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REVIEW

ALEXITHYMIA AND IMMUNE DYSREGULATION: A CRITICAL REVIEW

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Abstract

Alexithymia presents a deficit in identifying and expressing emotions, paucity of fantasies, and an externally oriented cognitive style. Numerous recent studies have documented that alexithymia is significantly related to dysregulation of immune functions. These findings implicate that stressors related to alexithymia could underlie the process of immune dysregulation that likely presents a significant risk factor in pathogenesis of several psychosomatic illnesses. In this article various findings on immune dysregulation in alexithymia are reviewed and discussed.

Key words: Alexithymia; Psychosomatic illnesses; Immune dysregulation

INTRODUCTION

Recent evidence indicates that dysregulation of an emotional experience and its expression have negative effect on health of the individual (Taylor, 1987; Kiecolt-Glaser et al., 2002; Guilbaud et al., 2003). Already Alexander (1943, 1950) has proposed that some specific changes of mental functions and typical alterations in cognitive and affective functioning may cause psychosomatic diseases. Alexander suggested that not only onset, but also a course of many somatic illnesses is influenced by repression of certain conflicting ideas and related emotional disturbances. Further research has shown that processes related to psychosomatic symptoms may present a final result of stress-induced internal psychic arousal (Nemiah, 2000). It was also proposed that a deficit in capacity of symbolization of emotions, verbal behavior, fantasies, and dreams can cause spectrum of symptoms, including physiological deficits that may result to various illnesses, dispositions to impulsive behavior, discomfort or avoidance of social relationships and decreased capacity for self-care and self-regulation (Nemiah & Sifneos, 1970).

An important explanation of these psychosomatic disorders presents the concept of alexithymia proposed by Sifneos in 1972, that is shortly described as: "no words for feelings". Alexithymia is frequently characterized by a deficit or developmental arrest of capacity of symbolic representation of emotions and it is hypothesized that it may present a basic dysfunction in psychosomatic patients (Nemiah & Sifneos, 1970; Lane et al., 1997). For example Bermond (1997) proposed that alexithymia could be defined as an inability of complete emotional experience, which mean that the person is not able to experience various feelings, differentiate between them, verbalize, reflect and analyze emotional experiences. As a consequence of this disturbed mental experience, alexithymia frequently leads to disconnected response between the emotional state and physiological arousal and increases risk of stress-related illness (Lumley et al., 1996; Friedlander et al., 1997; de Timary et al., 2008). These findings are in agreement with the assumption, that alexithymia poses a causal role in the pathogenesis of psychosomatic illnesses (Sifneos, 1975).

In close relationship with above mentioned data it was hypothesized that responses of autonomic nervous system (ANS) to emotion-evoked stimuli in alexithymic subjects are exaggerated or excessively persistent (Nemiah, 1975; Papciak et al., 1985; Martin & Pihl, 1985). In agreement with this assumption sympathetic over-activation in alexithymic persons has been found (Martin et al., 1986; Martin & Pihl, 1986; Rabavilas, 1987; Infrasca, 1997; Fukunishi et al., 1999; Gundel et al., 2002). This sympathetic over-activation frequently disturbs the autonomic, neuroendocrine and immune systems, and may result to tissue pathology. Recent findings also indicate that a main factor in this process present HPA axis (hypothalamo pituitary adrenal) and SAM system (sympathetic adrenal medullary), which

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significantly influence functioning of the immune system by regulation of pro-inflammantory and anti-inflammantory cytokines.

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According to recent findings glucocorticoides and catecholamines present key stress hormones produced by HPA and SAM system, that prompt the production of anti-inflammantory cytokines such as IL-4, IL-10 and TGF-β, whereas they inhibit production of pro-inflammantory cytokines, such as IL-12, TNF-α (Tumour Necrosis Factor Alpha) and INF-γ (Interferon Gamma) (Elenkov & Chrousos, 2002). According to recent evidence, cytokine production may be also directly stimulated by stressful experiences and negative emotions (Kiecolt-Glaser et al., 2002) and conversely cytokines may be responsible for influence of the HPA and SAM system (Zarkovic et al., 2008; Marques et al., 2009; Locatelli et al., 2010). Recent findings suggest that interleukine dysregulation presents important factor responsible for chronic impairment of pro/anti-inflammatory cytokine balance in alexithymia with psychological and somatic adverse effects (Corcos et al., 2004). Guilbaud et al. (2003) suggests that immune dysregulation observed in alexithymia, in many aspects seems to follow the same pattern as in subjects afflicted with chronic stress with a predominance of depressed cell-mediated immunity and a skewed Th1/Th2 ratio towards Th2 response. Contemporary studies also demonstrated that acute stress increases cardiac sympathetic activation and plasma catecholamine levels, while chronic stress is associated with a higher blood pressure and plasma levels of ACTH (Adrenocorticotropic Hormone) and diminished cellular immune response with decreased levels of interleukin-1β (Caioppo et al., 1998). According several studies acute stress seems to induce cell-mediated immunity (Th-1 immune response) while chronic stress induces humoral (Th-2) immune responses (Elenkov et al., 1996; Marshall et al., 1998; Glaser et al., 2001; Agarwal & Marshall, 2001). From this perspective and according to PubMed search, there are only a few studies examining immune response in alexithymia.

For example, a study performed in 17 healthy young women demonstrated that alexithymia (measured by Toronto Alexithymia Scale - TAS) was significantly positively correlated with serum levels of IL-4 (Corcos et al., 2004). In this context increased level of IL-4 was hypothesized as an important factor responsible for chronic impairment of pro/anti-inflammatory cytokine balance in alexithymia with psychological and somatic adverse effects (Corcos et al., 2004).

Another investigation by Pedrosa Gil et al. (2007) compared 24 subjects with somatoform disorder (SFD) and clinically significant alexithymia (TAS) with 9 healthy controls. They found significant relationship of alexithymia with decreased Th1-mediated immune function and increased activation of Th2 immune function. These finding were confirmed by the augmented serum levels of IL-6 and IL-10, elevated immunoglobulin E, and decreased levels of IL-2 Ralpha. Similarly, in the study by Guilbaud et al. (2008) performed in fifty-one healthy 18-27 year old women significant correlations of alexithymic scores (TAS) with decreased interleukin 1beta, IL-2 and IL-4 production were found. Guilbaud et al., (2008) also found reduced ratios of Th1/Th2 (IL-2/IL-10) and CD4/CD8, as well as reduced CD4 percentages indicating that alexithymic women have altered immune function, with a predominance of depressed cell-mediated immunity and a skewed Th1/Th2 ratio towards Th2 response.

Also other authors have demonstrated altered cell-mediated immunity in alexithymia. For example, study of Dewaraja et al. (1997) performed in 97 male subjects has reported hypo-activation of Th1 immune functions with significantly lower numbers of the most cytotoxic natural killer (NK) subset and killer effector T cell count in alexithymic subjects (TAS). In further study by Todarello et al. (1994) performed in 62 women (36 healthy and 26 affected by cervical intraepithelial neoplasia CIN I, II, III), who were not aware of their condition, lower rates of almost all lymphocytic subsets in alexithymic women compared to non-alexithymic ones were found. These results were successfully replicated by Todarello et al. (1997) performed in bigger sample of 43 women affected by cervical dysplasia and 67 healthy women.

These studies by Todarello et al. (1994, 1997) are in agreement with results reported by other authors who hypothesized that a certain personality trait characterized by emotional inhibition is related to greater cancer vulnerability, and that type of personality might be an important factor responsible for the outbreak of cancer. Such relationship might be mediated by certain lymphocytic functions and alexithymic status. It was proposed that immune system has an important role as a possible mediator between personality and cancer and that lowered cytotoxic lymphocytes trigger a mechanism, that may be responsible for the association between alexithymia and psychosomatic illnesses (Dewaraja et al., 1997).

Also further studies demonstrated immune changes associated with alexithymia. For example, strong positive correlation was found between pro-inflammantory cytokine IL-18 levels and alexithymia score (TAS) in ischemic stroke patients, particularly in patients with right–hemisphere lesions (Bossù et al., 2009). In the study by Temoshok et al. (2008) performed in 200 HIV-infected subjects, alexithymic scores (TAS) were positive correlated with significantly lower stimulated production of HIV-inhibiting MIP-1 alpha. They also observed association of strong maladaptive Type C coping

with significantly higher IL-6 that presents a second key immune parameter in HIV pathogenesis. Close relationship between immune response and alexithymia was also found in the study by Lin et al. (2005) performed in 60 healthy male students where positive correlation of elevated alexithymic scores (TAS) with significantly lower levels of saliva IgA (Imunoglobulin A) one month before stress situation was observed. Recent study by Vadacca et al., (2008) found increased prevalence of alexithymia (TAS) in patients with rheumatoid arthritis (RA) (54%) and also in patients with systemic lupus erythematosus (SLE) (42%). Both groups of patients had increased values of IL-6 and TNF-alpha. Similar study (Bruni et al., 2006) reported association between alexithymia (TAS) and increased TNF levels in RA patients.

CONCLUSION

Recent results indicate significant relationships among stress, alexithymia and immune dysregulation, although there are certain limitations that mainly include relatively small sample sizes in several studies and heterogeneous patient populations.

In the majority of these studies alexithymia related reduction in Th1-mediated immune functions (Todarello et al., 1994, 1997; Dewaraja et al., 1997; Pedrosa et al., 2007; Guilbaud et al., 2008) and an increase in the activation of the Th2 immune functions have been observed (Pedrosa et al., 2007; Guilbaud et al. 2008). But also other support hypothesis of cytokine dysregulation in alexithymia (Corcos et al., 2004; Bruni et al., 2006; Vadacca et al., 2008; Temoshok et al., 2008; Bossù et al., 2009). In addition an influence of the neuroendocrine dysregulation on immune functions is relatively well documented (Elenkov & Chrousous, 2002). Open question is, to what extent alexithymia may be modified by psychotherapeutic interventions (Grabe et al., 2008). Reduction of alexithymic features by psychotherapeutic interventions was tested in the several studies with optimistic results (Beresnevaite, 2000; Kennedy & Franklin 2002; Simha-Alpern, 2007; Gay et al., 2008 & Grabe et al., 2008). In this context assumed biological effect of psychotherapy on the structure and functions of the brain (Kandel, 1988, Gabbard, 2000) could present an important topic for future research of alexithymia and its therapy.

REFERENCES

Agarwal, S. K., & Marshall, G. D. Jr. (2001). Dexamethasone promotes type 2 cytokine production primarily though inhibition of type 1 cytokines. *Journal of Interferon and Cytokine Research, 21*, 147-55.

Alexander, F. (1943). Fundamental concepts of psychosomatic research. *Psychosomatic Medicine, 5*, 205-10.

Alexander, F. (1950). Psychosomatic Medicine. New York: Norton.

Beresnevaite, M. (2000). Exploring the benefits of group psychotherapy in reducing alexithymia in coronary hearth disease patients. *Psychotherapy and Psychosomatics, 69*, 117-22.

Bermond, B. (1997). Brain and Alexithmia. In: Vingerhoets AJJM, van Bussel FJ, Boelhouwer A. JW, editors. *The (non)expression of emotions in health and disease*. Tilburg, The Nederlands: Tilburg University Press. p. 115-29.

Bossù, P., Salani, F., Cacciari, C., Picchetto, L., Cao, M., Bizzoni, F., Rasura, M., Caltagirone, C., Robinson, R. G., Orzi, F., & Spalletta, G. (2009). Disease Outcome, Alexithymia and Depression are Differently Associated with Serum IL-18 Levels in Acute Stroke. *Current Neurovascular Research, 6(3)*, 163-70.

Bruni, R., Serino, F. M., Galluzzo, S., Coppolino, G., Cacciapaglia, F., Vadacca, M., Nilo, S., Terminio, N., & Afeltra, A. (2006). Alexithymia and neuroendocrine-immune response in patients with autoimmune diseases: preliminary results on relationship between alexithymic construct and TNF-alpha levels. *Annals of the New York Academy of Science, 1069*, 208-11.

Caioppo, J. T., Berntson, G. C., Malarkey, W. B., Kiecolt-Glaser, J. K., Sheridan, J. F., Poehlmann, K. M., Burleson, M. H., Ernst, J. M., Hawkley, L. C., & Laser, R. (1998). Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. *Annals of the New York Academy of Sciences, 840*, 664-73.

Corcos, M., Guilbaud, O., Paterniti, S., Curt, F., Hjalmarsson, L., Moussa, M., Chambry, J., Loas, G., Chaouat, G., & Jeammet, P. (2004). Correlation between serum levels of interleukin-4 and alexithymia scores in healthy female subjects: preliminary findings. *Psychoneuroendocrinology, 29(4)*, 557-62.

De Timary, P., Roy, E., Luminet, O., Fille, C., & Mikolajczak, M. (2008). Relationship between alexithymia, alexithymia factors and salivary cortisol in men exposed to a social stress test. *Psychoneuroendocrinology, 33(8)*, 1160-4.

Dewaraja, R., Tanigawa, T., Araki, S., Nakata, A., Kawamura, N., Ago, Y., & Sasaki, Y. (1997). Decreased cytotoxic lymphocyte counts in alexithymia. *Psychotherapy and Psychosomatics, 66(2)*, 83-6.

Elenkov, I. J., Papanicolaou, D. A., Wilder, R. L., & Chrousos, G. P. (1996). Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. Proceedings of the Association of American Physicians, 108, 374-81.

Elenkov, I. J. & Chrousos, G. P. (2002). Stress Hormones, Proinflammantory and Antiinflammantory cytokines, and Autoimmunity. *Annals of the New York Academy of Sciences, 966*, 290-303 . Friedlander, L., Lumley, M. A., Farchione, T., & Doyal, G. (1997). Testing the alexithymia hypothesis: physiological and

subjective responses during relaxation and stress. *The Journal of Nervous and Mental Disease, 185(4)*, 233-9.
Fukunishi, I., Sei, H., Merita, Y., & Rahe, R. H. (1999). Sympathetic activity in alexithymics with mother's low care. *Journal of Psychosomatic Research, 46*, 579-89.
Gabbard, G., O. (2000). A neurobiologically informed perspective on psychotherapy. *British Journal of Psychiatry, 177*, 117-122.
Gay, M. C., Hanin, D., & Luminet, O. (2008). Effectiveness of an hypnotic imaginery intervention on reducing alexithymia. *Contemporary Hypnosis, 25*, 1-13.
Glaser, R., MacCallum, R. C., Laskowski, B. F., Malarkey, W. B., Sheridan, J. F., & Kielcolt-Glaser, J. K. (2001). Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. [published erratum appears in Journal of Gerontology: Medical Sciences, 56(11), M673]. *Journal of Gerontology: Biological Sciences, 56*, M477-82.
Grabe, H. J., Frommer, J., Ankerhold, A., Ulrich, C., Groger, R., Franke, G. H., Barnow, S., Freyberger, H. J., & Spitzer, C. (2008). Alexithymia and outcome in psychotherapy. *Psychotherapy and Psychosomatics, 77(3)*, 189-94.
Guilbaud, O., Corcos, M., Hjalmarsson, L., Loas, G., & Jeammet, P. (2003). Is there a psychoneuroimmunological pathway between alexithymia and immunity? Immune and physiological correlates of alexithymia. *Biomedicine and Pharmacotherapy, 57(7)*, 292-5. Guilbaud O, Curt F, Perrin C, Chaouat G, Berthoz S, Dugré-Le Bigre, C., Wallier, J., Strebler, M., Touitou, C, Jeammet, P., & Corcos, M. (2009). Decreased immune response in alexithymic women: A cross-sectional study. *Biomedicine and Pharmacotherapy, 63(4)*, 297-304.
Gundel, H., Greiner, A., Ceballos-Baumann, A. O., Von Rad, M., Forstl, H., & Jahn, T. (2002). Increased level of tonic sympathetic arousal in high versus low alexithymic cervical dystonia patients. *Psychoterapy and Psychosomatics, 52*, 461-8.
Infrasca, R. (1997). Alexithymia, neurovegetative arousal and neuroticism. An experimental study. *Psychotherapy and Psychosomatics, 66(5)*, 76-280.
Kandel, E. R. (1998). A new intellectual framework for psychiatry. *American Journal of Psychiatry, 155*, 457-469.
Kennedy, M., & Franklin, J. (2002). Skills-based treatment for alexithymia: An exploratory case series. *Behavioral Changes, 19*, 158-171.
Kiecolt-Glasser, J. K., McGuire, L., Nobles, T. F., & Laser, R. (2002). Psychoneuroimmunology and Psychosomatic Medicine: *Back to the Future, Psychosomatic Medicine, 64*, 15-28.
Lane, R. D., Ahern, G. L., Schwarz, G. E., & Kaszniak, A. W. (1997). Is alexithymia the Emotional Equivalent of Blindsight? *Biological Psychiatry, 42*, 834-44.
Lin, S., Zhao, S. F, & Yan, F. H. (2005). The influence of alexithymia in stress on secretory IgA and cortisol in saliva. *Shanghai Kou Qiang Yi Xue, 14(6)*, 561-4.
Locatelli, V., Bresciani, E., Tamiazzo, L. & Torsello, A. (2010). Central Nervous System-Acting Drugs Influencing Hypothalamic-Pituitary-Adrenal Axis Function. *Endocrine Development, 17*, 108-120.
Lumley, M. A., Stettner, L., & Wehmer, F. (1996). How are alexithymia and physical illness linked? A review and critique of pathways. *Journal of Psychosomatic Research, 41*, 505-18.
Marques, A. H., Silverman, M. N. & Sternberg, E. M. (2009). Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. *Annals of the New York Academy of Sciences, 1179*, 1-18.
Marshall, G. D., Agarwall, S. K., Lloyd, C., Cohen, L., Henninger, E. M., & Morris, G. J. (1998). Cytokine dysregulation associated with exam stress in healthy medical students. *Brain, Behavior, and Immunity, 12*, 297-307.
Martin, J. B., & Pihl, R. (1985). The stress-alexithymia hypothesis: Theoretical and empirical considerations. *Psychotheraphy and Psychosomatics, 43*, 169-176.
Martin, J. B., & Pihl, R. O. (1986). Influence of alexithymic characteristics on physiological and subjective stress responses in normal individuals. *Psychotherapy and Psychosomatics, 45*, 66-7.
Martin, J. B, Pihl, R. O., Zouny, S. N., Ervin, F. R., & Tourjman, S. V. (1986). Prediction of alexithymic chracteristics from physiological, personality, and subjective measures. *Psychotherapy and Psychosomatics, 45*, 133-40.
Nemiah, J. C. & Sifneos, P. E. (1970). Affect and fantasy in patients with psychosomatic disorder. In: Hill OW, editor. Modern Trends in Psychosomatic Medicine, vol. 2. New York: Apple-ton-Century-Crofts. 26-34.
Nemiah, J. C. (1975). Denial revisited: Reflections on psychosomatic theory. *Psychotherapy and Psychosomatics, 24*, 140-7.
Nemiah, J. C. (2000). A Psychodynamic View of Psychosomatic Medicine. *Psychosomatic Medicine, 62*, 299-303.
Papciak, A. S., Feuerstein, M., & Spiegel, J. A. (1985). Stress reactivity in alexithymia: decoupling of physiological and cognitive responses. *Journal of Human Stress, 1*, 135-42.
Pedrosa, Gil F., Nickel, M., Ridout, N., Schwarz, M. J., Schoechlin, C., & Schmidmaier, R. (2007). Alexithymia and interleukin variations in somatoform disorder. *Neuroimmunomodulation, 14(5)*, 235-42.
Rabavilas, A. D. (1987). Electrodermal activity in low and high alexithymic neurotic patients. *Psychotherapy and Psychosomatice, 47*, 101-104.
Sifneos, P. E. (1972). *Short-Term Psychotherapy and Emotional Crisis*. Cambridge, MA: Harvard University Press.

Sifneos, P. E. (1975). Problems of psychotherapy of patients with alexithymic characteristics and physical disease. *Psychotherapy and Psychosomatics, 26*, 65-70.
Simha-Alpern, A. (2007). „I finally have words!“ Integrating a psychodynamic psychotherapeutic approach with principles of emotional intelligence training in treating trama survivors. *Journal of Psychotherapy Integration, 17, 293-313.*
Taylor, G. J. (1987). *Psychosomatic medicine and Contemporary Psychoanalysis*. Madison (CT): International Universities Press.
Temoshok, L. R., Waldstein, S. R., Wald, R. L., Garzino-Demo, A., Synowski, S. J., Sun, L., & Wiley, J. A. (2008). Type C coping, alexithymia, and heart rate reactivity are associated independently and differentially with specific immune mechanisms linked to HIV progression. *Brain, Behavior, and Immunity, 22(5)*, 781-92.
Todarello, O., Casamassima, A., Marinaccio, M., La Pesa, M. W., Caradonna, L., Valentino, L., & Marinaccio, L. (1994). Alexithymia, immunity and cervical intraepithelial neoplasia: a pilot study. *Psychotherapy and Psychosomatics, 61(3-4)*, 199-204.
Todarello, O., Casamassima, A., Daniele, S., Marinaccio, M., Fanciullo, F., Valentino, L., Tedesco, N., Wiesel, S., Simone, G., & Marinaccio, L. (1997). Alexithymia, immunity and cervical intraepithelial neoplasia: replication. *Psychotherapy and Psychosomatics, 66(4)*, 208-13.
Vadacca, M., Bruni, R., Cacciapaglia, F., Serino, F., Arcarese, L., Buzzulini, F., Coppolino, G., Rigon, A., Terminio, N., & Afeltra, A. (2008). Alexithymia and immunoendocrine parameters in patients affected by systemic lupus erythematosus and rheumatoid arthritis. *Reumatismo, 60(1)*, 50-6.
Zarković, M., Ignjatović, S., Dajak, M., Cirić, J., Beleslin, B., Savić, S., Stojković, M., Bulat, P. & Trbojević, B. (2008). Cortisol response to ACTH stimulation correlates with blood interleukin 6 concentration in healthy humans. *European Journal of Endocrinology, 159*(5), 649-52.