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An unusual recurrence of antitubercular drug induced hepatotoxicity in a child

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Hepatotoxicity secondary to antitubercular drug therapy is uncommon in children. Tuberculosis is a commonly acquired infectious illness in developing countries like India. Since antitubercular therapy is frequently used, there is a need to educate physicians on the causes and management of drug induced hepatotoxicity in children.

Case Details

A two-and-half-year-old child was admitted to our institution with complaints of fever since 6 days and a dry spasmodic cough for 4 days prior to admission. Her respiratory complaints began at the age of 6 months when she was admitted for bronchiolitis for 4 days. Thereafter, she had repeated episodes of cough and breathlessness requiring oral medications and nebulizations (nebulized medications not known) on multiple occasions and admission on four occasions. At one-and-half years of age, she was diagnosed as persistent asthma and was started on metered dose inhaler therapy with salmeterol and fluticasone. However, her respiratory symptoms continued till she was two-and-half years of age when she was admitted to our institute with the above complaints. Apart from recurrent respiratory symptoms, her past history was also significant for repeated episodes of febrile convulsions starting at 6 months of age till one-and-half years of age when she was started on oral sodium valproate (25 mg/kg/day). On examination, at the time of admission, she was afebrile and hemodynamically stable. Chest examination revealed bilateral rhonchi scattered over the lung fields and the rest of the general and systemic examination was unremarkable.

Investigations revealed a total leukocyte count of 33,000 cells/mm^3. Chest radiograph was suggestive of bilateral basal consolidation [Figure 1]. A high resolution computed tomograph (HRCT) of the chest was done in view of many previous chest radiographs showing hyperinflation of the lung fields. It confirmed the chest radiograph finding of bilateral basal consolidation with a possibility of pulmonary tuberculosis [Figure 2]. The Mantoux test was negative and sputum did not grow acid fast bacilli. Immunoglobulin profile (IgA, IgG, and IgE) was normal and the ΔF508 mutation study for cystic fibrosis was negative. A 2D-echocardiography was done to rule out congenital heart disease and was normal.

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The child was started on daily 4-drug antitubercular therapy comprising isoniazid, rifampicin, pyrazinamide and ethambutol which was planned to be continued for a period of 2 months, followed by isoniazid and rifampicin for a period of 4 months. Additionally, the child was also started on metered dose inhaler therapy with salbutamol and budesonide for hyper-reactive airway disease diagnosed . The child was discharged on the above treatment along with nutritional supplements and oral sodium valproate was continued.

The child completed her intensive phase of 4-drug antitubercular therapy with no adverse effects. Oral sodium valproate was stopped on day 25 of her intensive phase of antituberculous drug therapy. However, 3 weeks into her continuation phase with isoniazid and rifampicin, she developed jaundice with mild grade fever. Her liver function tests revealed elevated transaminase levels – serum glutamic pyruvate transaminase (SGPT) 1482 U/L (normal range 5–40 U/L), elevated bilirubin levels with a total of 5.4 mg/dL and a direct fraction of 2 mg/dL. Her complete blood count revealed leukocytosis with a total count of 23,500 cells/mm^3 with eosinophils of 37%. Her hepatitis A IgM antibody level was negative and hepatitis B surface antigen test was also negative.

A diagnosis of antitubercular drug induced hepatotoxicity (with possible intercurrent infection) was made.

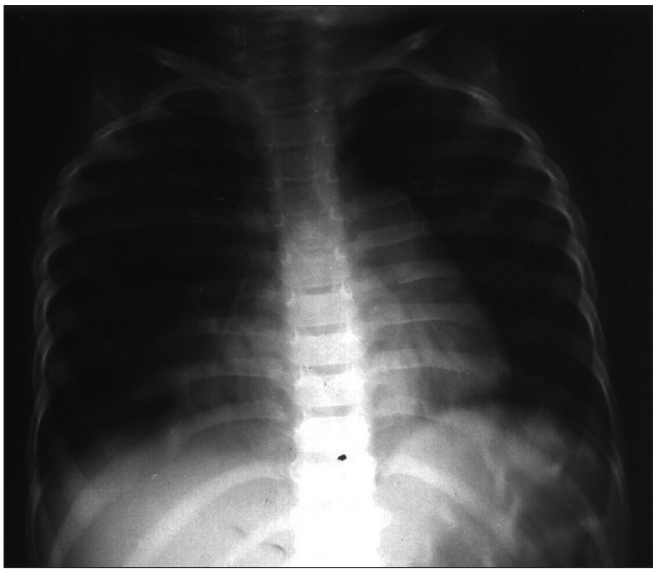

Figure 1: Chest radiograph showing bilateral basal consolidation

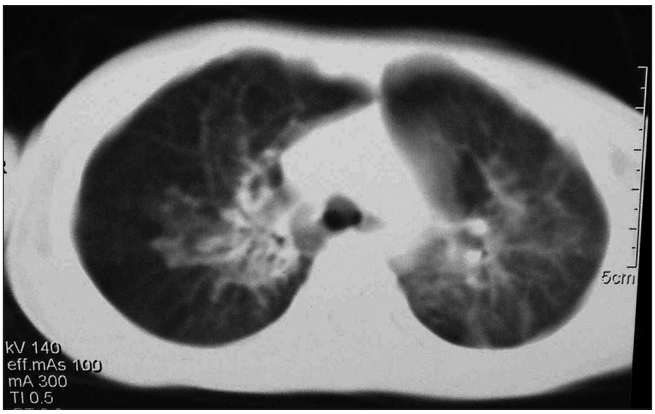

Figure 2: High resolution computed tomograph chest confirms the findings of bilateral basal consolidation

How common is antitubercular drug induced hepatitis in children, especially in those less than 5 years of age?

Reply: Hepatotoxicity secondary to antitubercular drug therapy is uncommon in children. It is reported in approximately 15% of adult patients with tuberculosis; however, in children, its incidence is much lower (3–10%), with serious jaundice occurring in only 0.6% cases.[1,2] However, in a study by Tsagaropoulo-Stinga *et al.*, in children with a mean age of 4.5 years treated with isoniazid and rifampicin, 82% experienced a serum glutamic oxaloacetate transaminase (SGOT) elevation greater than 100 U/L and more than 40% had symptomatic hepatitis with jaundice.[3] In a South Indian study published in the year 1986 on 1686 patients of all ages with TB, 16–39% of children with tuberculous meningitis developed hepatitis and "nearly always with jaundice".[4]

What are the pre-disposing factors for antitubercular drug induced hepatotoxicity?

Reply: Hepatic injury with antitubercular drugs is age related and is more likely to occur in adolescents, in those with associated severe malnutrition, and in patients with severe form of the disease such as miliary and CNS tuberculosis.[5,6] The incidence of hepatotoxicity in the above-mentioned study from South India was much higher than the 2–8% seen in the multi-age cohorts with pulmonary or spinal TB.[4] In another retrospective study, severe antitubercular drug induced liver injury was associated with age younger than 5 years, extra-pulmonary tuberculosis, and with use of pyrazinamide.[7] Dose of isoniazid more than 10 mg/kg/day is also reported to be associated with higher incidence of hepatic injury.[8,9] However, use of isoniazid for chemoprophylaxis even at the dose of 10 mg/kg/day elevated transaminases in 7.5% children.[10] Besides slow acetylator status and genetic polymorphisms of CYEP2E1, concomitant rifampicin administration increases the likelihood of hepatotoxicity with isoniazid as does the use of other hepatotoxic drugs.[11] Female gender, pre-existing chronic liver disease due to hepatitis B, hepatitis C, and HIV infection add to hepatotoxicity due to antitubercular drugs.[12]

How is antitubercular drug induced hepatotoxicity classified? What is clinically significant hepatotoxicity?

Reply: It has been suggested that if the transaminase levels are less than five times the upper normal limit, the toxicity is considered mild. When the transaminase levels are increased to five to ten times the normal, the toxicity is considered moderate. Elevation of transaminases to more than 10 times the upper normal limit suggests severe toxicity.[13] A progressive derangement in liver functions associated with symptoms of jaundice and hepatitis is highly significant, warranting intervention – rather than transient disturbances which are fairly common during the course of antituberculosis therapy.[12]

What are the clinical manifestations of antitubercular drug induced hepatotoxicity?

Reply: The clinical features of antitubercular drug induced liver injury closely mimic those due to viral hepatitis and range from transient asymptomatic elevations of liver enzymes to acute liver failure and fulminate hepatitis.[14]

What is the mechanism of hepatic injury due to isoniazid and rifampicin?

Reply: Isoniazid produces a hepatitis-like picture with elevation of liver enzymes, especially SGPT, with/without elevation of serum bilirubin, whereas rifampicin by inhibition of bile salt exporter pump produces cholestasis with predominant rise in serum bilirubin with/without elevation of alkaline phosphatase and/or gamma glutamyl transferase.[15,16] Formation of hydrazine from isoniazid is considered to be the cause for isoniazid induced hepatotoxicity and the production of hydrazine is increased following concurrent administration of rifampicin, an enzyme inducer.[17]

Case details (continued)

Isoniazid and rifampicin were stopped and the child was put on ethambutol and ciprofloxacin. Her liver enzymes repeated after 2 weeks of the modified regime had normalized (SGPT 29.2 U/L and SGOT 36.5 U/L). She was re-started on isoniazid

at half dose (2.5 mg/kg/day). Liver enzymes repeated another week later were still normal (SGPT 54.9 U/L and SGOT 65.7 U/L); so, isoniazid was increased to its full dose (5 mg/kg/day) and rifampicin was added at half dose (5 mg/kg/day). Liver enzymes repeated a week later were elevated (SGPT 319.5 U/L and SGOT 223.5 U/L). Isoniazid and rifampicin were again stopped in view of elevated transaminases and ethambutol with ciprofloxacin was re-started.

Liver enzymes repeated 2 weeks later normalized again (SGPT 38.4 U/L and SGOT 36.4 U/L); hence, half dose isoniazid was re-started. The enzymes remained normal after 2 weeks of re-starting isoniazid; so, half dose rifampicin was added. However, within a week, transaminases again rose (SGPT 150.6 U/L and SGOT 122 U/L). Both isoniazid and rifampicin were again stopped. A summary of the above has been presented in Table 1.

What is the Naranjo score for adverse drug reaction (antitubercular drug induced liver injury) in this case?

Reply: According to Naranjo's algorithm of causality assessment, the hepatotoxicity in this case falls into the category of definite (Naranjo score = 9) adverse drug reaction due to antitubercular therapy as both de-challenge and re-challenge are positive with adequate literature evidence of antitubercular drug induced liver damage.[18]

What are the recommendations for monitoring liver function tests in patients on antitubercular drugs?

Reply: There are no uniform guidelines for monitoring liver functions in pediatric patients who receive drug therapy for tuberculosis. A baseline pre-treatment liver function profile which includes a baseline alanine transaminase (ALT), serum bilirubin, hepatitis screen along with serum creatinine and platelets is a must for all patients; however, the American Thoracic Society does not recommend baseline liver function measurements for healthy asymptomatic patients who receive isoniazid or rifampicin.[19] Baseline and thereafter a 2 weekly liver function assessment in the first 2 months of treatment is recommended for high-risk patients, i.e. those suffering from chronic liver disease, HIV patients on anti-retroviral therapy, and those who are malnourished.[12,19] ALT is the preferred liver enzyme for detecting and tracking liver injury in those patients who develop clinical features of hepatotoxicity. Other liver function parameters such as aspartate transamianse (AST), alkaline phosphatase, and serum bilirubin levels are useful adjuncts to monitor chronic liver disease, cholestasis, and severe hepatocellular injury.[19] The upper limit of normal for the liver enzyme is as per the specific laboratory performing the assay.[19]

At what level of hepatic dysfunction is intervention warranted?

Reply: All potentially hepatotoxic drugs should be withheld if ALT is at least three times the upper limit of normal when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the upper limit of normal in the absence of symptoms and liver functions monitored weekly thereafter.[19,20] An isolated increase in the transaminase values to less than three times the upper limit of normal requires weekly monitoring of the liver enzymes.[20] With an isolated elevation of serum bilirubin without a concomitant rise in transaminases, antitubercular drugs can be continued with weekly monitoring of liver function tests.[20] The hyperbilirubinemia with antitubercular therapy is usually transient and is secondary to the impaired bilirubin excretion caused by rifampicin.[20] Hyperbilirubinemia persistent after 2 weeks requires withdrawal of rifampicin.[20] An associated transaminase elevation greater than twice the upper limit of normal is highly suggestive of hepatotoxicity and requires stoppage of isoniazid.[20] If there is clinical hepatitis or biochemical evidence of significant liver dysfunction due to antitubercular therapy, particularly impairment of synthetic function (most commonly a fall in serum albumin or an impaired prothrombin time), all medications should be stopped immediately.[20]

Case details (continued)

In view of recurrent hepatotoxicity secondary to antitubercular therapy, a modified regimen comprising ethambutol (20 mg/kg/day) and ciprofloxacin (20 mg/kg/day) (ciprofloxacin was replaced by ofloxacin after a month in view of better safety profile) was given as a continuation phase to complete the therapy, after which there was no derangement of transaminases. At present, the child has completed 4 months of modified therapy with ethambutol and ofloxacin (20 mg/kg/day) with no clinical or biochemical evidence of liver injury. Figure 3 gives a graphical depiction of the temporal association of liver enzymes with the days of anti-tubercular therapy received by

Table 1: Details of liver enzymes and anti-tubercular therapy

Date	Day of ATT	SGOT (U/L)	SGPT (U/L)	Action taken
23/07/2009	-	55 (Baseline)	26 (Baseline)	ATT started on 28/07/2009
26/10/2009	Day 91	88	1482	INH and R stopped; ETB and ciprofloxacin added
09/11/2009	Day 105	36.5	29.2	INH re-started at half dose (2.5 mg/kg)
16/11/2009	Day 112	65.7	54.9	INH increased to full dose (5 mg/kg); R added at half dose (5 mg/kg)
23/11/2009	Day 119	223.5	319.5	INH and R stopped; ETB and ciprofloxacin re-started
07/12/2009	Day 133	36.4	38.4	INH re-started at half dose (2.5 mg/kg)
23/12/2009	Day 149	61	30	R added at half dose (5 mg/kg)
01/01/2010	Day 155	122	150.06	INH and R stopped; ETB and ciprofloxacin added
01/02/2010	Day 185	46.9	51.2	Ciprofloxacin changed to ofloxacin; ETB continued
20/05/2010	Day 294	25	41	ETB and ofloxacin continued

ATT: Antitubercular therapy; INH: Isoniazid; R: Rifampicin; ETB: Ethambutol, SGOT: Serum glutamic oxaloacetate transaminase, SGPT: Serum glutamic pyruvate transaminase

the patient. An HRCT of the chest repeated after 4 months of modified therapy is suggestive of post-tubercular sequelae with traction bronchiectasis and a persistent partial collapse of the posterior segment of right upper lobe [Figure 4].

What are the recommendations for managing antitubercular drug induced hepatotoxicity and restarting the therapy?

Reply: It is essential to rule out other causes of liver injury, most commonly hepatic injury due to viral infections and that due to other non-antituberculous hepatotoxic drugs, before a diagnosis of antitubercular drug induced hepatitis is made and drug therapy for tuberculosis is modified.[19] Guidelines regarding management of hepatotoxicity due to antitubercular drugs and the order in which drugs should be added in such a case are not uniform.

Seth recommends stopping all antitubercular drugs in a setting of clinically evident hepatitis and starting a combination of ethambutol and streptomycin till the liver functions are restored to normal.[21] Once transaminases have decreased to less than twice the upper limit of normal, rifampicin should be started in the dose of 5 mg/kg and ethambutol along with streptomycin continued. A first rechallenge with rifampicin is due to it being the least hepatotoxic and the most potent antitubercular drug.[21] Transaminases should be estimated weekly, and if found to be normal after a week, the dose of rifampicin can be increased to 10 mg/kg and isoniazid reintroduced. Dose of isoniazid should not exceed 5 mg/kg/day, even in tuberculous meningitis and 10 mg/kg in intermittent regimens.[21] In patients with

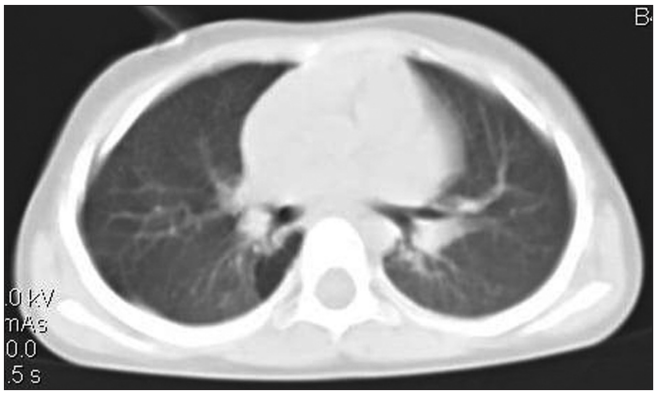

Figure 4: High resolution computed tomograph (HRCT) chest showing post-tuberculosis sequelae with traction bronchiectasis and partial collapse of posterior segment of right upper lobe

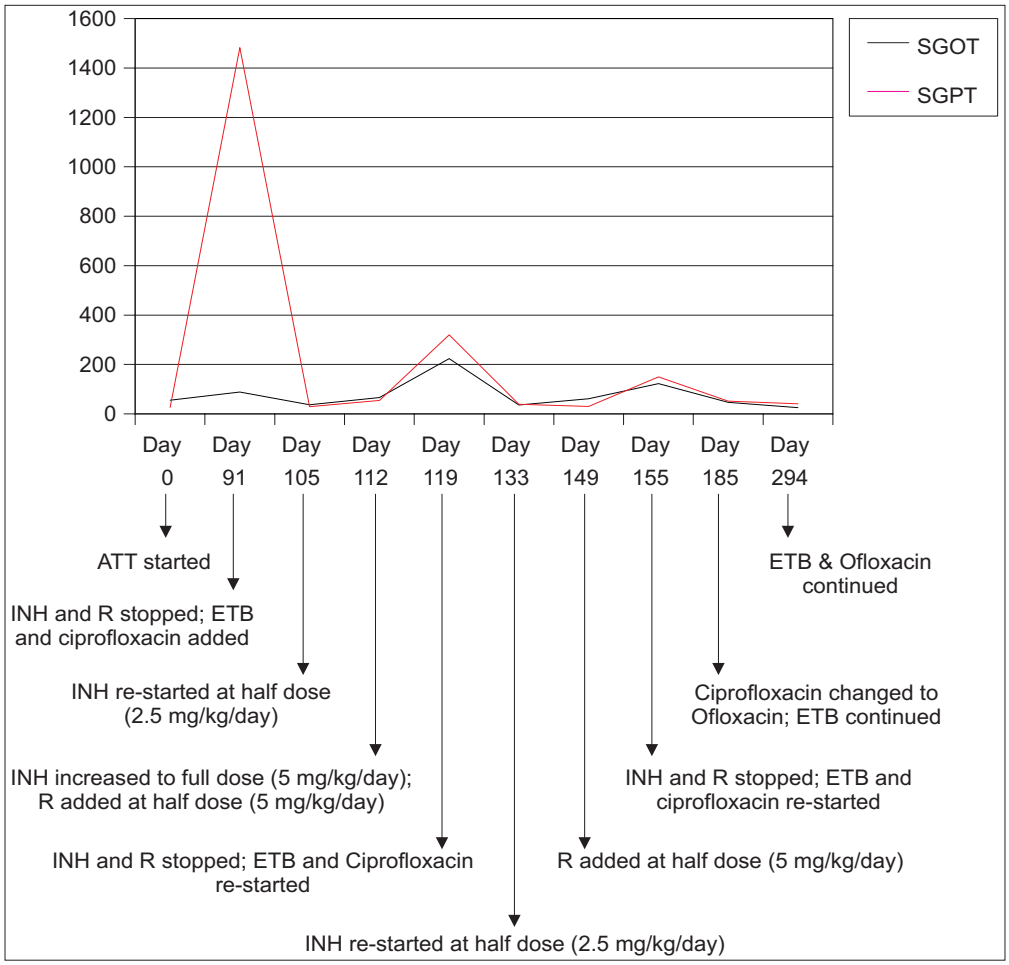

Figure 3: Graphical depiction of the temporal association of liver enzymes (SGOT, SGPT) with days of antitubercular therapy in the patient (X-axis: days of antitubercular therapy; Y-axis: liver enzymes (SGOT, SGPT) in U/L). ATT= Antitubercular therapy; INH = Isoniazid; R = Rifampicin; ETB = Ethambutol

tuberculous meningitis, miliary and osteoarticular tuberculosis, pyrazinamide can be added at 20 mg/kg with regular monitoring of transaminases.[21]

The American Thoracic Society guidelines are similar to that given by Seth as far as the order of re-introducing antitubercular drugs is concerned, i.e. rifampicin followed by isoniazid.[19] In addition, the American Thoracic Society states that in case of symptom recurrence or a rise in transaminase, the last drug added should be stopped. It also states that in case of patients with prolonged or severe hepatotoxicity who tolerate rifampicin and isoniazid, addition of pyrazinamide may be hazardous.[19] In such cases, it is advisable to discontinue pyrazinamide completely and to extend the duration of therapy to 9 months.[19]

A suggested regimen by WHO in such patients is a 2-month initial phase comprising daily streptomycin, isoniazid and ethambutol, followed by a 10-month continuation phase of isoniazid and ethambutol (2SHE/10HE).[22]

British Thoracic Society recommends no treatment in case a well patient or a patient with a noninfectious form of tuberculosis experiences drug induced heptotoxicity till the liver functions normalize.[23] However, if the patient is unwell or the sputum smear is positive within 2 weeks of starting therapy, use of ethambutol along with streptomycin is advised. Once the liver function becomes normal, challenge dosages of the original drugs can be reintroduced sequentially in the order isoniazid, rifampicin, pyrazinamide, with daily monitoring of the patient's clinical condition and liver function.[23] Isoniazid should be introduced initially at 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued. After a further 2–3 days without reaction, rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued. Finally, pyrazinamide is added at 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (<50 kg) or 2 g (>50 kg). If there is no further reaction, standard chemotherapy can be continued and any alternative drugs introduced temporarily can then be withdrawn.[23]

What is the possible explanation for the recurrences of hepatotoxicity in this case?

Reply: Probably every time, the reintroduction of isoniazid in this patient before rifampicin resulted in the recurrences of hepatotoxicity by isoniazid. Ideally, rifampicin should be restarted first and then isoniazid should have been added thereafter, and if hepatotoxicity recurred, isoniazid should be stopped and rifampicin should be continued for rest of the treatment period. Literature search clearly pictures that rifampicin is the single most essential antituberculous agent as it is the best tuberculocidal agent against slowly multiplying bacilli (i.e. during continuation phase) than any other antituberculous drug currently available.[24] Also, a case report was published by Askgaard *et al.*, where a 35-year-old woman developed hepatotoxicity following re-administration of rifampicin with isoniazid already started, whereas after dechallenging both the drugs and then when rifampicin was restarted, there was no recurrence of hepatotoxicity.[25]

A recent study[26] with an aim to determine the overall incidence of severe and mild isoniazid (INH) hepatotoxicity in children with TB and latent TB and the effect of age on liver injury in children did not demonstrate any age-specific difference for hepatotoxicity. There was no statistical difference in the incidence of overall liver toxicity in age groups of children in their study, i.e. aged <5 years, 5–10 years, ≥10 years. The authors concluded that severe hepatotoxicity in children is lower (0.57%) than reported before. Also, they state that age has no effect on Isoniazid hepatotoxicity in children (as against in adults); however they do caution toward the potential of antitubercular drugs to cause hepatotoxicity and liver failure in children.[26]

Conclusion

Antitubercular drug induced hepatotoxicity is not so common in children. However, if it occurs, as suggested by either a clinical or a biochemical evidence of liver injury, it requires stopping all the potential hepatotoxic antitubercular drugs with a systematic and regular monitoring of liver enzymes. A fluroquinolone-containing regimen may be preferred if there is recurrence of hepatotoxicity to first-line anti-tubercular drugs. Baseline liver function assessment before starting therapy for tuberculosis and parent education by the treating pediatrician for early identification of features of clinical hepatitis in their children will be useful in the appropriate management of these cases.

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