

Acute relapse of Multiple Sclerosis (MS) in an adolescent patient after Tuberculin skin test (TST): a case report

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Abstract

Activation of MS as a result of bacterial and viral infections is proposed by various studies. However, immune responses initiated by a bacterial antigen can rarely lead to the activation or occurrence of MS. Hereby, we report a unique case of Multiple Sclerosis (MS) relapse following a Tuberculin skin test (TST). After one year of MS remission, a 13-years old female, presented with symptoms supporting tuberculosis (TB), although TST denied TB infection. Two weeks later, the patient returned with symptoms indicating MS relapse, confirmed by magnetic resonance imaging (MRI). A series of immune system interactions, starting with the activation of Toll-like receptors (TLRs) by Mycobacterial components, may expose the central nervous system (CNS) to autoimmune reactions. TST-induced type IV hypersensitivity can be another parallel mechanism in light of MS being a CD4 T-cell mediated disease. This case report highlights the importance of environmental factors such as bacterial agents in the pathophysiology of MS.

Keywords: Multiple Sclerosis, Tuberculin Test, Tuberculosis, Case report

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Introduction

Multiple Sclerosis acquires complex pathophysiology, which results from the interplay of numerous genetic and environmental factors. The role of infectious agents in the etiopathogenesis of MS has been marked by recent studies (1). Activation of MS as a result of bacterial and viral infections can happen via Toll-like receptor (TLR) activation and cytokine secretion (2). However, mere antigen exposure leading to MS autoimmunity is a relatively rare finding.

Tuberculin Skin Test (TST) is based on a delayed-type hypersensitivity reaction in response to the exposure to the purified protein derivative (PPD) antigen. Some rare complications following TST in patients with and without tuberculosis (TB) have been previously reported, though none indicate an acute MS relapse (3-5). Here we report the relapse of a previously diagnosed and inactive MS in a 12-year-old girl with negative TST.

Case presentation

In April 2021, a 12-year-old girl was admitted to Firooz Abadi Hospital (Iran University of Medical Sciences) with fatigue,

vertigo, and loss of strength in the left upper limb. On the physical examination, nystagmus was noticed, while the mental state was normal.

Infectious etiologies were ruled out by Polymerase Chain Reaction (PCR) test for varicella-zoster virus, herpes simplex virus, and cytomegalovirus. Nevertheless, differential diagnoses were considered, including infectious, inflammatory, and neoplastic disorders, neurogenetic metabolic disease, and vascular conditions.

Further examination revealed positive oligoclonal bands (OCB) in the cerebrospinal fluid (CSF). Brain and spinal cord magnetic resonance imaging (MRI) with and without gadolinium contrast showed lesions in the brainstem, corpus callosum, and one enhancing area along the right optic radiation (Figure 1). Hence, MS was the diagnosis of choice.

Pulse therapy with methylprednisolone significantly improved the patient's symptoms. The patient had no clinical learning or cognitive disabilities and remained stable for one year without treatment.

One year after diagnosis, the patient was readmitted due to symptoms including cough, weight loss, diaphoresis, and fever

demonstrated TST-induced uveitis in a 16-year-old girl without TB infection 13 days after receiving intradermal PPD

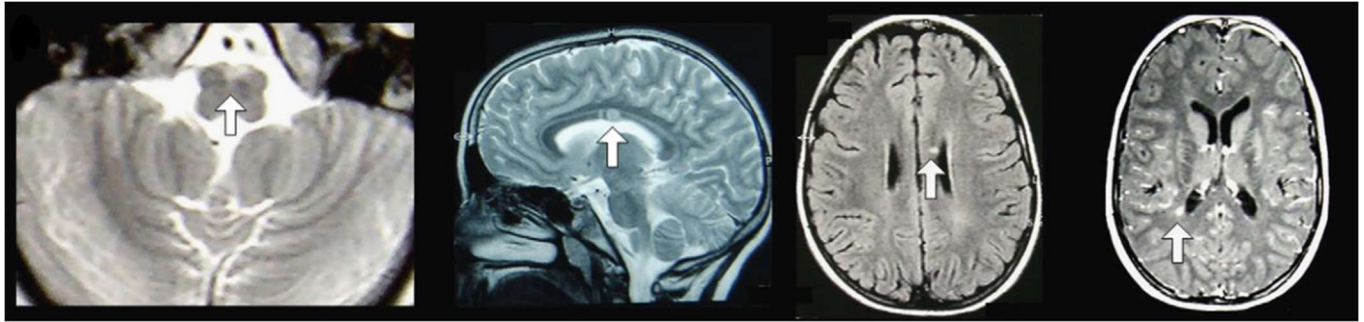


Figure 1. Lesions in brainstem, corpus callosum and one enhancing area along right optic radiation

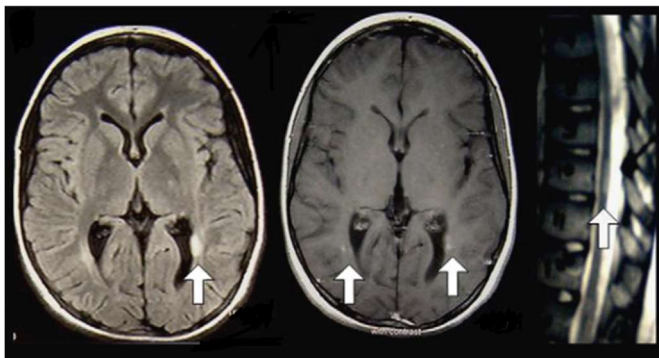


Figure 2. New hyperintense left posterior periventricular lesion, an increase in volume of a right posterior periventricular area and a decrease of the left cortical area, this latter area enhanced after contrast; a new contrast-enhancing lesion was also present in dorsal cord In Flair images

in favor of TB infection. A tuberculin skin test (TST) was performed, which showed a negative result. Two weeks after TST, the patient developed dysesthesia and increasing weakness.

MRI indicated new lesions; a new hyperintense left posterior periventricular lesion, an increase in the volume of the right posterior periventricular area, and a decrease in the left cortical area were evident (Figure 2-left side). The left cortical area was enhanced after contrast (Figure 2-center); a new contrast-enhancing lesion was also present in the dorsal cord (Figure 2-right side).

Treatment with oral steroids exerted partial recovery.

Discussion

To our knowledge, this is the first case of acute MS relapse following TST. Previous literature regarding unexpected complications of TST mainly indicates adverse reactions in patients with either latent or active TB infection. However, this case occurred in the absence of a TB infection. A previous case of severe irreversible optic neuritis in a 12-year-old girl with MS and following TST had been reported by Linssen and associates. However, optic neuritis developed instantly in this case (20 minutes after the skin test). Similarly, the patient had a negative TST result (3). Another case report has

(6).

Type IV hypersensitivity seems to be the connecting node between TST, and MS. TST recruits tuberculin antigen to stimulate a type IV hypersensitivity reaction and identify *Mycobacterium tuberculosis* infection. While the immune reaction is normally localized to the site of injection or scratch, systemic reactions such as fever, syncope, and focal reactions can happen in rare cases (5).

Accumulating evidence suggests considering MS as a CD4 T-cell mediated disease (7-9). Both the cellular immune response in MS and type IV hypersensitivity in TST can be traced back to CD4 T-cells. Production of various cytokines including IL-1 alpha, IL-1 beta, IL-6, interferon-gamma (IFN-gamma), and tumor necrosis factor-alpha (TNF-alpha) in the site of TST, can subsequently modulate CD4 T-cell responses, which mediate the autoimmune reaction leading to MS (9, 10).

In addition, Mycobacterial components have been recognized as potent activators of Toll-like receptors (TLRs) in naïve CD4 T-cells. Activation of TLR2 and TLR4 leads to the production of IL1, IL6, and IL12, thereby inducing the differentiation of naïve CD4 T-cells to Th1 and Th17 cells. Subsequent cytokines produced by these cells facilitate leukocyte transmigration across the blood-brain barrier and expose the central nervous system (CNS) to autoreactive responses by the innate immune system (11).

The present and several previous case reports of TST-induced CNS lesions point to the influence of pathogen-host interactions in MS. These studies provide evidence that challenges the current understanding of MS and acknowledges the environmental arm of its etiopathogenesis. Changing the current paradigms in MS pathophysiology would possibly lead to new treatment approaches focusing on the modification of environmental factors.

Declarations

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Conflict of interest

The authors have no conflicts of interest to disclose.

Consent for publication

This manuscript has been approved for publication by all authors.

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