Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i6.6514

ETHAMBUTOL INDUCED OPTIC NEUROPATHY IN ANKLE TUBERCULOSIS PATIENT- A CASE REPORT

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Abstract

Introduction: Tuberculosis is mainly treated by antitubercular therapy with 2month of intensive regimen with Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol, followed by 4months of maintenance therapy with Isoniazid, Rifampicin and possible extended therapy for ankle tuberculosis. Ethambutol is a potent bacteriostatic antitubercular agent. It is known to cause Ethambutol induced optic neuropathy.

Case: A 61year old female patient was diagnosed with ankle tuberculosis and on anti-tubercular therapy for 2months had complete joint damage, underwent left ankle arthrotomy with biopsy and ankle arthrodesis. After 3 months of antitubercular therapy patient had blurring of vision. Patient ophthalmological examination showed optic neuropathy. Since there being no identifiable reason for optic neuropathy it was attributed to ethambutol.

Conclusion: Though ethambutol is categorised as drug with mild adverse effects it can cause serious visual loss with no definitive treatment and variable recovery. Hence clinicans should be observant and prevent visual loss by early diagnosis and withdrawal of the drug immediately.

Key Words: Ankle tuberculosis, antitubercular therapy, Ethambutol, Optic Neuropathy.

Introduction

India accounts for about 25% of global TB burden, with an estimated TB incidence of 2.77 million in 2022.[1] Mycobacterium Tuberculosis mainly effects the respiratory system but it can also effect extra pulmonary tissues. Approximately 10% of extra pulmonary cases of TB are musculoskeletal in origin. The foot and ankle tuberculosis, represents only 0.13%[2].

Chemotherapy of tuberculosis includes 2months of intensive regimen of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (EMB), followed by 4 months of maintenance therapy of Isoniazid and Rifampicin.[3] Current recommended treatment with anti-TB drugs is 6 months course, duration may be extended for musculoskeletal tuberculosis[4]. For ankle tuberculosis 2months of

HRZE and 10-16 months of HRE is recommended as per TB Index guidelines[5]. Though all these drugs considered as safe, but they have many side effects[6].

EMB is a potent bacteriostatic antitubercular drug that interferes with the biosynthesis of arabinogalactan in the cell wall of Mycobacterium Tuberculosis and inhibits multiplication by bacilli[7]. This bacteriostatic effect is combination with other drugs known to give good results. Side effects of ethambutol include peripheral neuropathy, hepatotoxicity and mental confusion[8]. It is known to cause Ethambutol induced optic neuropathy (EON) in a dose and duration dependent manner[9]. The toxicity typically occurs between 3-5months of usage, though it may present as early as within 1month and as late as 12months of use[10]. Initiation dose prescribed by the WHO is 15–20 mg/kg body weight/day, which has an incidence of 1%–3% EON[11].

This is a case report of patient who developed diminution of vision and optic neuropathy with the use of ethambutol for the treatment of ankle tuberculosis.

Case history

A 61y old female, 60kg weight had history of pain in the left ankle with associated swelling since 1years. Pain was insidious in onset and slow in progression. Initially pain was dull aching type which did not hinder her normal activities. Pain was slowly progressing for which she took symptomatic treatment, later she was suspected left Ankle tuberculosis and started with anti-tubercular regimen 2months prior to presentation. Since 1½ months pain and swelling aggravated which caused her difficulty in walking and performing her normal activities even after starting anti-tubercular therapy. Since there was no improvement in the treatment, patient came to us for further evaluation and management. Patient is also a known case of Type II diabetes mellitus and was on medications since 3 years. Patient had undergone bilateral cataract surgery 4months ago.

Systemic examination was within normal limits. Local examination of left ankle showed rise of temperature with tenderness and swelling causing painful, restriction in range of movements without neurovascular deficit. Blood investigations showed normal blood picture with elevated ESR. Blood sugar levels and Hb1AC were increased. No other abnormality was found in the other routine investigations. Preoperative x-rays were taken shown in (Fig 1)

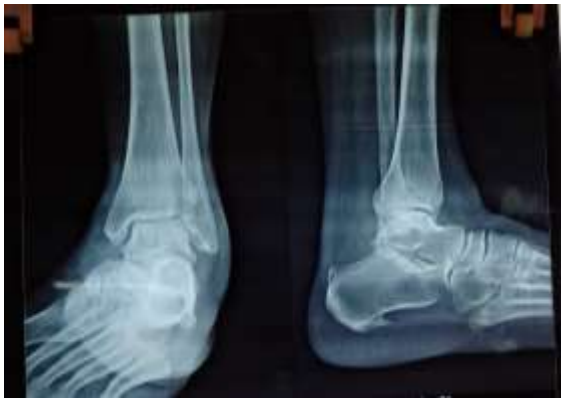

Fig 1: Pre-operative X-ray of ankle

Left ankle MRI was done and radiologist reported as Features suggestive of osteomyelitis with chronic infective arthritis of left ankle joint. This correlated to ankle tuberculosis.

Appropriate analgesics were initiated with continuation of antitubercular regimen and injectable insulin was started as per physician and pulmonologist opinion. Patient was continuously monitored for abnormalities in sugar levels. After anaesthesia opinion, patient underwent left ankle arthrotomy, debridement, biopsy and ankle arthrodesis with 6.5mm cc screws as the ankle joint was completely damaged.

Patient post operatively was continued with anti-tubercular therapy. Regular dressings were done and closely monitored for surgical complications and all the antitubercular drug complications. Patient post op care was uneventful. Patient post-operative X-ray was satisfactory (Fig 2).

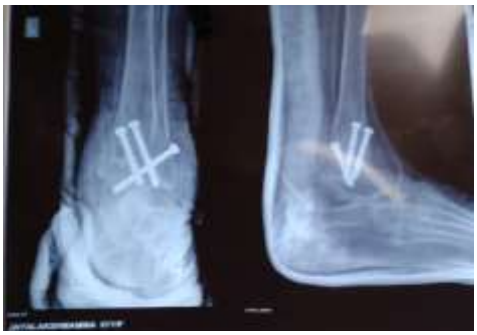

Fig 2: Post op X-ray showing arthrodesis of left ankle

Biopsy report by pathologist showed caseating granuloma tissue composed of lymphocytes, plasma cells, epitheloid cells, occasional multinucleate giant cell and thin walled blood vessels with few necrotic bone tissue. Which was consistent with tuberculosis.

General well-being of the patient improved. Pain and swelling of ankle decreased. Patient was discharged with non-weight bearing cast on left ankle and advised to continue antitubercular drugs and insulin and to follow up in 2weeks time for suture removal.

Patient was informed about all the side effects of antitubercular drugs. She had mild gastrointestinal symptoms with vomiting episodes initially which was a gastrointestinal side effect of antitubercular drugs which reduced with appropriate medication. Patient was under ophthalmological check-ups regularly as she was operated for cataract surgery and had good vision without visual aids. Patient was alright at the time of suture removal. Patient follow up picture shown (Fig 3)

Fig 3: patient`s standing without support
Fig 4: Ophthalmological examination

Patient one month post-surgery had blurring of vision in both eyes. Patient didn't seek medical advice for 3days. When the diminution progressed patient came to us and referred to an Ophthalmologist. Ophthalmology examination is shown (fig 4).

On initial examination, her BCVA (best corrected visual acquity) was 1 ½ meter in both eye. The Intra ocular pressure in both eye were 12mmHg (right eye) and 14mmHg (left eye) (Perkins tonometer) respectively. On slit lamp examination of both eyes anterior segment was normal. There was no RAPD but sluggish reaction of pupils in both eyes were seen. Both eye fundus appeared pale suggestive of progression of optic atrophy. Colour vision was reduced in both eyes (Ischira plates). Visual field couldn't be assessed due to very less vision. It was suspected to be ethambutol toxicity and drug was stopped immediately. Patient retinal picture is depicted in Fig 5

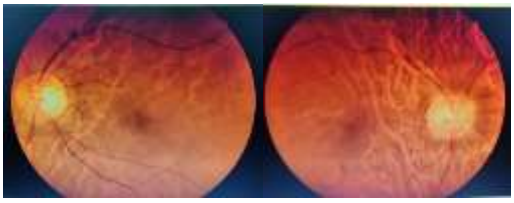

Fig 5: retinal changes

Steroid was started as per pulmonologist, ophthalmologist and neurologist opinion. Immediately she was started on intravenous Methylprednisolone one gram for 3 days and continued with 8mg methylprednisolone was treated accordingly as optic neuropathy. Patient was advised to continue Rifampicin, Isoniazid and Levofloxacin was added instead of Ethambutol. Discontinuation of ethambutol was reported to health authority. Patient was started on B complex with Zinc (20mg) combination. Patient was later referred to higher ophthalmology centre for further evaluation and management.

In higher center Ophthalmological center Fundus examination with Optical Coherence Tomography was done which showed pale disc with disc thinning in the inferior quadrant with thinning of retinal nerve fibre layer. Visual evoked potential showed both eyes increased latency and decreased amplitude. Patient was suspected ethambutol induced optic neuropathy. Patient ophthalmologist report is shown (fig 6).

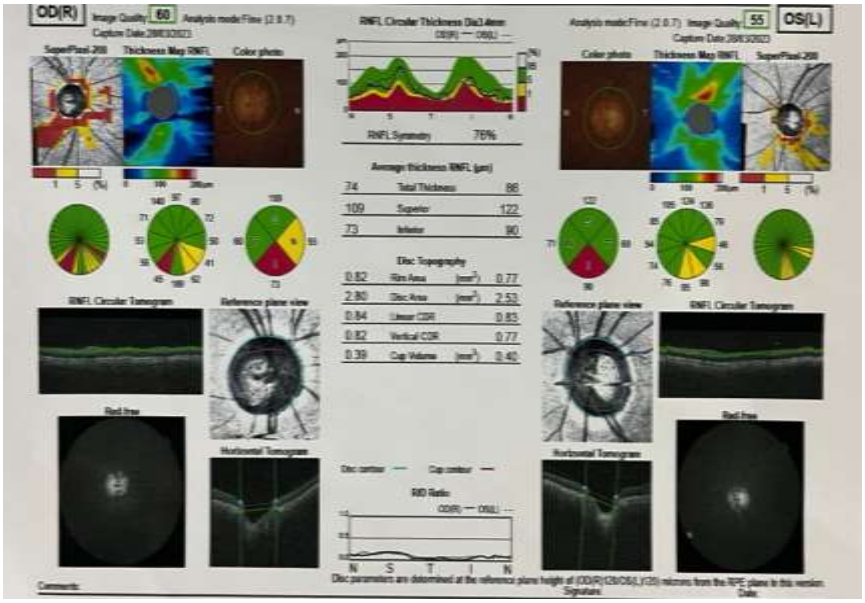

Fig 6: patient`s Ophthalmological report

Every effort was made to find out any other cause for optic atrophy we could not find any. In presence of drug known to cause optic atrophy and there being no identifiable reason for optic atrophy it was attributed to ethambutol.

Discussion

Tuberculosis disease primarily infects pulmonary system. It also effects other organs and tissues termed extra pulmonary TB[12]. Extra pulmonary tuberculosis can affect skeletal, nervous, lymphatic and genitourinary systems. Spine is the most frequently affected site in the musculoskeletal system. The foot and ankle is affected in only 0.13% cases of extra pulmonary TB. Indolent course of infection and heterogeneity of its presentation along with the difficulty in early diagnosis often causes significant delays in its treatment and hence results in a considerable disability[2]. Our patient had 1 year delay in diagnosis probably was treated symptomatically as early osteoarthritis.

Patients with suspected musculoskeletal tuberculosis can benefit from being evaluated using imaging modalities such as conventional radiography, CT, MRI, CT-guided fine needle aspiration biopsy, microbiological and histopathological examination[12]. Since there are no pathognomonic radiographic signs, tissue biopsy and/or culture data are typically used to make the diagnosis[13]. To prevent function and mobility loss, it is crucial to get a proper diagnosis and start treatment as soon as possible, if the diagnosis is established early enough, full restoration of function without deformity can be safely expected[14]. Our patient had delay in early diagnosis which had already damaged the joint requiring surgery which was confirmed on MRI

Skeletal tuberculosis is always a secondary infection from a primary focus elsewhere, most frequently after pulmonary infection. Tuberculosis generally presents as periarticular granuloma, central granuloma and may manifest as synovitis, tenosynovitis and bursitis. The basic histologic lesion is a tubercle, which exhibits an area of caseation necrosis surrounded by epithelial cells, Langhans giant cells and lymphocytes, and develops as a response to the tubercle bacillus[15]. Our patient was microbiological and histopathalogical proven case of ankle tuberculosis.

Tuberculosis treatment is initially started with anti-tubercular therapy, which slow down the progression toward sequelae. The majority of lesions heal within 6-12 weeks under medical treatment. The current standard of care treatment for drug-sensitive (DS) TB is 6 months and consists of two phases of drug treatment: four drugs isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) given for 2 months followed by two drugs (HR) for 4 months[16]. For ankle tuberculosis 2months of HRZE/ 10-16 months of HRE is recommended[5]. Our patient had received 2 months of anti-tubercular therapy and our patient continued to take 3drugs (HRE) as per newer guidelines of NTEP programme, but pain and swelling persisted.

Ethambutol is a potent bacteriostatic drug against tuberculosis[17]. Ethambutol should not be used alone as monotherapy but rather in tandem with at least one other anti-TB drug. Ethambutol shows a specific effectiveness against the Mycobacterium tuberculosis (MTB) and atypical/non-tuberculous mycobacteria such as Mycobacterium avium complex bacteria (MAC) that cause pulmonary infection non-tuberculosis and lymphadenitis, but not against other bacteria or other pathogens, such as viruses and fungi[8]. EMB interferes with the biosynthesis of arabinogalactan in the cell wall of MTB and inhibits multiplication by bacilli. The polymerization of cell wall arabinan from arabinogalactan and lipoarabinomannan is inhibited by blockade of arabinosyl-transferases and enhance the accumulation of D-arabinofuranosyl-P-decaprenol, an intermediate in arabinan biosynthesis. This results in decreased bacterial growth[18].

Anti-tubercular therapy has adverse effects that are sometimes serious, mainly occurring during the first intensive phase of treatment. About 60% of patients on anti-tuberculosis have adverse reactions, one third of which are related to immune sensitization[19]. Multidrug therapy for tuberculosis would increase the risk of serious adverse reactions such as hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgia, and neurological disorders[20]. Our patient had mild gastrointestinal symptoms and vomiting episodes but reduced with appropriate medication.

Side effects of ethambutol include peripheral neuropathy, hepatotoxicity and mental confusion. The most well-known and major adverse effects of EMB is optic neuropathy. It is currently reported that 1%-3% of patients receiving ethambutol may develop EON[21]. It is dose-related, and 40% of adult patients develop optic neuropathy at doses greater than 50 mg/kg[22]. Dosage in our patient was 1375mg for 60kg body weight and had continued ethambutol for 2months.

Ocular effects of ethambutol includes bilateral, painless and typically symmetric loss of visual acuity and abnormal colour vision[23]. However, the onset may be unilateral, but eventually both eyes are involved[24]. Loss of colour vision is typically reported for green and red, although blue–yellow colour changes may also occur[25]. Our patient had counting fingers at one and half meter in both eye. Ishihara's plates could not be read which indicated that patient had developed colour blindness. Normal anterior segment and normal intraocular pressure. In our patient had delayed in presentation.

Visual field test usually reveals central or par central scotoma and less commonly includes peripheral constriction, altitudinal field defects, and bilateral temporal field defects[26]. There are no pathognomical fundal features for ethambutol toxicity. The optic disc may appear normal; however, as the disease progresses, it eventually develops into a pale optic disc[27]. In our patient On Fundus examination with Optical Coherence Tomography showed pale disc with disc thinning in the inferior quadrant with thinning of retinal nerve fibre layer. Visual evoked potential showed both eyes increased latency and decreased amplitude.

EMB is included in the category of TB drugs with mild adverse effects[7]. There are several mechanisms proposed for ethambutol induced optic atrophy. Some patient with genetical mutations of mitochondrial fusion protein may be predisposed for ethambutol induced optic neuropathy. Ethambutol increases the chelation of copper, which is related to the mechanism of EMB-induced optic neuropathy[28]. A study of 231 patients found that age > 65 years, hypertension, and kidney disease were also risk factors for the development of EON[29]. In our patient risk factors were old age and diabetic mellitus which could have attributed to toxicity. Our patient had blurring of vision at 3rd month of antitubercular therapy.

Surgical intervention is needed when medical management fails, pain doesn't subside even after 8 weeks, advance disease with damaged joints[12]. When the joint is damaged including articular surface and unlikely to return to normal after chemotherapy surgical fusion of the ankle is indicated to relieve pain and to get a stable joint[30]. In our case joint damage was identified on MRI and we opted for chemotherapy and fuse joint with debridement and CC screw fixation. Patient follow up were good and no any abnormality in the surgical wound were observed. Eventually ankle fusion was achieved, patient had no complaints of pain and swelling at the end of 10 months after surgery and walking without support.

Further our patient was evaluated by super speciality hospital for optic atrophy since no other cause attributed to vision loss it was suspected ethambutol induced optic neuropathy.

There is no active treatment for Ethambutol induced neuropathy other than stoppage of drug itself. Recovery of visual functions is most often partial and incomplete, though complete recovery has been shown in several cases over 1 to 6 months when ethambutol was stopped early[31]. In our patient her visual acuity was counting finger 3meters after 12 months.

Conclusion

Though ethambutol is categorised as drug with mild adverse effects it can cause serious visual loss with no definitive treatment and variable recovery. Hence clinicans should be observant and prevent visual loss by early diagnosis and withdrawal of the drug immediately.

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