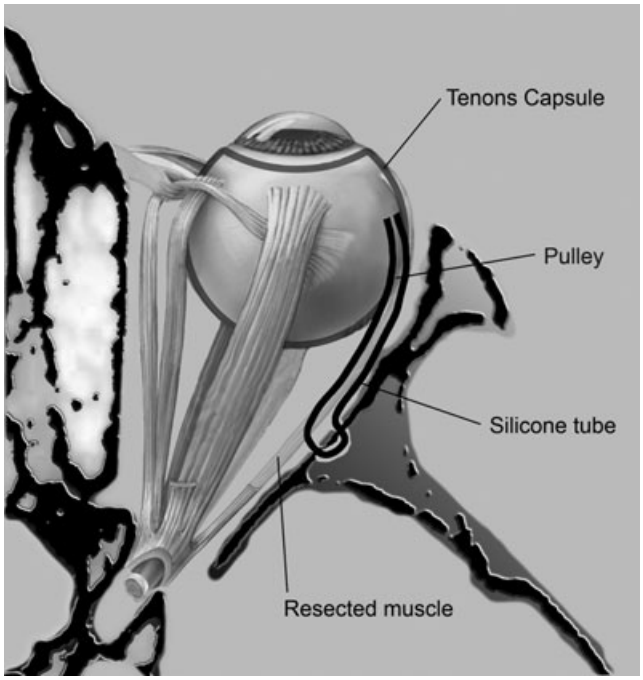

Figure 3. Diagram showing a silicon tube, which was fixed to the lateral orbital wall, then directed through the empty pulley in Tenon's capsule and sutured to the former insertion site of the lateral rectus muscle.

Taking the advanced stage of the disease with systemic metastases into consideration, palliative surgery to preserve vision in the only eye was performed. The lateral mid-facial approach included osteotomy of the lateral orbital wall and the zygoma. Upon opening the periorbit, the brown tumour infiltrating the muscle was visible. The optic nerve and its nutritive vessels were completely preserved. The lateral rectus tendon was then severed through a limbal incision. After subtotal removal of the metastasis and the rectus superior muscle, a straight position of the eye was restored using a 1-mm silicone tube. Through two burr holes, this tube was fixed to the lateral orbital wall. The tube was then threaded through the empty pulley, that is, the hole in Tenon's capsule, which remained after the lateral rectus muscle was removed. The tube was sutured to the former insertion site of the lateral rectus muscle (Fig. 3). In this way the globe was positioned in an abduction of approximately 5°.

After surgery, chemosis rapidly disappeared and visual acuity recovered up to 0.63 within 2 weeks. The visual field was not impaired. Upgaze was reduced to 15°, abduction to 5°; and adduction was possible up to 10°. The histopathological findings verified the diagnosis of a malignant melanoma, which correlates to the primary tumour.

Systemic metastases of choroidal melanoma predominantly appear in the liver. Lung, bone, skin and lymph nodes are often involved, mostly in patients with liver metastases. Our patient also had liver, lung and lymph node metastases before the orbital metastasis. Metastatic melanoma of the orbit, in contrast to recurrence of a melanoma in the ipsilateral orbit due to extrascleral seeding of the tumour, develops in the terminal stages of the disease. The life expectancy of the patient is short, and therefore treatment should be palliative.[2] Radiotherapy is an accepted treatment for intraocular tumours.[4,5] In literature, radiotherapy is described as a treatment for similar cases with bilateral choroidal melanoma.[6]

In our patient, we decided to decompress the optic nerve by removing the tumour. A xenotransplant was used to reposition the eye. We applied a method similar to the one described by Kolling for treatment of 6th nerve palsy,[7] and comparable to the recently described periosteal anchor of the medial rectus for treatment of 3rd nerve palsy.[8] Hummelsheim transposition was discussed as an alternative. This would, however, have included a significant risk of ischaemia in our case, owing to the interruption of anterior ciliary vessels of three neighbouring rectus muscles.

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Characterizing ethambutol-induced optic neuropathy with a 3D computer-automated threshold Amsler grid test

Ethambutol is commonly used in treatment against tuberculosis and *Mycobacterium avium* complex infections. Optic nerve toxicity is among the more serious adverse effects associated with ethambutol use and occurs in 6% of patients taking the drug.[1,2]

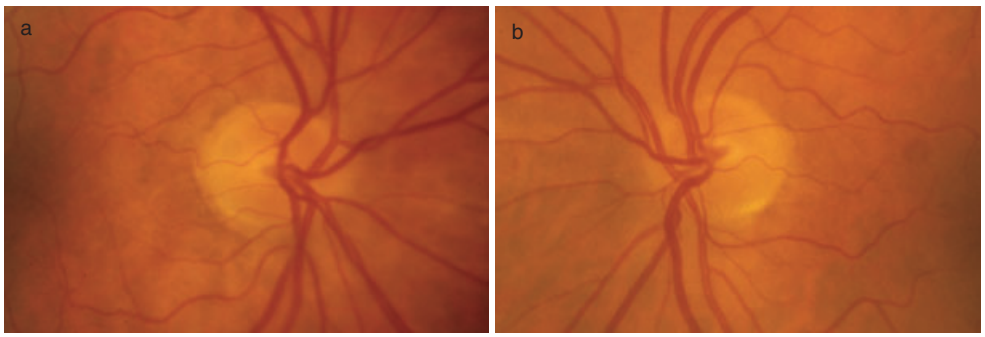

Figure 1. Colour fundus photographs showed very subtle temporal pallor OU with mild reduction of fibres in the papillomacular bundle region OU, (a) right and (b) left eyes, respectively. OU, both eyes.

Ethambutol-induced optic neuropathy manifests as decreased visual acuity, diminished colour vision and contrast sensitivity, and central scotoma.[3]

As ocular toxicity is dose- and duration-dependent, prompt recognition of declining visual function and early cessation of ethambutol therapy is important in preventing further progression of vision loss.[2] Current standard methods for monitoring ethambutol use include visual acuity assessment, visual field testing, funduscopy, and most sensitive, colour vision testing. However, these tests may not detect early, subtle changes in vision and remain non-specific.

The pathophysiology of ethambutol-induced optic neuropathy is unclear. One possible explanation for vision loss is that ethambutol chelates copper in the retinal ganglion cells and their fibres in the optic nerve. This decreases the levels of copper available for cytochrome C-oxidase in the electron transfer chain, leading to mitochondrial insufficiency and impaired axonal transport in the optic nerve.[4,5] Papillomacular bundle fibres are particularly affected in ethambutol-induced optic neuropathy.[6]

We applied 3D computer-automated threshold Amsler grid testing (3D-CTAG),[7,8] to gauge visual function in a patient with ethambutol-induced optic neuropathy.

A 71-year-old woman reported colour defects and decreased visual acuity 2 months after initiating ethambutol treatment for *Mycobacterium avium* infection. The patient had been taking ethambutol at a dose of 1200 mg/day (24 mg/kg/day) for 2 months when she first noticed diminished green colour perception and difficulty reading. The symptoms progressively worsened, up to the patient's first clinic visit. The patient had no prior ophthalmologic illness and had 6/6 corrected vision both eyes (OU) before beginning ethambutol.

On examination, the patient had best corrected visual acuity of 6/60 right eye (OD) and 6/12 + 2 left eye (OS). The patient had decreased colour vision bilaterally, scoring 4.5/8 OD and 5/8 OS on Ishihara pseudoisochromatic colour plates. The patient described a sense of decreased brightness OD compared with OS. Pupils were equal, round and reactive to light with no afferent pupillary defects. Slit-lamp examination was unremarkable. Funduscopy revealed sharply delineated optic discs with subtle temporal pallor OU (Fig. 1). Visual fields were assessed by Humphrey Visual Field 30–2 (SITA Fast) test (foveal sensitivity of 33db; Fig. 2), tangent screen at three feet and standard Amsler grid. All showed normal visual fields OU. The patient was recommended for assessment via 3D-CTAG. USC IRB approval was obtained.

Already successfully used in several clinical pilot studies,[9,10] 3D-CTAG displays a grid upon a black computer screen at a series of user-defined grayscale (i.e. contrast) levels. While maintaining their gaze on a central fixation marker, patients trace scotomas directly on the touch screen for each contrast level. The contrast levels and the angular resolution (i.e. spatial frequency) of the grid can be defined for each testing session. The same cathode ray tube monitor was exclusively used for all testing with an unchanged brightness/luminance setting. To ensure stability, the monitor was turned on at least 30 min prior to the testing sessions. The patient was presented with grid lines 0.5° apart as opposed to the 1° spacing of a standard Amsler grid, at five progressively higher levels of contrast (20%, 40%, 60%, 80%, 100%). Each eye was tested separately. The results of each tested level were recorded and afterwards displayed as a 3D depiction of the central hill-of-vision (i.e. 25° radially from fixation), both as topographical contour rings and 3D wire diagrams. Areas of 0% contrast sensitivity corresponded to the inability of the patient to recognize an Amsler grid at 100% contrast difference, and areas of 100% contrast sensitivity to the ability to recognize it at the lowest preset contrast, that is, the darkest grid.[9,10]

3D-CTAG with 0.5° grid spacing revealed relative scotomas that had been missed both by standard visual field testing methods and 3D-CTAG with 1° grid spacing: Figure 3 shows visual field defects predominantly in the central and temporal regions, bilaterally. The 3D depictions of visual field loss demonstrate a step-like pattern with increasing scotoma area as grid contrast approaches zero.

The ethambutol was discontinued, and the patient's condition was reassessed two months later. The patient had mild improvement in colour vision, scoring 5/8 OD and 6/8 OS on pseudoisochromatic colour plates. Visual acuity improved to 6/18 OD and 6/12 OS. A year after the initial diagnosis, the patient showed excellent recovery of visual function with normal colour vision and visual acuity of 6/7.5 OU. This recovery of function may speak more to retinal nerve fibre layer dysfunction rather than an absolute loss.

Using 3D-CTAG, we were able to distinguish visual field deficits consistent with ethambutol-induced optic neuropathy. Due to its greater sensitivity 3D-CTAG may reveal small depressions, which are variants of normal (i.e. lesser specificity). However, 3D-CTAG conducted at 0.5° grid spacing detected large-scale field defects not found on Humphrey Fisual Field 30-2 test, tangent screen perimetry, and conventional Amsler grid. This selective impairment of higher spatial frequency function suggests that currently used lower frequency tests may not be sensitive enough to detect ethambutol toxicity.

Conflict or commercial interest: Drs Fink and Sadun may have proprietary interest as patents on the 3D computer-automated threshold Amsler grid test technology used in this study are issued. Dr Kim, Dr Fahimi, Dr Nazemi and Dr Nguyen have no proprietary interest.

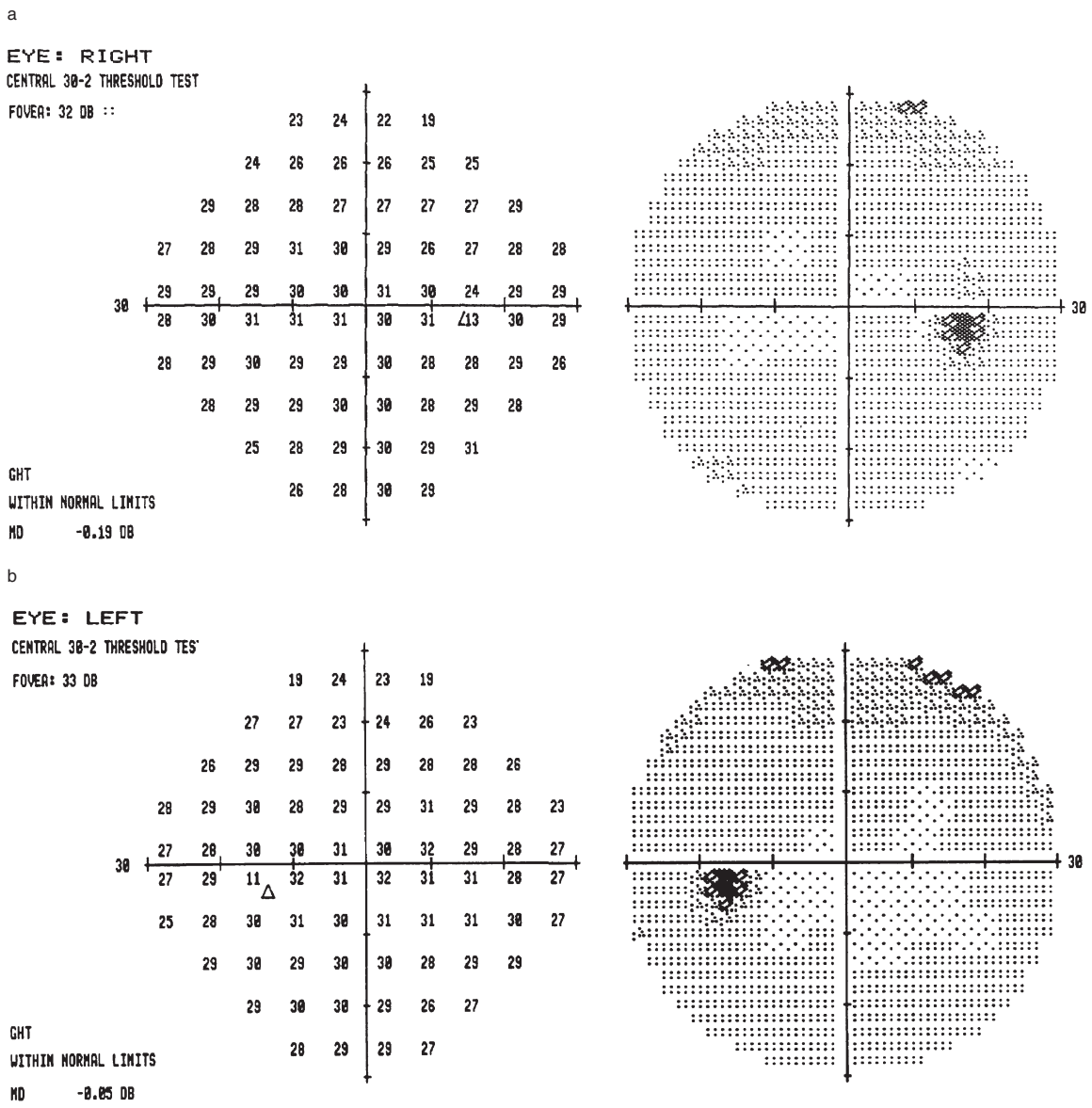

Figure 2. Normal Humphrey Visual Field 30-2 (SITA Fast) test at foveal sensitivity of 33db for (a) right and (b) left eyes, respectively.

The pattern of ethambutol toxicity of bilateral visual acuity loss and diminished colour and contrast sensitivity, along with its predominant involvement of the papillomacular bundle, strongly support a metabolic aetiology associated with mitochondrial dysfunction.[6] As in other mitochondrial optic neuropathies, the papillomacular bundle is preferentially sensitive in ethambutol toxicity. It is composed of smaller parvocellular axons that fire more frequently yet have fewer mitochondria.[6] These P cells detect change at higher spatial frequencies. That the scotomas were detected only at a higher spatial frequency of 0.5° *versus* 1° grid spacing is consistent with P cell dysfunction.

In our patient, 3D-CTAG identified a pattern of visual field loss consistent with ethambutol-induced optic neuropathy that was not detected using standard visual field tests. 3D-CTAG may be a useful complement to standard examination methods for early detection, accurate evaluation and monitoring of ethambutol toxicity. Further studies are needed for validating 3D-CTAG as a screening tool.

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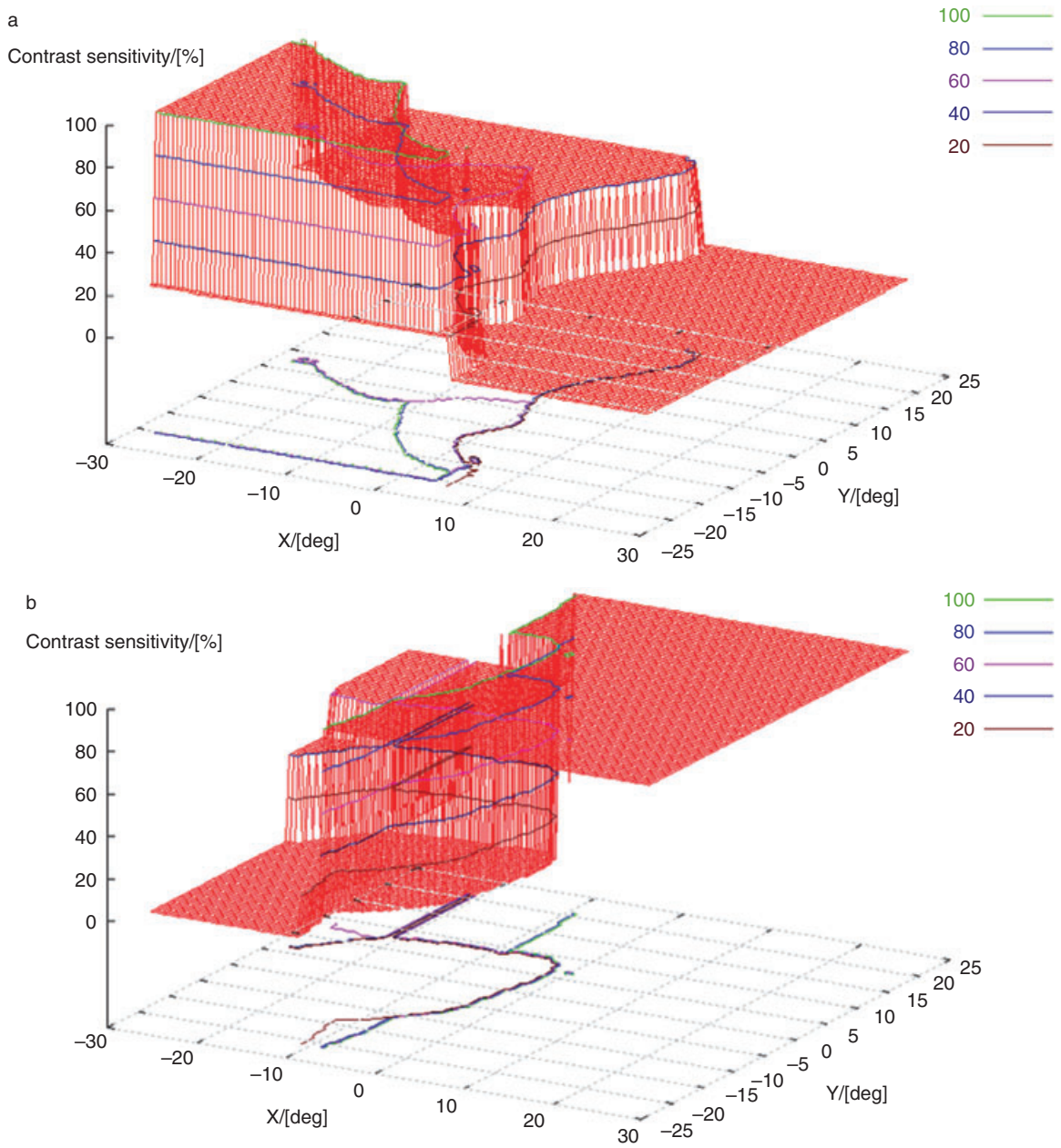

Figure 3. 3D computer-automated threshold Amsler grid testing results. At lower levels of contrast, Amsler grid lines appear fainter on a black background, allowing unmasking of subtle field defects. This tests for *high* contrast sensitivity. At 100% contrast, Amsler grid lines are white on a black background and test for *low* contrast sensitivity. The red regions represent the grid areas visible to the patient, plotted over the x/y (i.e. horizontal/vertical) plane of the visual field. This resembles a terrestrial contour map with contour rings, where higher altitudes indicate better contrast sensitivity and the valleys demonstrate depressed contrast sensitivity. The stepwise slopes represent stages of impaired contrast sensitivity, which become worse towards the temporal visual field of (a) right and (b) left eyes, respectively.

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Bilateral anterior optic neuropathy associated with use of terbinafine

Terbinafine is an antifungal drug used to treat onychomycosis of toenail and fingernail. Several side-effects have been associated with its use, including systemic lupus erythematosis,[1] generalized pustular psoriasis[2] and development of green vision.[3] To our knowledge, optic neuropathy has not been previously recognized. Herein we report a patient who developed bilateral optic disc swelling during oral terbinafine therapy for onychomycosis.

The 43-year-old man had noticed decreased vision of the right eye (OD) 2 months after starting terbinafine hydrochloride (Lamisil, Novartis, Istanbul, Turkey). Two weeks later, the vision of the left eye (OS) was also affected. He had neither significant headache nor other neurological symptoms. The patient was using only terbinafine HCl on high dose (500 mg/day instead of 250 mg) for onychomychosis as systemic medication. There was no history of ingestion of toxins like alcohol or tobacco. The visual acuities (VA) of the OD and OS were 0.8 and 1, respectively, on the Snellen chart. He could detect eight figures OD and 12 figures OS from 12 Ishiara colour plates by the OD. Fundus examination revealed bilateral low-grade disc oedema: Frisen scale stage 1 for OD (Fig. 1a) and for the OS (Fig. 1b). Lumbar puncture (LP) was planned, but the patient refused the procedure. One month after first admission, the patient presented with VA of 0.3 in both eyes (OU). The pupillary light reflexes were weak in OU, but colour vision was 6/6. The right optic disc was slightly pale (Frisen stage 2; Fig. 1C) and the left one was oedematous with a splinter haemorrhage on the superior pole (Frisen stage 4; Fig. 1D). The visual fields by Humphrey Visual Field Analyzer of OU were concentrically constricted (Fig. 2). The fundus fluorescein angiography of OU was normal except for the leakage beyond the optic disc margins. His blood pressure was normal. Intracranial pressure was not elevated which was measured as 120 mm H_2O during the LP. The MRI, MRA and MRV were all within normal limits. The results of spinal fluid and serum biochemistry were not significant. The chest X-ray, serum ACE, vitamin B_{12} levels, PPD, sputum and smear were within normal limits. The lyme, Bartonella and viral serologies in serum were all normal. The titres of the autoantibodies specific for lupus, scleroderma, polymyositis, dermatomyositis and Wegener's granulomatosis were not signifying an autoimmune pathology. The only systemic medication, terbinafine which was found out to be used at a relatively high dose was stopped and the patient was followed for 8 days. He was discharged with VA of 0.5 in OU. Five days later, the vision was 0.8 OU. Right optic disc oedema had resolved and the temporal side of left optic disc was slightly oedematous. One month later, the VA was again 0.8 OU and the borders of both optic nerves were regular with slight pallor of the left optic disc (Fig. 1e,f for OD and OS respectively) and the visual fields of OU were still concentrically constricted.

Several drugs including amiodarone[4] and perhexilene maleate[5] may cause toxic optic neuropathies with disc oedema.[4]

In cases with bilateral optic disc oedema and slight VA and visual field changes, it is important to exclude increased intracranial pressure by LP. Our patient did not report any headache and he had normal intracranial pressure, cerebrospinal fluid biochemistry and normal serological markers. His colour vision was not affected markedly. In toxic optic neuropathies, as the papillomacular bundle is preferentially affected, usually central visual field defects are reported though some exceptions.[6] A possibility of retinal toxicity with mild disc oedema may also be expected according to these observations. Optic disc oedema may cause generalized constriction of the visual field as in our patient. Normal MRI, lack of pain and the slow progression of the visual loss were not in favour of a demyelinating optic neuropathy.

When we analyse Hill's criteria[7] for causality of drug effect in this case, we observe a temporal relation and a clinically reasonable response on withdrawal (de-challenge) of terbinafine. However, with just one observed case, the strength, consistency and

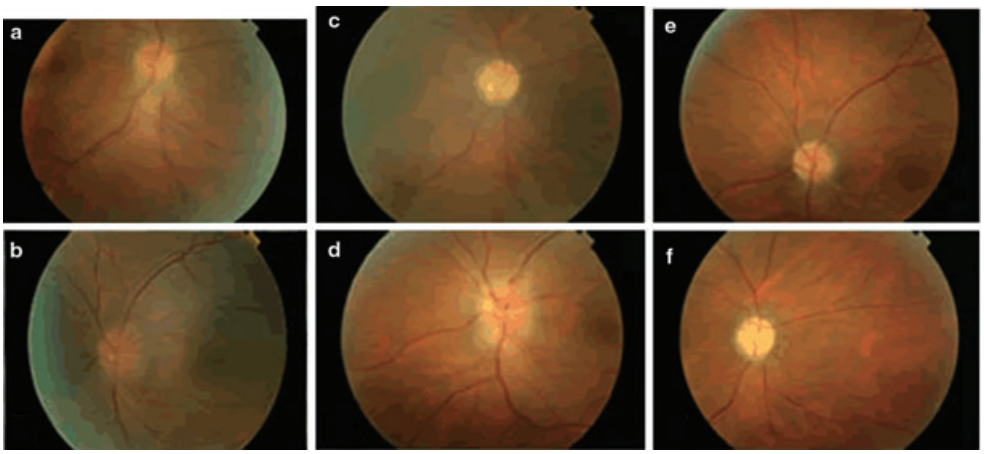

Figure 1. At presentation bilateral low-grade disc oedema was observed: Frisen scale stage 1 for right eye (a) and for the left eye (b). One month after first admission slightly pale right optic disc (Frisen stage 2) (c) and oedematous left one with a splinter haemorrhage on the superior pole (Frisen stage 4) (d). One month after discharge from hospital the borders of both optic nerves were regular with slight pallor of the left optic disc (e: right eye; f: left eye).