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Abuse in Childhood and HPA Axis Functioning in Mentally Ill Patients

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1. Introduction

In 1986 The European Council described family abuse as 'each activity or negligence of one of the family members that are life- threatening and can jeopardise physical and psychological integrity or freedom of another member of the same family or they seriously harm the development of his personality'. Ney et al. (1987)¹ ranked the types of violence and negligence according to the extent of destruction of an individual. The most traumatic forms of violence are:

- physical violence: hitting on the face, asphyxiation, striking with a belt, agitation, burns, bone fractures
- verbal violence: intimidation, blaming, embarrassing, discrimination
- sexual violence: gang rape, oral sex, forced masturbation, forced intercourse, forced participation in pornography

The epidemiological data point out the existence of the problem of abuse and using violence by parents towards children. It was stated that in the USA, from 11% to 62% of women (McCauley et al., 1997; Wyatt 1985)^{2,3} and from 3% to 39% of men (Kercher et al., 1984)⁴ were victims of sexual abuse in childhood. Different forms of abuse such as physical and emotional violence were believed to be an epidemic in the USA. What was researched were the traumatic experiences from childhood and later psychopathology. It was stated that sexual abuse in female children can later result in PTSD occurrence and concerns 10% of women in the USA (Kendler et al., 1995)⁵.

¹ Ney, P.G. (1987). Does verbal abuse leave deeper scars: a study of children and parents. *Canadian Journal of Psychiatry*, Vol. 32, pp. 371-377, ISSN 0706-7437.

² McCauley, J, Kern, D.E. et al. Clinical characteristics of woman with a history of childhood abuse: unhealed wounds. *JAMA*. 1997, 277; 1362- 1368, ISSN 0098-7484.

³ Wyatt, G.E. (1985). The sexual abuse of Afro- American and white- American women in childhood. *Childhood Abuse Neglect*, vol.9, pp. 507- 519, ISSN 1097-6256.

⁴ Kercher, R.C. & McShane M. (1984). The prevalence of child sexual abuse victimization in adult sample of Texas residents. *Childhood Abuse Neglect*, vol.8, pp. 495-502, ISSN 0145-2134.

⁵ Kendler, K.S.; Kessler, R.C.; Walters E. et al. (1995). Stressful life events, genetic liability and onset of an episode of major depression. *American Journal of Psychiatry*, vol.152, pp. 833- 842, ISSN 0002-953X.

Cawson's research (Cawson et al., 2000; Cawson, 2002), which was carried out on a population of 2869 young British adults aged 18- 24 chosen randomly, found that maltreatment was experienced by 16 per cent of them⁶. Serious physical abuse by parents was experienced in the childhood of seven per cent of those researched, and six per cent of them experienced emotional maltreatment. Serious absence of care was experienced by six per cent of the sample; whereas five per cent of them suffered a serious absence of supervision. Childhood sexual abuse by parents was reported by 1 per cent of the sample. At the same time, 15 per cent experienced sexual abuse by other relatives or a known person, four per cent by a recently met stranger. Intermediate sexual abuse by parents affected 14 per cent of the sample in their childhood and intermediate absence of care- nine per cent, intermediate absence of supervision was experienced by 12 per cent (Cawson et al. 2000 & 2002). In the United States, it has been estimated that 11- 62% of women (Wyatt 1985; McCauley and Kern, 1997)^{7,8} and 3- 39% of men (Kercher & McShane, 1984)⁹ have been victims of sexual abuse in childhood. Other forms of maltreatment such as physical and emotional abuse are regarded as widespread in the US.

While conducting research over various kinds of violence, Ney (1997) concluded that verbal violence, more than any other kind of it, influences the alteration of self- and world perception in the researched children. Verbal violence causes symptoms of fear of abandonment in children, mood disorders, difficulties in establishing and maintaining relationships, a feeling of guilt as well as auto- destructive behaviours. Children who are subject to physical violence are more aggressive, have a low self- esteem, impaired ability of achieving happiness in their lives, difficulties in expressing empathy, and - in case of a long-lasting violence - a connection can be noted between physical violence and the suppression of intellectual development, depression and aggressive behaviours (Heim et al., 2001; Ney, 1987; Ney, 1997; Rossman, 1985)^{10,11,12,13}.

The outcomes of a variety of nowadays' scientific research indicate that there is a sound impact of some stressful events from childhood (trauma) on mental health (Ossowska 2002, Twardowska & Rybakowski 1996))^{14,15}. The research mainly concern sexual abuses,

⁶ Cawson P., Wattam, C.; Brokers, S.& Kelly, G. (2000). *Child maltreatment in the United Kingdom*, NSPCC, ISBN 1-84228-006-6, London, United Kingdom.

⁷ See 3

⁸ See 2

⁹ See 4

¹⁰ Heim, Ch. & Nemeroff, Ch.(2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders; preclinical and clinical studies. *Biological Psychiatry*, Vol.1, No. 49, pp. 1023-1039, ISSN 0006-3223.

¹¹ See 1

¹² Ney, P.G. & Peeters M.A. (1997). *The centurion's pathway*, Pioneer Publishing, ISBN 9780920952061, Victoria, USA.

¹³ Rossman, P.G.(1985). The aftermath of abuse and abandonment: a treatment approach for ego disturbance in female adolescence. *Journal of American Academy of Child and Adolescent Psychiatry* , Vol.24, pp. 345-352, ISSN 0002-7138.

¹⁴ Ossowska, G.(2002). *Poszukiwanie leków zapobiegających następstwom stresu przewlekłego. Nowy model „depresji” u szczurów*. Praca habilitacyjna, Akademia Medyczna w Lublinie, Zakład Poligraficzny BiS, Lublin, Poland.

¹⁵ Twardowska, K. & Rybakowski J. (1996). Oś limbiczno - podwzgórzowo - przysadkowo - nadnerczowa w depresji (przegląd piśmiennictwa), *Psychiatria Polska*, Vol. 5, pp. 741 - 756, ISSN 0033-2674.

violence, lack of emotional support, loss of parents, separation, lack of parental warmth, familial conflicts, mental illnesses and psychoactive substance abuse by parents. The influence of sexual abuse and physical violence on a child's development has been put into a meticulous scrutiny here.

The experience of abuse in childhood is closely related to an increased number of traumatic experiences during a lifetime. The abuse may also enhance the susceptibility to the later development of PTSD through the change of psychological (e.g. the development of patterns of affection) and biological (the disruption of HPA axis functioning) developmental processes, including the interaction with genetic factors. In spite of the fact that different (except for abuse) types of traumatic experiences in childhood (e.g. a house burn-down or participation in a traffic accident), can force us to speculate that they will have an adverse effect on development, most of the current research points out childhood abuse and the linked stressful familial/ interpersonal events in life in the predictability of a wide range of later psychological and somatic problems.

The reasons for this state of matters are not yet fully understood, however, some of the potential explanations are the following:

1. In comparison to different types of traumatic events, childhood abuse happens more often in the context of the family ,
2. Every type of abuse in childhood is connected with an increased probability of exposure to another types of abuse and with an increased intensity of stressful situations connected with family/ parental dysfunctions (e.g. the psychoactive substance abuse by parents) , and
3. In comparison to some different types of exposure to trauma, childhood abuse is a frequently repeated experience, not only a single episode (e.g. multiple episodes of sexual abuse by the exact same tormentor for several years).

In McEven's work (2003)¹⁶ it was described that one of the most important factors influencing a life- long health is the stability in the early period of life. Unstable parent-child relationships as well as an explicit abuse in childhood may lead to the development of behavioural and physical problems in childhood that also persist in the adult life. In people who experienced abuse in childhood, there was an increased mortality and morbidity of various diseases. On the other hand, however, the less extreme familial environmental features also cause an increased risk of somatic and mental disorders in children. As it was stressed in the current review of research, in families that are characterised by the lack of warmth and support or an insufficient supervision of the parents, there is an increased risk of somatic and mental disorders. The consequences of childhood abuse and familial dysfunction in an early period of life include a significant increase in substance abuse, depression and suicidal tendencies; promiscuity; an incidence of heart disease, cancer, chronic lung disease, extreme obesity, skeletal fractures and liver disease.

Abuse and negligence in early childhood is also connected with neuro- chemical imbalance which is related to low levels of serotonin as well as the development of hostility, aggression, substance abuse and suicide. Research on primate apes have shown than an early maternal deprivation lowers the levels of serotonin in the brain and it also enhances the tendency towards alcohol and aggressive behaviours. It also lowers affiliate behaviours.

¹⁶ McEven,B.S. B.S.(2003). Early life influences on life-long patterns of behavior and health. *Mental Retardation and Developmental Disabilities Research Reviews*, Vol. 9, pp.149-154, ISSN 1080-4013.

Data from the research on humans point out similar patterns of an altered physiological function in children who were brought up in 'risky families' (i.e. families that are characterized by aggression, lack of parental warmth or an excessive/ insufficient regulation). Children from such families show irregular HPA axis activity, especially the increased levels of activity in this specific hormonal system.

In the Easton et al. research ¹⁷(2000) from Yale University School on the group of 105 addicts, a high incidence of abuse in childhood was observed. It was shown that 14% of the group were victims of family violence. The addicts that experienced this form of abuse showed a greater severity of depression symptoms that were estimated with the use of Beck's Depression Scale and more aggravated symptoms of addiction researched by Michigan Alcoholism Screening Test. They also required a more intensive individual therapy.

A lot of research was conducted that associated traumatic experiences from childhood with the later psychopathology.

Using violence towards children creates a possibility of occurrence in the adult life of the following: depression (Briere & Runtz, 1990; Wyatt 1985; Sweet et al. 1990)^{18,19,20} anxiety disorders (Agid et al. 2000)²¹, addictions (Agid et al. 2000, Kedler et al. 1995)^{22,23} and personality disorders (Herman et al. 1989, Ogata et al. 1990)^{24,25}.

Analysing the impact of various kinds of stress on mental state, it is important to divide them into those taking place during the recent time and in the past, including childhood. In the light of the latest work of Heim et al., the trauma experienced in the early years of childhood can cause a preserved biological state that can be the risk factor for mental disorders development in the later life. For this reason, the ascertainment of childhood abuse should be considered as a crucial risk factor of the occurrence of mental disorder just as tobacco smoking is the risk factor of lung cancer²⁶.

2. Trauma as a chronic stress and its pathogenic role

The occurrence of a long- lasting activation of HPA axis, autonomic system and various executive centres during chronic stress causes many adverse effects of the organism, it

¹⁷ Easton , C.J. (2000). Prevalence of family violence In clients entering substance abuse treatment. *Journal of Substance Abuse Treatment*, Vol.18, pp.23-28, ISSN 0740-5472.

¹⁸ Briere ,J. & Runtz, M. (1990). Differential adult symptomatology associated with three types of abuse. *American Journal of Psychiatry* , Vol. 14, pp. 357, ISSN 0145-2134.

¹⁹ See 3 Wyatt

²⁰ Sweet, C.; Surrey, J.; Cohen, C. (1990). Sexual and physical abuse histories and psychiatric symptoms among male psychiatric patients. *American Journal of Psychiatry*, Vol. 147, pp 632, ISSN 0002-953X.

²¹ Agid, O.; Kohn, Y.; Lere, B. (2000). Enviromental Sterss and psychiatric illness. *Biomedical Pharmacotherapy* vol. 54, pp. 135, ISSN 0753-3322.

²² See 16.

²³ See 5.

²⁴ Herman, J.L; Perry, J.; Kolk B.A. (1989). Childhood trauma in borderline personality disorder. *American Journal of Psychiatry*, Vol. 146, pp. 490, ISSN 0002-953X

²⁵ Ogata, S.N.; Silk K. (1990). Childhood sexual and physical abuse in adult patients with borderline personality disorder. *American Journal of Psychiatry*, Vol. 147, pp. 1008, ISSN 0002-953X.

²⁶ Heim, Ch.; Newport, D.J.; Stacey, H.; Graham, Y.(2000). Pituitary-adrenal and autonomic response to stress in woman after sexual and physical abuse in children. *JAMA* Vol.,2, pp. 592-597, ISSN 0098-7484.

predisposes to the development of pathological processes that are mostly linked with chronic hypercortisonism and the activation of autonomic system. Stress activates many of the organism's systems, including the HPA axis and noradrenergic brain system, is also controls autonomic input. Chronic stress can lead to the development of numerous kinds of disorders. In the case of chronic stress, the number/ sensitivity of the corticosteroid G receptors decreases which maintains the existing stress reaction. This is how it comes to an eventual weakening of the vital mechanism that naturally reduces its severity- the negative feedback, due to which the increased cortisol inhibits the activity of superior stress centres. Chronic stress, therefore, in contrast to an acute stress, should be considered as a non-adaptive reaction. Thus, through the persistent hyperactivity of the HPA axis and its accompanying neuro- hormonal imbalance, it leads to the occurrence of disorders in organism functioning. The persistent hypercortisonism and hyperactivity of sympathetic system or its imbalance during chronic stress can lead to:

- Weakening of memory processes (most probably connected with the degeneration of CA₃ cells in hippocampus)
- Immunosuppression
- Inhibition of sex hormones production and osteoporosis
- Hypertension, tachycardia , decrease in the variability of heart rhythm/ cardiac dysrhythmia

The above processes favour the development of various diseases of the cardiovascular system, as well as metabolic, endocrine and neoplastic diseases. Chronic stress plays a major role in the pathogenesis of insulin resistance syndrome. It is characterised by:

- Hyperinsulinemia, glucose intolerance and hyperglycemia
- Hypertension
- Decrease of fraction HDL cholesterol density and increase of triglyceride concentration
- Abdominal obesity

Insulin resistance syndrome predisposes to various metabolic and cardiovascular diseases such as diabetes type II, atherosclerosis as well as ischemic heart disease (Lewandowski 2001)²⁷.

Persistent increased level of corticotrophin- releasing hormone (CRF), causes such symptoms as deterioration of mood and sexual drive, anxiety, sleep and eating disorders. The pathogenic action of chronic stress happens also on the level of genetic expression. After entering the cell, corticosteroids together with the receptors, create a complex that, after activation, enters the cell's nucleus and induces the genetic transcription through binding to the regulation site of specific genes. Under the influence of chronic stress, on a one hand, an increase in cortisol concentration appears , on the other, however, there is a decrease in the number/ sensitivity of corticosteroid receptors which is why it can contribute to the occurrence of disorders concerning these processes and the activation of genetic predisposition towards some diseases (Budziszewska & Lasoń,2003)²⁸. The coincidence of subsequent stressful events in the adult life with the existing sensitivity of the HPA axis results in disorders of an enhanced production of cortisol and corticotrophin- releasing hormone (CRF) production reuptake in brain. CRF is a neuropeptide that influences the

²⁷ Landowski, J. (2001). Depresja jako przewlekły stres. *Dyskusje o Depresji*, Vol 17, pp.2.

²⁸ Budziszewska, B.; Lasoń W. (2003). *Neuroendokrynnne mechanizmy działania leków przeciwdepresyjnych*, ISBN 83-917041-3-0, Wrocław, Poland.

production of ACTH through the pituitary gland, it is simultaneously a neuromodulator of many different neurotransmitter systems. It also has a significant influence on the brain adrenergic system through the locus coeruleus by altering the secretion of noradrenalin, serotonin and dopamine. The tonic activity of locus coeruleus changes into a fluctuating one, causing alterations in secretion of monoamines and subsequent anxiety symptoms (changes in 5-HT secretion), anhedonia as well as slowness and difficulties in concentration (changes of DA secretion) (Harro & Orleand 2001)²⁹. Thus, a compilation of stresses in adult life on the childhood- originated sensitization in the range of the endocrine axis, Hypothalamus- Pituitary- Brain (HPA) can lead to a start of a cascade of abnormalities in monoaminergic systems which can be manifested by various clinical symptoms (Strickland et al. 2002)³⁰.

3. Hypothalamus- pituitary- adrenal axis

Monoaminergic neurotransmitters - noradrenalin (NA), serotonin (5-HT) and dopamine (DA) play an important role in various brain processes, including the limbic system functioning. The hypothalamus controls endocrine and vegetative systems. The Hypothalamus- Pituitary- Adrenal axis is a neuroendocrine system, in which there are mutual connections between the brain, hormones and various bodily organs. This system is engaged in the organism's reactions to stress. The activity of HPA axis shows 24 hour- long variations which are controlled by the central clock of suprachiasmatic nucleus, sending direct and indirect projections to the hypothalamus (Herbert J et al. 2006)³¹.

Under the influence of stress and hence, various transmitters such as noradrenalin (NA), gamma- amino- butyric acid (GABA), serotonin (5-HT) as well as acetylcholine (ACH), hypothalamus produces, through the synthetic pathway, a hormone called Corticotrophin- Releasing Factor (CRF) that stimulates the anterior pituitary which leads to the synthesis and release of an adrenocorticotrophic hormone (ACTH). By the means of ACTH, there occurs secretion of hormones called corticosteroids in the adrenal gland. The main representative of this group of hormones in humans is cortisol (which is believed to be the main hormone of the sympathetic nervous system). The presence of cortisol in blood inhibits production of ACTH and corticotrophin- releasing hormone (CRF). The inevitable condition for an appropriate adjustment for stress is the termination of the stress reaction after the termination of the stimulus causing it. The defect of the stress reaction expiration or a situation of exposure to chronic stress may lead to pathological phenomena³² (Parker et al. 2003). Naturally, homeostatic mechanisms in healthy people regulate an excessive physiological excitement. Abnormalities in HPA axis functioning may lead to prolongation

²⁹ Harro, J.; Oreland, L. (2001). Depression as a spreading adjustment disorder of monoaminergic neurons: a case for primary implication of the locus coeruleus. *Brain Research Review* , Vol. 38, pp. 79-128, ISSN 0165-0173.

³⁰ Strickland, P.; Dekin, W.; Percival C. (2002). Bio-social origins of depression in the community. Interactions between social adversity, cortisol, and serotonin neurotransmission. *British Journal of Psychiatry*, Vol. 180, pp.168, ISSN 0007-1250.

³¹ Herbert J.; Goodyer, I.M.; Grossman ,A.B. (2006). Do corticosteroids damage the brain? *Journal of Neuroendocrinology* Vol.18, pp. 393-411, ISSN 0953-8194.

³² Parker, K.; Schatzberg A.; Lyons D. (2003). Neuroendocrine aspects of hypercortisolism in major depression. *Hormones and Behavior* , Vol. 43, pp. 60-66 ,ISSN 0018-506X.

of stress; they also seem to play a vital role in the pathogenesis of some somatic diseases and mental disorders (e.g. affective disorders) (Ehlert et al. 2001 & Porter et al. 2006)^{33,34}.

The dynamics of stress response in the HPA system consist of three phases:

1. Basal activity which reflects the non- stress- stimulated HPA activity
2. Stress activity in which the cortisol level increases above the basal level, indicating the beginning of the stressor activity.
3. Stress recovery in which the cortisol level returns to the basal level, indicating the expiration of the stressor (Burke et al. 2005)³⁵.

The consequences of stressful events in childhood are the disorders of neuroendocrine hypothalamus- pituitary- adrenal (HPA) axis' functioning manifested by its excessive activity (sensitisation) in an adult life.

In response to the stressor stimulus, an organism mobilises mechanisms of defence. The most important mechanism related to the organism reaction to stress is a proper functioning of the axis Limbic System- Hypothalamus- Pituitary- Adrenal (LHPA). Corticosteroids, which are produced by adrenal glands, inhibit the production and secretion of hormones by the superior centres: corticotrophin- releasing hormone (CRF) by the hypothalamus and adrenocorticotrophic hormone (ACTH) by the pituitary gland. This process takes place due to the corticosteroid receptors localized in the hypothalamus, pituitary or the limbic system, especially in the hippocampus. The most essential role in the control system is played by the prefrontal cerebral cortex as well as limbic system.

An increased concentration of corticosteroids may be also responsible for changes of a neurodegenerative nature in hippocampus as well as distortions in neuronal plasticity. In the research conducted on animals it was stated that corticosteroids in high concentrations:

- enhance neurodegenerative changes in hippocampus caused by various factors
- inhibit the formation of new cells (neurogenesis) in the Ammon's horn
- cause the decrease of the length and number of branching of apical dendrites of pyramidal cells of CA3 region in hippocampus (Lyons et al. 2001)³⁶.

The HPA axis enables an organism to adjust to the physiological and psychosocial changes in its environment. Both of the above systems were frequently examined in disorders associated with stress and depression. Scientific data suggest that those systems are interconnected by the corticotrophin- releasing hormone (CRH). It is believed that anxiety disorders activate neuroendocrine systems in brain, however, it is not clear whether the situation is similar in case of depression .

On the basis of extensive basal and clinical results it was stated that the corticotrophin-releasing hormone and a group of related substances seem to play a key role in stress-related disorders, such as anxiety and depression.

³³ Ehlert, U.; Gaab, J.; Heinrichs, M. (2001). Psychoendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. *Biological Psychology*, Vol. 57, pp.141-152, ISSN 0301-0511.

³⁴ Porter, R.J.; Gallagher, P. (2006). Abnormalities of the HPA axis in affective disorders: clinical subtypes and potential treatments. *Acta Neuropsychiatrica*, Vol. 18, pp. 193-209, ISSN 0924-2708.

³⁵ Burke, H.M.; Davis, M.C.; Otte, C.; Mohr, D.C. (2005). Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology*, Vol.30, No.9, pp. 846-56, ISSN 0306-4530.

³⁶ Lyons, D.M.; Yang, C; Sawyer-Glover, A.M.(2001). Early life stress and inherited variation in monkey hippocampal volumes. *Archives of General Psychiatry*, Vol. 58 pp.1145-1154, ISSN 0003-990X.

CRH is thought of as a brain fundamental mediator of stress response in relation to its participation in producing a neuroendocrine, autonomic and behavioral response to a stressful situation (Reul i in. 2005)³⁷.

Another hormone that participates in reaction to stress is dehydroepiandrosterone (DHEA) belonging to a group of steroid hormones and it is synthesized in the zona reticularis of the adrenal cortex from pregnenolon. Dehydroepiandrosterone is found in human blood plasma in the form of DHEA steroid of low plasma saturation stability and sulphate (DHEA- S) with half- life around 10- 12 hours.

The secretion of DHEA hormone is stimulated in similar way to the cortisol, i.e. by CRH and ACTH. In the brain, DHEA works as an agonist of the receptors of gamma- amino- butyric acid type A (GABA A), it protects neurons from the toxicity of glutamates and beta- amyloid peptides that secrete neurotoxic amino acids (Ritsner et al. 2004)³⁸ , blocks the excitability of neurons, having an anxiolytic, tranquilizing, sleep- inducing, mood- and cognition- improving effect.

DHEA- S, however, works antagonistically to the GABA A receptors through stimulation of the central nervous system, increasing its plasticity and susceptibility to convulsions. It also takes part in releasing pituitary and hypothalamic neuropeptides.

Another function of DHEA- S is enhancing the release of dopamine, noradrenalin and acetylcholine in the frontal lobes and limbic system what intensifies the memory and learning processes. DHEA- S works protectively in relation to the neurotoxicity of cortisol, especially in the hippocampus region (Goodyer et al. 2001, Załuska & Janota, 2009)^{39,40}.

It is exactly the hippocampus as well as the limbic region where the concentration of DHEA is very high. However, it has not yet been agreed whether it is being produced there despite of the fact that there were quite a few reliable research reports completely devoted to its neurosteroidal genesis. Unfortunately, they also did not explain the mechanisms regulating the activity of cells producing neurosteroids (Holka- Pokorska 2005; Ritsner et al. 2004)^{41,42}.

The research conducted both in the laboratorial and natural conditions, allow a conclusion to be formulated in the range of the meaning of DHEA- a hormone circulating not only in the blood, but also in the brain, that regulates the neurogenesis in the hippocampus as well as it modulates the lowering of elevation of corticosteroids, especially cortisol, thus influencing the formation of new neurons and increasing their survival (Herbert 2007).⁴³

³⁷ Reul, J.M.& Holsoer, F.(2005). Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Current Opinion in Pharmacology*, Vol. 2, No.1, pp.23-33, ISSN 1471-4892.

³⁸ Ritsner, M.; Maayan, R.; Gibel, A.; Strous, R.D.; Modai, I.; Weizman, A. (2004). Elevation of the cortisol/dehydroepiandrosteron ratio in schizophrenia patients. *European Neuropsychopharmacology*, Vol. 14, pp.267-273, ISSN 0924-977X.

³⁹ Goodyer, I.M.; Park, R.J.; Netherton, C.M.; Herbert, J. (2001). Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. *British Journal of Psychiatry*, Vol. 179, pp..243-249, ISSN 0007-1250.

⁴⁰ Załuska, M.; Janota, B. (2009). Dehydroepiandrosteron (DHEA) w mechanizmach stresu i depresji. *Psychiatria Polska* , Vol.3. No.43, pp.263-274, ISSN 0033-2674.

⁴¹ Holka-Pokorska,J. (2005).Dehydroepiandrosteron w leczeniu depresji. *Wiadomości Psychiatryczne*, Vol. 8, No.3, pp.149-155, ISSN 1505-7429.

⁴² See 38

⁴³ Herbert, J. (2007). DHEA , In: *Encyclopedia of stress*, Eds. G. Fink (Ed.) 788-791,, Academic Press, ISBN 978-0-12-088503-9 ,London, United Kingdom.

Dehydroepiandrosterone serves a neuromodulating function as an agonist of GABA A receptors and an antagonist in relation to the action of cortisol, which is why the hypothesis of its vital importance in terminating the stress reaction and restoration of organism homeostasis is often supported. The hormone achieves it by the improvement of the strategy of handling stress (Zańska & Janota, 2009)⁴⁴.

The ratio of two steroid hormones (cortisol and DHEA) is an important indicator of their relative activity. A natural cortisol level and a lowered DHEA level can cause a harmful ratio for the brain's functioning. The ratio of hormones is described with the use of the term 'endocrine risk' with a greater probability of the occurrence of depression in a short period of time, more significantly in the afternoon measurements of cortisol levels than every single value considered separately.

The proportion of cortisol/ DHEA may be used as an indicator of the ability to maintain homeostasis when in stress. The available research results describe the influence of stress and the values of cortisol to DHEA ratio. In an acute stress, levels of both of the hormones (cortisol and DHEA) are subject to elevation and in chronic stress, a decrease of the concentration of cortisol, DHEA and DHEA- S can be observed, most probably as a sign of adaptive changes of an organism (Meewisse et al. 2007; Yehuda et al. 2006)^{45,46}.

4. The influence of cortisol on the formation of fear symptoms

Fear arises as a result of a distortion of an interaction between the hippocampus system (conscious memory) and amygdale (emotional memory). Cortisol, being a stress hormone, leads to the decrease of the cohesion and density of hippocampus cells, impairing its function. This process is happening in the following way: a stressor that acts on individual and is emotionally recognised by the amygdale as a dangerous one, also stimulates both the hypothalamus and pituitary, leading to an elevation of the acetylcholine level, which subsequently increases the cortisol level. If a high cortisol level is maintained for a longer period of time (an induced one), it has an adverse effect on the hippocampus, interfering with the ability of conscious learning and memorising. The cortisol level, being an endocrine designatum of stress, lowers 'the possibility of creation in the hippocampus of a long-lasting strengthening of synapses, which is a metabolic substrate of conscious memorising'. In the research "the shrinkage of neuronal fibres in hippocampus during a forceful, even a short lived stress" was also proved (Herzyk 2003)⁴⁷.

What was described in the literature and research were the events of experiencing stress that positively influences the ability of conscious memorising, so called flash light effect, which is the result of the adrenalin action as a consequence of stress being rated by an individual as moderate. If, however, in the aftermath of a stressful event, the cortisol level is elevated, it

⁴⁴ See 37

⁴⁵ Meewisse, M.L.; Reitsma, J.B.; De Vries, G.J., Gersons, B.P. & Olff, M. (2007). Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *British Journal Psychiatry*, Vol. 191, pp.387-392, ISSN 0007-1250.

⁴⁶ Yehuda, R.; Brand, S.R.; Golier, J.A. & Yang R.K.(2006). Clinical correlates of DHEA associated with post-traumatic stress disorder. *Acta Psychiatrica Scandinavica*, Vol. 114 No.3, pp.187-193, ISSN 0001-690X.

⁴⁷ Herzyk, A.(2003). *Mózg, emocje i uczucia. Analiza neuropsychologiczna*. Wydawnictwo UMCS, ISBN 83-227-2152-8 ,Lublin, Poland

will subsequently amplify the activity of amygdala and the emotional subconscious memory, which influences destructively on the conscious memory. This is most probably the reason why the fear memory, encoded in the amygdala structure, remains for the whole life in human brain, being out of the reach of the consciousness. (Herzyk 2003)⁴⁸.

5. The genetics of stressor resistance

A hypothesis could be developed that any trauma experienced in childhood models the neuroplasticity of the brain, depending on the genetic basis (the genetic liability to stressors).

Some people have the ability of managing the most extreme kinds of stress, i.e. they have a high resilience to stress. In others, however, the influence of stressors from childhood and the piling up of another in the later adult life gives rise to a number of mental disorders such as PTSD, depression, anxiety disorders or others. The research concerning the gene liability to falling ill under the influence of chronic stressor factors can be of use while explaining personal differences. Polymorphisms of different genes were examined. The research of Binder and others (2008) concerning the polymorphisms of genes that regulate the activity of the glucocorticosteroid receptor (GR) gave very interesting results. The pre-clinical research point out that the FKBP5 gene localized on chromosome 6 modulates the binding of glucocorticosteroids with an appropriate GR receptor, thus regulating the response to stress. Protective alleles (RS 9296158 as well as RS 9470080) were found that have the ability to protect from falling ill. What was also found where the alleles of the risk of falling ill (RS 3800373 and RS 1360780) for this gene (4 from 8 SNP).

Different research suggests the role of a transcription factor (Δ FosB) which is induced by reward and stress in the nucleus accumbens (NAc). The activity of Δ FosB simplifies the creation of synaptic connections and adaptive behaviours by the reduction of an emotional load with NAc, thanks to the repression of excitement of the glutaminergic system. Experience induces the activity of the Δ FosB gene which leads to the increase of resilience to stress (Vialou 2010)⁴⁹.

6. Disturbances in reaction to stress in depression

Many research concerning the risk factors of depression was performed. The inheritance factors, gender and personality features have vast influences over the occurrence of depression. Except for the constitutional predisposing factors, an important role in the pathogenesis of depression is played by the environmental factors. Many works indicate a relationship between the psychosocial stress and the incidence of depression. Research proved that stress caused by some exceptional life events that happened in a specific, short period of time is of great importance for the development of depression (Bilikiewicz et al. 2002)⁵⁰. It was also shown that there exists a connection between chronic stress (linked with e.g. work or marital problems) and the occurrence of depression.

⁴⁸ See 36

⁴⁹ . Vialou, V et al. (2010). Δ FosB in brain reward circuits mediates resilience to stress and antidepressant responses. *Nature Neuroscience*, Vol. 13, pp.745, ISSN 1097-6256.

⁵⁰ Bilikiewicz, A.; Pużyński, S.; Rybakowski, J.& Wciórka, J. (2002). *Psychiatria, tom I*, , Wydawnictwo Medyczne Urban & Partner, ISBN 83-87944-67-X, Wrocław, Poland.

A greater risk of major depression occurrence in adults that were molested in childhood was stated. For instance, in women who were victims of such abuse, the possibility of occurrence of major depression is 4 times as high and as for the risk of suicidal attempts, it is 44 times greater than in general population(Heim et al. 2001)⁵¹.

What was also concluded was that the earlier in childhood the stress took place, the earlier the depression can occur in the adult life. In these particular cases the depression disorders have the tendency to be longer and the incidence of remission is lower. On the basis of the research conducted in the United States, it can be drawn that various marital problems, parental divorce, abuse in the family, psychoactive substance abuse and many various mental disorders of parents are the result of a greater risk of falling victim of depression in the offspring (Nemeroff, 2002)⁵². According to other research there is a connection between the loss of parents and the development of depression in an adult age. There are research data suggesting that an increased susceptibility to depression in people who had lost their parents, occurs only in the case when they were left without a proper supervision in childhood. Also, a longer separation from parents might be the factor directly predisposing to becoming depressed. There is also a linkage between the lack of an appropriate mother care and the occurrence of depression (Twardowska & Rybakowski 1996, Nemeroff 2002)^{53,54}.

A great number of data coming from different researches points out that traumatising experiences in childhood are strictly connected with a greater frequency of occurrence of depression in an adult life. Traumatising events before the 17th year of age include:

- lack of contact with mother for over a year
- staying in a hospital for over two weeks
- parents' divorce
- a long period of parent's unemployment
- experiences so traumatic that memories of them lasted for several years
- an abandonment without parental care because of one's bad behaviour
- alcohol or other psychoactive substances abuse by parents which caused problems in the family
- physical abuse (Bremner et al. 2000, Heim et al. 2001)^{55,56}.

In comparison to children that were not exposed to maternal stress (especially depression in mother), children in the age of 4,5 year that were exposed to it showed a significantly higher cortisol concentration in saliva, but only in the case when the maternal stress was present in the infancy of the child, as well as in the period preceding the examination. In comparison to the 4,5- year old children with a lower cortisol concentration, the children with a higher level of it were subject to a greater risk of mental disorder occurrence, especially the

⁵¹ Heim, Ch.; Owens, M. (2001). Znaczenie negatywnych wydarzeń z dzieciństwa w patogenezie depresji, In. *WPA Bulletin on Depression*, Vol.22, No.5, pp.3-7.

⁵² Nemeroff, Ch., Wainwright, N.W.J; Surtees, P.G . (2002). Childhood adversity, gender and depression over the life-cours. *Journal of Affective Disorders*, Vol. 72, pp.33-44, ISSN 0165-0327.

⁵³ See 51

⁵⁴ See 15

⁵⁵ Bremner, J.D.; Vermetten, E.; Mazure, C.(2000). Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: The Early Trauma Inventory. *Depression and Anxiety*, Vol. 12, pp. 1-12, ISSN 1091-4269.

⁵⁶ See 26.

internalizing symptoms. These results show that the maternal stress is the factor that sensitises the infants that experience, in later life, the hyperactivity of the HPA axis during the exposition to a stressful situation from their mothers. An elevated concentration of cortisol in children with both: early- and later- occurring proneness to stress might be a marker of disorders in the stress response system that are clearly manifested in such developmental challenges as e.g. beginning school. It may lead to the increase of the risk of depression as well as anxiety disorders (Essex et al. 2000)⁵⁷.

In people with depression, signs of hyperactivity of the limbic system- hypothalamus-pituitary- adrenal axis (LHPA) can be observed, which is manifested by an elevated CRF level in the cerebrospinal fluid, an elevated cortisol level in blood, daily alterations in its secretion, lack of the cortisol response to the inhibiting action of dexamethasone (Ossowska 2002)⁵⁸ as well as a hypertrophy of the pituitary and adrenal glands. An autopsy research states the increase of CRF mRNA in the hypothalamus and a decrease of the number of CRF receptors; it also shows an elevation of mRNA encoding proopiomelanocortin in the pituitary. The persisting hyperactivity of the HPA axis in depression can result from a defect concerning the stress- activated mechanisms leading to the expiration of a stress reaction. There are certain premises that claim that there is a virtual malfunction of the action of corticosteroid receptor in the limbic system that might be responsible for the inability of the stress reaction to expire. (Ossowska 2002, Heim 2002)^{59,60}. There was also a decrease of the number of these receptors on lymphocytes in people with depression. The distortion of action of the limbic system and hypothalamus by a chronic hypercortisonism leads (by a rule of vicious circle) to a further over- secretion of cortisol.

In the majority of cases of depression, one can find features of hyperactivity of the adrenal cortex, which are manifested by an excessive secretion of cortisol (hypercortisonism), changes in a daily cortisol secretion (longer and more frequent periods of secretion) as well as an increase urine elimination of the 17- hydroxysteroids and free corticosteroids. In recent years, in CT studies - structural signs of hyperactivity in the adrenal cortex were also noted in depression (an increase in the volume of the glands) (Heim et al. 2001, Twardowska & Rybakowski 1996)^{61,62}.

7. HPA axis functioning disorders in depression

Psychosocial stress activates the HPA axis, however, it does not pose a mechanism of causing depression by stress. Depression occurs in the situation of the lack of a persisting hypercortisonism and the depressive patients usually have a lowered morning cortisol levels, which might be linked with a coexisting anxiety. The lead of 5- HT2 on the central level is strengthened in depression and is related to random events. It is compatible with the notion that the serotonergic system is responsible for the CUN level response to some unpleasant life events.

⁵⁷ Essex, M.J. et al. (2002) . Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biological Psychiatry* Vol.52, pp.776-784, ISSN 0006-3223

⁵⁸ See 14

⁵⁹ See Ossowska

⁶⁰ See heim

⁶¹ See 26

⁶² See 15

Strickland et al. (2002) study revealed an elevated cortisol level in the afternoon, after the action of some serious stress of the psychosocial kind in a current period of time; what is important, however, it was only observed in the female patients. It might mean that there is a primary dysregulation in the HPA axis in some types of social depression which may result in an excessive reaction of cortisol secretion in a response to some stressful and solidified life difficulties. The primary dysregulation of the axis might be responsible for the often reported elevated cortisol levels in the in- patients (hospitalized for depression), in whom the stress connected with the hospitalization might have co- existed with the HPA axis hyperactivity.

An increased activity of the HPA axis seems to have the most significant meaning in the pathogenesis of depression as well as in the mechanism of antidepressant drugs action. In the experimental research it was stated that corticosteroids and/ or the corticotrophin-releasing hormone may influence and intensify most of the changes observed in animals' models of depression.

In some of the depressed patients there is an elevated concentration of cortisol observed in the blood, urine and the cerebrospinal fluid, changes in the daily profile of cortisol secretion as well as an elevated corticotrophin- releasing hormone concentration in the cerebrospinal fluid. An increased activity of the HPA axis in depression is caused by hypersecretion of the corticotrophin- releasing hormone. In depression, there is a dysfunction of the HPA axis, which might have a genetic basis, however, the meaning of the past life events is also not excluded. The signs and symptoms that are characteristic for depression, include the changes in the HPA system, which in the majority of the patients, results in the alteration of corticotrophin (ACTH) regulation and a change in the secretive activity of cortisol. More detailed analyses of the HPA system have revealed that the signal of the corticosteroid receptor (CR) is distorted in severe depression, which leads, among all, to an increased production and secretion of corticotrophin- releasing hormone (CRH) in various regions of the brain, which is considered to be one of the main causes of depression (Holsboer, 2000)⁶³.

What also accompanies depression is the activation of the HPA axis and a lowered sensitivity to the negative feedback, when in the anxiety disorders it seems that the functioning of the HPA axis stays correct. (Young and others 1991, 1993, 2000, 2004; Abelson and Curtis, 1996).

8. Neuroendocrine mechanisms of antidepressive drugs action

What underlies the antidepressants' action are the adaptive changes in the neurotransmitter systems that occur under the influence of their constant administration. These changes include:

- decreased density and reactivity of β - adrenergic receptors
- increased density of α_1 - adrenergic receptors
- decreased density of α_2 - adrenergic receptors
- changes in density and reactivity of serotonin (5HT_{1A}, 5HT_{2A} and dopamine (D2/ D3) receptors, the calcium channels type I dependent on the voltage and glutaminergic receptors

⁶³ Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, Vol. 23, pp. 477-501, ISSN 0893-133X.

A long- lasting period of antidepressant administration lowers the concentration of corticotrophin- releasing hormone in the hypothalamus, corticosterone and ACTH in blood (especially during stress), they also inhibit some of the corticosteroid and stress effects (7).

Tricyclic antidepressants, fluoxetine and tianeptin lower the hyperactivity of the HPA axis that is caused by the activation of the immune system (the administration of LPS, endotoxin of Gram- negative bacteria increasing the synthesis of proinflammatory cytokines).

The normalizing effect of antidepressants on the HPA axis activity has led to drawing a hypothesis that they can increase the density or functional activity of corticosteroid receptors engaged in the inhibition mechanism of the negative feedback. Two types of corticosteroid receptors were distinguished in the central nervous system:

1. Type I (mineralocorticoids, MR)
2. Type II (glucocorticosteroids, GR)

The MR receptors, with a high affinity for the natural glucocorticosteroids (cortisol and corticosterone) and a mineralocorticoid (aldosterone), are found in a high concentration in the hippocampus (a concentration similar to the GR one) and the prefrontal cortex (1/3 of the GR's concentration). In other regions of the brain, they are encountered in concentrations that are ten times lower if compared to the GR one. The type II receptors are relatively uniformly spaced in the brain.

The GR connection increases by about 10% in basic conditions (with a low blood concentration of corticosterone) to up to 70 - 90% during stress or in the period of maximal secretion of this steroid in the daily cycle. The MR stimulation (with the use of aldosterone or low concentrations of corticosterone) enhances the excitability of neurons, amplifies the stimulating activity of stimulant aminoacids and it lowers the inhibiting action of serotonin to the activity of neurons in the CA1 region of hippocampus proper. Conversely, the activation of GR inhibits the excitability of neurons as well as it weakens the stimulating action of the stimulant aminoacids and noradrenalin. While examining the participation of GR and MR in the regulation of the HPA axis' activity it was found that in its inhibition during stress there are engaged mainly the GR whose connection with corticosterone increases depending on the concentration of the steroid.

The observed weakening of the inhibition mechanism of the negative feedback in depression is explained by the lowering of the density or sensitivity of the GR. Damage in the hippocampus or the frontal part of the cerebral cortex causes hypercortisonism, whereas the implantation of corticosterone to these regions of brain lowers the ACTH concentration and corticosterone which are elevated during stress. The GR receptors located in the amygdala are engaged, on the other hand, in positive feedback reaction and they also enhance the activity of the HPA axis. In spite of the fact that the HPA axis hyperactivity might be the result of density changes of the receptors localized in different brain structures, the GR show their most intense activity in the hippocampus proper⁶⁴.

The majority of antidepressant normalize the activity of the HPA axis by:

- increasing the density of the GR receptors in the hippocampus, thus strengthening the inhibition mechanism of the negative feedback
- lowering the synthesis of proinflammatory cytokines which release CRF from the hypothalamus
- directly repressing the gene encoding the CRF

⁶⁴ Yehuda, R. (1999). Linking the neuroendocrinology of post-traumatic stress disorder with recent neuroanatomic findings. *Seminars in Clinical Neuropsychiatry*, Vol 30, pp.1031-1048 ISSN 1084-3612..

9. Own research concerning the HPA axis disorders in depression and anxiety- depressive disorders

Numerous studies confirmed elevated cortisol and CRF levels in people suffering from depression if compared to the healthy ones. Next to the excessive secretion of this hormone, the researchers also observed distortions in its regulation. Many of the works regarded the Dexamethasone Suppression Test (DST). Originally, the researchers pointed out the test as being a useful diagnostic tool (Carrol & Feinberg, 1981; Holsboer, 2000)^{65,66}. In patients with depression, there were changes in the secretion of cortisol and the pituitary- dependent hormones (Pfohl et al., 1985)⁶⁷. The research suggests that the depressed patients have an elevated cortisol level for the whole day, not only in the morning, as it happens in the healthy controls. The recent studies have considerably widened the knowledge about the pathomechanism of stress and depression, especially in the range of the role of the hypothalamus- pituitary- adrenal (HPA) axis. It has been proved that as much as in the acute phase of depression an excessive secretion of CRH, ACTH and cortisol occurs, in the chronic depression, the secretion of ACTH decreases. It is most probably the result of a strong negative feedback inhibiting the influence of cortisol.

Own empirical research was performed concerning the connection of the HPA axis- functioning disorders with stressors and clinical symptoms in the depressed patients, if compared to the healthy ones.

9.1 The group under study

94 people were examined (66 women and 28 men), including 36 people with depression (according to ICD 10 F.32.), 22 of whom were treated due to the anxiety- depressive disorders (according to ICD 10- F. 41) and 36 healthy people, not treated at all as a control group.

The average age of the population was 34.9 (SD= 12.8). Patients with depression were, on average, 42.8 years old (SD=12.6), those with neurosis- 34.8 (SD=11.9) and the healthy ones- 27.5 (SD=8.4) years old. In the subgroups of the healthy individuals and those with neurosis, prevailed singles (58.3% and 59.1%, respectively), whereas among the depressed ones 52.8% were married.

The cross- section of the education level varied in every group. In the group of the depressed, 1/3 of them was on pension, whereas the other 1/3 was vocationally active. In the subgroup of the people treated for neurosis, approximately 1/4 constituting every of the following was respectively: employed, pensioners and unemployed.

9.2 Method

Blood samples were taken twice a day, at 08:00 (K1) and 16:00 (K2) in order to measure the cortisol level. On the next day, the Dexamethasone Suppression Test was made by administering orally 1 mg of dexamethasone (Dexamethasone tablets 1mg, Polfa Pabianice

⁶⁵ Caroll, B.J.; Feinberg, M.(1981). A specific laboratory test for the diagnosis of melancholia : Standardization, validation, and clinical utility. *Archives of General Psychiatry*. Vol. 38, pp. 15-22, ISSN 0003-990X.

⁶⁶ See 63

⁶⁷ Pfohl B.; Sherman B.; Schlechte. J.; Stone, R. (1985). Pituitary adrenal axis rhythm disturbances in psychiatric depression. *Archives of General Psychiatry*, Vol.42, pp.897-903, ISSN 0003-990X.

PL) at 23:00 hour. On the next day, the blood samples were taken again in order to measure the cortisol level, at 08:00 and 16:00 (K3 and K4). All of the patients considered were acquainted with the examination procedure and gave a written consent for it. The research was approved by the University Bioethical Committee. The marking of the concentration in the blood was made with the use of Elisa method.

The load of the stressful childhood events was examined with the use of the Early Trauma Inventory which was developed by the J.D. Bremner's group in the 2000⁶⁸. The inventory examines 4 aspects of abuse in the childhood period:

General traumatic experiences (ETI I), Physical abuse (ETI II), Emotional abuse (ETI III), Sexual abuse (ETI IV).

Childhood Trauma Load Index was used for statistical calculations. The index is the sum of all the Indexes of all the above individual subscales (ETI S).

The level of anxiety and depression was assessed with the use of HADS Scale which was developed by Zigmond and Snaith. The Scale includes separate scores for anxiety- A (HADS A) and depression- D (HADS D). The severity of depression was measured with Beck's Scale for Measurement of Depression (BECK). The level of anxiety as a state (x- 1) and as a feature (x-2) was scaled with Spielberger's Inventory (STAI).

In order to assess the impact of stressors experienced in the last 12 months on the mental state, the PsychoSocial Stress Scale was used which was developed in 1967 by Holmes and Rahe. The Scale states that from 250 points there is an excessive stress load (STRES).

The obtained results of the research were subject to the statistical analysis, a U- Mann-Witney's test, a test of the validity of correlation coefficient of R Spearman, which was a non- parametric equivalent of a variation analysis test ANOVA of the Kruskal- Wallis' range.

9.3 Results and discussion

A naturalistic level of cortisol in blood at 08:00 should fall into the range of 60- 285 ng/ml (K1), whereas at 16:00 (K2) it should range from 40 to 150 ng/ml according to the laboratory norms.

An average morning cortisol concentration before the dexamethasone suppression proved to be the lowest for depression: K1= 185.7ng/ml, whereas the afternoon one for neurosis and depression: K2= 84.5 ng/ml. These results did not differ statistically in any significant way.

The threshold was agreed to be 40 ng/ml of the value of cortisol after the administration of dexamethasone, which was an indication of whether the suppression of cortisol secretion is correct or impaired; if the value was below the threshold, it meant a correct suppression.

The weakest suppression was found in the depressed patients with the K3 being 40.8 ng/ml and K4- 31.8 ng/ml. Therefore, an average morning cortisol level in depression patients after suppression (K3) was higher than the threshold value and indicates impaired cortisol suppression in the researched group. The strongest suppression occurred in the control group: K3= 12.1 ng/ml and K4= 18.1 ng/ml. The healthy people, with no clinical symptoms were characterized by a correct feedback inhibition of cortisol secretion after dexamethasone administration, which means an appropriate handling of an excessive supply of cortisol.

The anxiety- depressive patients achieved medium results that were similar to the results obtained by the healthy group. Only the morning cortisol level, before and after the administration of dexamethasone at 08:00, proved to be higher in anxiety- depressive

⁶⁸ See 55

patients than in the healthy ones. Thus, it seems that people with anxiety- depressive disorders might be characterized by less severe disorders of the HPA axis than the depressed ones. Nonetheless, there can also appear some abnormalities in functioning of the stress axis in this group.

The differences between the groups did not seem to be statistically significant (see: table 1).

Group		Number of results	Min.	Max.	Mean	Standard deviation
Control group	K1	35	79.40	358.00	198.1486	54.59455
	K2	35	10.55	187.00	84.9717	44.91104
	K3	32	3.37	122.00	12.0597	20.42394
	K4	28	4.53	105.87	18.0975	26.04248
Depression	K1	36	65.22	332.02	185.7139	64.87991
	K2	36	7.74	231.02	86.9161	44.02321
	K3	33	4.37	239.58	40.8391	61.36999
	K4	32	5.24	151.45	31.8594	39.31164
Neurosis	K1	20	90.52	329.35	217.0290	73.67715
	K2	18	13.13	200.31	84.5167	46.59056
	K3	20	4.13	208.08	20.6395	45.18454
	K4	15	3.72	162.97	19.0120	40.04291

Table 1. Average cortisol levels before (K1 and K2 and after dexamethasone suppression (K3 and K4) in individual groups of the people under examination in ng/ml.

A differentiating tendency in the morning cortisol concentration after suppression K3 ($p=0.06$) was observed in people with depression compared to the control group.

Statistical analyses were conducted in order to find differences in reactions to dexamethasone (DST) depending on the gender.

In table 2 results concerning the cortisol concentration in relation to the gender were shown. The feature of gender did not significantly statistically differ between the researched groups. The morning cortisol concentration (K1) was the highest in both men ($K1=241.9$ ng/ml) and women with anxiety- depressive disorders (217.6 ng/ml). Similarly, the afternoon cortisol concentration was the highest in men with anxiety- depressive disorders ($K2= 104.1$ ng/ml). The cortisol suppression by dexamethasone influenced the cortisol levels quite differently depending on the gender of the researched. In women with depression there was the lowest suppression and thus the highest morning cortisol concentration $K3=6.3$ ng/ml in comparison to the patients with anxiety- depressive disorders ($K3=6.3$ ng/ml) and the healthy ones ($K3= 8.8$ ng/ml). The difference was statistically valid on the level of $p=0.03$. Those differences, however, were not observed in the male group.

The afternoon cortisol concentration after suppression in women with depression was also the highest ($K4=34.7$ ng/ml). In the male group, the patients with the anxiety- depressive disorders showed the lowest tendency towards cortisol suppression, where $K3=39$ ng/ml and $K4=30.7$ ng/ml, those differences, however, were not statistically valid.

It is therefore correct to state that the HPA axis functioning disorders in women with depression, in comparison to men, may have a different character. In the research on

Gender		Group	Mean	Standard deviation	N
Women	K1	Healthy	210.9000	53.25796	20
		Depression	189.0058	64.46846	26
		Neuroses	217.6429	87.80601	7
		General	201.0500	63.80486	53
	K2	Healthy	91.2750	38.30435	20
		Depression	89.0304	35.32379	26
		Neuroses	68.5600	37.10318	7
		General	87.1738	36.73782	53
	K3	Healthy	8.7970	4.62600	20
		Depression	43.4262	64.65060	26
		Neuroses	6.3486	2.08270	7
		General	25.4615	48.32329	53
	K4	Healthy	18.5310	28.63269	20
		Depression	34.7012	42.01123	26
		Neuroses	7.5986	4.86375	7
		General	25.0196	35.42213	53
Men	K1	Healthy	174.0667	66.76546	6
		Depression	179.1200	41.86135	6
		Neuroses	241.9071	61.88564	7
		General	200.6563	63.66812	19
	K2	Healthy	89.6500	52.28678	6
		Depression	75.6150	20.34181	6
		Neuroses	104.1071	49.93306	7
		General	90.5442	43.02977	19
	K3	Healthy	25.6100	47.24780	6
		Depression	31.5650	55.14208	6
		Neuroses	39.0771	74.78656	7
		General	32.4521	57.98278	19
	K4	Healthy	19.3483	22.75644	6
		Depression	19.5450	23.08311	6
		Neuroses	30.6971	58.35932	7
		General	23.5916	38.18667	19

Table 2. Cortisol concentration levels in the researched group with the division of gender

animals it was proved that the female gender predisposes to a greater reactivity and a longer time of the HPA axis’ reaction to stress. These differences in people, however, would result from the influence of the gender- related steroids and the differences in the organisation of the brain structure (Kudelka et al.)⁶⁹. In the research it was confirmed that in

⁶⁹ Kudelka, B.M. & Kirschbaum, C (2005). Sex differences In HPA axis responses to stress: a review. *Biological Psychology*, Vol.69, pp.113-132, ISSN 0301-0511.

comparison to men, women with depression had a weaker ability of self- regulation after the action of cortisol.

The assessment of the intensity of anxiety and depression with clinical scales (HADS, STAI, BECK) has shown increased, statistically valid intensifications of anxiety and depression in the group of patients with depression and the anxiety- depressive disorders in comparison with the healthy people from the control group, which is consistent with the clinical symptoms profile. The psycho- social stress level (STRES) proved to be the highest among the depressed- 158.3 points (SD=98.8) and it differed in a statistically significant way in comparison with the healthy individuals ($p<0.05$). Recurrences of depression in the course of affective unipolar disorders might be dependent on the triggering stress factors experienced in the last twelve months.

In table 3 average results of the childhood trauma load (ETI) in the studied subgroups were shown.

Group		N	Min.	Max.	Mean	Standard deviation
Healthy	ETI I	36	0	28	6.83	6.648
	ETI II	36	0	186	50.39	52.166
	ETI III	36	0	258	52.33	67.496
	ETI IV	36	0	30	2.33	6.770
	ETI SUM	36	1	484	111.61	115.867
Depression	ETI I	36	1	31	14.81	7.191
	ETI II	36	0	216	77.39	65.057
	ETI III	36	0	348	113.72	117.884
	ETI IV	36	0	126	12.50	25.632
	ETI SUM	36	1	538	218.31	180.604
Neuroses	ETI I	22	0	52	13.50	11.538
	ETI II	22	0	300	83.73	84.741
	ETI III	22	0	679	152.95	186.645
	ETI IV	22	0	182	19.45	45.654
	ETI SUM	22	12	880	269.64	280.553

Table 3. Childhood trauma load (ETI) in the studied subgroups.

It was stated that the statistical differences in the intensity of the childhood trauma load between people with depression and those suffering from anxiety- depressive disorders in the range of general traumatic events (ETI I), psychological violence (ETI III) and summary trauma (ETI SUMA) were on the level of $p< 0.05$. The highest wholesale intensities of childhood trauma load (ETI SUMA) were diagnosed in people with depression as well as with the anxiety- depressive disorders. Similarly, psychological abuse in childhood (ETI III) and general traumatic events (ETI I), afflicted patients from both groups significantly more often than healthy ones. These results are consistent with the results of other studies. Research suggests that exposing laboratory animals in their early period of life to stressor factors leads to lasting changes in the HPA axis activity and disturbances in functioning of

the noradrenergic as well as serotonergic systems (Manji et al. 2001)⁷⁰. The disturbances in the functioning of the above systems are expressed as symptoms of anxiety and depression. Therefore, the dependencies between the HPA axis functioning and clinical symptoms were analysed.

In table 4 the dependencies of the cortisol concentration on other examined features are shown on the statistically valid level (Rho Spearman's) for the entire researched group (**Correlation is valid on the 0.01 level (bilaterally))

			K1	K2	K3	K4
Whole group	HAD A	Correlation coefficient	.037	-.083	.289(**)	.215
	HAD D	Correlation coefficient	-.014	-.095	.340(**)	.249(*)
	STAI X- 1	Correlation coefficient	.291(*)	-.026	.318(**)	.302(*)
	STAI X- 2	Correlation coefficient	.298(*)	.089	.254(*)	.194
	BECK	Correlation coefficient	.214	-.053	.299(*)	.192

Table 4. Statistically valid (Rho Spearman's) dependencies of the cortisol concentration on other examined features for the whole group.

The morning cortisol level before the suppression (K1) was positively correlated for the whole group with the feature and state of anxiety (STAI). We can therefore conclude that the actual experience of anxiety (STAI X-1) and the apprehensiveness' feature (STAI X- 2) are correlated with an increased release of morning cortisol from the adrenal glands in every person in the group.

What was also observed for the entire group were statistically significant positive correlations ($p<0.05$) of the level of depression (HADS D, BECK) and anxiety (HADS A, STAI) with the morning cortisol level after the dexamethasone suppression (K3). The afternoon cortisol concentration after suppression (K4) was essentially dependent on the intensity of depressiveness (HADS D) and the anxiety state (STAI X- 1) for the entire group. It was proved that the greater the depression and anxiety intensity, the greater the cortisol levels after dexamethasone suppression, which means a weaker suppression. This proves the connection of the anxiety symptoms and depression with the HPA axis functioning disorders and its feedback inhibition for the whole group.

In table 5 there are the dependencies of cortisol concentration from different examined features shown. They are statistically valid (Rho Spearman's) for the subgroups of the studied people.

In the control group it was stated that the greater the anxiety state (STAX- 1), the higher the afternoon cortisol concentration after suppression K4 (weaker suppression). A currently

⁷⁰ Manji, H.K.; Drevets, W.C.; Charney D.S.(2001)The cellular neurobiology of depression. *Nature Medicine*, Vol. 7, pp. 541–547, ISSN 1078-8956.

Group			K1	K2	K3	K4
Healthy	STAI X- 1	Correlation coefficient	.142	.104	.168	.430(*)
Depression	STRES	Correlation coefficient	-.413(*)	-.318	-.287	-.299
	ETI IV	Correlation coefficient	-.023	-.177	-.451(**)	-.440(*)

*Correlation is valid on the 0.05 level (bilaterally), **Correlation is valid on the 0.01 level (bilaterally)

Table 5. Statistically valid (Rho Spearman’s) dependencies of the cortisol concentration from different examined features for the whole group.

experienced feeling of anxiety or fear causes a distortion in the feedback inhibition of the HPA axis as well as its hyperactivity in the form of the persisting elevated cortisol level in healthy people.

The morning cortisol concentration before suppression (K1) was negatively connected with the level of psychosocial stress (STRES) in depression. It can be therefore concluded that the resilience to the current stressors (that occurred during the last 12 months) is lowered in people with depression. Usually, an appropriate reaction in stressful situations is the release of cortisol and its concentration increases in blood which is an adaptive reaction of an organism to fight the stressor. In people with depression, however, there is a lowering of the cortisol level under the influence of stressor factors which might be associated with an insufficiency in fighting any traumatic events. As it was given in the introduction, the HPA axis in people with depression is insufficient which may be the result of some developmental and plasticity disorders of the brain in some of the depressed, which is subsequently the result of trauma experienced during childhood. The piling up of another stressor factors in the adult life influences the intensity of depression symptoms. As the research reveals, especially sexual abuse (ETI IV) in childhood, had a significant impact on cortisol suppression (K3 and K4) in people suffering from depression ($p<0.05$). In the people with neuroses the dependencies that would be statistically valid were not found. The data concerning the influence of sexual abuse in childhood on the HPA axis are consistent with previous reports. The experience of sexual abuse in early childhood in people with affective disorders, increases the risk of an earlier occurrence of the symptoms, coexistence of different disorders (especially drugs and alcohol) as well as a more severe course of illnesses (Leverich et al. 2002)⁷¹.

9.4 Conclusions from the research

1. The greater depressiveness and anxiousness, the weaker the cortisol suppression (higher K3 and K4 levels) for the whole studied group.
2. In people with depression, however, the current stress factors (STRES) and sexual abuse in childhood (ETI IV) worsened the suppression (higher results of K3 and K4).

⁷¹ Leverich ,G.S.; McElroy, S.L.; Suppes, T, et al(2002).Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biological Psychiatry*, Vol.51 No. 4, pp. 288-297, ISSN 0006-3223.

3. The weakening of cortisol suppression in the DST test in women suffering from depression in comparison to the healthy ones seemed to be especially statistically valid (for K3, $p=0.03$)
4. The results confirm the data regarding the association between the HPA axis disorders and stressors in people with depression and anxiety- depressive disorders if compared to the healthy people

10. Further research directions- different symptoms, common pathomechanism

What has been presented above is an attempt to find an aetiology that would fit into a broad trend of different research currently taking place over the influence of trauma on the incidence of mental disorders.

Literature concerning various traumatic events has documented a great variety of different symptoms that are often associated with an interpersonal abuse in the childhood and adult ages (e.g. an earlier sexual maltreatment of a child, rape or beating the spouse). The connection between these symptoms, which are less closely related with PTSD, and both of the traumatic persecutions (a childhood life- and adult life- related ones) have led to the fact that a lot of scientists have started to perceive the psycho- traumatic disorders, which include neither PTSD nor ASD as such (e.g. Herman, 1992) in a much broader way. More important in this case are: anger because of the persecution, depression, dissociation, sexual problems, interpersonal difficulties, self- mutilation and an excessive or disordered sexual activity. The research presented above fits into the range of influence of trauma on the occurrence of anxiety and depression symptoms in the adult life. Depressiveness is one of the symptoms of complex PTSD.

The term of 'Complex PTSD' was introduced in 1992 by J.L. Herman⁷². It includes PTSD, the diagnosis of which is present in ICD- 10 and DSM- IV classifications, accompanied by additional disorders such as: somatisation, dissociation, prolonged depression and personality disorder of broader- line type⁷³.

In American researches (Seng, 2005) the probability of Complex PTSD occurrence among children and female teenagers suffering from serious somatic illnesses was analysed. Increased frequency of Complex PTSD occurrence was found among young girls suffering from parasitic infections, endocrine, metabolic and immune system disorders. The presence of cardiovascular and skin diseases also increased the risk of complex PTSD occurrence⁷⁴.

Other American researches including women treated for mental disorders, both in ambulatory care and hospitalised indicated the occurrence of high levels of alexithymia among patients with PTSD coexisting with dysregulation, dissociation and somatisation

⁷² Herman, L. (1992). Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *Journal of Traumatic Stress*, Vol. 5, pp. 377-391, ISSN 0894-9867.

⁷³ Allen, J.G. (2001). *Traumatic Relationships and serious mental disorders*. John Wiley & Sons, ISBN 0-471-49102-0, Chichester, England

⁷⁴ Seng, J.S.; Graham- Bermann, S.A. ; Clark, M.K.; MaCarthy, A.M.; Ronis, D.L. (2005). Posttraumatic stress disorder and physical comorbidity among female children and adolescents: results from service-use data. *Pediatrics*, Vol.116, No.6, pp.767-76, ISSN 0031-4005.

(Complex PTSD) (McLean et al. 2006)⁷⁵. German researches conducted on patients hospitalized in Psychiatric Ward for the accused revealed that 59% of them were neglected in their childhood, 75% were mentally and 52% physically abused. Complex PTSD developed among 44 per cent of the abused (Spitzer et al. 2006)⁷⁶. PTSD patients during MRI examination appeared to characterize with a decreased volume of hippocampus, mostly its left side, subthalamic- pituitary- suprarenal axis disorders in the form of decreased cortisol concentration and increased night- and- day level of noradrenalin and adrenalin secretion. In comparison, endogenic depression patients have increased cortisol level in blood circulation system. Neurochemical examinations indicated an increased level of interleukins: IL- 1 and IL- 6 among PTSD patients (Bilikiewicz 2002)⁷⁷.

The disorders in the range of humoral response and interleukins level were also observed in depression.

In some of the studied people with depression or anxiety- depressive disorders with childhood trauma load, there can be a comorbidity recognised, i.e. Complex PTSD symptoms, where the superior unit seems to be the Complex PTSD diagnosis. Depression in different patients may have a different profile of symptoms, yet it still is a 'bag' of such symptoms as pyrexia in contagious diseases. It is therefore vital that the aetiology of either depression, anxiety- depressive disorders or any other disorders, such as the dissociation ones is not yet known. It seems that in some of the patients with depressive symptoms, the aetiopathogenesis of illness after taking into account all the criteria and factors other than only the symptomatic ones, as in ICD- 10, can be established.

A common aetiopathogenetic path for a part of depressive, anxiety or even psychotic disorders could be:

1. Genetic liability
2. Early traumatic experiences tend to change the route of brain development under the influence of the neuroplasticity alterations which are made by hormones secreted during the activity of chronic environmental factors in childhood
3. Lasting HPA axis functioning disorders in adulthood
4. The piling up of stressor factors in the adult life distorts the relative and delicate balance, causes the occurrence of an illness' symptoms and a growth of abnormalities in the HPA axis functioning.
5. Environmental factors modeling the aetiopathogenetic path leading to falling ill; with the negative piling up of stressors, they may protectively influence the development of mental disorders. According to current results these are:
 - an adequate care in childhood
 - social support

⁷⁵ Mclean, L.M.; Toner, B.; Jackson, J.; Desrocher, M.; Stuckless, N. (2006). The relationship between childhood sexual abuse, complex post-traumatic stress disorder and alexithymia in two outpatient samples: examination of women treated in community and institutional clinics. *Journal of Child Sexual Abuse*. Vol.15, No.3, pp.1-17, ISSN 1053-8712.

⁷⁶ Spitzer, C.; Chevalier, C.; Gillner, M.; Freyberger, H.J.; Barnow, S. (2006). Complex posttraumatic stress disorder and child maltreatment in forensic inpatients. *Journal of Forensic Psychiatry & Psychol.* Vol.17, No.2, pp.204-216, ISSN 1478-9949

⁷⁷ See 50

- psychotherapy and antidepressive drugs
- health- promoting personality factors such as the sense of coherence (developed by Antonovsky)

Antonovsky has developed the term of the sense of coherence which includes all three of the following: clearness, controllability (sense of resourcefulness) and reasonability. Clearness is associated with a cognitive aspect of a situation that a person is in. Controllability (sense of resourcefulness) is the sense of the disposal with abilities of handling life's challenges, an active influence on a situation in which one is found. Reasonability is a sense being expressed as a conviction that engaging into things is worth the attempt of investing energy in one's own life and challenges it brings. People differ among each other by the level of the sense of coherence. The greater sense of coherence, the greater the probability of fighting an likely illness, including depression⁷⁸.

In conclusion, it is high time to leave the routine thinking based on symptomatic classifications of mental illnesses and start searching aetiopathogenetic paths leading to the occurrence of an illness in a particular patient. It is postulated that it would be advisable to head towards a personalized medicine, which is already happening in case of oncology for instance. Going through the history of a patients' life, his/ her genotype and the actual symptoms will disallow the disrespectful classification of a patient as a disorder unit, moreover, it will make it possible to recognize the aetiology of his/ her illness and subsequently treat the patient in an adequate way.

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⁷⁸ Antonovsky, A. (1995). *Rozwikłanie tajemnicy zdrowia. Jak radzić sobie ze stresem i nie zachorować*. Fundacja IPN, ISBN 83-85705-24-4, Warszawa, Poland.

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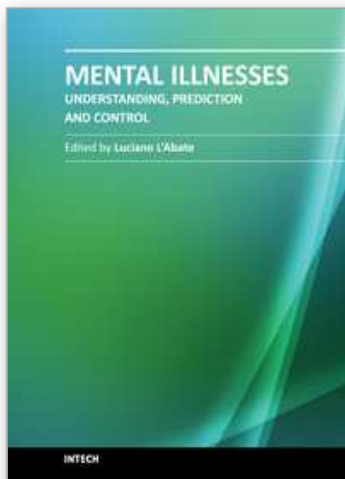
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In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

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