## Commentary: Dysthyroid optic neuropathy

Dysthyroid optic neuropathy (DON) is the most severe sight-threatening complication of thyroid eye disease (TED) and is reported in 5%–8.6% of patients.[1] The prevalence reported in India seems to be higher, with a group from southern India reporting DON in 14% of TED patients.[2] The same group reported a 19% prevalence of visual morbidity in TED, which included DON, exposure keratopathy, and double vision.[2]

DON is clinically diagnosed in TED in the presence of a decrease in visual function (acuity or field) not attributable to other ocular comorbidities, decrease in color vision, relative afferent pupillary defect (RAPD), and optic nerve head edema.[1,3] Making a clinical diagnosis of DON may sometimes be difficult given that 50%–70% of patients have visual acuity ≥20/40 and 70% have bilateral disease with no RAPD.[1] The sensitivity and specificity of visual acuity in diagnosing DON in the current series were 80% and 53%, color vision at 46% and 10%, and RAPD at 80% and 77%, respectively.[3] Eyelid droopiness is a new sign reported by Weis *et al*. in DON.[4] Therefore, clinicians often resort to corroborating the clinical diagnosis of DON with investigations and imaging. Investigations done to support a clinical diagnosis of DON include visual field and visual evoked potential.[1,3] A variety of visual field defects have been reported in DON: central and cecocentral defects and other breakout patterns with or without generalized reductions in

sensitivity.[1] The visual field shows a remarkable response to medical or surgical therapy in DON and predates recovery seen in optic nerve edema.

Orbital imaging is valuable in supporting a diagnosis of DON.[1,5] Apical crowding described by Nugent as effacement of the orbital fat around the optic nerve has a high correlation with DON.[5] Though apical crowding is one of the most common imaging characteristics reported in the literature, the position in the orbit where the coronal cross-section is to be taken has not been described. One must also remember that 16 of the 124 TED patients who did not have DON showed severe apical crowding in Nugent's study, highlighting the importance of correlation of imaging with clinical characteristics before making a definitive diagnosis.[5] Fat prolapse into the superior orbital fissure was reported to have high specificity at 100% but a low sensitivity at 20% in DON by the European Group on Graves Orbitopathy (EUGOGO).[6] In the setting of several volumetric indices described for DON, muscle index and bony orbital wall angle described by Chan *et al*.[7] has 73% sensitivity and 90% specificity. This volumetric index takes into account both the soft tissue (muscle) crowding and narrowed bony anatomy at the orbital apex that possibly has a role in DON.[7]

MRI of the orbit is suited to highlight soft-tissue characteristics.[1,8] MRI can help detect water content in the orbital tissue, suggestive of active inflammation in the orbit.[8] T2-weighted sequences along with short tau inversion recovery sequences (STIR) have been reported to correlate well with clinical activity scores in TED patients.[8] Extraocular muscles that are inflamed in an active phase of TED show high signal intensity in STIR sequences.[8] Furthermore, signal intensity ratios calculated by comparing the signal intensity generated from extraocular muscles with non-orbital tissues such as temporalis muscle have been used to differentiate active from inactive TED.[9] It is important to differentiate edema present in active TED from water content present in congestive TED with reduced venous flow, and this differentiation has been described using T1W sequences with contrast and fat suppression.[10] Dodds *et al*.[11] studied the optic nerve diameter at multiple points in serial coronal sections in DON to look for compression. There was a reduction in optic nerve diameter in DON, but a considerable overlap with controls made conclusive evidence difficult in these measurements.[11]

Older age, male gender, chronic smoking, and diabetes mellitus have been found to be significant risk factors predisposing disease severity.[1,2,12] In the Indian subcontinent, several large retrospective series have shown older age and male gender to be risk factors in DON.[1,12,13] It is particularly striking that diabetes mellitus, particularly type 2, has been implicated with severe TED in several parts of the Indian subcontinent in the recent past.[12,13] This is not surprising given DM has a high prevalence, with 1 in 5 adults >20 years old in India shown to have diabetes mellitus or pre-diabetic status.[14] Our retrospective series of 201 TED, of which 49 were diabetic, showed that those with DM had double the risk of developing DON in the first year compared to TED patients without diabetes.[12] In addition, TED with DM had a significantly higher risk of bilateral and recurrent DON.[12] In the current series, all patients who had recurrent DON were diabetic.[3] Furthermore, the risk of developing DON gets compounded in the presence of both smoking and DM, with the risk of poorer visual outcomes necessitating prompt and appropriate management.[12]

Compression at the orbital apex, ischemia, and inflammation have been proposed to play a role in the mechanism of DON in TED.[1,12] By far, compression theory is the most accepted. Compression at the orbital apex is caused by the enlargement of the extraocular muscles or even high intraorbital pressure after fat enlargement in TED.[1] This theory is supported by some evidence gained from the dramatic improvement in visual function documented even hours after apical decompression in DON.[1] Vascular insufficiency playing a role in DON may be understood from the significantly higher risk of DON seen in diabetes mellitus.[12] The hypothesis postulated for the increased risk is microangiopathy noted in diabetes mellitus.[12] Optic nerve stretch has been postulated to be an independent risk for the development of DON.[1,15] Bain *et al*.[15] performed an interesting set of experiments in guinea pig optic nerves to find that neuropraxia occurs when nerves sustain 18% stretch and immunohistochemical changes appear at 21% stretch from baseline. These experiments give credence to the optic nerve stretch mechanism proposed in DON; thus, orbital decompression to relieve the optic nerve stretch seems the most reasonable modality in such scenarios. Inflammation as a cause of DON though plausible seems most difficult to have supporting evidence given the constraints of tissue biopsy in active DON.

Corticosteroids remain pivotal in the management of DON with dramatic responses seen with intravenous corticosteroids.[1,12,16] EUGOGO protocol recommends 12 weekly cycles of intravenous corticosteroids with orbital decompression reserved for TED patients with DON who show poor or no response to corticosteroids.[16] Oral corticosteroids are sometimes used in tapering doses after intravenous or even between weekly cycles, which the authors in the current series have acknowledged.[3] Orbital decompression, primarily bony and even fat decompression, has shown good responses in DON recalcitrant to intravenous corticosteroids.[1,12,16] Comparison of medial wall versus deep lateral wall orbital decompression in DON has shown comparable visual outcomes, though the deep lateral decompression techniques fare better in proptosis reduction.[17] However, orbital decompression in "hot" orbits as is often the case in DON is likely to cause new-onset or worsening of existing diplopia.

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