Dysthyroid optic neuropathy

Dysthyroid optic neuropathy: a clinical diagnosis or a definable entity?

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The diagnosis of DON should be made correctly; those affected should be treated promptly and those unaffected spared the risks associated with treatment.

Optic neuropathy is the most feared complication of thyroid eye disease (TED). Thankfully, it is rare, affecting perhaps 4–8% of patients with TED,^{1,2} but when diagnosed requires urgent treatment with medical (eg, high-dose intravenous steroids) or surgical decompression to avoid permanent or progressive visual loss.³ However, both these treatments carry a considerable risk of morbidity. Hence, it is essential that the diagnosis is made correctly in order that those affected are treated promptly and those unaffected are spared the risks associated with treatment.

Several features are used to make the diagnosis of dysthyroid optic neuropathy (DON) (table 1).^{1,2,4} The assumption is generally made that if any of these features are present in an individual with dysthyroid eye disease and no other explanation of the defect is apparent, then the individual has DON. Unfortunately, alternative causes for visual impairment are often present in TED—estimated at 20% or more of cases.^{5,6} Several of these may be linked to the TED itself (eg, keratopathy or glaucoma due to increased orbital venous pressure),⁷ whereas others are coincidental (eg, amblyopia, uncorrected refractive errors or cataracts). This poses a considerable problem: if the alternative causes are not identified, then DON may be inappropriately diagnosed, whereas if alternative causes are present, visual impairment might be inappropriately ascribed to them when in fact DON is present.

So is it possible to improve our diagnostic accuracy for DON? The large survey from the European Group on Graves' Orbitopathy (EUGOGO) collaboration reported in this issue of *BJO* contributes further information to this debate (see page 455).⁸ Clinical features are reported for 94 eyes in 47 patients with TED, 77% of which were clinically considered to have DON. Of 47 patients, 13 (28%) had ocular comorbidity including glaucoma, cataract, amblyopia and corneal ulcer.

The survey also emphasised that the presence of other features of TED—soft-tissues signs, signs of clinical activity, proptosis or dysmotility—does not help confirm or refute the diagnosis of DON, and indeed such features are not infrequently absent. For example, 25% of patients with DON had a clinical activity score of <3 and 33% of eyes with DON did not have proptosis >21 mm. These features confirm previous reports.^{1,2,4}

When it comes to features that might be specific for DON (table 1), these were generally absent in patients not considered clinically to have DON, giving them a relatively high specificity (70–100%).⁸ However, few of them were present in >50% of all cases, giving individual criteria a low sensitivity (table 1).

The three exceptions were radiological evidence of optic nerve compression, reduced visual acuity and impaired colour vision. This is interesting, but it must be remembered that there was no defined "gold standard" for the diagnosis of DON in this survey, so the apparently high prevalence of, say, impaired colour vision or change in visual acuity might arise from the fact that these are the features that clinicians traditionally take into account most in making a "clinical" diagnosis of DON. Crowding of the orbital apex performed particularly well as a predictive factor, and this is of interest as it has the potential to be more objective. Fat prolapse through the superior orbital fissure carried a greater specificity of 100% (but a sensitivity of only 20%) suggesting that it may also be a useful sign where present. In the EUGOGO Survey it was not made clear whether all scans were reassessed by a limited number of experts and, if so, whether the experts were unaware of the clinical diagnosis, but similar findings have been reported previously.² Visual evoked potentials (VEPs) have been claimed to have up to 96% diagnostic accuracy for DON, especially if the N75-P100 amplitude for 15° checks is used.⁹ However, the authors of this study

concede that patients with concomitant conditions that might affect VEPs were excluded, which is likely to result in a much lower diagnostic specificity in the real world. Importantly, there was also a significant false-negative rate associated with the use of VEPs in the EUGOGO Study.

Could response to treatment be used as part of the criteria to define the diagnosis of DON? Although initially this seems an attractive way of distinguishing visual loss due to DON from that due to concomitant ocular pathology, it has several disadvantages. Firstly, it could only be used as a criterion for diagnosing DON in retrospective series, not in prospective studies in which criteria are being sought to determine whether treatment should be given or not. Secondly, there are reasons why DON may be present but not respond: up to 50% of eyes may fail treatment with medical decompression depending on the regimen used³; and if optic nerve compression has been insidiously present for some time, recovery of function may be limited even after surgery. Thirdly, it is possible that treatment may simultaneously improve concomitant conditions, such as exposure keratopathy, choroidal folds and raised intraocular pressure, and hence result in benefit not attributable to the presence of reversible DON.

If the diagnosis of DON is subject to the difficulties of varying presentation and confounding comorbidities, and all the clinical and electrophysiological features used to diagnose this condition are subject to significant false-positive and false-negative rates, is there any way we can improve on defining this condition or will it remain a clinical judgement? One approach is to synthesise what we know about the clinical, radiological and electrophysiological features of DON from the EUGOGO Group and others into a diagnostic algorithm such as that shown in fig 1. In the first step of the algorithm, it is assumed that although individual features of TED are frequently absent, it is unusual for no feature to be present if visual impairment is due to TED. A marker of new-onset impairment of visual function is then required (any of impaired colour vision, reduced acuity, visual field abnormality, relative afferent pupillary defect, abnormal VEPs or optic disc swelling). If no alternative cause of visual impairment is present and radiological assessment suggests apical crowding or fat prolapse through the superior orbital fissure, then DON is likely. If there is no radiological evidence of optic nerve compression, or radiological compression is evident but an alternative cause for nerve compromise is

Figure 1 Diagnostic algorithm for dysthyroid optic neuropathy (DON). TED, thyroid eye disease.

Table 1 Features used to diagnose – EUGOGO DON study^a

Clinical criteria used to diagnose DON	Clinically diagnosed DON cases in which criteria are present (%) ^a
Impaired colour vision	70
Optic disc swelling/atrophy	45
Abnormal visual acuity	75
Relative afferent pupillary defect	48
Abnormal VEPs	42
Crowded apex on scanning	88
Abnormal visual fields	42

DON, Dysthyroid optic neuropathy; VEP, visual evoked potentials.

present, then DON remains “likely but not proven”. In all other circumstances, DON is unlikely. In future, more widespread availability of high-resolution scanning for optic nerve compression and optical coherence tomography assessment of the retinal

nerve fibre layer may further improve on the radiological diagnosis, which is the key novel element of such an algorithm.

This is a hypothetical scheme intended to stimulate debate and further study. Investigators such as EUGOGO who have

managed to accumulate significant numbers of cases of possible DON are in a position to determine how well such a scheme might work in the field and how to improve on it. Progress in being able to accurately define DON will help to ensure that those who need sight-saving treatment for DON receive it in a timely manner, whereas those who do not need it are spared the unnecessary risk of side effects. At the same time, improved diagnostic criteria are essential for progress in developing improved treatments for DON, by ensuring that all clinical trials are treating the same entity.

Br J Ophthalmol 2007;**91**:409–410.

doi: 10.1136/bjo.2006.110932

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Competing interests: None declared.

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