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Assessment of Optic Nerve Changes in Patients Receiving Anti-Tuberculosis Drugs at Different Time Interval

Shakila Abbas, Sonia Abdul Sammad, Mariyam Akhtar¸ Syeda Tasneem Zahra, Syeda Najam Gulzar, Ayesha Kiran

ABSTRACT:

Objectives: To assess optic nerve changes in patients receiving anti-tuberculosis drugs and to assess optic nerve changes at different time intervals of therapy.

Study design and settings: Descriptive cross-sectional study was conducted from August 2021 to November 2021 in Madinah Teaching Hospital, Faisalabad.

Methodology: 200 eyes of 100 patients receiving anti-tuberculosis therapy since 2-month, 4-month, 6 month and 8 months were taken. Patients did not have any systemic disease other than Tuberculosis. Indirect Ophthalmoscopy was performed to assess changes in fundus and optic nerve head. Optical Coherence Tomography was performed for assessment of retinal nerve fiber layer thickness and cup to disc ratio. Data was analysed by using descriptive statistics and chi-square test with SPSS version 20.

Results: In 2 months there was 16(66.66%) normal fundus, 8(33.33%) glaucomatous optic disc cupping. In 4 months, there was 12(15.38%) normal fundus, 16(20%) optic atrophy, 16(20%) optic neuropathy, 4.00(5%) optic neuritis and 30(38%) glaucomatous optic disc cupping. In 6 months, there was 7(21%) normal fundus, 4(12.5%) optic atrophy and 21(50%) optic neuropathy. In 8 months, there was 24(36%) optic atrophy, 34(51.5%) optic neuropathy, 4(6%) optic neuritis and 4(6%) Glaucomatous optic dis cupping (P 0.00). Result of this study also shows that retinal nerve fiber layer thickness is normal in 83(41.5%), increase in 4(2.0%) and decrease in 113(56.5%).

Conclusions: This study concluded that anti-tuberculosis drugs responsible for optic nerve changes and severity of optic nerve changes increase when duration of therapy increases.

Key words: Ethambutol, Isoniazid, Optic Neuropathy, Optic Nerve, Tuberculosis

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INTRODUCTION:

Tuberculosis is a contagious infection that is caused by "mycobacterium tuberculosis" and spreads from one person to another through an air droplet and person just needs to inhale a few germs to be infected. It is a chronic disease and can be curable and preventable. It can involve more than one part of the body such as the brain, intestine, spine or kidney. [1] It is the first infectious disease declared as a global health emergency by the World Health Organization. In developing countries tuberculosis is the leading cause of mortality and morbidity. Tuberculosis most commonly occurs in the poorest section of the community. It most frequently occurs among people living in crowded areas, poor hygienic condition, poor ventilation and poor nutrition may lead to alteration of the immune system which increases the risk of transmission of disease. WHO estimated globally 10 million cases of tuberculosis in 2019. Tuberculosis kills 1.4 million people which make it the second leading cause of death as compared to the HIV and AIDS. [2] In the world Pakistan has fifth highest tuberculosis prevalence. [3]

Tuberculosis most commonly occurs in the poorest section of the community and it has a well-recognized association

between tuberculosis and poverty. [4] Chemotherapy for tuberculosis was discovered in the 1940s and in the 1980s standardized short courses were adopted for its treatment. It is assumed that it was diminished worldwide but the decline was not observed in developing countries. The implementation of (DOTS) Directly-Observed Therapy has been an advancement in the treatment of tuberculosis. [1] Tuberculosis is treated with first line drugs' including ethambutol isoniazid, rifampin and pyrazinamide and streptomycin. [5] It is difficult for the patient to stick with the treatment in case of long-term therapy, if treatment is discontinued during this time patients do not cure from the disease and they develop drug resistance. WHO endorsed the DOT. There are four drugs that are likely to be efficacious to compose the regimen; out of these at least two are core drugs while the other two are compensation drugs.[6]

The role of core drugs is that in any of its metabolic phase it has the capability to kill mycobacterium tuberculosis while the role of companion drug is that it supports the core drug. The core and the companion drug maintain the entire duration of treatment as one of the core drugs has fine bacteriostatic activity while the other drug should have good sterilizing activity. The drug that has bactericidal activity minimizes the bulk of rapidly growing bacteria, avoid disease progression and decrease infection.[6] In the chemotherapy of tuberculosis ethambutol play an important role although it has various side effects including blur vision, headache dizziness, nausea, breathlessness, swelling of face, numbness and tingling of fingers and toe, rashes, loss of appetite, vomiting and stomach pain. Anti-tuberculosis drugs have adverse effects on visual functions including decreased visual acuity, blur vision, scotomas and reduced ability to detect green and red color. Color vision defect are the initial sign of ocular changes. Even color vision is affected before visual field and visual acuity. [7] Isoniazid has been a key treatment drug since 1952. It has adverse reactions, are hepatotoxicity and neurotoxicity. [8] Optic disc swelling is associated with isoniazid toxicity. Optic nerve is composed of the retina ganglion cells axons. They're distributed in an organized pattern. It is the only tract of the body that is clinically visible and has a cranial cavity. The retina of the eye is the thin layer of tissue continuous posteriorly with the optic nerve. There are approximately 1.2 million ganglion cells per retina and approximately 4-6 cones and 100 rods per ganglion cell. [9]

Pupillary abnormalities are observed in patient receiving antituberculosis drugs. Binocular Indirect Ophthalmoscope is an instrument and it is clinically applicable for the diagnosis and early intervention. With it structure that are lying in the innermost of the globe is visible including retina, optic disc, macula, retinal blood vessels, optic nerve head. [10] Optical coherence tomography (OCT) is an instrument used to see the retina; it is a non-invasive method used to measure the thickness of retinal nerve fiber layer. It provides the cross-sectional view of the retina along with the axial resolution of 8 to 10 micrometer. OCT can identify and measure the loss of retinal nerve fiber layer and measure the changes in thickness of retinal nerve fiber layer. Hence, clinically identifies optic nerve changes in patients and describes ocular changes in early stages caused by the anti-tuberculosis drug which was not visible with the ophthalmoscope. OCT provides two dimensional images of retinal layers by optical scattering. It is used in the detection of a variety of disease. OCT directly corresponds to the histological findings. [11] The rationale of the study is to rule out optic nerve changes during anti-tuberculosis treatment and to educate the community to undergo timely screening while receiving anti-tuberculosis therapy to avoid preventable blindness.

METHODOLOGY:

A descriptive cross-sectional study was conducted from August 2021 to November 2021 in a Medina Teaching Hospital, Faisalabad in which outpatients referred to eye OPD and receiving anti tuberculosis drugs were selected through a non-Probability purposive sampling technique. The research was approved by institutional ethical review board of The University of Faisalabad (TUF/IRB/005/2021). Sample size was calculated from WHO calculator by taking 95% confidence interval and 5% margin of error. The sample size was determined by WHO formula was 200. A total of 100 with 200 eyes of patients, ranging from 16 to 55 years of age were selected. Tuberculosis patients had been already receiving anti tuberculosis treatment since 2-month, 4-month, 6 month and 8 months were included. Patients with ocular pathologies like diabetic retinopathy, hypertensive retinopathy, glaucoma due to another ocular diseases e.g., myopia, systemic diseases other than tuberculosis like migraine, arthritis, multiple sclerosis and taking any systemic medication other than anti-tuberculosis drug were excluded from this study.

After taking written and informed consent, all patients underwent detailed clinical history, examination and investigations. Torch light examination was performed to assess the relative afferent pupillary defect. [12, 13] It is a condition in which when light is shown to the pupil of both eyes then both pupil does not show equal response. Patients seated comfortably and examiner stood at arms length then light was shown at one eye and pupil response was noted and at the same time light was swing to the other eye and response of the other eye was noted. It was noticed that if the both pupil shows equal response or different. Pupils respond differently to light stimuli shown in one eye at a time showed patients had unilateral relative afferent pupillary defect. Relative afferent pupillary defect clearly showed that patient had any defect in optic nerve and light is unable to pass up to occipital lobe safely. Binocular Indirect ophthalmoscopy (MSL model number MSL25C) was performed to assess changes in fundus and optic nerve head. Optic disc and blood vessels of fundus were also assessed.

Indirect ophthalmoscopy was also necessary to check any papillary oedema any change in fundus colour and swelling of the optic disc. Optical Coherence Tomography (NIDEK) was performed for assessment of optic nerve fibers. Optical Coherence Tomography was performed to check the thickness of retinal nerve fiber layer and to access the cup to disc ratio. To perform Optical Coherence Tomography (OCT), the patient was seated comfortably in front of OCT machine, the head rested on head rest to keep it motionless. The patient was simply looked into the lens of device at small, blinking target; the equipment quickly scaned the eye. After that interpretation was performed and diagnosis was made. After the collection of data descriptive statistics and chi-square test was used with P <0.05 was considered and used IBM SPSS-20 version to get a statistical result.

RESULTS:

The total of 200 eyes of 100 patients was included. The study showed that 100(50%) were male and 100(50 %) were females with mean age 32.93**.** Out of 200 eyes of 100 patients, there was 44(17.5%) normal fundus. There was increased frequency of optic neuropathy during anti-tuberculosis therapy as described in Figure 1. The result of this study also shows that relative afferent pupillary defect was positive in 131(65.5%) and negative in 69(34.5%), optic disc color was pinkish orange in 57(28.5%), grey in 37(18.5%) and pale in 106(53%), optic disc shape was oval in 39(19.5 %), horizontally oval in 40(20 %) and round in 121(60.5%), arterial and venous changes shows normal arteries and veins in 83(41.5%), thick in 4(2.0%) and thin in 113(56.5%), optic disc edema is present in 48(24%) and absent in 152(76.0%) patients taking anti tuberculosis drugs.

Assessment of optic nerve changes with different age group was done. 55 patients were assessed having age range of 16-23 in which 11(20%) had normal fundus, 16(29%) had optic atrophy, 8(14%) had optic neuropathy, 8(14%) had optic neuritis, and 12(21%) had glaucomatous optic disc cupping. 43 patients were assessed having age range of 24-31 in which 23(53%) had normal fundus, 12(27%) had optic neuropathy and 8(18%) had glaucomatous optic disc cupping.

44 patients were assessed having age range of 32-39 in which 14(31%) had optic atrophy, 20(45%) had optic neuropathy and 10(22%) had glaucomatous optic disc cupping. 43 patients were assessed having age range of 40-47 in which 8(18%) had optic atrophy, 20(46%) had optic neuropathy and 10(23%) had glaucomatous optic disc cupping. 15 patients were assessed having age range of 48-55 in which 1(6%) had normal fundus, 6(40%) had optic atrophy, 6(40%) had optic neuropathy, and 2(13%) had glaucomatous optic disc cupping. The result of this study shows, as age increase severity of optic nerve changes also increase with p<0.05 (0.00).

Figure 1: Frequency of optic nerve changes in subjects receiving anti-tuberculosis drug

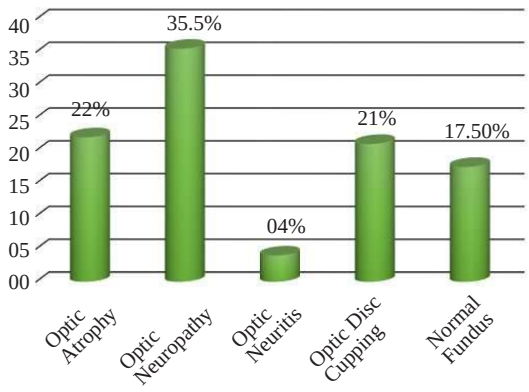

Table 1: Assessment of optic nerve changes with duration of anti-tuberculosis drugs N=200

Duration of therapy	Normal fundus	Glaucomatous optic dis cupping	Optic neuritis	Optic neuropathy	Optic atrophy	P-value
2 months	16 (66.6%)	8 (33.33%)	0	0	0	0.000
4 months	12 (15.38%)	30 (38%)	4 (5%)	16 (20%)	16 (20%)	
6 months	7 (21%)	0	0	21 (50%)	4 (12.5%)	
8 months	0	4 (6%)	4 (6%)	34 (51.5%)	24 (36%)	

Table 2: Assessment of retinal nerve fiber layer thickness with the duration of anti-tuberculosis therapy N=200

Duration of therapy	Normal	Increase	Decrease	P. value
2 months	20(83.33 %)	0	4(16.66 %)	0.000
4 months	38(48.71%)	4(5.12%)	36(46.15%)	
6 months	11(34.37%)	0	21(65.62%)	
8 months	14(21.21%)	0	52(78.78%)	

Comparison of frequency of optic nerve changes with different time intervals of therapy. The result of this study show, as duration increase severity of optic nerve changes also increase with $p<0.05$ as described in Table 1.

For assessment of retinal nerve fiber layer thickness, out of 200 eyes of 100 subjects, the retinal nerve fiber layer thickness was normal in 41.5% (83), increase in 2% (4) and decrease in 56.6% (113).

We compare retinal nerve fiber layer thickness with different time interval of therapy. Results showed that as duration of anti-tuberculosis drugs increases there is decrease in retinal nerve fiber layer thickness with $p< 0.05$ i.e. (0.00) as described in Table 2.

DISCUSSION:

In this study we assess the optic nerve changes due to anti-tuberculosis drugs. Analysis of the optic disc in current study found 19.5% oval, 20.0% horizontally oval and 60.5% round in shape. Arties and veins changes were found 41.5% normal arteries and veins, 2.0% thick arties and veins and 56.5% thin arteries and veins. Optic disc swelling was also observed in 24.0% eyes. Present study also examined Cup to disc ratio. A large number 21% of subjects have increase cup to disc ratio. In previous study they observed optic neuropathy due to ethambutol. They observed ethamnutol cause retibal changes and retinal nerve fiber layer thickness decrease.[14]

The result of present study showed 35.5% patient was optic neuropathy. There were greater chances of optic neuropathy during anti-tuberculosis therapy. Previous study on longitudinal evaluation of subclinical ethambutol induced optic neuropathy was conducted in 2019. They concluded that ethambutol-induced optic neuropathy was found in a total 22 eyes of 14 patients and duration of medication was shown to be a greater risk factor for subclinical toxicity.[15]

Present study explains the parameter that cause visual impairment like glaucomatous disc cupping. Optic nerve is a main point that carries information from retina to brain if any changes occur at this level result visual impairment. Present study observed these changes during treatment periods. 20% optic nerve changing i.e., optic neuropathy occurs at four-month 50% optic nerve changing observed at six month and 51.5% optic nerve changing occur at eight months. In previous study they assessed incidence of visual impairment. According to this study using of anti-tuberculosis drugs 2 to 9 months caused visual impairment in 19.2/1000 persons and permanent visual impairment in 2.3/1000 persons. [16]

A study was conducted on retinal nerve fiber layer analysis in subjects taking anti-tuberculosis therapy. They concluded retinal nerve fiber layer thickness was reduced.[17] The results of present study also showed 56.6% retinal nerve fiber layer loss from optic nerve. Torch light examination was performed to assess pupillary reaction and there was 65.5% positive relative afferent pupillary defect. It will show defect in optic nerve therefore improper information send from optic nerve to brain. There are 21% subjects as cup to disc ratio increases. 53% pale optic disc color was observed.

A study of visual function in subjects on ethambutol therapy for tuberculosis was conducted in 2016. They observe significance difference in visual acuity, fundus changes and visual filed after follow-up of first two months of therapy. [18] Present study result showed that in 2-month therapy (33.33%) have glaucomatous optic disc cupping. At 4-month optic nerve changes were assessed in which 12 patients (15.38%) have normal fundus and 30 patient (38%) have glaucomatous optic disc cupping. Present study describes retinal nerve fiber layer thickness decrease in more (56.5%) then half subjects and increase thickness in few (2.00%) subjects and less (41.5%) then half subjects had normal thickness during eight months of treatment. In present study 12% optic nerve changing in first 2 months of treatment was observed. Optic disc color is grey (18.5%) and pale (53%) and observed disc shape is horizontal oval (20.0%) and round (60.5%). Punit Kumar Singh and Prasnnta in 2020 reported a study and they observed only retinal nerve fiber layer thickness and no remarkable changing observed through ophthalmoscope within starting 2 months of treatment.[19] Present study describes retinal nerve fiber layer thickness decrease in (56.5%) subjects and (41.5%) subjects have normal thickness during treatment. The study had limitation that the time duration was limited and some people did not give complete information related to therapy. Our results coincide with a study on assessment of ocular toxicity in patient receiving ethambutol therapy which was conducted in 2020. They observed significance difference in visual acuity, contrast sensitivity and retinal nerve fiber layer from baseline and first two and six months of treatment. They concluded that retinal nerve fiber layer thickness decreased.[20]

CONCLUSIONS:

The study concluded that there was increased frequency of optic neuropathy as duration of anti-tuberculosis therapy increase. When duration of therapy increases changes become severe. Anti-tuberculosis drugs are responsible for optic nerve changes; patients must undergo optic nerve evaluation and the physician should be fully aware of the diagnosis and clinic evaluation of ocular toxicity caused by anti-tuberculosis drugs, as soon as optic nerve changes are diagnosed intervention should be performed to prevent irreversible blindness.

Authors Contribution:
Shakila Abbas: Concept of study, Conceptualization of study design, data analysis, data interpretation
Sonia Abdul Sammad: Data collection, acquisition of data, data analysis
Mariyam Akhtar: Data collection, acquisition of data, write-up
Syeda Tasneem Zahra: Data collection, write-up
Syeda Najam Gulzar: Literature search, write-up
Ayesha Kiran: Literature search, write-up

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