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# The Effects of Pyridoxine on Retinal Nerve Fiber Layer in Tuberculous Treatment

## Piridoksinin Tüberküloz Tedavisinde Retina Sinir Lifi Tabakası Üzerindeki Etkileri

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**ABSTRACT**

**Aim:** Ethambutol and isoniazid, two of the main drugs used in the treatment of tuberculosis, can lead to optic neuropathy. Optical coherence tomography (OCT) is a non-invasive, repeatable, high resolution imaging technique used in the diagnosis and follow-up of optic nerve diseases. The purpose of this study was to investigate the effect of pyridoxine added to antituberculous therapy on retinal nerve fiber layer (RNFL) thickness and the effectiveness of OCT in the early diagnosis and monitoring of optic neuropathy.
**Material and Methods:** Twenty four patients diagnosed with pulmonary or non-pulmonary tuberculosis were included in the study. Patients divided into two groups. One group received antituberculous therapy alone, and the other group received 50 mg pyridoxine in addition to antituberculous therapy. RNFL thickness in both eyes was measured using OCT before treatment and 2-month after treatment.
**Results:** The change in the second month of treatment according to baseline in terms of average RNFL thicknesses in the right eyes, showed a statistically significant difference between the groups using and not using pyridoxine (p=0,038). However, there was no significant difference in the left eyes in terms of RNFL thickness in any of the quadrants between the groups.
**Conclusion:** Despite a decrease in RNFL thickness in patients receiving antituberculous therapy alone, no change in RNFL thickness occurred in patients receiving pyridoxine in addition to antituberculous therapy. We think that early ototoxicity can be detected with RNFL thickness measurement using OCT in asymptomatic patients and that the addition of pyridoxine to antituberculous therapy prevents ototoxicity.
**Keywords:** Isoniazid; optical coherence tomography; retinal nerve fiber layer thickness.

**ÖZ**

**Amaç:** Tüberküloz tedavisinde kullanılan başlıca ilaçlardan ikisi olan etambutol ve izoniazid, optik nöropatiye yol açabilir. Optikal kohorens tomografi (OCT), optik sinir hastalıklarının tanı ve takibinde kullanılan noninvaziv, tekrarlanabilir, yüksek çözünürlüklü bir görüntüleme yöntemidir. Bu çalışmanın amacı, antitüberküloz tedavi ile birlikte verilen piridoksinin, retinal sinir lifi tabakası (RNFL) kalınlığı üzerindeki etkisini ve OCT'nin, optik nöropatinin erken tanı ve takibindeki etkinliğini araştırmaktır.
**Gereç ve Yöntemler:** Çalışmaya pulmoner veya pulmoner olmayan tüberküloz tanısı alan yirmi dört hasta dahil edildi. Hastalar iki gruba ayrıldı. Bir gruba sadece antitüberküloz tedavi uygulandı, diğer gruba ise antitüberküloz tedaviye ek olarak 50 mg piridoksin verildi. Her iki gözde de RNFL kalınlığı tedaviye başlamadan önce ve tedaviye başladıktan 2 ay sonra OCT cihazı kullanılarak ölçüldü.
**Bulgular:** Sağ gözlerde ortalama RNFL kalınlıkları bakımından başlangıca göre tedavinin 2. ayındaki değişim, piridoksin kullanan ve kullanmayan gruplar arasında istatistiksel olarak anlamlı bir farklılık göstermekteydi (p=0.038). Bununla birlikte, olguların sol gözlerinde ise gruplar arasında hiçbir kadranda RNFL kalınlıkları açısından anlamlı bir farklılık bulunmadı.
**Sonuç:** Sadece antitüberküloz tedavi alan hastalarda RNFL kalınlığında bir azalma olmasına rağmen, antitüberküloz tedaviye ek olarak piridoksin de alan hastalarda RNFL kalınlığında herhangi bir değişiklik olmadı. Asemptomatik hastalarda OCT cihazı kullanılarak yapılan RNFL kalınlık ölçümü ile erken ototoksisitenin saptanabileceğini ve antitüberküloz tedaviye piridoksin eklenmesinin ototoksisiteyi önlediğini düşünüyoruz.
**Anahtar kelimeler:** İzoniazid; optikal koherens tomografi; retina sinir lifi tabakası kalınlığı.

## INTRODUCTION

Although the cause of tuberculosis is known, and despite the fact it is possible to treat and protect against the condition, it remains one of the most fatal diseases worldwide (1). It progresses with multisystemic involvement, and most commonly affects the lungs. It is mainly seen in developing countries. The most important feature distinguishing the treatment of tuberculosis from other infections is long-term multidrug use. Drug side-effects are therefore an important problem. The antituberculous drug isoniazid causes several neuropsychiatric side-effects, such as hallucination, convulsion, transient diplopia, peripheral neuropathy, aggression, memory loss, anxiety and depression (2). Although isoniazid-induced optic neuritis is not common, it can lead to optic neuropathy in adults (3,4). It is difficult to exactly determine the optic nerve toxicity that can emerge during antituberculous therapy including isoniazid, and the incidence thereof, due to the variation in symptoms and the different approaches adopted by clinicians. In addition, malnutrition, alcohol use and existing brain diseases all increase the neurotoxic effect (5). Although the physiopathological basis of isoniazid is still not completely certain, the probable mechanism involves accumulation of isonicotonic acid hydrazide preventing metabolism of active pyridoxine through inhibition of pyridoxine-dependent enzyme systems (6-8). Optic coherence tomography (OCT) is a non-invasive, repeatable, high resolution imaging technique used in the diagnosis and monitoring of glaucoma and various retinal diseases (9). Retinal nerve fibers (RNF) in the internal part of the retina consist of ganglion cell axons. These fibers transmit impulses from photoreceptors to the central visual cortex through the optic nerve. Axonal injury is characterized by thinning of the retinal nerve fiber layer (RNFL). Decreased visual acuity may result from RNFL thinning. Several neurodegenerative (10,11) and some metabolic diseases (12,13) affect RNFL thickness.

Very few studies have used RNFL thickness measurement with OCT in the diagnosis and monitoring of optic neuropathy and the preventive effect of pyridoxine against optic neuropathy in patients receiving antituberculous therapy. The purpose of this study was to investigate the effect of pyridoxine administered together with antituberculous treatment on RNFL thickness and the effectiveness of OCT in the early diagnosis and monitoring of optic neuropathy.

## MATERIAL AND METHODS

This study was performed at Recep Tayyip Erdoğan University Medical Faculty Chest Diseases and Eye Diseases clinics, Turkey. The study protocol followed the guidelines of the Declaration of Helsinki. Recep Tayyip Erdoğan University Clinical Researches Ethics Committee approval (07.10.2016 and 2016-65) and signed informed consent forms from patients were obtained before the study began. Thirty patients diagnosed with pulmonary or non-pulmonary tuberculosis between January 2014 and December 2016 were included. Before starting on antituberculous therapy, patients received corrected visual acuity examination, standard ophthalmological examination, fundoscopy and visual field examination at the Eye Diseases Clinic. Two patients meeting exclusion criteria were excluded. Fifty milligrams pyridoxine was administered to half of the remaining 28 patients, but not the other half. Four patients receiving pyridoxine were excluded due to not using the drug regularly over a 2-month period. The study was completed with 24 patients, 10 subjects receiving pyridoxine and 14 not receiving it. RNFL thickness of 48 eyes of these 24 patients was measured using an OCT device before treatment. Patients were started on antituberculous therapy consisting of isoniazid 5 mg/kg, rifampicin 10 mg/kg, ethambutol 15 mg/kg and pyrazinamide 25 mg/kg. When treatment was completed after 2 months, RNFL thickness measurements were repeated. Ethambutol and pyrazinamide were discontinued after 2 months' treatment. Isoniazid and rifampicin therapy was completed in 6 months.

### Exclusion Criteria

Patients with diseases affecting RNFL thickness, such as diabetes mellitus, obstructive sleep apnea syndrome, multiple sclerosis and Parkinson's, with high myopia (<-6 diopters) or hypermetropia (>6 diopters), with a history of intraocular surgery, glaucoma, uveitis or ocular trauma or with intraocular pressure exceeding 21 mmHg in both eyes were excluded from the study.

### RNFL Thickness Measurement

RNFL thickness was measured using a Cirrus HD spectral domain OCT (Carl Zeiss Meditec, Dublin, CA) device. Measurement was performed in the superior, inferior, nasal and temporal quadrants in the peripapillary region. Mean RNFL thickness was also determined.

### Statistical Analysis

Statistical analyses were performed with IBM-SPSS (SPSS version 22; SPSS Inc., Chicago, IL, USA) software. Normality assumption of variables were determined using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation and categorical variables as frequency and percentage. The analysis of variance with repeated measures was used to compare pre and post-treatment RNFL thicknesses in patients receiving treatment with and without pyridoxine. A p value of $<0.05$ was regarded as statistically significant.

## RESULTS

Twenty-four patients with tuberculosis, 6 (25.0%) female and 18 (75.0%) male, were included in the study. Patients' mean age was 37.8±14.2 years. Mean age was 34.4±12.2 and 40.3±15.4 in groups using and not using pyridoxine, respectively. There was no statistically significant difference between the two groups in terms of age ($p=0.327$). Ten (41.7%) of the 24 patients were using pyridoxine together with antituberculous therapy. The remaining 14 (58.3%) patients received antituberculous therapy only. In terms of smoking status, 13 (54.2%) patients were still smoking, 3 (12.5%) had quit and 8 (33.3%) had never smoked. Six (25.0%) patients used alcohol regularly. All these were male, and all consisted of patients who were still smoking. Additional diseases were present in three patients. Four patients were receiving treatment for psychiatric disorders, while hypertension was present in two. Based on the site of involvement, pulmonary tuberculosis was present in 19 patients, pleural tuberculosis in three and tuberculous lymphadenitis in two. Patients' demographic characteristics are shown in Table 1.

RNFL thickness was measured using OCT, before and at the end of the second month of treatment, in 48 eyes of the 24 patients enrolled, 10 using pyridoxine and 14 not using pyridoxine. The change at the second month of treatment according to baseline in terms of average RNFL thicknesses in the right eyes, showed a statistically significant difference between the groups using and not using pyridoxine (p=0.038). The change amount at the second month of treatment according to baseline in terms of average RNFL thicknesses in the group not using pyridoxine was higher than the pyridoxine group (Figure 1). No significant change in other quadrant RNFL thickness in the right eye was determined between the groups with and without receiving pyridoxine, at the second month of treatment according to baseline (Table 2). However, no statistical significance occurred in the second month of treatment according to baseline in left eyes in terms of average or superior, nasal, inferior or temporal quadrant RNFL thickness between the groups using pyridoxine and not using pyridoxine (Table 3).

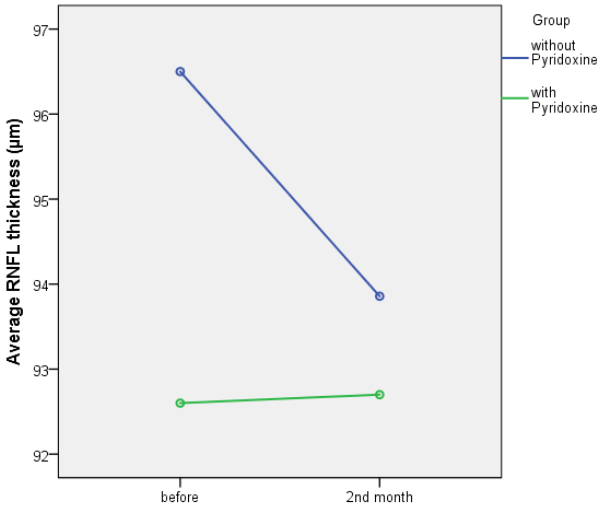
## DISCUSSION

Various researchers have long emphasized that induced polyneuropathy and optic neuropathy occur immediately following the use of isoniazid in the treatment of tuberculosis. The incidence of this induced polyneuropathy has been shown to be closely associated with isoniazid dosage. Biehl et al. (6,14) reported that neuropathy developed in 44.0% of patients receiving high-dose isoniazid and in 2.0% of those receiving low doses. In addition to the dose of isoniazid, factors such as patients' nutritional status and the rate of acetylation also increase the risk of neuropathy (15-18). With the effect of all these factors, an increased blood concentration of isoniazid raises the drug's side-effect potential (7,19-21).

Optic neuropathy occurs as RNFL thickness decreases as a result of several neurodegenerative and metabolic-toxic diseases. Although isoniazid-induced optic neuritis is generally seen in adults, it may very rarely also be seen in childhood (3,4,22-29). Optic neuropathy developing in tuberculous patients receiving isoniazid therapy is reported to take place together with a decrease in pyridoxal phosphate synthesis which depletes neurotransmitter flow (3). There are studies showing that the need for pyridoxine supplementation in tuberculous patients receiving isoniazid therapy, as in the present study, in order to prevent this (22).

**Table 1.** Patient characteristics

| | |
|---|---|
| Age (years), mean±standard deviation | 37.8±14.2 |
| Sex, n (%) | |
| Female | 6 (25.0%) |
| Male | 18 (75.0%) |
| Smoking status, n (%) | |
| Still smoking | 13 (54.2%) |
| Quit | 3 (12.5%) |
| Never smoked | 8 (33.3%) |
| Alcohol use, n (%) | 6 (25.0%) |
| Site of involvement | |
| Lungs | 19 (79.1%) |
| Pleura | 3 (12.5%) |
| Lymphadenitis | 2 (8.3%) |
| Comorbidities, n (%) | |
| Hypertension | 2 (8.3%) |
| Psychiatric disease | 4 (16.6%) |




RNFL: Retinal Nerve Fiber Layer

**Figure 1.** Average RNFL thickness in the right eye before and 2nd month of the treatment

**Table 2.** Comparison of RNFL thicknesses (µm) in the right eye before and 2nd month of the treatment

| | | Without Pyridoxine (n=14) | With Pyridoxine (n=10) | p |
|---|---|---|---|---|
| Superior | Before | 123.07±14.05 | 111.70±17.24 | 0.059 |
| | After | 115.71±12.14 | 110.20±15.10 | |
| Inferior | Before | 120.71±15.68 | 119.80±11.39 | 0.247 |
| | After | 116.71±15.07 | 119.30±11.06 | |
| Nazal | Before | 75.21±10.23 | 75.10±12.06 | 0.588 |
| | After | 76.64±11.42 | 78.00±13.71 | |
| Temporal | Before | 66.93±6.87 | 63.60±5.54 | 0.353 |
| | After | 63.64±8.98 | 62.80±5.01 | |
| Average | Before | 96.50±7.59 | 92.60±9.06 | **0.038** |
| | After | 93.86±7.30 | 92.70±8.43 | |

RNFL: Retinal Nerve Fiber Layer

**Table 3.** Comparison of RNFL thicknesses (µm) in the left eye before and 2nd month of the treatment

| | | Without Pyridoxine (n=14) | With Pyridoxine (n=10) | p |
|---|---|---|---|---|
| Superior | Before | 122.86±11.30 | 121.80±17.81 | 0.407 |
| | After | 118.93±11.77 | 112.50±30.37 | |
| Inferior | Before | 118.64±9.95 | 120.50±10.22 | 0.082 |
| | After | 111.21±15.23 | 121.00±11.41 | |
| Nazal | Before | 74.21±10.75 | 72.80±9.45 | 0.614 |
| | After | 70.71±11.09 | 71.00±15.28 | |
| Temporal | Before | 63.50±8.23 | 61.20±8.11 | 0.527 |
| | After | 63.29±7.98 | 62.70±6.91 | |
| Average | Before | 95.50±6.95 | 93.60±7.89 | 0.671 |
| | After | 92.00±7.50 | 91.00±12.27 | |

RNFL: Retinal Nerve Fiber Layer

However, many physicians do not give patients a pyridoxine combination, due to the idea that neuropathy is rare at standard isoniazid doses, cost and effect analysis and that there may be a decrease in the antibacterial effect of isoniazid.

Carlson et al. (30) and Ross RR. (31) showed that the administration of pyridoxine together with isoniazid can prevent this neuropathy. Low-dose pyridoxine has been shown to prevent neuropathy complications without obstructing antibacterial activity (32).

Kulkarni et al. (33) reported that following the development of bilateral optic neuritis during antituberculous therapy including isoniazid due to tuberculous meningitis, the symptoms and findings of optic neuritis resolved entirely when isoniazid was discontinued and pyridoxine support given. Those authors also suggested that pyridoxine combination therapy in patients with tuberculosis receiving isoniazid should be reviewed in favor of such administration and that it is vitally important for such cases to be reported through active pharmacovigilance programs and medical journals.

No reliable data are available that can fully determine the effect of individual metabolic enzyme levels and pyridoxine requirement for the evaluation of early diagnosis and monitoring and response to treatment of optic neuropathy that may develop in patients receiving isoniazid therapy. Visual symptoms during optic neuropathy may develop after the 10th day of tuberculous therapy or after 3 months (3,4,34). Vision loss, impaired color vision and scotomas at perimetric examination may occur (3,4). Normal findings are generally present in the early period in addition to pathological changes at fundoscopic and perimetric examination (3). It is difficult to detect these symptoms and findings in the early period, and assessment is more subjective. It is not possible to predict toxicity, and toxicity may also be overlooked since a significant proportion of patients are not symptomatic. RNFL thinning may be detected as an indication of early toxicity more fundus changes become pronounced.

Isoniazid used in tuberculous therapy is known to cause optic neuropathy, but the number of studies objectively revealing its effect on RNFL thickness is limited. RNFL measurement, an objective and quantitative method, can identify optic nerve toxicity in the early period in patients receiving tuberculous therapy, and potential permanent complications can thus be prevented. Kim et al. (35) assessed RNFL thickness using OCT in five patients developing visual impairment in association with tuberculous therapy. Although that research involved a low number of patients, it is one of the rare studies to show the effect on RNFL thickness of drugs used in tuberculous therapy. Chai et al. (36) reported a decrease in RNFL thickness in eight patients with ETB-related optic neuropathy. In our study, we observed thinning in the RNFL in the superior and inferior quadrants of the 14 patients not given pyridoxine. Some previous studies have measured RNFL have shown that optic nerve damage commences in the superior and inferior quadrants, particularly in glaucomatous optic neuropathy. However, there are no fully agreed studies concerning which quadrants are most affected by toxicity. Although some studies have reported that the temporal quadrant is affected, we think that this finding may be a late-stage symptom of papillomacular bundle fiber involvement. The common features of the two studies cited above are that RNFL thickness was evaluated after development of toxicity and their low patient numbers. Apart from these two studies, we encountered no other publications in the literature monitoring RNFL thickness using OCT in optic neuropathy developing in association with antituberculous drugs.

Our measurement of RNFL thickness using OCT before and 2 months after treatment in tuberculous patients receiving isoniazid therapy between with and without receiving pyridoxine groups showed a significant difference in average RNFL thickness in the right eye. We evaluated RNFL decreases in the group not receiving pyridoxine as a finding of early toxic optic neuropathy (Figure 1). We interpreted this as a potential effect of isoniazid on the optic nerve in association with pyridoxine metabolism. Consequently, we considered this difference between groups as a reflection of the positive effect of pyridoxine on RNFL thickness.

Genotypic screening is not routinely used because screening of Nat-2 levels before isoniazid therapy does not always show toxicity, and due to the restricted availability of genetic analysis in developing countries and high costs (37). However, we think that monitoring RNFL using OCT will be very advantageous in clinical practice, both because of its easy and rapid application at all levels and to its low cost, in the early diagnosis of optic neuropathy associated with toxicity that may develop in tuberculous patients receiving isoniazid and in follow-up after treatment with pyridoxine. For that purpose isoniazid combined with pyridoxine support must be provided in tuberculous patients with regular toxicity monitoring with RNFL measurements, and that isoniazid must be stopped in patients in whom thinning in the RNFL is observed despite this.

We recommend frequent and close follow-up with OCT of patients with decreased RNFL thickness. OCT is a good, non-invasive imaging technique capable of assessing retinal microstructure with high sensitivity. It must be used in the early diagnosis and monitoring of potential optic neuropathy associated with tuberculous therapy.

## CONCLUSION

In conclusion, although isoniazid-related optic neuritis exhibits severe progression accompanied by pronounced symptoms and findings, we recommend RNFL measurement with OCT for the detection of optic neuropathy that may develop at the subclinical level. While isoniazid should be stopped in the event of a marked optic neuritis attack, we think that optic neuropathy involving latent symptoms and findings at the subclinical level, RNFL monitoring with pyridoxine support is important in the effective administration of antituberculous therapy and in the prevention of optic nerve function disorders such as impaired contrast sensitivity and color vision that may occur in the late period in patients developing subclinical optic neuropathy.

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**Conflict of Interest**

The authors report no conflicts of interest exist.

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