caused by intervertebral lumbar disc herniation confirmed by MRI assessment. For biochemical assessment of serum CRP levels, the blood samples of 5 ml volumes were collected and analyzed according to common procedures.

4. Results

4.1. The results indicate that CSF-IL-8 is significantly correlated to TAS-20 (Spearman R = 0.46, p = 0.007) and SAS (Spearman R = 0.44, p = 0.009) but not to BDI-II (Spearman R = 0.15, p = 0.39). These correlations show that CSF-IL-8 exhibits relatively strong relationship to alexithymia, anxiety but not to depression. The results show that statistical comparison using Mann- Whitney test between groups of the NIND patients with values of CSF-IL-8 higher and lower than median distinguishes the groups of individuals with higher and lower alexithymia (TAS- 20).

4.2. Because data did not show presence of significant clusters, the patients (N = 66) were divided into three groups according to the presence of neuropathic pain component [i.e. neuropathic pain patients N=29, ambiguous group with possible neuropathic pain component N=18 and non-neuropathic group N=19]. All the differences are statistically significant for alexithymia (TAS-20) [at $p<0.01$, $z>4.1$], depression (BDI-II) [at $p<0.01$, $z>3.9$], anxiety (SAS) [at $p<0.01$, $z>4.9$], and pain score

(PD-Q) [at $p<0.015$, $z>2.8$]. Also we have found statistically significant differences in CRP levels between patients with neuropathic and non-neuropathic pain, and between patients with neuropathic and ambiguous pain [at $p<0.01$, $z>3.8$].

5. Discussion

5.1. Results of the present study are in agreement with recent evidence that various interactions between nervous and immune system are important in the pathophysiology of alexithymia (Todarello et al., 1997; Pedrosa et al., 2007; Guilbaud et al., 2009). In this context, findings of this study show that heightened level of alexithymia within the group of the NIND patients is associated with increased CSF-IL-8. The results also show that CSF-IL-8 level significantly increases with heightened occurrence of anxiety, which is in agreement with findings that patients with anxiety disorder exhibit disturbances in IL-8 production (Hoge et al., 2009). In addition we have found that alexithymia and anxiety in their specific interaction is linked to increased levels of CSF-IL-8 and that alexithymia and anxiety are tightly linked together.

5.2. Results of this study indicate that increased neuropathic component in sciatica pain is associated with elevated levels of alexithymia, depression, anxiety and serum CRP. Based on literature search the results of this study present the first finding documenting relationship between neuropathic pain and alexithymia in sciatica pain patients. These findings are in agreement with the current data documented in non-selected LBP patients that has shown significant association between neuropathic pain and the higher ratings of pain intensity, depression and anxiety symptoms (Freynhagen et al., 2006).

6. Conclusions

The result suggests that IL-8 could have exceptional role in mediation of the relationship of psychopathological symptoms and inflammantory response. An important explanatory role in this relationship between IL-8 and alexithymia could play corticotropin-releasing hormone (CRH) that is closely related to locus ceruleus-norepinephrine autonomic neurons of the hypothalamus and brainstem and regulate sympathetic nervous activity, and also immune responses (Elenkov et al., 2000; Elenkov and Chrousos, 2002). It corresponds to findings of several recent studies suggesting dysregulation of the HPA (hypothalamic-pituitary-adrenal) axis and SAM (sympatho-adreno-medullary reactivity) in alexithymic subjects (Lindholm et al., 1990; Finset et al., 2006; De Timary et al., 2008). In addition, IL-8 was identified in different brain areas (e.g. paraventricular nucleus of the hypothalamus and hippocampus) involved in the HPA axis regulation through the ACTH [adrenocorticotropic hormone] (Lucinio et al., 1992; Rosténe et al., 2010). In this context, results of this study present contribution to current findings that also cytokines participating in regulation of predominantly innate immunity may play an important role in pathophysiology of immune dysregulation in alexithymia (Pedrosa et al., 2007; Guilbaud et al., 2009). These findings present a new research direction which is complementary to the recent hypothesis that alexithymia is related to Th1/Th2 cytokines balance dysregulation reflecting disturbances in adaptive immunity (Pedrosa et al., 2007; Guilbaud et al., 2009).

In addition the result indicating significant elevation of serum CRP levels in the neuropathic sciatica patients is in line with recent studies strongly suggesting that several inflammatory mediators may potentiate neuronal activity and play a role in neuropathic pain generation (Pabreja et al., 2011; Takahashi et al., 2011). In this context, it is known that depression (Miller et al., 2009; Dowlati et al., 2010), as well as alexithymia (de Berardis et al., 2008; Honkalampi et al., 2011) are related to increased levels of CRP, therefore the inflammatory-cytokine pathway might be responsible for the relationship between neuropathic pain and some psychopathological symptoms in neuropathic pain patients.

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List of original publications

1. publications *in extenso* with relationship to the subject of disseration

a) with IF

Tomáš Uher, Petr Bob, Radek Ptáček, Alexithymie a psychosomatická onemocnění, Československá psychologie, ročník LIV, 2010. (IF = 0,295)

Tomas Uher, Petr Bob**,** Cerebrospinal fluid IL-8 levels reflect symptoms of alexithymia in patients with non-inflammatory neurological disorders, Psychoneuroendocrinology. 2011 Sep;36(8):1148-53. (IF = 5,168)

b) without IF

Tomas Uher**,** Alexithymia and immune dysregulation: A critical review, Activitas Nervosa Superior 2010;52:1,40-44

Total cumulative IF = 5.463

2. publications *in extenso* without relationship to the subject of dissertation.

a) with impact factor --

b) without impact factor --