Case Report / *Olgu Sunumu*

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Psychosomatic Change Due to Isoniazide: Case Report

İzoniazide Bağlı Değişen Psikosomatik Değişiklik: Olgu Sunumu

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Abstract

Latent tuberculosis infection is a state of sustained immune response to *Mycobacterium tuberculosis* antigen stimulation without evidence of clinically evident active tuberculosis (TB). Although there is no symptom of active TB, preventive treatment is recommended because there is a risk of conversion to active disease. The first treatment option in latent tuberculosis prophylaxis is isoniazid (INH). We presented a child who developed sleepiness, weakness and aggressive mood while taking isoniazid (INH) prophylaxis for latent TB in our clinic. The clinician should be aware that there may be serious side effects of INH, including the central nervous system. Patients should be evaluated for drug side effects during follow-up and the patient should be informed.

Keywords: Latent tuberculosis infection, isoniazid, side effect, central nervous system

Öz

Latent tüberküloz enfeksiyonu klinik olarak belirgin aktif tüberküloz (TB) kanıtı olmadan *Mycobacterium tuberculosis* antijen uyarısına karşı devam eden immün yanıt durumudur. Aktif TB hastalığına dair hiçbir bulgu olmamasına rağmen aktif hastalığa dönüşme riski olduğu için koruyucu tedavi önerilir. Latent tüberküloz profilaksisinde ilk tedavi seçeneği izoniazid (INH)'tir. Kliniğimizde latent tüberküloz nedeniyle INH profilaksisi alırken uykuya eğilim, halsizlik, saldırgan ruh hali gelişen bir çocuk hastayı sunduk. INH'nin merkezi sinir sistemi dahil ciddi yan etkilerinin olabileceği klinisyen tarafından bilinmelidir. Hastalar takiplerde ilaç yan etkileri için değerlendirilmeli ve hastaya bilgi verilmelidir.

Anahtar Kelimeler: Latent tüberküloz enfeksiyonu, izoniazid, yan etki, merkezi sinir sistemi

Introduction

Tuberculosis (TB) remains a major health problem worldwide, with high rates of morbidity and sequelae. It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis (M. Tuberculosis)* although the exact proportion is unknown. Latent tuberculosis infection (LTBI) is a condition in which a persistent immune response is induced by *M. tuberculosis* antigens without clinically evident evidence of active TB (1).

People with LTBI have no complaints, physical examination or laboratory findings of active TB disease. LTBI is not contagious. Not all individuals infected with *M. tuberculosis* develop active TB. An average of 5-10% of infected individuals may develop active TB disease during their lifetime, usually within the first five years after the first infection (2). The risk of active TB disease after infection depends on several factors, the most important of which is immunologic status. Preventive treatment is recommended for LTBI patients at high risk of developing active disease. Antituberculosis (anti-TB) drugs such as INH, rifampicin (RIF) and rifapentine (RPT) are used in preventive treatment (3). Side effects of anti-TB drugs are rarely reported. INH has been widely used in TB treatment since the early 1950s. The most commonly reported toxicities include liver enzyme elevation, cutaneous findings and rarely nervous system findings. In this article, we report the development of sleepiness, fatigue and aggressive mood due to INH use in LTBI prophylaxis.

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Case Report

A seven-year-old male patient presented with complaints of night sweats and subfebrile fever for two years. It was learned that his father had been treated for pulmonary TB 12 years ago, and prophylaxis was given to the household at that time. Currently, his father was being examined by chest diseases with a prediagnosis of active TB due to cough with intense sputum. There were no other significant findings in his personal and family history. Physical examination was normal except tonsillopharyngitis. Bacillus Calmette-Guerin (BCG) vaccination scar was present. Tuberculin skin test (TST) was 20 mm. Two-way chest radiography and contrast-enhanced thorax tomography were normal. No acid-resistant bacilli (ARB) were observed in the gastric lavage (GL), which was tested for three consecutive days because the patient was unable to produce sputum. GL TB culture and PCR test were ordered. Other laboratory tests including transaminases were normal. Active TB was not detected in the father. The patient who had no evidence of active TB disease at the outpatient clinic control and whose GL TB culture, ARB and PCR tests were negative was evaluated as LTBI since his TST was 20 mm, and INH prophylaxis was started at a dose of 10 mg/kg/day. The patient, who came for monthly follow-up visits, complained of weakness, fatigue, increased drowsiness, aggressive behavior incompatible with his personality, vomiting 1-2 times a week, and occasional headache in the fourth month of prophylaxis. The patient, who was not malnourished and had normal examination including ophthalmologic and neurologic system, was observed to fall asleep immediately when no verbal or tactile stimulus was given. Routine blood tests were normal and INH prophylaxis was interrupted for one week. INH was restarted to the patient whose complaints completely resolved. At the follow-up visit ten days later, it was learned that the patient's complaints, especially tendency to sleep and excessive irritability, recurred. The clinical picture was thought to be due to INH. Treatment was changed to RIF. The patient who attended the follow-up visits regularly did not develop any additional complaints, and no side effects related to RIF were observed.

Discussion

Although there is no gold standard test for the diagnosis of LTBI, TST and/or interferon gamma release tests (IGST), especially T-SPOT.TB (ELISPOT) or QuantiFERON-TB Gold In-Tube (QFT-GIT) (ELISA), which show that the immune system is stimulated by *M. tuberculosis* antigens, are used in practice. In children under five years of age, TST should be preferred. In children older than five years of age who have received BCG vaccine and in patients who are difficult to visit a health center to have a TST read, IGST is preferred. If the result of the first test of a patient who has undergone TST or IGST is uncertain or negative, but there is a clinical suspicion of active TB disease, another test should be performed (4).

The aim of LTBI treatment is to prevent the return to active TB disease. According to the Ministry of Health 2019 Tuberculosis Diagnosis and Treatment Guideline, it is recommended that LTBI treatment be given to those under the age of 34 who have close contact with infectious disease, to those with positive TST at the age of 0-4 years and to children with positive TST or IGST at the age of 5-14 years (3). LTBI treatment includes daily INH for 6-9 months, daily RIF for 3-4 months, daily INH + RIF for 3-4 months, and weekly RPT + INH for three months regimens. The World Health Organization primarily recommends six-month INH monotherapy in both children and adults, both in countries with high and low TB disease rates (1). A randomized controlled trial published in 2017 showed that those given six months of INH prophylaxis in LTBI treatment had a significantly greater reduction in TB incidence than those given placebo (5).

In our seven-year-old patient with BCG vaccination scar, TST was positive and lung imaging was normal, GL TB culture, ARB and PCR tests were negative. We diagnosed LTBI in our patient who had no evidence of active TB disease, and INH prophylaxis was started at a dose of 10 mg/kg/day.

INH is a widely used anti-TB drug since the early 1950s. The reported side effects of INH commonly include skin reactions and liver toxicity. Both the peripheral and central nervous systems (CNS) are sensitive to the effects of INH. These CNS effects include restlessness, insomnia, headaches, psychiatric symptoms, seizures, peripheral neuropathy, optic neuropathy. It has been observed that the effects of INH on the neurological system are more common in the presence of predisposing factors such as liver failure, diabetes mellitus, genetic causes such as slow acetylation status, alcoholism, and a family history of psychosis.

Peripheral neuropathy, a frequently reported side effect among INH-associated neurologic side effects, develops as a result of INH-associated antagonism of pyridoxine (vitamin B6). INH causes excessive excretion of pyridoxine, leading to a decrease in pyridoxine levels in the blood. This antagonism causes axonal degeneration affecting both myelinated and unmyelinated nerve fibers. Patients with INH-induced peripheral neuropathy show symptoms of burning and numbness in the lower extremities. Upper limb involvement and muscle weakness are rarely observed. On examination, such patients show impairment in pain, temperature and light touch sensation and weakness and/or absence of Achilles reflexes (6). Pharmacokinetic studies show that children may experience pyridoxine deficiency while receiving INH, but are less vulnerable to pyridoxine-related toxicities of INH than adults. Therefore, routine supplementation is not recommended for children unless they receive INH at particularly high doses, are malnourished, show other diseases predisposing to pyridoxine deficiency, or are breastfed by a

mother receiving INH treatment (7). Pyridoxine level cannot be measured in our hospital. Pyridoxine deficiency was not considered in the patient because pyridoxine is a cofactor of transaminases and the patient's transaminase levels were at normal levels and clinical findings compatible with pyridoxine deficiency (stomatitis, glossitis, depression, seborrheic dermatitis, anemia, seizure) were not found in the patient (8).

Psychosis is a rare but dramatic side effect of INH treatment. The mechanism of action is not fully understood. Decreased production of pyridoxyl phosphate may lead to decreased levels of dopamine, noradrenaline and serotonin. Pyridoxyl phosphate is an important coenzyme in the metabolism of the neurotransmitter building blocks tryptophan and tyrosine. However, reductions in these neurotransmitters are not traditionally thought to cause psychosis. Another hypothesized mechanism of action is that INH may function as a monoamine oxidase inhibitor (MAOI), disrupting the breakdown of serotonin and catecholamines and thus triggering psychosis (9). Weirdorn et al. have reported that INH-induced acute psychosis developed in five patients in a study (10). In another study, 38 cases of INH-induced psychosis with preliminary symptoms have been reported (11). INH is a common cause of drug-induced seizures. Seizures caused by INH have been reported to typically occur due to INH overdose in both adults and children, but they can occur with prolonged ingestion above therapeutic doses (12). A study evaluating the experience of the California Poison Control Center in 2003 showed that INH was responsible for 5.9% of drug-induced seizure cases brought to this center in one year (13).

Among other reported neurologic side effects, a prospective study have described INH-induced memory impairment evaluated by special memory tests. It has been reported that the symptoms disappeared a few months after treatment was discontinued (14). In a case reported by Peter et al. convulsion, encephalopathy and spasticity in extremities have been observed to be related to INH. One year after discontinuation of the drug, it has been reported that gait did not return to normal even though the clinical picture improved to a great extent (15).

It was thought that our patient's symptoms may have been related to the effect of INH, which could not be evaluated laboratory, to function as MAOI or may have occurred because our patient was a slow acetylating drug.

It is important to know the side effects that may develop in all drug therapies and to monitor them closely in order to provide an appropriate approach to patients. Although liver toxicity and peripheral neuropathy are the most well-known side effects in INH users, serious CNS side effects should be kept in mind and patients should be closely monitored.

Informed Consent: Patient consent was obtained.

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