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Review

Quality of life and neuropsychiatric disorders in patients with Graves' Orbitopathy: Current concepts

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ABSTRACT

Graves' disease (GD) is an autoimmune chronic thyroiditis frequently associated with development of Graves' orbitopathy (GO) characterized by proptosis, strabismus, impairment of visual function, ocular surface inflammation and dry eye. As consequence, patients with GO experience impairment of quality of life and social function and could develop a neurobehavioral syndrome, ranging from anxious to depressive or psychotic disorders. To date, the pathogenic mechanism underlying neuropsychiatric disorders in patients with GD has not been clearly understood. In fact, the development of neuropsychiatric disorders in patients with GO has been associated with both the detrimental effects of the altered circulating thyroid hormones on the nervous system, and with the psychological discomfort caused by poor quality of life, reduced social interactions and relapsing course of the disease. This paper summarizes current evidence on neuropsychiatric abnormalities in Graves' disease focusing on its impact on QoL and psychosocial function. We remark the importance of a multidisciplinary approach and we emphasize the potential benefit of neuropsychiatric approach on disease perception, patient compliance to medical and/or surgical treatment and clinical outcomes.

Contents

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1. Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, it is characterized by decreased levels of serum thyroid-stimulating hormone (TSH) and/or increased serum levels of triiodothyronine (T3) and thyroxine (T4) [1]. It accounts for 60–80% of all cases of hyperthyroidism in adults, and it can be familial, isolated or associated with other autoimmune diseases [2]. GD is 6–7 times more common in women than in man, with an annual incidence of 2.7% in women and 0.3% in men in the United Kingdom [3]. This difference, which is common for autoimmune diseases, is generally ascribed to the difference between males and females in the immune and endocrine systems [4–6].

Environmental factors are also known to influence the development of GD, with some clear risk factors having been identified, including: increased iodine intake, deficiency in selenium and vitamin-D levels, and smoking, - with the risk being proportional to the number of cigarettes smoked daily. Also, exposure to radiation, viral infections – especially parvovirus B19 and hepatitis C virus - and intestinal dysbiosis may cause hyperthyroidism [7–9]. The most frequent and typical manifestation associated with this condition is Graves' orbitopathy (GO) [10]. Specifically, several evidence showed that 25–50% of patients with GD develop GO. Rarely, GO is also observed in Hashimoto thyroiditis, euthyroid or hypothyroid patients [1,10]. The presence of GO is associated with poor clinical outcomes, impaired quality of life and socio-economic status. It has been shown that early identification of the different phenotypical expression of GO by clinicians and researchers lead to a better management and outcome of the disease [11].

The pathogenic mechanisms of GO have not yet fully understood. It is well known that antibodies against the TSH receptors (TRAb) binding to TSH receptor (TSH-R), inhibit, interfere or stimulate intracellular signaling playing an important role in GO development. In fact, these receptors are highly expressed not only by the thyroid but also by the extra ocular muscles and retro bulbar fat tissue [12]. It has been suggested that circulating TRAb stimulates inflammation and activation of orbital fibroblasts, inducing intraorbital swelling and, at a later stage, fibrotic reaction [13].

The most common symptom of GO is a noticeable change in the appearance of the eyes, including redness and swelling of the eyelids, strabismus and disfiguring proptosis. As consequence, GO severely affects quality of life and social function of the patients and is often associated with neuropsychiatric disorders more than other chronic autoimmune ophthalmic conditions that induce more severe impairment of the visual acuity. In addition, psychological problems of patients with GD may be related not only to the consequences of the ocular impairment but also to the detrimental impact of altered circulating thyroid hormones on the nervous system.

In fact, several studies in healthy human brain revealed that TSH-R are significantly expressed in cortical and limbic areas– amygdala, cingulate gyrus, frontal cortex, hippocampus, hypothalamus and thalamus – suggesting a cross-talk between endocrine and neuropsychiatric systems [14,15]. In patient with GD, whether or not with associated orbitopathy, antibodies binding to cerebral TSH-R may play a role in the development of neuropsychiatric disorders, such as cognitive deficit and emotional impairment [16,17].

A multidisciplinary approach, including endocrinologist, ophthalmologist, psychiatrist and neurologist should be considered to customize the therapeutic strategy in order to improve the quality of life (QoL) of patients, the ocular disease perception and the compliance to medical and/or surgical treatment.

2. Graves' orbitopathy

The ocular involvement in GD is generally bilateral, and, most often, occurs simultaneous with hyperthyroidism or within the first 18 months of thyroid disease [18]. In fact, in clinical practice, the apparently unilateral cases usually show a subclinical contralateral eye involvement as evidenced by orbital imaging. It has been shown that nearly 70% of adult GD patients have magnetic resonance or computed tomographic evidence of extra ocular-muscle enlargement, confirming that GO is a very common occurrence [3,10].

The hallmark of GO is the presence of proptosis, which is related to the orbital soft-tissue enlargement (Fig. 1). This is associated with fat expansion, mostly reported in younger patients, and ocular-muscle swelling which is more pronounced in older patients [19]. The typical symptoms of GO are burning, swelling, sensation of pressure behind the eyes and diplopia, that are related to the inflammation of the muscles and periorbital tissues [10]. However, several conditions associated to GO, such as dry eye and exposure keratopathy, are frequently underdiagnosed but can induce severe detrimental effect on QoL and visual function [20,21]. Exposure keratopathy is related to both proptosis and eyelid retraction, but dry eye may be also observed in absence of GO. Other symptoms of GO include ocular dryness, grittiness, photophobia, pain, redness and vision impairment, [22] related to eyelid retraction and lagophthalmos, decreased blinking rate, increasSSed tear evaporation and corneal epithelial defects or ulcers [10,23,24] (Fig. 1).

Finally, the most severe, insidious and alarming complication of GO is the disthyroid optic neuropathy (DON) which may be associated with permanent visual loss [25].

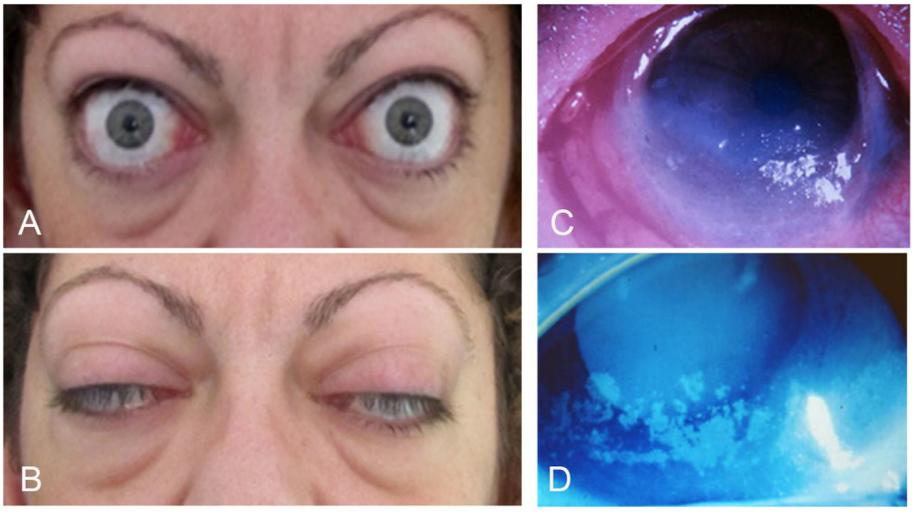

Fig. 1. A patient with GO showing severe proptosis (A), lagophthalmos (B) and inferior epithelial defects (C) stained with fluorescein (D).

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