Ophthalmologic manifestations of celiac disease

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Abstract

- Celiac disease is an autoimmune disorder that affects the small intestine of genetically predisposed individuals. Ophthalmic manifestations are within the extra-intestinal manifestations, and can be divided into those of autoimmune disorders or those due to absorptive disabilities. This article reviewed the ophthalmologic manifestation of celiac disease. Ophthalmic symptoms are rare, but should be investigated in patients with celiac disease and taken into consideration as the first systemic manifestation.

- KEYWORDS: ophthalmology; celiac disease; review

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INTRODUCTION

Celiac disease is an autoimmune disease that affects the small intestine of genetically predisposed individuals. This disease can be asymptomatic and can have gastrointestinal or extra-intestinal symptoms. The classic symptoms are part of a malabsorptive syndrome with diarrhea and weight loss. Approximately 50% of the patients present with atypical or extra-intestinal symptoms, such as anemia, osteoporosis, neurological disorders and dermatitis herpetiformis [1-3]. Symptoms vary according to the genetic predisposition, immune status, gender and age at onset [4]. Diagnosis is made when there is the presence of the genetic factor (HLA DQ2/8), with a positive biopsy and the presence of antibody serology [5]. The typical form of the disease presents with crypt hyperplasia and villous atrophy in a malabsorptive syndrome. The atypical form of the disease is characterized by a positive serology, small changes in the mucosa of the small intestine, or no gastrointestinal symptoms associated with extra-intestinal symptoms, including osteoporosis, peripheral neuropathy, anemia and infertility [6-7]. The ophthalmic manifestations are within the extra-intestinal manifestations, and can be divided into autoimmune disorders and absorptive disabilities. The manifestations related to malnutrition are correlated to the low levels of vitamin A, vitamin D and calcium. It could cause retinopathy, cataract, dry eye and pseudotumor cerebri. The manifestations related to autoimmune disorders are orbital myositis, uveitis, thyroiditis associated with orbitopathy and brain calcification.

Ophthalmologic Manifestations Related to Malnutrition

Retinopathy Retinopathy is characterized by yellowish to white punctate lesions in the peripheral retina. Electroretinogram (ERG) changes can occur, and vitamin A levels are usually reduced in these patients [8-9]. A normal vitamin A metabolism is important for the function of the cones. The vitamin A deficiency can lead to night blindness (nyctalopia) associated with ERG changes. Nyctalopia is usually the first symptom in patients with vitamin A deficiency, which may precede the symptoms of dry eye by several months. Typically, visual function improves after one to four months of vitamin A reposition[10].

Cataract Cataracts associated with celiac disease have been reported in the literature[11-12]. Malabsorption can be caused by chronic diarrhea. A severe vitamin D deficiency due to the malabsorptive syndrome interferes with the absorption of calcium, and the resulting hypocalcemia contributes to the development of cataracts. Chronic diarrhea can also lead to dehydration, which would alter the osmotic flow between the lens and the aqueous humor, with alkalosis and high levels of urea and ammonia. The lens maintains a good level of hydration in an environment with calcium between 10-12 mg/100 mL. Low levels of calcium in the aqueous humor change the permeability of the lens epithelium, causing an imbalance in the osmotic equilibrium and leading to lens opacification. Hypocalcemia lasting 10-12 mo is sufficient to generate cataracts[13].
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Pseudotumor cerebri Pseudotumor cerebri, also known as idiopathic intracranial hypertension, may be associated with vitamin A deficiency, and is characterized by increased intracranial pressure of unknown cause[16-15]. It may be caused by nutritional, metabolic, endocrinological or hematological disorders[16-17]. The association between vitamin A and pseudotumor cerebri is more commonly reported associated with vitamin A poisoning[18]. High levels of vitamin A may damage the granulation of the arachnoid, hindering the absorption of cerebrospinal fluid[19]. However, a few case reports have described the relation between pseudotumor cerebri and low levels of vitamin A[20-22]. The clinical picture is characterized by the presence of papilledema with normal radiological images and no other cause of increased intracranial pressure[2]. The mechanism by which vitamin A deficiency results in increased intracranial pressure is still not fully understood. It was demonstrated, in animal models, that vitamin A deficiency can increase the rate of the absorption of cerebrospinal fluid, causing increased intracranial pressure[23]. Studies have confirmed this mechanism demonstrating fibrosis and increased arachnoid granules in animal vitamin A deficiency[24]. One study suggested a different mechanism of increased intracranial pressure caused by vitamin A deficiency[24]; they found a decrease in the volume of the cranial cavity and brain compression by excessive cranial bone growth in dogs with vitamin A deficiency. This increase in bone growth was noted in the bones of the posterior fossa, thus affecting the cerebellum, the pons and the medulla oblongata. Similar bone deformities were demonstrated by scientists, who found an increase in osteoblast activity in the periosteum, which led to a bone deposit in the skulls of birds with vitamin A deficiency[25]. Vitamin A deficiency can be treated with oral supplementation or, in the case of poor lipid absorption, with muscular injection. Additional doses of vitamin A may be required in patients with protein deficiency.

Dry eye Vitamin A is necessary to maintain the proper functioning of the ocular epithelium surface. In the conjunctiva, the loss of goblet cells, and the metaplasia of the squamous cells can lead to dry eye condition in patients with vitamin A deficiency. Bitot spots due to keratinization of the perilimbal conjunctiva may be seen. In more severe cases, liquefactive necrosis of the cornea (keratomalacia) may occur[26]. Topical retinoic acid 0.1% can promote anatomical improvement of the conjunctiva and the cornea[27].

Ophthalmologic Manifestations Due to Dysimmunity

Orbital myositis An association has been reported between celiac disease and inflammatory myopathies. High levels of anti-gliadin antibodies were found in patients with myositis[28]. Celiac disease has also been associated with neutrophil myositis[29]. An association between celiac disease and dermatomyositis has been reported in patients, and these two conditions may have a common immunological basis[30]. The pathophysiology of this disease is not yet clear, but it is usually related to eosinophil and granulomatous infiltration[31]. Patients with orbital myositis usually have diplopia, pain with eye movements and exophthalmos. It is more common in women and affects only one extra-ocular muscle[20]. This condition is well treated with corticosteroids[32-33].

Uveitis A recent study showed an association between idiopathic uveitis and patients with celiac disease[34]. Uveitis is an inflammation of the uvea, which can lead to vision loss. Early diagnosis and prompt treatment is important to preserve vision.

Thyroiditis associated with orbitopathy The etiology of Hashimoto's disease is unknown, but patients usually have a genetic predisposition, with the presence of HLA-DR3/DR4 or HLA-DQ2/DQ8[33-35]. The pathogenesis of Hashimoto's thyroiditis is multifactorial[41]. Endogenous hormones and external factors are suspected to trigger the manifestations of the disease[42].

Gastrointestinal immune diseases, such as celiac disease, are more prevalent in patients with Hashimoto's thyroiditis. Patients with celiac disease have four times more risk to develop Hashimoto's thyroiditis. The pathogenesis of the coexisting Hashimoto's thyroiditis and other autoimmune diseases, such as celiac disease, is still not completely understood[43-45]. The association between the orbital manifestation of the thyroiditis and celiac disease is due to a possible lymphoctic infiltration leading to tissue remodeling and fibrosis[46-49]. The local release of pro-inflammatory cytokines, tumor necrosis factors and interleukin-6 are present both in Hashimoto's thyroiditis and in celiac disease[47-48]. The presence of histocompatibility complex class II (MHC II) has been described in both thyroiditis and celiac disease[46-50].

Brain occipital calcification The neuro-ophthalmologic manifestations result in local inflammatory alterations and vasculitis caused by immunological mechanisms. Low vision is rare in celiac disease, but has been correlated with cases of cortical calcification in the occipital region[51-52].

A study indicated that HLA, predisposing to celiac disease, is the same gene that is associated with bilateral occipital calcification[53]. The cerebral calcification may be associated with a reduction in the concentration of folate in the central nervous system, due to poor absorption of folate and transportation difficulties through the blood-brain barrier[54-56]. However, the pathophysiology of this alteration has not yet been definitely determined. Folic acid deficiency is not present in all patients with celiac disease and cerebral calcification[57]. Another hypothesis is that the brain calcification is due to an immune complex associated with endothelial inflammation[55-58]. Further studies are needed to elucidate the pathophysiology of occipital calcification.
CONCLUSION
Celiac disease has intestinal and extra-intestinal manifestations, caused by immune malabsorption or by nutrient malabsorption. The ophthalmic symptoms are rare within the extraintestinal manifestations, but should be investigated in patients with celiac disease and taken into consideration as the first systemic manifestations of the disease[9-46].

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