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Graves' ophtalmopathy and dysthyroid optic neuropathy: Imaging studies for diagnosis

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ABSTRACT

The diagnosis of Graves' ophtalmopathy (GO) is based on clinical examination, laboratory tests (indicating thyroid dysfunction and inflammatory and autoimmune unbalance) and imaging studies (such computed tomography, magnetic resonance imaging, ultrasound and colour Doppler imaging). Imaging studies can be helpful in establishing the certain diagnosis of GO, because they provide objective morphological findings of the orbital structures. An important role of imaging studies is revealed in differential diagnosis versus other orbital diseases and can be also used to evaluate the progression of the disease and follow-up after clinical or surgical treatment.

Keywords: Graves' ophtalmopathy, computed tomography, magnetic resonance imaging, ultrasonography, colour doppler ultrasonography, radionuclide-based imaging

INTRODUCTION

Graves' ophtalmopathy (GO) is an autoimmune inflammatory process that affects the orbital and periorbital tissue, occurring in 25-50% of patients with Graves' disease. Approximately 6% of patients with Graves' ophtalmopathy develop optic neuropathy (ON), a potentially blinding complication [1].

ON is often subclinical and may be masked by other symptoms of myopathy, inflammation and orbital congestion. ON may also occur without proptosis and visual loss may be rapid and irreversible [1,2]. The disease has a self-limited active phase that usually lasts 18 to 24 months and abates slowly (characterised by lymphocytic infiltration, interstitial oedema and glycosaminoglycans deposition in enlarged extra-ocular muscles and retroorbital fat) followed by an inactive phase (with fibrosis and fat infiltration of the orbital tissues). Despite improved diagnostic tests, the diagnosis of ON remains heavily dependent of clinical findings [4].

The clinical manifestation of the thyroid ophtalmopathy include periorbital soft tissue inflammation, lid retraction, lid lag, proptosis, restrictive myopathy, corneal exposure leading to corneal erosion, conjunctival injection, conjunctival oedema and compressive optic neuropathy (5-10% of patients) [11]. Compressive optical neuropathy expressed by occurring double vision, afferent pupillary defect, loss of visual acuity, dyscromatophsia, central or paracentral scotoma, nerve head swelling or optic atrophy [12].

Various imaging features have been associated with the diagnosis of optic neuropathy, such as the degree of enlargement of the extra-ocular muscles, volumetric increase in orbital fat, radiologic evidence of apical optic nerve compression and the presence of intracranial fat prolapse [5-9].

Based on imaging studies (especially CT and MRI), it is possible to establish the degree of extra-ocular muscle and orbital fat enlargement, exclude coexisting orbital pathology, clarify a confusing clinical picture and perform surgical planning [10].

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IMAGING TECHNIQUES IN GRAVES' ORBITOPATHY

Computed tomography (CT)

Computed tomography (CT) scanning is an accurate imaging procedure for the diagnosis of thyroid ophtalmopathy. CT finding in thyroid orbitopathy is fusiform configured enlargement of the extra-ocular muscles with normal tendinous insertions on the ocular globe (different from cylindrical configuration in idiopathic inflammation of the muscles or myositis). Muscle involvement is generally bilateral (90%) and asymmetric (70%) [13].

CT can distinguish normal from abnormal structures of different tissue density based on their differing X-ray absorption properties. Fat and water have low densities and therefore appear black on CT images, in contrast to denser muscles, the optic nerve and bony structures. Acting as a natural contrast medium, the presence of orbital fat allows good spatial and density resolution of orbital structures [14].

The tissue differences inherent in the orbit obviate the need for intravenous contrast in some cases. After digital recording the data are converted via an arithmetic procedure into different grayscale. Compared with isodense tissues (e.g., the brain), tissues with high absorption values (e.g., bone) appear hyperdense, whereas tissues with low absorption values (e.g., water or fat) appear hypodense [15].

A CT scan with positive findings is included in many sets of diagnostic criteria for GO. GO presents un unusual imaging pattern. The extra-ocular muscles appear to be the primary area of orbital involvement. The assessment of muscle enlargement is often subjective and requires comparison with the opposite orbit or prior qualitative experience. Patients with GO usually present symmetrical, multiple extra-ocular muscle enlargement in both orbits, although asymmetrical muscle involvement can occur. Unilateral orbital involvement is uncommon, occurring in only 6-10% of patients [17]. The muscle most frequently affected are the medial and inferior rectus (Fig. 1).

Selection of the CT scanning plane is an intrinsec issue in the assessment of orbital content. Extra-ocular muscles are measured perpendicularly to the orbital wall in the parallel planes to their course: in axial scans (medial rectus, lateral rectus), in coronal scans (inferior rectus, superior group, superior oblique).

Individual volume elements obtained from axial slices can be reformatted in any plane to produce coronal, saggital, paraxial or parasaggital oblique images.

Post processed planar reconstructions enable the consultant to perform a survey of the orbits while the scanning is performed in single plane acquisition.

Enlargement of the extra-ocular muscle diameter as well as density decrease was pertinent to all muscle groups, implying that fat and inflammation in dysthyroid ophtalmopathy usually do not incorporate individual orbital elements, but the entire orbit compartment.

Computed tomography imaging enables highly sensitive and specific diagnostic of the development of optic neuropathy with apical crowding induced by the muscles and/ or fat tissue that seems to be the most appropriate indicator of intraorbital pathology [19].

In a study with a series of 116 CT scans of patients with GO in different stages of the disease, 85% of the patients displayed definitive enlargement of the extra-ocular muscles [20]. The inferior rectus was enlarged in 77% of the cases and the medial rectus in 75% cases. This two groups of muscles were the most severely enlarged. The lateral rectus (51%) and the superior rectus (50%) were involved less frequently and less severely [21].

Many studies suggest that expansion of the orbital fat compartment also represent s a major component of the disease process, although the extra-ocular muscles have been described as the "shock organ" of GO [22].

Graves' orbitopathy ia associated with a wide spectrum of radiological findings in addition to extra-ocular muscles and fat tissue enlargement, as described in literature [23,24,25].

CT findings may include bone changes, especially in lamina papyracea of the ethmoid, with bowing resulting from muscle pressure. Exophthalmos, lacrimal gland displacement and enlargement, anterior soft tissue swelling and superior optic vein dilatation may be revealed in imaging studies, but these are unspecific findings that do not support the diagnosis of GO [25,26,27].

Several studies have shown that CT scan parameters increase the suspicion of dysthyroid optic neuropathy (DON). Approximately 6% of patients with Graves ophtalmopathy develop optic neuropathy (ON), a potentially blinding complication [1]. This is primarily attributed to an apical orbital crowding and optic nerve compression. A subgroup of patients is believed to have optic nerve stretching secondary to increased orbital volume and a narrow orbital apex, which may lead to earlier compressive features without other significant manifestations [1].

The most important mechanism of stretching of the optic nerve is orbital apical crowding by the enlarged extra-ocular muscles, although there is one more possible pathogenic mechanism for stretching optic nerve by increased orbital fat with axial proptosis [29-31].

Barrett [28] described a simple method of quantifying extra-ocular muscle impingement of the optic nerve space. The study showed that a muscle index of 67% or greater indicated compressive neuropathy with a diagnostic sensitivity of 67%, although no patient with DON had a muscle index of less than 50%.

Chan et al. [32] highlighted the importance not only of extra-ocular muscle enlargement but also the role of the bony orbit and its usefulness as a predictor of DON. The bony orbit capacity was quantified using standardised orbital angles on axial scans. The study authors calculated an index of orbital muscular crowding in combination with lateral and medial orbital wall angles that had 73.3% sensitivity and 90% specificity.

Changes observed with CT in sequential measurements of the extra-ocular muscles may be related to clinical activity. Muscular involvement occurs early in GO and subsides together with other clinical signs [33].

Nevertheless, MRI is preferred for studies assessing disease activity because its better performance in the evaluation in soft tissues.

Magnetic resonance imaging (MRI) in Graves' ophtalmopathy (GO) diagnosis

MRI estimates disease activity based on the water content of the tissues.

In GO, strongly T2-weighted and fat-suppressed images obtained using the turbo inversion recovery magnitude (TIRM) and short tau inversion recovery (STIR) sequences have been shown to be useful in detecting extra-ocular muscle oedema [34].

To differentiate active from inactive GO, inflammatory oedema of the extra-ocular muscles must be distinguished from fibrous end-stage disease with fatty degeneration using the T2 relaxation time, which is shorter for fibrous tissue than for inflammatory tissue [35].

Some authors (Mourits and the Amsterdam orbitopathy group) [36] described correlations between clinical activity scales (such as clinical activity score CAS) and MRI images.

VISA classification described by Dolman and Rootman [37] can be very helpful in assessing disease activity. The combination of MRI studies and clinical scores would improve diagnostic accuracy. Other researches have not found evident correlations between MRI findings and CAS scores. However, MRI is considered to be useful for monitoring the response to Graves orbitopathy treatment, using measurements like the signal intensity (SI) and signal intensity ratio (SIR).

It is an important aspect of differential diagnosis based on MRI images because it is possible to distinguish inflammatory oedema from congestive venous outflow in burned-out disease, when gadolinium is combined with fat saturation techniques.

Not-fat-saturated T1w images are also useful in the detection of fatty muscle degeneration. These fatty or fibrotic muscle changes display no contrast enhancement on matched fat-saturated T1w images.

Very few MRI studies have directly assessed DON. Dodds et al. [40] assessed DON in a high - resolution MRI study in which they compared the diameter of the optic nerve at seven different positions from the ocular globe to the prechiasmal region in three groups (control, GO with DON, GO without DON).

The results showed that the optic nerve diameter was significantly smaller in the group with DON. But the authors admitted that the reduction in optic nerve size in the GO with DON group, neural compression could not be demonstrated as a pathogenic mechanism. It was also observed the reduction in the optic nerve diameter in the absence of enlarged extra-ocular muscles, suggesting that the optic nerve compression results from the increase of the infraorbital pressure due to the increased fat volume.

Ultrasonography (US) in Graves' orbitopathy

Standardised diagnostic US for eye disease is performed using high frequencies (8MHz) and small wavelengths to visualise ocular small structure.

It is performed both types of trans-ocular scanning A and B.

A-scan are used to assess the tissue characteristics based on the reflected acoustic waves.

This technique is sensitive for identifying the thickening or thinning of the muscles and for differentiating diagnostics. The reflectivity of the extra-ocular muscles may change as a result of tissue oedema and cellular infiltration [3].

Using B-scan is easier to visualise the orbital structures. B-scans are very helpful in topographic evaluations and to establish which individual rectus muscles are enlarged.

The use of US has also been proposed for evaluating disease activity.

Prummel et al. [41] demonstrated extra-ocular muscle reflectivity changes in the inflammatory phase of GO, suggesting that US is an reliable tool to evaluate disease activity. In the inflammatory phase (active) the extra-ocular muscles have a lower internal reflectivity, due to oedema. In the end-stage (inactive) muscles showed irregular high reflectivity from echogenic fibrotic scar tissue.

Not all studies have found correlations between clinical activity score (CAS) and US reflectivity [38,42].

It is required that the adequate measurements of the muscles reflectivity to be performed by an experienced examiner with a standardised A-wave US equipment.

US has been rarely used to identify the presence of DON, suggesting that US can detect DON- related enlargement of the subarachnoid space of the optic nerve [15].

Color Doppler imaging (CDI) in Graves' orbitopathy

CDI is an ultrasonic imaging modality that allows the assessment of blood flow in real time on a gray-scale B-mode background.

CDI have been recently introduced as an adjunct to the clinical examination and cross- sectional imaging for evaluating several pathological conditions in the orbit.

CDI assessed the blood flow in the orbital vessels and detect changes in the perfusion of the orbital arteries and veins [43].

CDI produces conventional grayscaleUS images together with informations about the direction and the velocity of the blood flow.

CDI is used to investigate changes in blood flow parameters in disorders like ischemic optic neuropathy, central artery occlusion, central vein occlusion, glaucoma, diabetes mellitus, ocular ischemic syndrome, uveitis and endophtalmithis.

In orbital pathology, CDI is performed for the evaluation of cavenous-carotid fistula, orbital varix, orbital tumors, orbital cellullitis and orbital inflammatory conditions [44,45].

CDI is also used as a tool for diagnosing GO and Assessing disease activity.

Several studies have compared the orbital blood flow in GO patients and control subjects [46,47].

Benning et al. [46] found that the flow velocity in the right ophtalmic artery was much increased in subjects with clinically active GO than control subjects.

Other authors confirm this findings, which supports the assumption that orbital inflammation increases orbital blood flow [45].

Radionuclide-based imaging evaluation of Graves' ophtalmopathy

Octreoscan (octreotide scintigraphy) is an imaging modality to determine the phase of the disease in an individual patient [49]. It was observed that accumulation of ocreotide, a somatostatine analoque labelled with radioisotope indium-111, binds in the thyroid and the orbit to the somatostatin receptor in patients with active GO[50]. The octreoscan does does not provide information on inactive patients. Although several studies have found a relation between octreoscan uptake and severity of GO [51], the others did not find such a correlation [52].

'The positron emission tomography (PET) appears also as promising tool for diagnosting of active phase of GO. PET is a noninvasive diagnostic of active method that has been used as a mean for differential diagnosis of inflammatory and malignant processes and it offers the ability to perform functional and metabolic assessment in cases of the absence of any tissue structural alteration [53].

CONCLUSIONS

The nuclear medicine-based imaging continues to be important in the diagnosis and management of the thyroid-associated ophtalmopathy.

CT remains the main imaging modality in Graves' ophtalmopathy and can be used to establish the degree of extra-ocular muscle and orbital fat enlargement. In some cases CT can be great help in the detection of DON using linear, area or volumetric indexes of orbital apex crowding. However, CT provides little information about the disease activity.

Although CT is excellent for outlining bone details, MRI provides better soft tissue details and is useful for evaluating the extra-ocular muscles, optic nerve and fat and appears to be useful for monitoring the response to treatment using measurements such as the signal intensity (SI) and signal intensity ratio (SIR). Further studies are necessary in investigate the ability of MRI to detect DON, alone or in association with CT. MRI has become non-useful adjunct when GO related muscle involvement must be differentiated from other orbital conditions.

PET/CT imaging modalities are able to recognise the early active phase of the disease and to predict the response to anti-inflammatory treatment in majority of GO patients.

In clinical practice, US may be used to measure the extra-ocular muscles and to exclude other disease. CT and MRI performed an accurate evaluation of the orbital apex compared with US.

CDI evaluation may become useful in the management of GO, because is the most adequate technique that provides informations about orbital venous drainage.

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