Rev Dor. São Paulo, 2012 jul-sep;13(3):282-6

CASE REPORT

Depressive disorder and fibromyalgia: association to early life stress. Case report*

Transtorno depressivo e fibromialgia: associação com estresse de vida precoce. Relato de caso

Sandra Odebrecht Vargas Nunes[1], Luciana Vargas Alves Nunes[1], Juliana Brum Moraes[2], Vivian Uemura[2]

** Received from the State University of Londrina (UEL). Londrina, PR.*

SUMMARY

BACKGROUND AND OBJECTIVES: The association between depression, fibromyalgia and child abuse suggests that they divide the model of developmental traumatology. This study aimed at presenting a case of depressive disorder and fibromyalgia, associated to child abuse, as well as at discussing causes and consequences of both diagnoses.
CASE REPORT: Female patient, 54 years old, with fibromyalgia and recurrent depressive disorder, current severe episode, without psychotic symptoms, with somatic symptoms for approximately six months. With history of negative childhood events with loss of affective relationship, problems related to alleged child abuse and frightening childhood experience.
CONCLUSION: Early life stress may be the causal factor of painful symptoms in depression and fibromyalgia.
Keywords: Child development, Depressive disorder, Fibromyalgia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A associação entre depressão, fibromialgia e maus tratos infantis sugere que ambas, dividem o modelo de traumatologia do desenvolvimento. O objetivo deste estudo foi apresentar um caso do transtorno depressivo e fibromialgia relacionado aos maus tratos na infância, bem como discutir as causas e as consequências de ambos os diagnósticos.
RELATO DO CASO: Paciente do sexo feminino, 54 anos, apresenta fibromialgia e transtorno depressivo recorrente, episódio atual grave, sem sintomas psicóticos, com sintomas somáticos há cerca de seis meses. Com história de eventos de vida negativos na infância com perda de relação afetiva, problemas relacionados com abuso físico alegado da criança e experiência pessoal amedrontadora na infância.
CONCLUSÃO: O estresse de vida precoce pode ser responsabilizado como fator causal dos sintomas dolorosos na depressão e fibromialgia.
Descritores: Desenvolvimento infantil, Fibromialgia, Transtorno depressivo.

INTRODUCTION

Fibromyalgia (FM) is a clinical entity characterized by chronic pain lasting more than three months, presence of 11 out of 18 hypersensitive points referred as trigger points, and diffuse pain. It is more prevalent among females and is associated to insomnia, fatigue and psychological stress[1].
The prevalence of depression varies from 49% to 80% in FM. Depression worsens social and emotional functionality and the quality of life of FM patients[2].
In addition, history of child abuse has been found both in adults with FM[3] and in adults with depressive disorder[4].
Child maltreatment may bring consequences to adult life, such as: heart ischemic disease, cancer, irritable colon disease, chronic lung disease, FM, mood disorders, dietary disorders, anxiety, alcohol and drug abuse, post-traumatic stress, infertility, suicide behavior, learning deficit and sleep disorders[5].
Children born in stressing environments may change their neuropsychological structures as a way to adapt to toxic childhood experiences. Structural consequences of child maltreatment include corpus callo-

1. Associate Professor of Psychiatrics, State University of Londrina (UEL). Londrina, PR, Brazil.
2. Resident in Psychiatrics, State University of Londrina (UEL). Londrina, PR, Brazil.

Correspondence to:
Sandra Odebrecht Vargas Nunes, M.D.
Av. Adhemar de Barros, 625
86050-190 Londrina, PR.
Phone: 55 (43) 3323-8210
E-mail: sandranunes@sercomtel.com.br

Rev Dor. São Paulo, 2012 jul-sep;13(3):282-6

sum, left neocortex, hyppocampus and amygdala abnormalities, and reprogramming of the hypothalamic-pituitary-adrenal axis (HPA)[6].

Exposing developing brain to stress results in hyperfunctioning amygdala, decreased hyppocampus activity with altered negative feedback in glucocorticoid receptors, hypofunctioning dopaminergic mesocorticolimbic system and HPA axis hyperactivation[7].

Traumatology development model explains how early life stress leads to permanent developing brain modifications, with changes in neurotransmitters and hormones modulating the neuronal migration development processes, differentiation, synaptic proliferation which may affect the developing brain[8].

This study aimed at observing the association of early life stress to depressive disorder and to fibromyalgia, in addition to biological stress changes and relationships with depression and pain.

CASE REPORT

Female patient, 54 years old, Caucasian, married, housewife and Catholic. Born and raised in Paraná. For approximately 6 months, patient is waking up sad, anguished, with generalized pain and sensation that she will be unable to do was she has to do. She reported that for six months she spends most part of the day in bed or sitting and started crying more than normal.

She feels worse in the morning, has difficult to stand up, and does everything with major effort; she feels the body heavy as lead, perceives everything as nuisance, nothing is enjoyable and she does not have strength even to take a bath. She feels herself unable to chat and to do the services of the home. In the afternoon she feels better and is able to perform minor activities.

She reports frequent awakenings during the night; she wakes up around four o'clock in the morning and is no longer able to sleep due to pain. She brood things of the past with ideas of guilt and worthlessness. She believes that dying would relief her suffering. Food has no longer taste; she has difficulties to eat and has lost 4 kg in the last month.

Pain in the back, shoulders, elbows, wrists, knees, ankles, nape and head has worsened in the last six months. She has difficulties to perform normal activities and started to feel more tired with minor tasks, such as climbing stairs or carrying a box, and when doing the services of the home. She used to do manual work, but has abandoned due to pain which does not improve with common analgesics.

She describes an unhappy childhood. She would take care of home duties and of smaller siblings since very early because she was the oldest of six siblings. She studied until high school with good performance.

Patient refers that her drunken father would abused the family and threatened to kill the mother and children and so patient and siblings would run away and sleep outside home. Her father was denounced by neighbors for having physically abused the patient and since then she and her siblings started to be monitored by a tutelary council.

At 13 years of age her mother died and after this her father's violence has turned against her. Her adolescence was marked by several migraine crises. She married at 20 years of age and reported that her husband is sympathetic, but has lost sexual desire. She has three children, had postpartum depression episodes similar to current episodes, however of lower intensity.

Smoker since 18 years of age, she smokes 40 cigarettes a day being the first morning cigarette the most pleasant; she smokes more frequently in the morning. She denies alcohol and illicit drugs abuse or dependence. According to patient, her mother has probably died from depression because she stopped eating and became very weak.

Her father was alcoholic and died from the consequences of alcohol. She has two sisters who are being treated for depression.

At mental evaluation patient was alert, with preserved temporo-spatial orientation. Cooperative attitude, psychomotor retardation. Her mood is depressed, her affection is congruent. Thinking processes are logic with ideas of guilt and suicide ideation. She presents with anhedonia, anorexia, terminal insomnia, low libido, generalized pain which worsens in the morning. Her hands are unquiet and she has pain expressions at any movement.

Physical evaluation has shown no joint heat, redness or movement limitation. Normal muscle strength. Presence of 11 trigger points in cervical and scapular-humeral regions, arms, knees and lumbar region.

Patient had signs and symptoms compatible with clinical criteria for the following diagnoses, according to International Classification of Diseases (ICD-10): Recurrent Depressive Disorder, severe current episode, without psychotic symptoms, with somatic symptoms (F33.21), Tobacco Dependence (17.2) and Fibromyalgia (M79). Among contextual factors she presented: family history of drug abuse (Z81.1), loss of affective relationships during childhood (Z61.0), problems related to alleged physical abuse of the child (Z61.6), frightening personal experience in childhood (Z61.7). She presented labor incapacity and incapacity to perform the services of the home.

After three months under antidepressant duloxetine and

psychotherapy, she improved her depressed mood, was more interested and pleased in dressing up and making up the home, and had more energy to start the services of the home. She could keep attention to TV programs and maintain conversation with other people. Her appetite and sleep have improved, she does not wake up numerous times and pains were attenuated.

Patient was diagnosed with depressive disorder associated to FM and to negative childhood events. Patient's family has history of depressive disorder and alcohol dependence.

The prevalence of depression among FM patients is 32.9% for mild depression, 21.4% for moderate depression and 12.9% for severe depression[2]. FM is not only associated to more severity of current depression, but also to depressive disorder along life and family history of depression. These findings suggest that FM could be a depression variant[9]. In this clinical case, the patient had problems related to negative childhood events, such as: 1) loss of affective relationship in childhood (mother's death), 2) problems related to abuse (father abused the patient and was denounced by neighbors to the tutelary council), 3) frightening personal experience in childhood (witnessed death threats to her mother). The relationship between stressing situations in early life and the development of depression in adult life is well established. Early life trauma in genetically vulnerable individuals may trigger a depressive episode[10].

Results of handling versus maternal separation experiments with animals have reported that those handled had more binding capacity to hippocampus glucocorticoids receptors in adult life and were protected from the noxious effects of hypersensitive HPA axis[11]. Children maltreatment causes the permanent inactivation of the HPA axis, resulting in cortisol changes and hippocampus damage[12].

Decreased hippocampus volume in neuroimaging was observed in women victims of sexual abuse in childhood. Excessive HPA axis activation caused by stress produces a less efficient negative feedback system in the hippocampus resulting in decreased number and sensitivity of hippocampus glucocorticoid receptors[13].

Early life stress is related to HPA axis activation leading to changes in the amygdala-hippocampus complex. Hippocampus and prefrontal cortex inhibit HPA axis and the amygdala activates the HPA axis. Cortisol changes related to early life stress are a consequence of increased CRF levels and of increased HPA axis sensitivity to negative feedback[14].

HPA axis is abnormal in depressive disorder patients[15], as well as in FM patients[16] and in depressive patients. HPA axis changes contribute to changes in the neurotransmission of serotoninergic and noradrenergic pathways, which are closely related to the development of depressive and painful symptoms[15].

The presence of serotoninergic and noradrenergic pathways in the pain descending inhibitory pathway promotes pain perception modulation. If depression has decreased such neurotransmitters, there will be decrease in pain inhibition mediated by the spinal pathway, leading to further painful perception.

Neuroimaging changes show that chronic pain is followed by decreased gray matter in the dorsolateral prefrontal cortex bilaterally and in the right thalamus[17]. Depressive disorder also leads to decreased density of prefrontal cortex gray matter[18].

The system proposed as pain descending inhibitory system consists of central nervous system areas (CNS) interconnected by fibers going from cortical and diencephalic systems to the periaqueductal (PAG) and periventricular gray matter, and which are rich in encephalins and opioid receptors and, from there, they continue to areas of the rostroventral bulb, especially nucleus magnus of raphe (NMR) and adjacent nuclei, which, in turn, send serotoninergic and noradrenergic fibers, via dorsolateral funiculus, to spinal cord dorsal horn and the bulb, ending especially in laminae I, II and V, and inhibiting nociceptive neurons, interneurons and ascending tracts which project rostrally, including spinothalamic, spinoreticular and spinal-midbrain tracts.

The relationship between early life stress, physical, sexual, emotional abuse and negligence, and depression may be attributed to a dysfunctional HPA axis response. During acute stress, there are biochemical body adaptive responses, such as change in adrenocortical hormones secretion, especially cortisol, caused by decreased number and sensitivity of brain glucocorticoid receptors, with impairment of negative feedback.

Hippocampus is the brain structure responsible for episodic memory and learning, with high density of glucocorticoid receptors and persistent postnatal neurogenesis, which could be related to cognitive deficits secondary to hippocampus or prefrontal cortex malfunctioning[20]. When stressing experiences are very extreme or chronic, increased cortisol may be noxious, changing endocrine responses and brain structures functioning[21].

The impact of early adverse experiences also changes amygdala functioning, hyperactivating it. This brain structure is part of the neural circuitry which has regulatory effects on the HPA axis[22].

The presence of serotoninergic and noradrenergic pathways in pain descending inhibitory pathway promotes

painful perception modulation. If depression has decreased such neurotransmitters, there will be a decrease in pain inhibition mediated by the spinal pathway, leading to further painful perception.

The relationship between early life stress, depression and pain is summarized in figure 1. Early life stress would activate the HPA axis leading to changes in the amygdala-hippocampus complex. Hippocampus and prefrontal cortex inhibit HPA axis and the amygdala activates HPA axis. Decreased pain inhibition by serotoninergic and noradrenergic pathways.

Approximately two decades after the establishment of FM diagnostic criteria, there is still no consensus about its causes. The hypothesis of central pain processing deregulation and its underlying neurological mechanisms is gaining force. Pain amplification as etiologic FM mechanism encompasses from abnormal activation of postsynaptic N-Methyl-D-Aspartate (NMDA) receptors in spinal cord dorsal horn to the deregulation of pain modulation by the descending inhibitory system. NMDA receptors are important for neuronal excitotoxicity and plasticity[22].

PRACTICAL IMPLICATIONS

Early life stress may contribute to adult life diseases, such as depressive disorder and FM. Early life stress is related to HPA axis activation leading to changes in the amygdala-hippocampus complex. Hippocampus and prefrontal cortex inhibit HPA axis, while the amygdala activates HPA axis. Decreased pain inhibition by serotoninergic and noradrenergic pathways is implied as the causal factor for painful symptoms in depression and FM.

So, it is to be expected that increased norepinephrine and serotonin neurotransmission may be effective to control pain.

Noradrenergic and serotoninergic effects on pain descending inhibitory system related to stress and depression may bring the possibility of using new drugs.

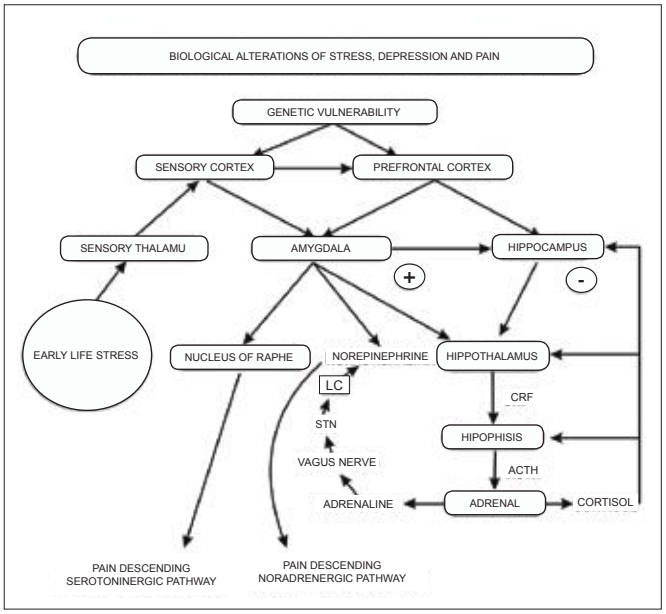

Figure 1 – Biologic alterations of stress related to depression and pain.
PVN = paraventricular nucleus; LC – locus ceruleus; STN =solitary tract nucleus; CRF = corticotrophic factor; NR = nucleus of raphe; ACTH = adrenocorticotrophic hormone.

CONCLUSION

Early life stress may be implied as causal factor for painful symptoms in depression and FM.

REFERENCES

1. Taud R. Fibromyalgia pain: do we know the source? Curr Opin Rheumatol. 2004;16(2):157-63.
2. Berber J, Kupek E, Berber S. Prevalência de depressão e sua relação com a qualidade de vida em pacientes com síndrome da fibromialgia. Rev Bras Reumatol. 2005;45(20):47-54.
3. Anderberg UM, Marteinsdottir I, Theorell T, et al. The impact of life events in females patients with fibromyalgia and in female healthy controls. Eur Psychiatry. 2000;15(5):295-301.
4. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. Neuropsychopharmacology. 2004;29(4):641-8.
5. Krug EG, Dahlberg l, Mercy J, et al. Child abuse and neglect by parents and other caregivers. In: World Health Organization. World Report on Violence and Health. Geneva: WHO, 2002. p. 59-86.
6. Grassi-Oliveira R, Ashy M, Stein L. Psychobiology of childhood maltreatment: effects of allostatic load? Rev Bras Psiquiatr. 2008;30(1):60-8.
7. Charmandari E, Kino T, Souvatzoglou E, et al. Pediatric stress: hormonal mediators and human. Horm Res. 2003;59(4):161-79.
8. Bellis MD, Baum AS, Birmaher B, et al. Developmental traumatology part I: biological stress systems. Biol Psychiatry. 1999;45(10):1259-70.
9. Okifuji A, Tirk D, Sherman J. Evaluation of the relationship between depression and fybromyalgia syndrome: why aren't all patients depressed? J Rheumatol. 2000;27(1):212-9.
10. Zavaschi MLS, Satler F, Poester D, et al. Associação entre trauma por perda na infância e depressão na vida

adulta Rev Bras Psiquiatr. 2002;24(4):189-95.
11. Miller A, Maletic V, Raison C. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732-41.
12. Van Voorheers E, Scarpa A. The effects of child maltreatment on the hypothalamic-pituitary-adrenal axis. Trauma, Violence, Abuse. 2004;5(4):335-52.
13. Bremmer DJ, Vythilingam M, Vermetten E, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003;160(5):924-32.
14. Nunes, SOV, Watanabe MAE, Morimoto HK, et al. The impact of childhood sexual abuse on activation of immunological and neuroendocrine response. Aggression and Violent Behavior. 2010;15(6):440-5
15. Belmaker R, Agam G. Major depressive disorder. N Engl J Med. 2008;358(1):55-68.
16. Demitrack MA, Crofford LJ. Evidence for the pathophysiologic implications for hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann N Y Acad Sci. 1998;840:684-97.
17. Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004;24(46):10410-5.
18. Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci Biobehav Rev 2009;33(5):699-771.
19. Pires OC, Ashmawi HA, Constantino E, et al. Antagonistas serotoninérgico e noradrenérgico por via subaracnoidea aumentam a resposta álgica em ratos. Rev Bras Anestesiol 2011;61(2):202-10.
20. Carrion VG, Weems CF, Reiss AL. Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics. 2007;119(3):509-6.
21. Sheaa A, Walshb C, Macmillanb H, et al. Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and posttraumatic stress disorder in females. Psychoneuroendocrinology. 2004;30(2):162-78.
22. Abeles AM, Pillinger MH, Solitar BM, et al. Narrative review: the pathophysiology of fibromyalgia. Ann Intern Med. 2007;146(10):726-34.

Submitted in November 28, 2011.
Accepted for publication in May 08, 2012.