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Aspects of anorexia nervosa

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Abstract

Introduction: Eating disorders are severe psychiatric disorders. nervosa (AN) has a mortality rate among the highest of any psychiatric illness. Its etiology is multifactorial and not fully understood yet. Patients with AN have an intense fear of gaining weight and they continuously seek to their “ideal” weigh. Many studies focus on changes at the endocrine an neuronal level which can be a result of the illness or occur premorbid.

The aim of the study: The purpose of this systemic review was to collect and analyse available data about aspects of anorexia nervosa.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: anorexia nervosa, neuroimaging, endocrinology.

Description of the state of knowledge: Emotional and psychological aspects of anorexia nervosa are very important in understanding this condition. Food restrictions may have a compulsive quality which were compared to those of obsessive-compulsive disorder (OCD), but with the focus on eating, weight and shape. Another aspects concerns neuronal alterations. Many studies with the use of neuroimaging showed changes in the right inferior prefrontal lobe, the right superior prefrontal lobe and the right parietal region, insula and orbitofrontal cortex in patients with anorexia nervosa. Also there is a variety of changes in endocrine system such as disturbances on the axis of Hypothalamic-pituitary-gonadal or growth hormone axis.

Summary: The perception of anorexia nervosa has changed over year. It is known now that its etiology is complex. There are changes on many levels and it is still not known which one of them were premorbid. More studies are needed to have a better understanding of this condition and to be able to treat it better.

Keywords: anorexia nervosa, neuroimaging, endocrinology

1. Introduction

Eating disorders are severe psychiatric disorders that usually begin during adolescence and affect mostly women [1]. Anorexia nervosa has a mortality rate among the highest of any psychiatric illness [2]. The etiology is thought to be the result of interactions of multiple risk factors [3]. Anorexia nervosa is characterized by disturbance in eating habits leading to body weight below the recommended level for age and gender [4]. Patients with AN have an intense fear of gaining weight, their mind is occupied with weight and at the same time they

deny being ill [5]. They continue to lose weight to achieve their "ideal" weight [6]. Two types of anorexia nervosa can be distinguished: a restricting type (AN-R) characterised by food restriction and usually over-exercising and a binge-eating/purging type (AN-B/P) characterised by eating large amount of food in a short period of time which is called "binge eating" or taking compensating actions to prevent weight gain such as self-induced vomiting or use of laxatives or diuretics which is called "purging" [1]. Although anorexia nervosa can change its course. Crossovers occur both from anorexia nervosa to bulimia nervosa and from bulimia nervosa to anorexia nervosa. Low self-directedness may be associated with diagnostic instability in general [7]. Another aspect of anorexia nervosa is excessive or compulsive elements of exercise. This kind of behaviour is inappropriate when it conflicts person's life and persists despite injury or medical complications [8]. Furthermore, excessive exercise in AN has many associations, particularly with the purging subtype of AN but also with younger age, more obsessions and compulsions and higher levels of trait anxiety [9]. Precise pathophysiology of anorexia nervosa remains unclear, also mechanisms underlying many symptoms are not fully know, due to this the treatment is not easy and still needs improvement [10]. Dietary restriction in patients with AN tends to have compulsive quality. The compulsive behaviours in AN were compared to those of obsessive-compulsive disorder (OCD), but with the focus on eating, weight and shape [11]. There is high comorbidity between AN and OCD, mostly with the restrictive subtype of AN [11]. There are many risk factors for anorexia nervosa such as young age, female, having a history of being depressed, anxious, or having obsessive-compulsive disorder. Also having poor self-esteem and trying to be perfect [12]. The point of psychological aspect of AN is the extreme overvaluation of shape and weight [13]. In general, etiology of eating disorders is thought to be biopsychosocial. Although, there is a growing number of studies of genetic factors influencing liability to these disorders [14]. Emotional factors also contribute to develop of eating disorders. Pre-meal anxiety is what dictates individuals with AN the calorific value of the meal [4]. Body weight dissatisfaction is widespread among women with and without eating disorder [15]. Although, patients with AN tend to over emphasize the self-imposed standards [16]. In case to prevent reduction of one's self- esteem they continue dysfunctional eating habits [4]. Cognitive factors are related to self-perception. Individuals with AN overestimate their own body shape and body measurements. Another thing is different evaluation of meal portion sizes which may lead to smaller intake of food [4]. Anorexia nervosa is associated with anxiety disorders, as a vulnerability factor, commonly premorbid to the onset of AN [17]. The study of etiology of eating disorders may be very challenging since these are multifactorial diseases [3].

2. Neuroimaging in anorexia nervosa

Brain imaging techniques enable us to have an insight into brain activity and neuroreceptor function *in vivo* in humans. This can be used to find alterations in anorexia and bulimia nervosa, thus provide us more information about how to treat those diseases better [18]. Neuroimaging uses among others techniques of computerised tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT). One of the most commonly used is fMRI, which measures changes in local blood flow by BOLD

(blood-oxygen-level-dependent) during brain activation [19], and due to this is able to associate behaviour with specific brain activation [18]. PET and SPECT techniques are used to study neurotransmitter mechanisms and gain information about brain metabolism and chemistry [20,21]. One of the studies published in 2000 showed the association between activation in specific cortical regions and anxiety in patients with anorexia nervosa. In this study there were three gropus: patients with purely restrictive anorexia, patients with habitual binge/purge behavior and healthy female volunteers. SPECT was used to measure the regional cerebral blood flow (rCBF) before and after the subjects were asked to imagine food. Groups of patients with anorexia and habitual binge/purge behaviour showed significant increase of rCBF in the right-side areas of the brain, more precisely: the right inferior prefrontal lobe, the right superior prefrontal lobe and the right parietal region. This results were associated with heightened anxiety levels of the patients with anorexia and habitual binge/purge behavior [22]. Another region of brain linked to anorexia is insula. The insula is very important in functioning of human cognition and behavior [23]. It has been implied that feeling states arising from the insula influence cognition. Anterior insula makes association between salient information and feeling states, thus begins cognitive processes [24]. One of the studies examined relation between altered insula functioning and anorexia nervosa using fMRI. Participants were 15 females with restricting-type AN and 15 females with no history of psychiatric disorder. There were three types of trials in this focused awareness task: interoceptive attention (IA), anxious rumination trials and exteroceptive trials. Findings of this study showed an association between anorexia nervosa and abnormal visceral interoceptive activity in the insula. Moreover, during interoception trial, individual differences in dorsal mid-insula activity occurred and they might be linked to participants' anxiety and eating disorder psychopathology [25]. Another study compared a group of twenty-four women recovered from restricting-type anorexia nervosa with twenty-four healthy control women using diffusion weighted imaging of the brain. The results showed greater structural white matter fiber connections between insula, ventral striatum and orbitofrontal cortex in recovered group, although white matter integrity of those tracts was reduced. Authors of the study suggested some explanations of this occurrence. One is that white matter tracts need to be rebuilt during recovery, but readjustment is possible with more fibers and reduced quality. Another is that patients suffering from anorexia nervosa could have had more connections premorbid. It was also suggested that connectivity could be a marker for illness severity [26]. Another region which disturbance is associated with eating disorders is orbitofrontal cortex (OFC). A near-infrared spectroscopy (NIRS) study of this subject was performed on a group of females with extremely low body weight diagnosed with ED compared to a control group. As a result it showed malfunction of OFC in patients with ED which might be linked to their lack of insight and social isolation characterizing eating disorders [27]. The altered function of orbitofrontal cortex can be a reason of self-starvation since its valid role in terminating food intake [28]. A study of brain structures altered in patients with eating disorders showed that medial orbitofrontal cortex, insula and striatum are the altered ones. The research was made using structural magnetic resonance brain imaging on groups of restricting-type anorexia patients, bulimia nervosa patients, recovered restricting-type anorexia nervosa individuals and a healthy control women. Groups of anorexia, recovered anorexia and bulimia showed increased left orbitofrontal gyrus rectus gray matter volume implying this structure as

a potential marker [29]. In another study, with use of structural brain scans, participated groups of patients with current restricting-type anorexia nervosa, patients recovered from restricting anorexia nervosa and healthy control women. This study showed a relatively lower cortical thickness in superior frontal regions and relatively higher cortical thickness in the insula and orbitofrontal cortex in anorexia group. However, this alterations were not noticed in recovered group, suggesting those as a biomarker of the disorder [30]. Neuroimaging in eating disorders is valid and has a lot of potential, although it can not yet be used for diagnostic causes. There is a need for more studies. Also studies of brain structure at different points during recovery would be helpful in creating a better therapy [28,31].

3. Endocrine changes

3.1 Hypothalamic-pituitary-gonadal axis

In patients with anorexia nervosa we can observe hypothalamic amenorrhea. In women with amenorrhea and AN wide range of luteinizing hormone pulsatility patterns were found[32,33]. In these finding we observe changes such as apulsatility or patterns characteristic of early puberty, in which luteinizing hormone pulses occurred only during sleep. The luteinizing hormone distribution seems to have no simple dependence on the weight, because in those studies we observe that the adult circadian LH secretory pattern was not present in some women who had partially or totally achieved ideal weight. Moreover the degree of immaturity of pattern did not correlate reliably with the duration of illness, the degree of fatness, or the extent of deficit from ideal weight [33,34]. Changing in gonadotropin secretion has been associated with deceases in fat mass, a reflection of energy stores, changes in levels of hormones such as leptin, adiponectin (adipocytes hormones), ghrelin and cortisol [35]. Low level of estradiol and leptin in AN cause decreased secretion of LH [36,37]. Cortisol and ghrelin suppress LH gonadotropin secretion and their level is increased in AN [38,39]. In one study we observe immature LH secretion pattern in experimental starvation of healthy subjects [40]. The presence of complete amenorrhea or irregular periods may reflect changing energy status over time [35]. Data suggest that the most important element of resumption of menstrual function is an increase in fat mass. With increase in fat mass, menstrual functions resumes for most women with AN [35]. In one study in adolescents with AN found that all girls with body fat >24% resumed menstrual function, whereas all girls with body fat <18% had no menses [35,38]. One study on three males with AN found low morning levels of leptin, gonadotropin and testosterone with increase in these levels with weight gain [41].

3.2 Growth hormone axis

Adolescents and adults with AN have acquired growth hormone (GH) resistance. Those with the lowest BMI and fat mass have the highest level of GH. GH resistance is characterized by low systemic level of insulin-like growth factor 1 (IGF1) [42,43]. One study confirmed GH resistance by administrating recombinant human GH in women with AN. In this study we do not observe increase level of IGF1 after administration of supraphysiological doses of recombinant human GH [44].The alterations in secretion of GH seems to be related to weight loss and could be reversed by gain weight [42,43]. One of effects of GH is

gluconeogenesis. In state of low energy it is a beneficial effect, due to maintaining euglycemia [45]. GH resistance is important in impaired bone metabolism, due to low level of IGF1 [35].

3.3 Hypothalamic-pituitary-adrenal axis

In AN we observe high levels of adrenocorticotropic hormone and cortisol [45]. It seems to be caused by hypersecretion of CRH, which was confirmed by measurement of CRH level in cerebrospinal fluid from patients with AN [46]. Physical and psychological stress activate the hypothalamic-pituitary-adrenal axis with secondary anorectic effect [45]. Studies on animals show that central microinjections may lead to anorexia and this effect could be reversed by injection of CRH antagonist [47,48]. Somatostatin counteracts the anorectic action of CRH. Studies show that the somatostatinergic tonus may be impaired in AN [49]. However, there is also evidence that concentrations of somatostatin in cerebrospinal fluid in patients with anorexia nervosa, both at low weight and after weight recovery, were similar to those in controls [50]. Hypersecretion of CRH, increased concentration of ACTH and cortisol could be also caused by increased level of ghrelin, because it stimulates their secretion [51,52]. Those with the lowest BMI, fat mass and fasting glucose and insulin levels have the highest level of cortisol. It could be an adaptive mechanism to maintain euglycemia in state of low energy [53].

3.4 Hypothalamic-pituitary-thyroid axis

After losing weight there is adaptive decline in circulating levels of T3, T4 and thyroid-binding-globuline to slow down the rate of metabolism [45,54]. In AN TSH level is usually normal or low normal, but TSH response for exogenous TRH is weakened and delayed [55]. Low level of T3 is associated with lower leptin level and BMI, and higher levels of ghrelin and cortisol [56,53].

3.5 Insulin, gut peptides and adipokines

In studies lower BMI, weight and glucose levels are associated with lower fasting insulin levels than in controls [57]. Secretion in a 1:1 ratio with insulin - amylin is also reduced in AN. Due to low insulin levels, mechanisms such as glycogenolysis, lipolysis and gluconeogenesis are intensifying. Lower insulin and amylin levels help preserve euglycemia [35]. The most well-studied gut peptides are cholecystokinin, peptide YY, glucagon-like peptide-1, oxyntomodulin and ghrelin. Those act directly on neurons in hypothalamic and brainstem centers of appetite control and influence short-term and long-term energy balance. All of these hormones act to increase satiety, except ghrelin [45]. Peptide YY performs function in satiety, also by reducing appetite stimulation by ghrelin. There are contradictory data from studies. One study shows increased plasma level of peptide YY, while another shows its decreased plasma level [58,59]. There is also study, which shows unchanged level of peptide YY in patients with AN [60]. Ghrelin is an orexigenic hormone. Its levels increase before meals. Patients with AN have higher fasting and overnight ghrelin levels, associated inversely with BMI, fat mass, and insulin [56,61,62]. Obestatin is product of ghrelin gene, it inhibits appetite and gastric motility. Its level is increased in patients with AN [63]. There are studies which implicate that ghrelin gene polymorphism such as genetic variation of the

ghrelin activator gene ghrelin O-acyltransferase may be etiological factor of AN. However, another study did not confirm these results [64,65,66]. Higher ghrelin concentration is an adaptive mechanism to increase food intake, in one study on five woman with AN who were given twice daily ghrelin infusion, led to reduced gastrointestinal symptoms, and increased hunger and caloric intake [67].However, this study was small and not placebo-controlled, more further studies is needed to confirm those findings. After weight gain, the level of ghrelin decreases, but can be higher than in normal weight controls [56]. In patients with AN basal and pulsatile secretion of leptin is reduced and it is associated with low fat mass. In one study, mean overnight serum leptin levels were 71% lower in adolescent girls with anorexia nervosa than in healthy adolescents [68]. Another studies seems to confirm those findings [69,70]. Leptin increases level of GnRH and hypoleptinaemia might contribute to hypothalamic amenorrhea in anorexia nervosa and to elevated levels of physical activity in women with anorexia nervosa for whom compulsive exercise is a component of the psychiatric syndrome [34,71]. In one study 17 of 18 adolescent girls with AN, who achieved normal weight, had higher leptin levels than controls [72]. There are conflicting data in studies about adiponectin. In studies its levels were normal, higher or lower, compared to controls [57,73,74].

3.6 Posterior pituitary hormones and renal function

Studies have reported altered osmoregulation in AN, due to abnormalities in osmoregulation of vasopressin, intrinsic renal defects and the effects of antidepressants [75]. Hyponatremia is very common in AN and may lead to complications such as vomiting or seizures [45]. Women with AN have lower osmolality and level of sodium, higher levels of antidiuretic hormone (ADH) and more concentrated urine than normal-weight controls [76]. One study found elevated ADH level in cerebrospinal fluid, reduced pituitary sensitivity to ADH [77]. Another causes of low plasma sodium level, except inappropriate secretion of vasopressin are excessive water consumption, hypovolemia due to inadequate nutrition and purging, impaired renal sodium reabsorption in the setting of malnutrition and the use of psychotropic medications [34]. Hyponatremia is generally not severe in women with anorexia nervosa but sometimes severe or acute hyponatremia may lead to seizures without any alarm symptoms, therefore measuring levels of serum sodium is important in these patients [34,78]. Patients with AN who develop hyponatremia often have hypovolemia, SIADH or are overload of water, cause of excessive water consumption [34]. Except hyponatremia there are other electrolyte abnormalities: hypokalemia, hypomagnesaemia and hypophosphatemia. Hypokalemia is present in 20% women with AN and seems to be caused by vomiting, laxative use or diuretic consumption (with the exception of women who abuse potassium-sparing diuretic, then hyperkalemia may occur) [79]. During nutritional rehabilitation may occur refeeding syndrome - carbohydrate intake induces insulin release, which leads to cellular uptake of potassium, magnesium, and phosphate [80]. In AN also occurs dysregulation of oxytocin secretion, which is an anorexigenic hypothalamic hormone [34]. Overnight levels of oxytocin are lower in women with AN, compared to controls, but postprandial plasma oxytocin levels are higher in women with active and weight-recovered AN than in normal-weight woman [81,82].

4. Summary

The etiology of anorexia nervosa is a combination of many factors such as psychological, developmental, sociocultural and biological which makes the study very challenging [3]. Yet strong biological factors predispose individuals to developing heating disorders [1]. Alterations in brain structure and functioning may have contribution in developing this condition. Knowledge of changes on another levels like endocrine system can be useful in creating new therapies. More studies are needed to have a better understanding of this condition and to be able to treat it better.

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