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Polyphagia as an accompanying symptom of various diseases - overview and treatment options

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ABSTRACT

Introduction and purpose

Polyphagia is a rare symptom described as an excessive food intake due to an abnormally strong and persistent sensation of hunger or desire to eat. Diseases that can lead to polyphagia are numerous and include several medical specialties, such as endocrinology, neurology and psychiatry. Polyphagia leads to overweight and severe obesity, reduces quality of life, has a negative impact on the patient's mental health and eventually causes premature death. Therefore identifying and addressing the root cause of polyphagia is crucial for effective management and treatment. This article aims to explore the most common causes, the latest research and potentials in the treatment of polyphagia.

Materials and methods

To write this article, data bases such as PubMed and Google Scholar were searched using the following terms: polyphagia, obesity, diabetes, insulinoma, Prader-Willi syndrome, frontotemporal dementia, binge eating disorder, Grave's disease, pharmacotherapy of obesity.

Description of the state of knowledge

Currently, pharmacotherapy offers a number of treatments for polyphagia, the effectiveness of which depends on the underlying cause. In type 1 diabetes, insulin therapy is applicable, while in type 2 diabetes oral antidiabetic drugs, particularly GLP-1 analogs, offer promising results. Good compensation of Grave's-Basedow disease with thyreostatic drugs, radioactive iodine therapy or surgical treatment makes it possible to control the accompanying polyphagia. In binge eating disorder, the first line of treatment is psychotherapy, while medications include lisdexamphetamine, serotonin reuptake inhibitors or anti-convulsants (topiramate and zonisamide) and anti-obesity medications (orlistat). Serotonin reuptake inhibitors are also used adjunctively in frontotemporal dementia. The most complex problem is the treatment of polyphagia in Prader-Willi syndrome. In this disease, in addition to the available pharmacological methods, surgical treatment in the form of bariatric surgery, as well as neurosurgical methods are used.

Summary

Polyphagia is a symptom of many diseases in various medical fields. For this reason, it often appears in clinical practice and requires a multidisciplinary approach. In most cases, the possibility of its cure depends on whether treatment for the underlying disease is available.

For patients affected by diabetes, insulinoma, binge eating disorder or Grave's disease there is an effective therapy. However, patients with Prader-Willi syndrome and frontotemporal dementia face more complex challenges. Due to the lack of causal management, they can only rely on symptomatic treatment. Luckily, in recent years, a number of studies have been conducted, offering hope for improving the quality of life for patients suffering from these conditions.

Keywords: polyphagia; obesity; diabetes; insulinoma; Prader-Willi syndrome; frontotemporal dementia; binge eating disorder; Grave's disease; pharmacotherapy of obesity

Introduction

Polyphagia is a rare symptom described as an excessive food intake due to an abnormally strong and persistent sensation of hunger or desire to eat [1]. Among the more than 80 medical conditions that can lead to polyphagia are diseases such as diabetes, Graves' disease, binge eating disorder (BED), insulinoma, frontotemporal dementia, as well as Prader-Willi syndrome [1]. Polyphagia leads to overweight and severe obesity, reduces quality of life, has a negative impact on the patient's mental health and eventually causes premature death. According to the WHO, obesity affects about 30% of the population of Poland, 60% population of Europe and 43% population worldwide. [2-4]. This, consequently, can contribute to premature death in about 1.2 million people a year in Europe and 2.8 million worldwide and can lead to a deterioration in patients' quality of life. Its objective measure is the disability-adjusted life years (DALY) index, which is 680 per 100,000 for obesity in the general population. [5-7]. Therefore identifying and addressing the root cause of polyphagia is crucial for effective management and treatment. This article aims to explore the most common causes, the latest research and potentials in the treatment of polyphagia.

Pathophysiology

As a growing number of people suffer from obesity, understanding the mechanisms by which various hormones and neurotransmitters have influence on energy balance is crucial. Food intake is a process closely regulated by both the central and peripheral nervous systems. The hunger center in the brain is stimulated by proteins such as ghrelin and orexin, whose action

activates the arcuate nucleus of the hypothalamus to produce neuropeptide Y and agouti-related peptide (AgRP) [8]. These in turn stimulate appetite (orexigenic system). Food consumption, in turn, leads to the production of anorectic neuropeptides such as cholecystokinin (CKK), peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). They stimulate neurons of the arcuate nucleus of the hypothalamus to produce proopiomelanocortin (POMC), melanotropin α (α-MSH), inducing a feeling of satiety (anorexigenic system) [9]. Peripheral stimuli such as gastric wall distension (mechanoreceptors), products of digestion of proteins, fats and sugars (chemoreceptors) and leptin secretion in the intestines and adipose tissue also lead to activation of the anorexigenic system.

From pathophysiological point of view, the causes of polyphagia include dietary errors in the form of a high-fat diet, increased stimulation of the orexigenic pathway and the dopamine-dependent reward system, as well as decreased feelings of satiety regulated by serotonin [10].

Overview of major conditions

Diabetes

Type 1 diabetes is an autoimmune disease in which the beta cells of the pancreas, responsible for insulin production, are damaged by the immune system, leading to an increase in blood glucose levels. Polyphagia is a common symptom of type 1 diabetes. Among children with ketoacidosis in the course of previously undiagnosed diabetes, preceding polyphagia occurs with a frequency of 76.8%. The pathomechanism of polyphagia is due to the lack of insulin, which is one of the main inhibitors of appetite. Its role is to downregulate the expression of NPY and AgRP and activate the POMC system [11].

In type 2 diabetes, polyphagia is observed in 23.9% of cases. Potential causes include an increase in ghrelin levels due to impaired glucose transport into cells, which stimulates the production of NPY and AgRP. Another possible cause is the overweight and obesity present in 90% of patients, which contribute to insulin- and leptin-resistance [12-13].

Grave's disease

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland. In this disease, antibodies against the TSH receptor are produced, which stimulates the thyroid to secrete supra-physiological amounts of peripheral hormones. This in turn leads to a number of metabolic changes, which include polyphagia. The mechanism of this phenomenon involves direct stimulation of NPY production, which is part of the orexigenic pathway [14].

Binge eating disorder (BED)

Binge eating disorder is a mental disorder characterized by recurrent episodes of overeating accompanied by a lack of control over the amount of food consumed [15]. Risk factors include increased body weight and the resulting negative comments from the environment, anxiety disorders, depression, insecure access to food, exposure to racist behavior and low socioeconomic status [16]. Obese patients planning to reduce weight are particularly predisposed to developing BED [17]. The pathophysiology of this disorder has not been fully elucidated. The causes could be excessive dopaminergic stimulation of the reward system, a mutation in the gene encoding the receptor for melanocortin 4, or the influence of the gut microbiota and dysregulation of the gut-brain axis [15].

Insulinoma

Insulinoma is one of the most common neuroendocrine tumors of the gastrointestinal tract. The annual incidence is about 4 cases/1 million people. In 6% of cases, it is a component of type 1 multiple endocrine neoplasia (MEN1). The neoplasm originates in the insulin-producing beta cells of the pancreas. It is characterized by Whipple's triad of symptoms, occurring after exercise, starvation or spontaneous bouts of hypoglycemia: symptoms (e.g., tachycardia, pallor, sweats, hand tremors, severe hunger) appear during starvation, are accompanied by hypoglycemia, and resolve after carbohydrate administration [18]. Episodes of hypoglycemia are a trigger for the production of orexin, which acts on the arcuate nucleus of the hypothalamus to stimulate the production of NPY and AgRP. The reward system is also stimulated, particularly by dopaminergic neurons in the paraventricular nucleus. The consequence is increased motivation to seek and eat food [19].

Frontotemporal dementia

Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disorder, clinically characterized by changes in cognition, personality, and behavior. Marked disturbances in eating behavior, such as overeating and preference for sweet foods, are also commonly reported. It is the second most common cause of dementia and is as common as Alzheimer disease in individuals with young onset dementia [20]. Three main clinical phenotypes of FTD are generally recognized based on clinical symptomatology at presentation: behavioral-variant FTD (bvFTD), semantic dementia, and progressive nonfluent aphasia. The hypothalamus plays a critical role in feeding regulation, as the patients with high feeding

disturbance exhibited significant atrophy of the posterior hypothalamus [21]. Yet the relation between pathology in this region and eating behavior in FTD is unknown.

Prader-Willi syndrome

Prader–Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region [22,41]. Clinical picture of PWS changes across life stages. The main clinical characteristics are represented by short stature, developmental delay, cognitive disability and behavioral diseases. Hypotonia and poor suck resulting in failure to thrive are typical of infancy. As the subjects with PWS age, clinical manifestations such as hyperphagia, temperature instability, high pain threshold, hypersomnia and multiple endocrine abnormalities including growth hormone and thyroid-stimulating hormone deficiencies, hypogonadism and central adrenal insufficiency due to hypothalamic dysfunction occur. Obesity and its complications are the most common causes of morbidity and mortality in PWS. Several mechanisms for the aetiology of obesity in PWS have been hypothesized, which include aberration in hypothalamic pathways of satiety control resulting in hyperphagia, disruption in hormones regulating appetite and satiety and reduced energy expenditure [23].

Treatment options

As described, polyphagia is a symptom of many different diseases. Therefore, in most cases, its treatment comes down to appropriate therapy for the underlying disease.

Diabetes management

The treatment of type 1 diabetes is insulin therapy, which directly affects the inhibition of NPY and AgRP expression and activation of the anorexigenic pathway. Therapy for type 2 diabetes is based on antidiabetic drugs. Of particular note are GLP1 analogs, which directly affect appetite by activating the GLP-1 receptor. They slow gastric emptying, inhibit the release of glucagon, and stimulate insulin production, therefore reducing hyperglycemia in people with type 2 diabetes. Among antidiabetic drugs, they have the strongest effect on weight reduction [24-26].

Grave's disease management

Treatment of polyphagia in Graves-Basedow disease consists of lowering the increased concentration of thyroid hormones. The first-line treatment is thyrostatic drugs such as thiamazole and propylthiouracil. In cases of relapse or if there are contraindications to first-choice treatment, as well as in elderly patients, patients with cardiac arrhythmias, and women

planning pregnancy, radioactive iodine therapy is an option. An alternative to radioiodine is surgical treatment - partial or total thyroidectomy, which should be considered in cases of moderate or severe orbitopathy, large goiter with compression of the respiratory froth, and when a malignant lesion is diagnosed or suspected. A reduction in the production of orbital hormones leads to a decrease in metabolic processes in the body and, consequently, a decrease in energy requirements and a reduction in food intake [27].

Binge eating disorder (BED) management

International guidelines recommend evidence-based psychological therapy as first-line care for BED. There are three main psychotherapies for BED which have evidence of efficacy from randomised controlled trials: cognitive behaviour therapy (CBT), interpersonal psychotherapy (IPT) and dialectical behaviour therapy (DBT) [15]. For patients who do not have access to psychotherapy or prefer to take medication, pharmacotherapy is applicable. For patients who do not have access to psychotherapy or prefer to take medication, pharmacotherapy is applicable. Lisdexamfetamine (a prodrug of d-amfetamine) is the only medication approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe BED in adults [28]. Other drugs that have been tested in at least one randomised controlled clinical trial in BED include second generation antidepressants, anti-convulsants (topiramate and zonisamide) and anti-obesity medications (orlistat) [29].

Insulinoma management

For single solitary insulinomas, curative surgical excision remains the treatment of choice and allows for a complete cure. However, it should be performed only when the diagnosis is certain and by a surgeon who is skilled in pancreatic surgery. For tumors expressing receptors for somatostatin that do not qualify for surgery, therapy with radioisotopes such as lutetium 177 (^{177}Lu) or yttrium 90 (^{90}Y) may be considered. Symptomatic treatment focuses on treating and preventing hypoglycemic seizures. Seizure interruption involves the supply of carbohydrates orally and glucose intravenously by injection or infusion. A continuous glucose monitoring system can support patients in recognizing hypoglycemic events and prevent serious complications, especially during the night Seizure prophylaxis involves the oral administration of diazoxide and the subcutaneous use of short- and long-acting somatostatin analogs in tumors having the appropriate receptors. Both forms of treatment -causal and symptomatic- affect hypoglycemic seizures, which induce polyphagia through stimulation of the orexigenic pathway [18, 30].

Frontotemporal dementia management

Unfortunately there's currently no approved disease-modifying therapy for frontotemporal dementia, although research into treatments is ongoing. Symptomatic treatment remains the only form of assistance for patients. Non-pharmacologic management includes: physical activity targeting cardiovascular fitness and mobility, speech therapy, and behavioral food modification techniques. The best-documented drug therapy is considered to be serotonin reuptake inhibitors, such as citalopram and trazodone. The use of these drugs for the treatment of eating disorders, including polyphagia, developing in FTD brings moderate improvement. An interesting solution for polyphagia in FTD is the use of topiramate. The likely mechanism in this case is an antagonist action against glutaminergic AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazo- lopropionic acid) receptors, which reduces stimulation of the reward system [31].

Prader-Willi syndrome management

A relevant aspect in the management of the patients with PWS is the adherence to a diet starting from the first months of life to favor a regular body growth and, subsequently, to cope with the incipient hyperphagia and to prevent or treat the excess of weight throughout the life span [32,33,34]. Over the years, several anti-obesity drugs have been used to support nutritional therapy in patients with PWS. Orlistat is a gastrointestinal lipase inhibitor that limits fat absorption to up to 30% of ingested fats without exerting central nervous system effects. It has demonstrated only modest efficacy in patients with PWS, likely due to poor compliance for gastrointestinal side effects [35]. Metformin is an oral hypoglycemic drug used for the management of T2D and pre-diabetes in individuals with obesity. A pilot study with metformin supplementation in 21 children and adolescents with PWS showed an improvement of the food-related distress and anxiety, evaluated by hyperphagia questionnaire, but no effects on body weight [36]. Similar effects were observed also after Topiramate and Diazoxid supplementation. An 8-week double-blind randomized placebo-controlled trial in 62 patients with PWS demonstrated an improvement of hyperphagia - evaluated as behavior and severity scores by Dykens Hyperphagia Questionnaire - after Topiramate group versus placebo group, with no effects on BMI [37]. A further therapeutic tool to consider in patients with PWS is bariatric surgery, which is proved to reduce the severity of polyphagia for 3 years after surgery. The likely mechanism in this case is a reduction in the concentration of ghrelin produced by the stomach [38,39]. Another option is neurosurgical management in the form of deep brain stimulation, transcranial direct current modulation, vagus nerve

stimulation or repetitive transcranial magnetic stimulation [40]. However, further studies are needed to determine the effectiveness of these methods [42].

Summary

This review underscores the need for a multidisciplinary and individualized approach to a patient with polyphagia. The treatment of polyphagia as a symptom mainly boils down to treating the disease whose pathomechanism contributed to its development. For this reason, proper diagnosis and differential diagnosis are important to rule out its increasingly rare causes. Continued research into innovative therapies and personalized treatment holds great potential in improving long-term outcomes for individuals affected by this condition.

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