H, an 18-month old boy was diagnosed with LTBI after his mother was diagnosed with TB infection. He was started on INH monotherapy 10mg/kg/dose. Prior to starting treatment, his baseline liver function test (LFT) showed aspartate aminotransferase (AST) 65 U/L, alanine aminotransferase (ALT) 30 U/L. He was also started on syrup Maltofer for iron deficiency anaemia (IDA). His LFT showed an increase in transaminases: AST: 104 U/L, ALT: 56 U/L two weeks later. Subsequent LFT in another two weeks showed a progressive increase in transaminases of AST 111 U/L and ALT 278 U/L. INH was stopped and repeated LFT two weeks later revealed the transaminases level had decreased. His LFT had normalised four weeks after stopping INH. Apart from that, he was asymptomatic throughout this incident. He is still under follow-up for LTBI.

INH is one of the main medications to treat tuberculosis (TB) infection including LTBI. However, drug-induced liver injury (DILI) is a known adverse effect of isoniazid. Serum transaminase elevation occurs in about 10% of children receiving INH monotherapy. Drug-induced liver injury can range from asymptomatic increase of aminotransferase to severe liver injury, or in some cases hepatic failure. Even though INH-induced liver injury has been known and extensively studied, its underlying mechanisms are still not fully understood. The liver injury comprises hepatotoxicity and a rarer form of hepatitis hypersensitive allergic reaction. Since the facility to do liver function (LFT) is widely available, monitoring liver function while on INH therapy is the wisest way of monitoring acute liver injury (ATLI).

**ABSTRACT**

ISONIAZID IN CHILDREN – ANY RATIONALE FOR POST ISONIAZID LIVER FUNCTION TEST?

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Isoniazid (INH) therapy remains the treatment of choice in latent tuberculosis infection (LTBI). However, drug-induced liver injury (DILI) is a known adverse effect of isoniazid. Serum transaminase elevation occurs in about 10% of children receiving INH monotherapy. Drug-induced liver injury can range from asymptomatic increase of aminotransferase to severe liver injury, or in some cases hepatic failure. Even though INH-induced liver injury has been known and extensively studied, its underlying mechanisms are still not fully understood. The liver injury comprises hepatotoxicity and a rarer form of hepatitis hypersensitive allergic reaction. Since the facility to do liver function (LFT) is widely available, monitoring liver function while on INH therapy is the wisest way of monitoring acute liver injury (ATLI).

**Keywords:** Isoniazid, Anti-TB drug-induced liver injury (ATLI), latent Tuberculosis infection (LTBI)

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Donald P.R. published an article which analysed eighteen papers that documented adverse events after INH chemoprophylaxis was prescribed [6]. Seven of the eighteen papers with a total of 2149 children had received an INH dosage of 4-6 mg/kg. Out of these, 461 children have their serum transaminase level tested regularly with 56 (12.1%) of them having increased transaminase level nonetheless none developed jaundice. Whereas, another four papers with a total of 1451 children received INH dosage of 10 mg/kg; 369 (25%) children had LFT routinely tested with 25 children (6.8%) had increased transaminase values with 1 child developed jaundice (0.27%). In the remaining seven studies with a total of 7528 children who received INH dose of 10-20mg/kg reported 17 (14.7%) out of 116 children had increase in transaminases with 4 (3.4%) developed symptoms of fever, nausea, vomiting, loss of appetite, skin rash and hepatomegaly but no jaundice. Thus, 5% to 14% of children had their transaminase level rise after starting on INH. Although the dose did not have much influence in the incidence of increase in transaminase level, those with higher dose were more symptomatic.

Two forms of liver injury linked with INH are hepatitis hypersensitive allergic reaction and INH hepatotoxicity [7]. INH hepatitis hypersensitive allergic reaction is a more serious liver injury than INH hepatotoxicity. The former is usually symptomatic and may be fatal. It is an idiosyncratic reaction that is not definitively related to dose or duration of therapy. The typical time of inception of injury usually ranges from 2 weeks to 6 months. It is usually insidious and resembles acute viral hepatitis with a prodomal period of nausea, anorexia, abdominal discomfort, and fatigue, notably followed by dark urine and jaundice [8]. Progressive jaundice in INH mediated liver injury is associated with liver transplant and death [8]. Thus, INH hepatitis hypersensitive allergic reaction should be suspected in any patients on INH therapy followed by fatigue, malaise, anorexia, nausea, and/or vomiting accompanied with elevated serum aminotransferases. The diagnosis is clinically determined, based on clinical manifestations and exclusion of other causes. Resolution of elevated aminotransferases within several weeks after discontinuation of therapy supported the diagnosis [8].

INH hepatotoxicity is defined in the guidelines of the American Thoracic Society as an increase in ALT > 3 times the upper limit of normal (ULN) with symptoms of hepatitis and/or jaundice, or ALT > 5 times ULN without symptoms [9]. In a retrospective study done by Chang et al that enrolled 1587 children (less than 18-year-old) who was treated withisoniazid for latent TB. In this cohort, 13 children developed hepatotoxicity (0.8%) in which 11 were symptomatic and another 2 were asymptomatic but the ALT was more than 5 times normal. The most common reported symptoms are abdominal pain, anorexia, vomiting, and nausea. All but 3 patients acquired hepatotoxicity within 6 months of starting INH. All the symptoms and abnormal transaminases level resolved after the isoniazid was stopped. The hepatotoxicity is not related to sex, age, or race. However, in this cohort the real prevalence of increased transaminases was not able to accurately determine due to no regular post liver function test done after isoniazid treatment in most of the cases [10].

Wu et al. conducted a study of a 10-year period, collected data from 84 centres which did liver transplant (age range between 1.3 years till 17 years with mean 9.8 years old). INH toxicity represented 0.2 % (8/4679) of all liver transplants and 14 % (8/56) of drug induced liver failure. The estimated incidence of INH causing liver toxicity resulting in liver transplant was 3.2/100 000 in children, slightly less than the adult frequency of 4.2–14/100 000 [11]. Out of 20 cases of INH-induced liver failure, 16 patients were scheduled for liver transplant; 2 recovered spontaneously, 4 died while awaiting liver transplant, and 10 underwent orthotopic liver transplantation (OLT) with 2 died and 8 survived. Liver specimens from 18 patients with INH toxicity revealed massive necrosis with parenchymal collapse and swollen residual hepatocytes. In one of the patients, another biopsy specimen taken 10 days after normalisation of serum transaminases showed mild chronic portal inflammation with focal peliosis. Even when INH was stopped promptly and appropriately, some children nevertheless progressed to liver failure. Overt signs and symptoms including jaundice, dark urine, and abdominal pain, may lag behind initial hepatocellular damage and thus may not be reliable early indicators. A retrospective study done among Taiwanese adult population wherein patients were divided into two groups; good monitoring and poor monitoring. This
study concluded that baseline LFTs and serial repeated LFT could be helpful to detect potential development and early identification of ATLI, especially because early detection of increased serum transaminases often leads to a close follow-up and may prevent progression to ATLI. Asymptomatic ATLI may be missed in the poor monitoring group, which can cause underestimation of the incidence of ATLI. Regular monitoring of liver function seems to increase the detection rate of ATLI [12]. 10 years earlier, in another study, Chih et. al. analysed severe ATLI patients who reported to the Taiwan Drug Relief Foundation and discovered that the non-monitoring group had more severe hepatotoxicity and a higher mortality rate compared with the monitoring group (odds ratio, 8.87; 95% CI 1.32 - 59.41; \( p = 0.024 \)) [13]. However, both studies were done in adults thus may or may not be applicable in the children population.

At the moment, the latest WHO guideline advice for baseline LFT and serial monitoring only in those with pre-existing liver disease. These patients should have regular LFT monitoring at weekly/biweekly intervals for the initial two months and followed by more widely spaced assessment whilst ongoing treatment [14]. Nonetheless, perhaps repeating LFT at least once after starting anti-tuberculosis medication may be a wise practice since the test is inexpensive and is readily available in this country as illustrated in this case above. This may help to detect early liver function derangement in children caused by INH which is thought to be rare but exists.

References


