Case Report

# RAPD as a clinical alert for early evidence of dysthyroid optic neuropathy

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## Abstract

Dysthyroid optic neuropathy (DON) is a serious manifestation of thyroid eye disease (TED) resulting in permanent visual loss. There is controversy regarding the diagnostic features of DON. Relative afferent pupil defect (RAPD) in TED is highly specific for DON. Our first patient, a 42-year-old male presented with proptosis and intermittent blurring of vision with best corrected visual acuity of 6/6 in both eyes and right RAPD as an early sign of DON. Our second patient, a 54-year-old female presented with proptosis and clinical activity score <3 at the time of presentation. She developed intermittent blurring of vision with left RAPD on her second presentation as clue of bilateral asymmetric DON in her eyes, though BCVA was 6/6 both eyes. Both cases of bilateral asymmetric DON had RAPD as early specific sign of DON, which prompted us to do detailed radio-imaging to confirm DON, hence highlighting the importance of RAPD.

**Keywords:** Apical crowding, dilated SOV, DON, RAPD, thyroid eye disease

## Introduction

Dysthyroid optic neuropathy (DON) is a dreaded complication of Graves orbitopathy. It has an incidence of 5%–8.6%.[1-3]

The diagnosis of DON can be based on variety of clinical features. The European Group on Graves' Orbitopathy (EUGOGO) survey found impaired visual acuity (<20/40) in 73%, colour vision impairment in 77%, visual field defects in 71%, relative afferent pupillary defect (RAPD) in 45% and optic disc swelling in 56% of eyes in patients, which were subsequently diagnosed to have definite DON.[4] The presence of DON may be subclinical and masked by more obvious signs of orbital congestion.[3,5,6]

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The visual acuity also often lags behind other symptoms and signs of DON.[7] In unilateral and bilateral asymmetric cases, RAPD may be an early alerting sign. Good visual acuity does not exclude the diagnosis of DON as 50–70% cases of confirmed DON have best corrected visual acuity (BCVA) of 20/40 or better and 76% are bilateral and symmetrical.[6]

We hereby discuss two cases of dysthyroid optic neuropathy who were suspected to have DON by using simple non-invasive clinical assessment of pupillary reactions. Informed written consent was taken from the patients, which were followed by approval from institution ethical committee for reporting of the cases.

## Case History

### Case-1

A 42-year old male, a known case of Grave's disease for 1 year on anti-thyroid medication (tablet Carbimazole 10 mg twice a day), presented to us with intermittent horizontal diplopia,



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intermittent blurring of vision and bulging of both eyeballs for the last 10 months. Ocular examination revealed best corrected visual acuity (BCVA) of 6/6 in both eyes, bilateral lid oedema and proptosis (28 mm-right, 24 mm-left). There was limitation of abduction and elevation in both eyes [Figure 1] with Right RAPD Grade I. Fundus revealed no optic disc changes. Colour vision (Ishihara) was normal; however, log contrast sensitivity (Pelli-Robson) in right eye was 1.2 and in left eye was 1.5. Diplopia charting revealed crossed horizontal diplopia.

Based on these findings, patient was advised Contrast Enhanced Computed Tomography (CECT) orbit, which showed bilateral bulky muscles [Figure 2] with internal hypodense nonenhancing stroma with relative sparing of lateral rectus. [Nugent score, right - grade 3, more than 50% effacement and left - grade 2, 25-50% effacement][8] [Figure 3a]. Contrast Enhanced Magnetic Resonance Imaging (CEMRI) orbit also showed bulky bilateral medial, superior and inferior recti and crowding in right orbital apex with intra-substance hyperintense signal in right optic nerve suggestive of compression [Figure 3b].

Visual Field Analysis (30-2 threshold) was within normal limits. Pattern reversal visual evoked potential (VEP) showed increased P100 latency and reduced amplitude in both eyes (Right-107.4 ms, 3.9 uV, Left-101.4 ms, 5.6 uV). Thyroid profile was deranged with free T3 – 72 ng/dl, free T4 – 4.8 μg/dl and TSH – 8.83 μIU/ml. Thyroid scan showed bilateral thyroid gland enlargement suggestive of diffuse toxic goitre.

With diagnosis of compressive optic neuropathy patient was given methyl prednisolone pulse therapy 1 g intravenously for 3 days under close monitoring followed by oral steroids 100 mg per day in tapering doses over 12 weeks. Improvement in pupillary reaction and log contrast sensitivity (1.8 in both eyes) was seen with pulse steroid therapy. Hertel's measurements also decreased to 25 mm-right and 22 mm-left with improvement in ocular motility over a period of 2-months. On 1-year follow-up patient was maintaining euthyroid status and there was no evidence of deterioration of visual functions, no significant diplopia or any clinical evidence of optic nerve dysfunction.

## Case-2

A 54-year-old female, a known case of Grave's disease for 1 year on anti-thyroid medication (tablet Carbimazole 10 mg once a day), presented to us with horizontal diplopia, redness of both eyes and bulging of both eyeballs for last 6 months. Ocular examination revealed BCVA of 6/6 in both eyes, bilateral lid oedema and proptosis (28 mm-right, 27 mm- left). There was limitation of elevation, adduction and abduction of both eyes [Figure 4] with normal pupillary reaction and bilateral normal optic disc with normal colour vision and log contrast sensitivity. Diplopia charting revealed crossed horizontal diplopia.

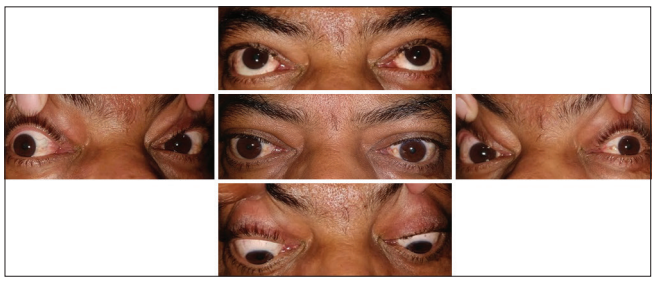

**Figure 1:** Case 1: Clinical photograph showing limitation of abduction and elevation in both eyes

Based on these findings, patient was advised CECT orbit, which showed bilateral bulky intraocular muscles with internal hypodense nonenhancing stroma consistent with thyroid ophthalmopathy. There was no crowding at orbital apex. Visual Field Analysis was within normal limits. Thyroid profile was within normal limits. Thyroid scan showed bilateral thyroid gland enlargement suggestive of diffuse toxic goitre.

Patient was advised prednisolone 80 mg orally once daily with continuation of anti-thyroid medications along with radiation therapy and a review after 3 weeks. However, she was lost to follow-up.

She presented 6 months later with increasing prominence of both eyes and intermittent blurring of vision. Ocular examination at this time revealed BCVA of 6/6 both eyes with bilateral lid oedema and proptosis (29 mm-right, 28 mm-left) and left RAPD Grade I. Retinal examination showed bilateral normal optic disc. However, there was reduced log contrast sensitivity in both eyes (right-1.4, left-1.2) with paracentral scotoma left eye on visual field analysis. Pattern VEP showed increased P100 latency and reduced amplitude in both eyes (right-114.3 ms, 4.4 uV, left-115.8 ms, 4.7uV). Thyroid profile was deranged with free T3 –7.08 ng/dl, free T4 – 2.06 μg/dl, TSH – 0.006 μIU/ml.

Based on these findings, patient was advised CECT orbit, which revealed bulky bilateral recti muscles [Figure 5] with bilateral optic nerve compression (Nugent score - Grade 2,

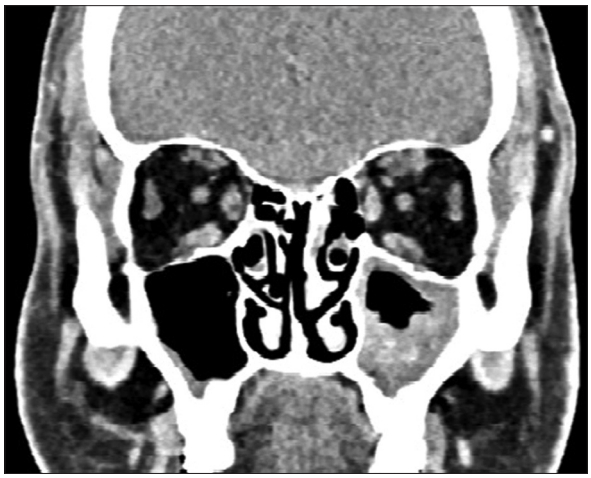

**Figure 2:** Case 1: CECT orbit coronal scan showing enlarged muscles, Right (Inferior rectus - 8.06 mm, medial rectus - 7.85 mm, superior rectus LPS complex - 5.76 mm, and lateral rectus - 3.18 mm), Left (Inferior rectus - 9 mm, medial rectus - 6.3 mm, superior rectus LPS complex - 6 mm, lateral rectus - 3.82 mm)

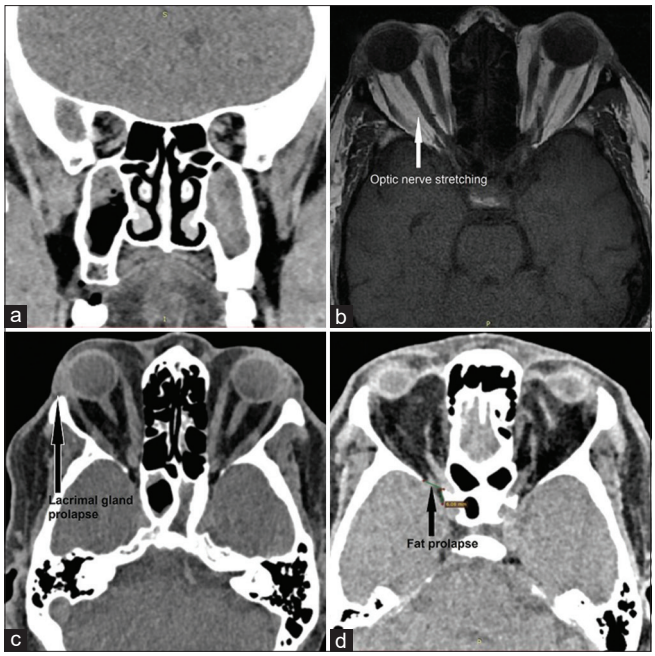


**Figure 3:** Case 1: (a). CECT orbit coronal scan showing effacement of perineural fat due to enlarged extraocular muscles at the orbital apex, Nugent score - Right more than 50% effacement (Grade 3), Left 25-50% effacement (Grade 2). (b). CEMRI orbit axial scan showing right optic nerve stretching. (c). CECT orbit axial scan showing lacrimal gland displacement anterior to frontozygomatic process on both sides. (d). CECT orbit axial scan showing intracranial fat herniation through superior ophthalmic fissure bilaterally, Right - 6.08 mm, Left - 3.28 mm

both eyes) [Figure 6a]. CEMRI Orbits also showed bilateral bulky inferior, medial, superior and lateral recti with optic nerve stretching and compression [Figure 6b].

With diagnosis of DON, patient was given methyl prednisolone pulse therapy 1 g intravenously for 3 days followed by oral steroids 80 mg per day in tapering doses over 12 weeks. There was improvement of optic nerve function after 2 days of pulse steroid therapy with normal left pupillary reaction and log contrast sensitivity improving to two in both eyes. Hertel's measurements also decreased to 28 mm-right and 26 mm-left with improvement in ocular motility over a period of 2 months. Patient is euthyroid and has not shown any worsening of her visual functions and orbital parameters till the last follow-up.

## Discussion

Multiple objective measures grade the physical signs, symptoms and severity of thyroid eye disease, including NO SPECS, CAS, VISA and EUGOGO; however, no single protocol completely characterises dysthyroid optic neuropathy.[9-12] While exact mechanisms of DON remain elusive, apical compression by enlarged extraocular muscles and/or fat (crowding), ischaemia due to increased retrobulbar pressure, mechanical stretch due to proptosis and perineural inflammation have been proposed.[7,13]

According to Tanner *et al.*,[14] RAPD is one of the few objective signs of asymmetric optic nerve compression but requires good

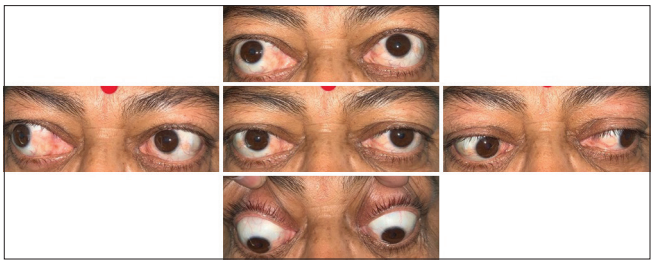

**Figure 4:** Case 2: Clinical photograph showing limitation of abduction, adduction and elevation in both eyes

examination technique; it is difficult to grade and is obviously of limited value in those with symmetrical disease processes. Neigel *et al.*[3] in their series of 58 patients with DON found bilateral DON in 63% patients. An afferent pupillary defect (APD) was found in 34.8% of the optic neuropathy group. In EUGOGO survey of 47 patients with DON, eyes having definite DON had RAPD in 45% patients and eyes with equivocal DON had RAPD in 40% patients.[4] In a study by Suttorp-Schulten *et al.*,[15] out of 25 patients who had DON, 11 had unilateral DON out of which three patients had DON with visual acuity less than 20/70 and RAPD as a clinical finding of DON. In a study by Rutkowska–Hinc *et al.*,[16] amongst 14 patients diagnosed with DON, five had unilateral DON and nine had bilateral DON, and amongst these nine bilateral cases, two showed RAPD suggestive of asymmetry. In a study by Trobe *et al.*,[5] 76% patients had bilateral DON, where pupils were uniformly equal in size in dim illumination, but a RAPD was present in all patients with asymmetric field loss, even in the presence of similar interocular acuity. Sears *et al.*[17] in their case series of 10 patients of DON had RAPD in all of their unilateral cases and asymmetric bilateral cases except in one. In our case 1, grade 1 RAPD was the earliest warning clinical indicator of DON, while in case 2 also, it was the clue to further evaluation for DON.

The pseudo isochromatic colour vision screening procedure rarely identifies an acquired colour defect in DON unless optic neuropathy is severe.[3] Trobe *et al.*[5] in their study of 21 patients tested with Ishihara chart found 10 patients with abnormal colour vision, but only when acuity was below 20/40. However, both our patients had normal colour vision as tested on Ishihara. Kuebler *et al.*[18] in their study of 48 patients found that blue yellow (tritan) deficiency is a sensitive indicator of DON (98.9%) even in the presence of relatively good BCVA and no visual field defects.

Contrast sensitivity may diminish in TED patients who do not show other signs of DON, indicating that this test may detect subclinical optic nerve damage early in the disease process with normal or near normal visual acuity.[19] Tanner *et al.*[14] found consistent decrease in chromatic discrimination sensitivity in all cases of DON and in patients with grade 5 (NOSPECS) disease who subsequently developed DON. Studies have shown that DON produces different pattern of contrast sensitivity abnormality and the discrimination amongst patients is much better if spatial frequencies less than 1 c/deg are tested.[15,20,21] In our patient 1 log contrast sensitivity was 1.2 in right eye

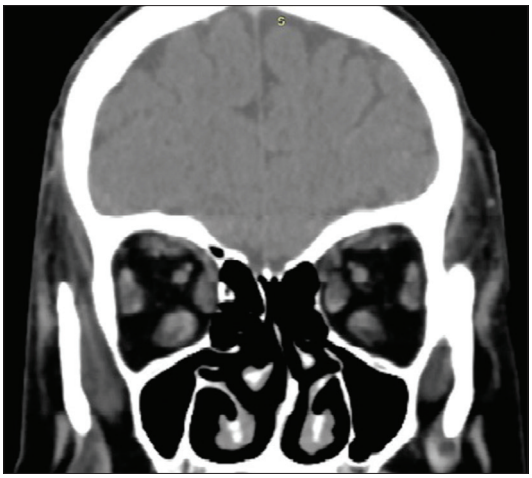

**Figure 5:** Case 2: CECT orbit coronal scan showing enlarged muscles, Right (Inferior rectus - 8.55 mm, medial rectus - 5.29 mm, superior rectus LPS complex - 6.34 mm, and lateral rectus - 8.39 mm), Left (Inferior rectus - 8.47 mm, medial rectus - 6.49 mm, superior rectus LPS complex - 6.35 mm, lateral rectus - 6.80 mm)

and 1.5 in left eye and in patient 2 it was 1.4 in right eye and 1.2 in left eye.

Although measurements of contrast sensitivity can be used to assist in the diagnosis of DON and in monitoring the treatment effects, they cannot by themselves be used to diagnose the condition. Complete evaluation by visual fields, VEP and CT scan is still recommended.[21] Electrophysiological testing in DON has shown that pattern reversal VEP (pVEP) is more reliable than flash VEP. Systematic review by Iao *et al.*[22] reported significant differences of pVEP parameters, with prolonged P100 latency in eyes with DON, to eyes without DON from TAO patients or eyes from TAO patients to control. Tsaloumas *et al.*[23] also demonstrated reduction in P100 amplitude (relative or absolute) in 11 out of 13 eyes with DON. In both our cases, latency and amplitude were reduced in both eyes. However, the eye with RAPD had more significant reduction.

Imaging studies are of great help in early identification of those with DON, thereby enabling timely treatment.[24] The following findings on orbital imaging are indicative of a possible optic neuropathy in TAO: severe apical crowding; optic nerve stretching, increased muscle diameter index; severe proptosis; dilated superior ophthalmic vein (SOV); anterior displacement of the lacrimal gland and intracranial fat prolapse.

Nugent *et al.*[8] graded the severity of apical crowding in patients with and without optic neuropathy based on effacement of perineural fat planes by enlarged extra ocular muscles. Volumetric measurements of extraocular muscle tissues can demonstrate the condition of apical crowding in a quantitative way and have been used as an indicator of DON.[25] Our case 1 right eye had grade 3 and left eye grade 2 apical crowding [Figure 3a]. In case 2, both eyes had grade 2 apical crowding [Figure 6a]. Rutkowska–Hinc *et al.*[16] found apical crowding or optic nerve

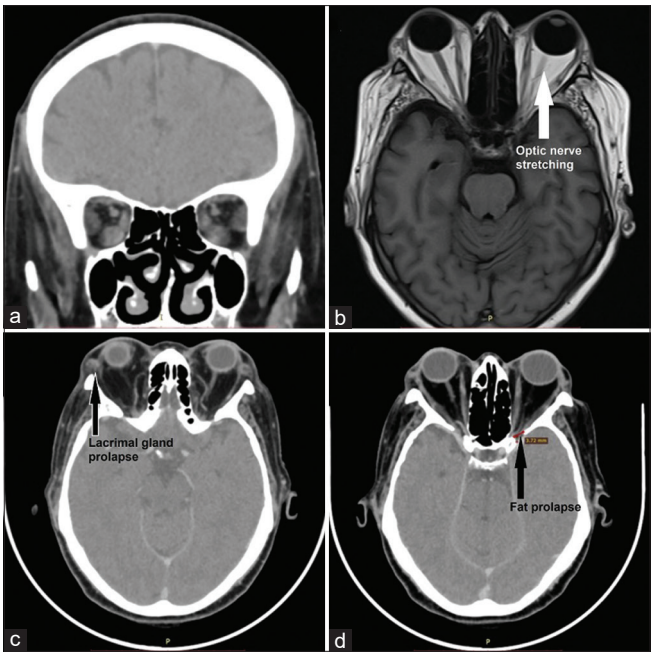


**Figure 6:** Case 2: (a). CECT orbit coronal scan showing effacement of perineural fat due to enlarged extraocular muscles at the orbital apex, Both eyes 25-50% (Grade2). (b). CEMRI orbit axial scan showing left optic nerve stretching. (c). CECT orbit axial scan showing lacrimal gland displacement anterior to frontozygomatic process on both sides. (d). CECT orbit axial scan showing intracranial fat herniation through superior ophthalmic fissure bilaterally, Right - 1.11 mm, Left - 3.72 mm

stretching in 22 (96%) and 16 (35%) eyes with very severe and moderate-to-severe GO, respectively. Our case 1 had optic nerve stretching in right eye [Figure 3b], whereas case 2 had it in left eye which could be correlated with RAPD [Figure 6b].

Enlargement of the superior ophthalmic vein (SOV) may also predict DON.[26] Similarly, an anteriorly displaced or enlarged lacrimal gland may also be seen in the setting of TED and possibly DON.[8] Neigel *et al.*[3] found dilatation of the superior ophthalmic vein in 33.3% of their cases and displacement of lacrimal gland in 64%. Nugent *et al.*[8] found anteriorly displaced lacrimal gland in 15 of the 18 optic neuropathy orbits (83.3%). In our patient 1 SOV diameter right was 2.53 mm and left was 2.49 mm. In patient 2, SOV diameter right was 1.98 mm and left was 1.82 mm. In both cases, lacrimal gland was displaced anterior to frontozygomatic process [Figures. 3c and 6c].

Birchall *et al.*[27] found that intracranial fat prolapse through superior orbital fissure in imaging studies also correlates closely to the presence of optic neuropathy in TAO, with up to 94% sensitivity, 91% specificity, a positive predictive value of 69% and a negative predictive value of 98%. This sign in combination with optic nerve crowding demonstrates a closer correlation to optic neuropathy as also found by Giaconi *et al.*[24] In our patient 1 intracranial fat herniation through superior ophthalmic fissure was 6.08 mm right orbit and 3.28 mm left orbit [Figure 3d], whereas in patient 2 it was 1.11 mm on right orbit and 3.72 mm on left orbit [Figure 6d].

Both our cases of bilateral asymmetric DON as diagnosed early with RAPD as the clinical sign on detailed radio-imaging had definitive DON. Our cases of bilateral asymmetric DON therefore highlight the importance of careful pupillary light reflex evaluation to detect RAPD as an early sign of DON. This early evidence of DON can then be confirmed on radio imaging and timely therapy instituted before development of permanent vision loss.

## Key-Messages

- Dysthyroid Optic Neuropathy (DON) can cause permanent vision loss in patients with thyroid eye disease and results from an orbital apex syndrome.
- RAPD in TED is highly specific for DON and can work as clinical alert for early evidence of DON.
- Good visual acuity and a normal colour vision do not exclude the diagnosis of DON
- Detection of RAPD requires good examination technique, may be difficult to grade but in unilateral and bilateral asymmetric cases it is an early alerting sign.
- In patients with bilateral DON, where pupils are uniformly equal in size in dim illumination, a RAPD is present in all patients with asymmetric field loss, even in the presence of similar interocular acuity.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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