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Use of contrast sensitivity measurement in the detection of subclinical ethambutol toxic optic neuropathy

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SUMMARY Contrast sensitivity was measured by means of Arden grating plates in 100 patients on medication for pulmonary tuberculosis. The scores were abnormal in 38·2% of the patients whose therapy included ethambutol for three months, and 36·7% of the patients on similar treatment for six months. In comparison with age matched groups of patients on a regimen where streptomycin replaced ethambutol a statistically significant number of the patients on ethambutol had abnormal scores. This study suggests that Arden contrast sensitivity plates would be effective in detecting subclinical toxic optic neuropathy due to ethambutol and therefore could be used for routine monitoring of ocular function of patients on ethambutol. Loss of contrast sensitivity may explain why some patients on ethambutol with normal visual acuity and colour perception may still complain of visual disturbance.

Ethambutol hydrochloride is an orally administered agent specifically effective against *Mycobacterium tuberculosis*. Carr and Henkind[1] initially reported optic nerve toxicity due to ethambutol in 1962, and further reports have established this side effect as a dose related retrobulbar optic neuropathy.[2] In most studies it appears that the degree of reversibility depends on early recognition of symptoms and signs of ocular toxicity.[3]

Since the introduction by Arden[4] of a series of contrast gratings of various spatial frequencies, contrast sensitivity has been used to assess visual function in a number of ocular diseases. In particular the Arden contrast sensitivity test has been used to assess visual function in diseases involving the optic nerve, for example, in chronic glaucoma[5] and optic neuritis.[6] This suggested that the Arden test might be useful in the early detection of ethambutol toxic optic neuropathy. It was also thought that an isolated loss of contrast sensitivity might explain why some patients on ethambutol with normal visual acuity and colour perception may still complain of visual disturbance.

Patients and methods

We examined 100 black inpatients suffering from pulmonary tuberculosis. Acid-fast bacilli had been identified in their sputa and chest *x*-rays were suggestive of tuberculosis. There were 38 females and 62 males.

At this tuberculosis hospital two medication regimens are used in the treatment of pulmonary tuberculosis. Patients on schedule 1 receive streptomycin 1 g daily, rifampicin 450 mg daily, and isoniazide 400 mg daily for six months and pyrazinamide 2 g daily for three months. When streptomycin cannot be administered, schedule 2 is used, which differs from schedule 1 in only one respect, in that ethambutol 25 mg/kg is given daily in place of streptomycin. As a general rule the younger patients are placed on schedule 1 and the older patients on schedule 2. Patients undergo a routine chest *x*-ray after three months and again after six months. After a full six-month period of treatment patients are discharged and followed up as outpatients.

This established policy conveniently allowed us to examine four groups of patients. These groups were based on whether the patient had received ethambutol or not, for a three-month or a six-month period. Groups 1 and 2 were patients receiving schedule 2 medication, and groups 3 and 4 were patients on schedule 1 medication. Group 1, 34 patients (mean age 40 years, range 23–63), had received ethambutol for three months; while group 2,

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30 patients (mean age 45 years; range 20–83), had received ethambutol for six months. Group 3, 22 patients (mean age 32 years, range 18–44), had received no ethambutol for three months; and group 4, 14 patients (mean age 31 years; range 19–43, had received no ethambutol for six months.

We further subdivided these four groups to enable us to compare age matched groups. The results of patients between the ages of 20 and 49 years (3rd, 4th, and 5th decades) were analysed. Group A (a subdivision of group 1) consisted of 26 patients with a mean age of 35·3 years (range 23–49); group B (a subdivision of group 2), 15 patients, with a mean age of 32·1 years (range 20–48); group C (a subdivision of group 3), 21 patients, with a mean age of 32·7 years (range 22–44), and group D (a subdivision of group 4), 13 patients, with a mean age of 31·3 years (range 20–42).

The patients were examined the day before their routine chest *x*-ray. Visual acuity was tested at distance and at near; colour vision was assessed (Ishihara's test), and ophthalmoscopy was performed. Patients with obvious eye disease were excluded from the study. (This meant that several patients with cataracts and two patients with chronic glaucoma were excluded.) An independent examination of the patient's contrast sensitivity was carried out with Arden contrast sensitivity plates by the method described by Arden.[4] Each eye was scored separately, and for each eye a total score consisting of the sum of the scores on each of the six plates was determined. A total score of more than 82 was considered abnormal,[4] and for analysis the lower score of the two eyes was used.

Results

The mean score of patients in group 1 was 80·3 and 38·2% had a total contrast sensitivity score of more than 82. This contrasted with patients in group 3, where the mean score was 63·0 and where 9% scored more than 82. There is a significant difference between the scores in these two groups ($p<0·005$ paired *t* test; $p<0·015$ by Fisher's exact test). The patients in group 2 had a mean score of 79·2, while 36·7% scored more than 82, compared with those patients in group 4, where the mean score was 62·0 and 7·1% scored more than 82. Once again these differences are statistically significant ($p<0·025$ by paired *t* test; $p<0·04$ by Fisher's exact test) (Table 1).

When the sex of the patients whose medication included ethambutol is considered, the mean age of the females was 41·5 years and the males 44·4 years (statistically comparable ages). Of the patients on ethambutol who scored more than 82, 44% were females and 33% were males. This difference, however, is not statistically significant (Table 2).

The histogram in Fig. 1 is an analysis of the 100 patients divided by age in decades. Statistically there is no difference between the mean age of the four groups of patients between the ages of 20 and 49. In group A 34·6% scored more than 82, and in group B 28·6% were abnormal. In group C 9·5% were abnormal, and in group D 7·7% were abnormal. On statistical analysis a significant number of patients on ethambutol scored more than 82, compared with those not on ethambutol ($p<0·015$ by Fisher's exact test). The mean scores were also significantly higher for patients on ethambutol ($p<0·005$ by paired *t* test) (Table 3).

When the patients between the ages of 20 and 49 who scored less than 83 were assessed, the mean scores of patients on ethambutol were similar to the mean scores of patients not on ethambutol. The 28 patients in groups A and B (mean age 33·1 years) had a mean score of 62·2 compared with the 31 patients in groups C and D (mean age 31·6 years) with a mean score of 59·8. There is no statistically significant difference between the mean scores of patients who scored less than 83, irrespective of whether they received ethambutol or not (Table 4).

In a comparison of the patients who were on ethambutol who scored more than 82, the mean score of abnormal patients in group 1 who had received ethambutol for three months was 105·6 (standard deviation 19·1), while for abnormal patients in group 2 who had received ethambutol for six months the mean score was 110·4 (standard deviation 16·8). There is no statistically significant difference between the scores of these two groups.

When the age matched groups are considered, no single spatial frequency was particularly effective in detecting the effect of ethambutol on the optic nerve.

Table 1 *Contrast sensitivity scores >82 and mean Arden grating scores*

	n	*>82*	*Mean*	*SD*
Group 1 Three months on ethambutol	34	13	80·3	25·4
Group 2 Six months on ethambutol	30	11	79·2	27·6
Group 3 Three months not on ethambutol	22	2	63·0	17·8
Group 4 Six months not on ethambutol	14	1	62·1	14·1

Table 2 *Sex distribution of patients with contrast sensitivity scores >82*

		Female		*Male*	
		n	*>82*	*n*	*>82*
Group 1	Three months on ethambutol	14	6	20	7
Group 2	Six months on ethambutol	11	5	19	6
Group 3 and 4	Not on ethambutol	13	2	23	1

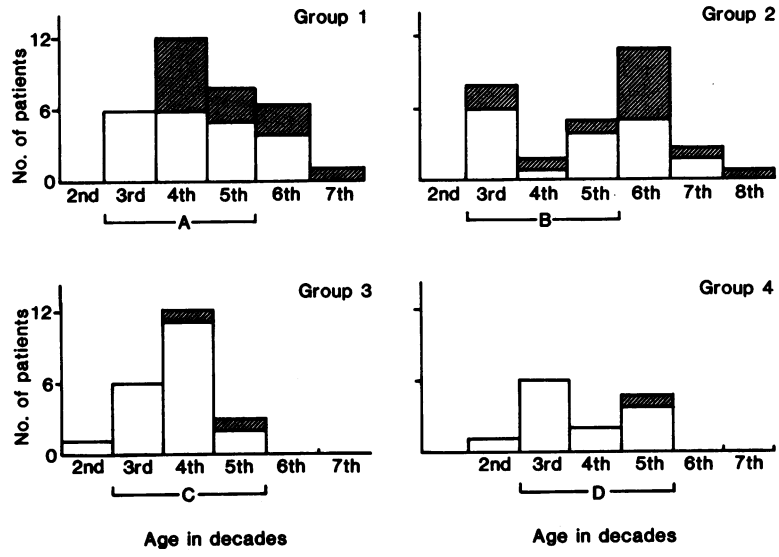

Fig. 1 *Histogram of 100 patients, divided by age in decades. Hatched areas show numbers of patients scoring more than 82. Clear areas show numbers of patients scoring 82 or less.*

The estimate of reliability using one spatial frequency was 0·6702133, while the estimate of reliability using all six spatial frequencies was 0·9242056.

Of this group of 100 patients five on ethambutol had a partial decrease in colour perception, with a contrast sensitivity score of more than 82. One of these patients had a reduction in Snellen acuity (R 6/9, L 6/12 best corrected). No abnormalities of their optic discs were observed. The remainder of the patients on ethambutol, including those with abnormal contrast sensitivity, and all the patients on streptomycin in place of ethambutol, had normal visual acuity, colour perception (Ishihara), and discs.

Discussion

Ethambutol, a dextrorotatory isomer of 2,2′-(ethylenedimino)-di-1-butanol, is a widely used oral agent effective against mycobacteria. Since its introduction in 1961 the clinical effectiveness and toxicity have been comprehensively documented.[7,8] The drug is well tolerated, although side effects like numbness in the lower limbs, nausea, and other gastrointestinal upsets have been described[8]. The major side effect is a dose-related retrobulbar neuropathy. Leibold[2] reported that in 59 patients treated with 35 mg/kg ethambutol per day optic neuropathy was seen in 18% of the patients. At 25 mg/kg per day the incidence of toxicity dropped to 2·25%. Citron[3] confirmed this low risk, finding an incidence of optic neuropathy of 6% among 34 patients receiving 25 mg/kg per day.

The ocular toxicity may have two forms, and it usually affects both eyes. Patients with central or 'axial' toxic effects have reduced visual acuity, impaired colour vision (especially on the red-green axis), and a central scotoma. Those with 'periaxial' toxic effects have a defect in peripheral isoptres of their visual field, with little or no decrease in visual acuity and normal colour vision. Most studies suggest that the neuritis is reversible if the drug is stopped and that the speed of recovery depends on early recognition of symptoms and signs.[3]

The exact mechanism by which ethambutol produces retrobulbar neuritis is unknown. Experimentally in animals it has been shown that the drug can cause depletion of copper and zinc, with a decrease in cytochrome C oxidase activity.[9] A relationship between these changes and ocular toxicity has not been established. It has also been suggested that, being a butanol derivative, ethambutol may cause toxic amblyopia by the same mechanism as alcohol.[10]

Table 3 *Contrast sensitivity scores >82, ages 20–49, and mean Arden grating scores*

		n	*>82*	*Mean age*	*Mean*	*SD*
Group A	Three months on ethambutol	26	9	35·3 yr	78·8	25·5
Group B	Six months on ethambutol	15	4	32·1 yr	72·9	24·7
Group C	Three months not on ethambutol	21	2	32·7 yr	63·9	17·7
Group D	Six months not on ethambutol	13	1	31·3 yr	61·3	14·4

Table 4 *Contrast sensitivity scores <83, ages 20–49, and mean Arden grating scores*

	n	*Mean age*	*Mean*	*SD*
Group A Three months on ethambutol	17	33·6 yr	63·4	12·2
Group B Six months on ethambutol	11	32·4 yr	60·5	12·8
Group C Three months not on ethambutol	19	32·4 yr	60·1	13·7
Group D Six months not on ethambutol	12	30·3 yr	59·3	12·8

Schmidt,[11] using high doses of ethambutol on monkeys (800 mg/kg) found demyelination of the optic nerve fibres.

There are two methods of reducing the risk of ethambutol induced toxic optic neuropathy. Firstly, the dose could be reduced to 15 mg/kg per day.[12] Secondly, the visual function of patients on ethambutol should be carefully assessed. Saroux *et al.*[13] recommended a monthly check with a Farnsworth-Munsell colour test, while Leibold[2] recommended regular visual acuities and visual field checks.

The use of routine visual tests during treatment is not optimal, because visual acuity, colour perception, fields, and optic discs may be normal in the presence of subjective visual disturbance[3]. It appeared from our study that only five patients (7·8%) might have been considered to have optic nerve disease by simple screening tests.

Yiannikas *et al.*[14] recently suggested that visual evoked potentials would be useful in detecting subclinical disturbances in optic nerve condition. They examined 14 patients all receiving less than 30 mg/kg ethambutol per day. In six patients (43%) the VEP showed changes in latency and amplitude of the P 100 component at the one- or three-month interval. Five of these six patients did not have other changes in visual function as measured with clinical neuro-ophthalmological examination.

Since Arden[4] introduced a rapid and simple method of testing contrast sensitivity, it has become clear that isolated loss of contrast sensitivity exists in certain diseases, and in many others loss of contrast sensitivity is more prominent and disturbing to the patient than the loss of visual acuity.

Using this test, Arden reported a normal population mean score of 69·8, and suggested that a patient scoring more than 82 should be considered abnormal. Because the values obtained from these plates are dependent on the tester, who must uncover the sheets at a constant speed, the results given in this paper are not directly applicable to all clinicians using the test. Our normal patients, however, scored a mean of 60·9, so any patient scoring more than 82 would be significantly abnormal. We found that 38·2% of the patients whose therapy included ethambutol for three months and 36·7% of the patients on similar treatment for six months had abnormal scores.

Because contrast sensitivity decreases significantly with age,[15 16] we compared four age matched groups of patients. Once again a statistically significant number of the patients whose medication included ethambutol had abnormal scores. Of the patients in the 3rd, 4th, and 5th decades of life, 34·6% were abnormal after three months and 28·6% abnormal after six months of ethambutol. 9·5% of the patients in the 3rd, 4th, and 5th decades who were not on ethambutol were abnormal after three months and 7·7% abnormal after six months. The three patients not on ethambutol who had abnormal contrast sensitivity scores were on a schedule that included streptomycin, isoniazide, rifampicin, and pyrazinamide. Two of these patients had normal eyes, and one was a corrected high myope who did not appear to have macular pathology on funduscopy. None had received previous tuberculosis treatment. The explanation for this finding may be that both isoniazide and streptomycin are optic nerve toxins, and, although use of either of these agents with ethambutol may lower the toxic threshhold, they may be toxic on their own.[17 18]

It has previously been reported that the toxic optic neuropathy secondary to ethambutol appears only after a latent period of 77 to 313 days following the beginning of treatment.[12] It might therefore have been expected that more patients would be abnormal at six months than at three months. A possible reason why an almost similar number of patients had abnormal contrast sensitivity at three and six months (with similar mean scores) could be the fact that all the patients gained weight while in hospital. The ethambutol dose was kept constant for the entire six-month period, so the mg/kg dose gradually fell over this period to a mean dose of 22 mg/kg per day at six months.

The potential severity of ocular toxicity attributed to ethambutol, and the reversibility of the reaction when the drug is stopped, necessitate a screening procedure capable of detecting ocular toxic effects before a deficit occurs. It would appear that, for routine monitoring of ocular function of patients on ethambutol, Arden contrast sensitivity plates would be simple and effective. However, further study is required using serial testing in individual patients, in an attempt to disclose the onset of ethambutol toxic optic neuropathy and to establish the precise place of the test in the management of these patients. Loss of contrast sensitivity may explain why some patients on tuberculosis treatment who have normal visual acuity and colour perception may still complain of visual disturbance.

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