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Case Report

Visual Loss following Daily Dose Regimen of Anti Tubercular Treatment

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Abstract

This article is to report on the increasing trend of visual loss following daily regimen of Anti Tubercular treatment. Review of 15 patients who presented with varying degrees of visual loss after starting Anti Tubercular treatment was done. The patients had variable time of presentation ranging from few weeks to 3 months. Pupillary reaction was bilaterally brisk but ill sustained in 80% cases. Fundus examination showed optic disc changes only in 20% cases. Ethambutol was stopped in all cases. 46.6% patients were given systemic steroids. Patients who presented early had better visual prognosis. No treatment was found to be effective in reversing the optic neuropathy except stopping of Ethambutol. Only early diagnosis could prevent total visual loss. Till the time the causes and risk factors get better elucidated it would be prudent to have a regular Ophthalmological evaluation of all patients who are started on daily regimen of anti-tubercular treatment.

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Keywords: *Tuberculosis, Visual Loss, Daily Dose Regimen*

Introduction

Tuberculosis, an infectious disease caused by Mycobacterium Tuberculosis has seen a resurgence since last few years. The presence of multi drug resistant Tuberculosis has also shown an upswing. In India, the diagnosis and treatment of tuberculosis is based on the Revised National Tuberculosis control program which was started in 1997, by the Government of India. Earlier all new patients received an initial intensive phase of four medications for eight weeks. It included Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. It was followed by continuation phase of two medications for sixteen weeks. This was under the WHO approved DOTS Regime (Directly observed Treatment, short course). The treatment was provided for three days a week and all drugs were given separately. This regimen was later found to promote relapse and generated drug resistant strains and the relapsed cases were also found to be difficult to treat.

In 2014 RNTCP recognized the need for daily dosing and the new regimen was implemented from February 2017. Under the new daily drug regimen Patients are given fixed dose combinations (FDC) of 4 drugs according to patients' weight, in a single pill on a daily basis. This is followed for 6-8 months. The patients are supervised by the DOTS strategy. They are given a combination of Isoniazid 5 mg/kg/day, Rifampicin 10 mg/kg/day, Ethambutol 14.5-21.4 mg/kg/day and Pyrazinamide 18.2-26.3 mg/kg/day. Maximum recommended dose of Ethambutol is 1500mg/day. Ethambutol toxicity has been identified as dose related. So patients receiving higher doses of ethambutol according to the new regimen of RNTCP should be at greater risk of developing Ethambutol induced adverse effects the most common of which is Optic neuropathy

Methods

This study is a retrospective chart review of 15 patients who developed visual loss after treatment with the daily regimen of Anti Tubercular Treatment (ATT)for a period ranging from 1 month to 1 year. They presented to the outpatient department of Ophthalmology of Government Medical College, Kozhikode, Kerala, India between January2018 to June 2019. Details regarding the age, gender, duration of ATT taken, comorbidities, renal status, smoking or alcohol dependence, time when the visual symptoms were noticed after starting ATT were noted. Clinical features included visual acuity, anterior segment findings, pupillary reaction, color vision, visual field, fundus findings at presentation and in last follow up, visually evoked potential(VEP), treatment given, fundus picture and visual acuity at last follow up and the time period that the patient has been on follow up were noted. Only those patients whose visual symptoms developed after the initiation of daily regimen of ATT and in whom the symptoms could be attributed to the Anti tubercular treatment and had been on follow up for at least 6 months were included in the study

Results

Demographic Characteristics- The age of the patients ranged from 34 to 75 years. 8 (53%) patients were male and 7(46.6%) patients were female. All patients presented with diminution of vision bilaterally which started after 1 month to 9 months of starting daily regimen of ATT treatment. They presented to the hospital within 15 days to 3 months of onset of symptoms. 5 patients (33%) had received ATT for pulmonary tuberculosis, 7 (46.6%) patients for Potts spine, 1 (6%) patient for laryngeal tuberculosis, 1 (6%) patient for intestinal tuberculosis and 1 patient (6%) for lupus vulgaris. 7(46.6%) patients had associated diabetes mellitus and hypertension, 1 (6%) patient had peripheral vascular disease, 1 (6%) patient had a seizure disorder, 1(6%) patient had a

Table 1: Master Chart showing the details of the 15 patients who developed visual loss following daily dose regiment of ATT

Column1	AGE	ORGAN	COMORB	DURATION OF ATT	TIME OF PRESENTATION	PUPIL	ANT SEGM	T/T	VEP	CV	FIELD	FUNDUS	MRI	ADDICTIONS	FINAL FUNDUS PICTURE	TIME TAKEN TO DEVELOP OPTIC ATROPHY	VA AT PRESENTATION	FINAL VA	Column2
CASE 1	54/F	SPINE	CKD	9 MTHS	3MTHS	LL SUSTA	WNL	PULSE THE	NOT DON	DEF BE	TARGET M	TEMPORAL	SMALL VE	NIL	STATUS QUO	AT PRESENTATION	2/60,1/2MCF	2/60,1/2MCF	
CASE 2	66/M	LUNG	DM-HT	9MTHS	3MTHS	LL SUSTA	WNL	INJECTAB	NO WAVE	DEF BE	TARGET M	MAC SCAR	NOT DON	SMOKER, ALCOH	STATUS QUO	DID NOT DEVELOP	2/60BE	2/60BE	
CASE 3	57/M	LUNG	PERIPH VASC	8MTHS	3 MTHS	LL SUSTA	WNL	PULSE THE	NOT DON	DEF BE	HEMIANO	BE DISC EDE	SMALL VE	NIL	OPTIC ATROPHY BE	3 MONTHS	2/60 BE	CFCF BE	
CASE 4	66/F	LUPUS VU	DM/HT	4MTH	3 MTHS	LL SUSTA	NS2-3	ORAL STE	NOT DON	DEF BE	TARGET M	NRR TEMP	NOT DON	NIL	STATUS QUO	AT PRESENTATION	CFCF,1/2MCF	CFCF,1/2MCF	
CASE 5	66/F	SPINE, PARAPLEGIA		9MTHS	3 MTHS	LL SUSTA	WNL	VITAMINS	NOT DON	NOT POSS	TARGET M	DISC EDEM	NOT DON	NIL	OPTIC ATROPHY BE	2 MTHS	1/60 BE	1/60 BE	
CASE 6	63/M	SPINE	CVA	7 MTHS	15 DAYS	LL SUSTA	WNL	VITAMINS	NOT DON	NOT POSS	NOT POSS	WNL	OLD INFA	NIL	WNL	DID NOT DEVELOP	N/O P/L	06-12P	
CASE 7	63/M	LUNG	NIL	6 MTHS	3 MTHS	LL SUSTA	WNL	VITAMINS	NO WAVE	NOT POSS	NOT POSS	WNL	NOT DON	NIL	WNL	DID NOT DEVELOP	PL, HM	HM BE	
CASE 8	34/F	SPINE	HT,DM	1 year	3 MTHS	LL SUSTA	WNL	VITAMINS	NO WAVE	DEF BE	FULL BE	MOD N/F DE	NOT DON	NIL	STATUS QUO	DID NOT DEVELOP	6/60,3/60	3/60,2/60	
CASE 9	55/F	LARYNGEA	NIL	6 MTHS	2MTH	LL SUSTA	WNL	VITAMINS	LOW AMP	DEF BE	SCOTOMA	TEMPORAL	NOT DON	NIL	STATUS QUO	AT PRESENTATION	3/60 5/60	6/60,6/36	
CASE 10	57/F	LUNG	DM,HT	6MTHS	2 WKS	LL SUSTA	NS3-2	VITAMINS	LOW AMP	DEF BE	SCOTOMA	WNL	NOT DON	NIL	TEMPORAL PALLOR BE	2 MONTHS	3/60,5/60	6/60, 6/36	
CASE 11	75/M	INTES TB	DM,HT	SAND HALF MTHS	3WKS	GR 1 RAPD	WNL	VITAMINS	NO WAVE	DEF BE	SCOTOMA	RE HYPEREA	NOT DON	NIL	OPTIC ATROPHY BE	2 MTHS	6/60,2/60	1/2MCF,CFCF	
CASE 12	55/M	SPINE	NIL	1.5 mths	1WEEK	GRADE 1 R	WNL	ORAL STE	NO WAVE	DEF BE	SCOTOMA	TEMPORAL	NOT DON	SMOKER, ALCOH	STATUS QUO	AT THE TIME OF PRESENTATION	1/2MCF, 6/18	1/2MCF, 6/18	
CASE 13	65/M	LUNG	NIL	8MTHS	11/2MTHS	GR 1 RAPD	WNL	ORAL STE	NO WAVE	DEF BE	SCOTOMA	BE TEMPOR	NOT DON	NIL	STATUS QUO	AT THE TIME OF PRESENTATION	3/60 6/24	3/60,6/24	
CASE 14	63/F	SPINE	SEIZURE, DM	7 MTHS	2MTH	GR 1 RAPD	WNL	INJECTAB	NO WAVE	DEF BE	SCOTOMA	RE NORM, L	NOT DON	NIL	RE STATUS QUO, LE OA	2 MTHS	6/60, CFCF	6/12,2/60	
CASE 15	53/M	SPINE	HT,DM	9MTHS	1 MTH	SLUGGISH	WNL	VITAMINS	NO WAVE	NORM,DE-FULL		RE WNL TEN	NOT DON	ALCOHOL, TOBA	STAUS QUO	AT PRESENTATION	6/9 6/18	6/9 6/18	

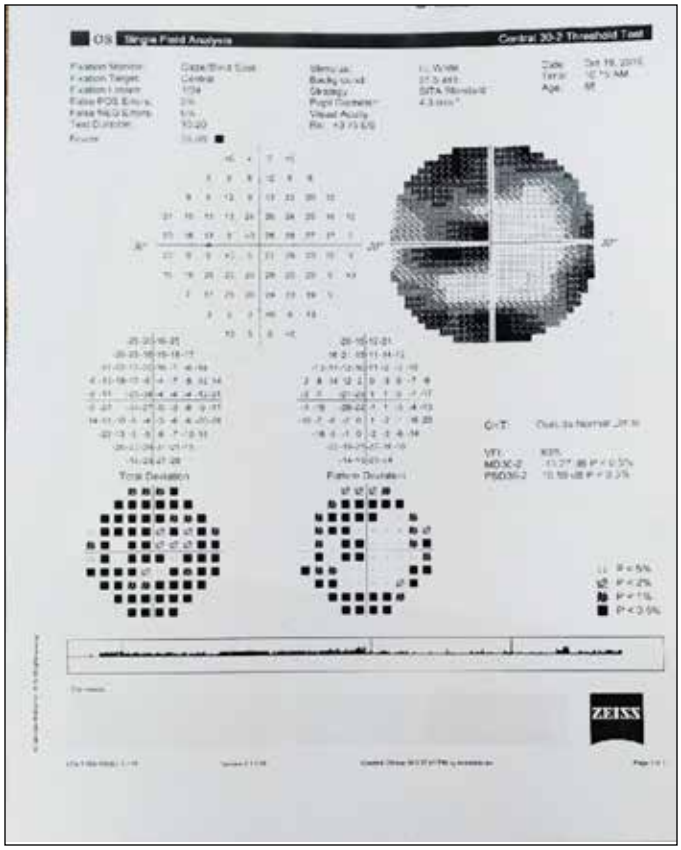

Figure 1: *Central & Centrocaecal Scotoma in a patient with Asymmetric* visual loss *due to Ethambutol induced optic neuropathy*

history of cerebrovascular accident and 1 (6%) patient had a chronic kidney disease. All diabetic patients had a normal renal profile. Only 3 (20%) patients had a history of smoking and alcohol consumption for many years.

Clinical features

Visual acuity- 7(46.6%) patients had a profound loss of vision in both eyes i.e. VA <3/60.3 (20%) patients had bilateral severe visual impairment (3/60 – 6/60). 4 patients (26.6%) had asymmetric presentation with one eye having profound vision loss and the other with a vision ranging from 6/60 to 6/18. 1 patient (6%) presented with visual acuity of 6/9 and 6/18 in RE and LE respectively with no further improvement. 6 (85.7%) patients out of 7 with profound loss of vision had presented late for ophthalmological evaluation at around 3 months. Rest of the patients presented between 2 weeks to less than 3 months. 1 patient with bilateral severe visual impairment did not reveal her history of ATT intake till 3 months even though she remained on continuous follow up for her diabetic retinopathy.

Anterior segment was unremarkable in all patients except 2(13.3%) who had nuclear sclerosis grade 2. Pupillary reaction was bilaterally brisk but ill sustained in 12 (80%) patients. 3 patients (20%) had Grade 1 relative afferent pupillary defect (RAPD) in the more severely affected eye while the other eye showed a sluggish pupillary reaction.

Color vision tested using Ishihara's color plates, was defective bilaterally in 11 (73.3%) patients while in 3(20%) patients it could not be tested due to profound loss of vision. In 1 (6%) patient there was a loss of color vision in only the severely affected eye.

Field examination showed a hemianopic field defect in 1 (6%) patient with profound loss of vision. Rest of the patients with profound loss of vision the field examination was not possible. Field examination showed central scotoma and centrocaecal scotoma (Figure 1) with peripheral field constriction in 9 (30%) eyes of 7 patients with bilateral severe visual impairment and patients with asymmetric loss of vision. 1 (6%) with minimal loss of vision did not have any visual field defect

12 eyes of 7 patients (40%) had minimal optic disc pallor at the time of presentation, 6 (20%) eyes of 4 patients had optic disc edema and 12 (40%) eyes of 7 patients had normal optic disc at presentation. 1 (6%) patient with normal optic disc had a macular scar bilaterally at the time of presentation and had a history of poor vision since young age. 1 (6%) had moderate non proliferative diabetic retinopathy with non-center involving macular edema in both eyes

VEP was done in 10 (66.6%) patients and it showed an absence of waves bilaterally in 8 patients (80%) and low amplitude with prolonged latency in BE of 2 patients (22.2%).

Magnetic resonance imaging of the brain was carried out in 3 patients (20%) which showed small vessel disease in 2 patients and an old infarct in the midbrain in 1 patient "Demographic and clinical features are further described in (Table 1)."

Treatment

All patients were advised to stop Ethambutol with immediate effect after consultation with their RNTCP physician. 2(13.3 %) patients with profound loss of vision who did not show any improvement even after stopping Ethambutol for 1-2 weeks were advised to stop Isoniazid. 7 patients (46.6%) were started on systemic steroid: 2 patients (13.3%) were given pulse therapy of methyl prednisolone 1 gram intravenously for 3 days and then oral steroids on tapering schedule. 2 patients (13.3%) were given injectable steroids 2cc intravenously twice a day for 5 days and then gradually tapered and 3 patients (20%) were given oral steroids 40- 60 mg twice daily for 5 days then tapered over a week. All were given methyl cobalamine and multi vitamin tablets.

At the last follow up at 6 months, 6(20%) eyes of 4 patients with optic disc edema went into secondary optic atrophy, 10(33.3%) eyes of 6 patients with normal optic disc continued to have a similar fundus picture at last follow up at 6 months 2 eyes (6%)of a single patient with normal disc at presentation developed temporal disc pallor. 12 (40%) eyes of 7 patients had persistent or worsened temporal pallor at the time of last follow up.

Only 8 (26.6%) eyes of 4 patients showed any improvement of vision. 2 eyes of single patient with profound loss of vision bilaterally showed an objective improvement in vision from no perception of light (No PL) to 6/12 in BE. 4 eyes of 2 patients with bilateral severe visual impairment showed improvement from 3/60 in RE and 5/60 in LE to 6/60 and 6/36 in RE and LE respectively in 6 months. One patient with asymmetric visual loss showed improvement in vision from 6/60 to 6/12 in right eye and while in left eye there was only a marginal improvement from CFCF to 2/60.

6 (20%) eyes of 3 patients showed deterioration of vision even after stopping ethambutol. 14 (46.6%) eyes of 7 patients showed stabilization of vision after stopping Ethambutol.

Discussion

Ethambutol induced optic neuropathy is a well-recognized adverse effect which is dose and duration related.[1] Prompt recognition of symptoms of diminution of vision could help in drastically reversing the optic neuropathy in 6.6% patients and marginally reversing it in 20% patients but rest of the patients did not show any improvement .The studies in the past have shown variability in the percentages of patients regaining their vision after stopping Ethambutol. This variability could be due to the difference in the follow up period of these patients apart from many known and unknown factors.[2,3]

The patients who recovered their vision came within 2 weeks to 1 month of their onset of visual symptoms.[4] All patients who reported late after their visual symptoms started did not benefit by stopping of Ethambutol. 13.3 % of patients were also advised to stop Isonazid when stopping of Ethambutol was not found to be effective after 2-3 weeks. These patients did not show any improvement but further loss of vision could be prevented.

In the patients who recovered their visual acuity 50% patients had no comorbidities while 50% were diabetic with normal renal functions(3). 6% patients had chronic kidney disease and did not recover any vision even after cessation of Ethambutol. Renal disease has been a known risk factor for development of optic neuropathy following ATT. There were 46.6% diabetic patients and hypertensive patients all of whom had normal renal profile at the time of presentation and during follow up too. Patients with altered renal status require more frequent follow up with their ophthalmologists as the risk of Ethambutol induced optic neuropathy is found to be more in patients with reduced glomerular filtration rate since ethambutol is mainly excreted through kidney.[2]

None of these patients who recovered their vision had any history of smoking or alcohol consumption. Only 20% of patients in this group had history of smoking and alcohol intake. All of them maintained their visual acuity following stoppage of Ethambutol.

Among the patients who recovered vision 12.5% eyes had unilateral optic disc edema 50% eyes had a normal fundus at presentation while 37.5% eyes had a mild temporal pallor. This was in contrast to the findings in previous studies in which presence of optic disc pallor was a poor prognostic indicator.

Only 25% patients among those who recovered vision were given systemic steroid intravenously which was gradually tapered while the other patients were given oral multivitamin and methycobalamine. Systemic steroids either orally or intravenously or as pulse therapy were given to 46.6% patients but only 14.2% patients out of these recovered some vision. Though Ethambutol induced optic neuropathy is supposed to be reversible but it was not found to be reversible in the majority of the patients in this group. 20% showed progression of visual loss even after stopping ethambutol.

Creating awareness among patients and Ophthalmologists is the need of the hour since patients may not associate visual loss to the anti-tubercular treatment and thus may fail to inform the ophthalmologist regarding their ATT.[5] This may result in unnecessary investigations and lead to loss of valuable time.

This study has a few limitations. The number of patients has been very few to fully understand the risk factors, causes and treatment of ethambutol induced optic neuropathy. The role of Isoniazid has not been investigated. The relationship between the cumulative dose of Ethambutol, the weight of the individual and the severity of the visual loss has not been studied. The role of contrast sensitivity in early diagnosis of optic neuropathy has not been looked into.[4] The follow up period is also a limiting factor in the study. The present daily dose regimen does not include tablet pyridoxine tablet which was earlier included in the regimen. Whether this had any role to play in the development of visual loss needs to be investigated

Conclusions

Adverse drug reactions to ATT has seen an increase following the daily regimen of Anti Tubercular treatment. This calls

for a more rigid regimen of ophthalmological evaluation and follow up for all patients who are started on this new regimen. This would help in early detection of drug induced optic neuropathy and other adverse drug reactions which may help in saving the vision of the patient before irreversible damage has happened. This article is a small step in this direction to create awareness among all ophthalmologists regarding this drug induced optic neuropathy following daily regimen of anti-tubercular treatment.

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