

## ETHAMBUTOL INDUCED CHOLESTASIS

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### ABSTRACT

Ethambutol induced cholestatic hepatitis is a rare and not a well known complication. The typical presentation of vomiting, right hypochondriac heaviness may not distinguish it from the usual hepatocellular damage commonly seen during antituberculous therapy. So detailed liver function test has to be done. Here we present a case of cholestatic hepatitis occurred after start of ATT and improved when ethambutol was omitted. Moreover it's a first case report of such disorder in this age of 14 years, in Pakistan.

**Key Words:** Ethambutol induced cholestatic hepatitis, Antituberculous therapy drug reaction. Ethambutol toxicity.

### INTRODUCTION

Ethambutol is the first line anti tuberculous drug which is part of tuberculosis treatment almost for 8 months. Optic neuritis is the recognized toxicity associated with its treatment, which may or may not be reversible.<sup>1,2</sup> The reported incidence of optic neuritis i.e. 1.5 % is more with dose of 25 mg/Kg.<sup>3</sup> This side effects is documented in various text books and reviews throughout medical indices.<sup>1,4,5,6</sup> We present a case of cholestatic jaundice which manifested as severe vomiting and right hypochondrium heaviness started after one month of anti tuberculous therapy including ethambutol despite having normal liver function tests checked prior to start of therapy and three weeks after therapy just for early detection of liver damage. Unique feature is that it happened in 14 years old boy.

### CASE REPORT

A male boy of 14 years of age presented with vomiting, right hypochondriac pain and lethargy for one week. He was on antituberculous therapy for last one month including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. Ethambutol was being given at dose of 15 mg/kg body weight. His liver function tests prior to starting treatment were within normal range. (Table I).

At the time of presentation with vomiting and

right hypochondriac heaviness he was apprehensive, and lethargic with Blood Pressure 110/75 and pulse 110/min, regular and weight of 40 Kg. However, he was afebrile. Patient did complaint of anorexia. There were no visual complaints and rest of the systemic examination was unremarkable.

Prior to this event he was improving and was having good appetite and feelings of well being. Considering his symptoms, his liver function tests were repeated (Table I). His ALT/Bilirubin was reported normal while alkaline phosphatase was markedly raised to 954. As there was no hepatocellular hepatitis. So he was asked to get ultrasound abdomen for any evidence of lymphadenopathy causing cholestasis and Gamma GT Serum Test which was high. He refused to be treated as in patient and he assured to get it done as outpatient and he was advised antiemetics (gravinate and Famotidine). He again lost to follow up and turned up after one week still symptomatic and looking dehydrated but conscious and oriented. His ultrasound was normal with no evidence of biliary obstruction. But the repeat LFTs showed further deranged Alkaline Phosphatase with normal ALT/Bilirubin. One case of cholestatic jaundice was reported in 1985 due to ethambutol, so antituberculous therapy was continued omitting ethambutol. Patient started improving so does the Liver Function Tests that gradually within 15 days came down to normal.

### DISCUSSION

Ethambutol is an important first line antituberculous medication, which according to WHO now is used throughout the length of tuberculosis treatment. Although ethambutol induced rise in alkaline phosphatase (ALP) has been reported once,<sup>7</sup> but from this area this is the first case report and also first in

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this age group in the world.<sup>6</sup> Its diagnosis is based on investigating the causes for vomiting while on antituberculous treatment.

This patient was active, ambulant and was improving on antituberculous treatment when after completion of one month of antituberculous therapy he started showing these symptoms, it was an unusual manifestation of ethambutol toxicity. According to one review its incidence is 1.52%.<sup>6</sup> And it starts rising after one month of ethambutol treatment and if its not discontinued it may keep on elevating ALP level till 6 month of therapy.<sup>6</sup> If such therapy is required to continue for more then 6 months then level of alkaline phosphatase may further rise.<sup>6</sup> Young women between 30-39 years of age are mostly affected. Risk from first year of life to 19 years of age is nil.<sup>6</sup> So this is the first case of 14 years old boy having high alkaline phosphatase level on ethambutol treatment.

This patient was not on any other medicine beside antituberculous therapy. The top co drugs which can contribute to such side effect are, Amikacin sulfate, Ganciclovir, Hydrocortisone sodium phosphate, Lamivudine, Zidovudine.<sup>6</sup> Uptill now just one case report is available.<sup>7,8</sup> The mechanism of ethambutol's such side effect is unknown and hypersensitivity has been attributed to it.<sup>8</sup> So we didn't re introduced the medication once ALP became normal after its withdrawal since the symptoms settled. However, earlier reported toxicity occurred after 2 months of start of therapy.<sup>7,8</sup> Recovery time frame is almost equal to the first reported patient as our patient improved in 15 days compared to 11 days in the first case. However, they rechallenged it by restarting ethambutol and we didn't because of this reason the further clinical course of our patient on Isoniazid, Rifampicin and Pyrazinamide is stable.

This case is unique in the sense that there was cholestasis at lower dose and younger age and despite initial improvement, patient deteriorated and started showing signs of cholestasis. Interestingly he was on 15 mg/Kg body weight dose of ethambutol. This is of concern as even optic neuritis is more common with higher doses of 25 mg/kg body weight.

We shared this observation for further debate on monitoring the alkaline phosphatase level as well

while on antituberculous therapy including ethambutol in addition to Alanine aminotransferase (ALT) which is a routine practice.

**Table I:**

**Repeated values of liver function tests**

S.No.	Date	Billirubin	ALT	Alk.Phosphatase
1	15 <sup>th</sup> March 2012	0.64	16	207
2	25 <sup>th</sup> April 2012	0.79	57	218
3	14 <sup>th</sup> May 2012	0.94	34	954
4	22 <sup>nd</sup> May 2012	0.75	19	1031
5	29 <sup>th</sup> May 2012	0.91	26	977
6	7 <sup>th</sup> Jun 2012	0.73	39	243

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