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Reversible magnetic resonance imaging findings in cycloserine-induced encephalopathy: A case report

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Abstract

Cycloserine is a broad spectrum antibiotic used as a second drug for treatment of drug resistant tuberculosis. Inappropriate usage in excessive doses can give rise to neurological problems. We report a case who developed aphasia, anxiety and seizure during anti-tuberculosis medication. MRI of the brain showed reversible cytotoxic edema in dentate nuclei. Clinical and MRI findings were consistent with cycloserine toxicity.

INTRODUCTION

Cycloserine is a broad spectrum antibiotic used as a second drug for the treatment of drug resistant tuberculosis. Its adverse effects on the nervous system include drowsiness, headache, dizziness, dysarthria, psychosis, seizure and coma.[1] Here, we report a pulmonary tuberculosis patient presenting with cycloserine-induced encephalopathy. This is not the first case depicting MR imaging changes of cycloserine toxicity[2], but MR imaging change at the dentate nucleus can be unusual and has not been reported.

CASE REPORT

A 26-year-old woman was admitted to our hospital for the evaluation of pulmonary tuberculosis not responding to 3-months first-line anti-tuberculous medication in February 2014. She was previously diagnosed with tuberculosis lymphadenopathy in her neck in 2011 and underwent a treatment with first-line anti-tuberculosis medication, including isoniazid, rifampicin, ethambutol and pyrazinamide. The patient presented with cough, fever, weight loss and sputum. The sputum acid-fast bacilli (AFB) smear was positive and AFB culture was reported to be resistant to all drugs except cycloserine. A diagnosis of extensively drug-resistant tuberculosis was made and the treatment was initiated with cycloserine (500 mg/day), amikacin (1000 mg), linezolid (600 mg), levofloxacin (250 mg/day), rifabutin (300 mg) and augmentin (625 mg). Aphasia and anxiety developed 21 days after the initiation of treatment. On the 22nd day of treatment, she suddenly felt dizzy with graying out of her vision followed by a generalized tonic seizure lasting for 5 minutes. This was witnessed by a nurse. Laboratory investigations including electrolyte and glucose were normal. A brain MRI was performed with gadolinium on a high-field-strength 3T system. It showed symmetrical high signal intensity in the dentate nuclei on diffusion-weighted images (DWI) and decreased apparent diffusion coefficient (ADC) values, suggesting a cytotoxic edema (Figure 1a and b). T2-weighted and fluid-attenuated inversion recovery (FLAIR) images demonstrated a corresponding high signal intensity on the same area (Figure 1c). The brain MR angiography was normal. No hemorrhage was seen on gradient echo images.

Electroencephalography (EEG) and cerebrospinal fluid analysis were normal. No antiepileptic medications were administered because the patient had no further seizures. Her clinical presentation and MRI findings were thought to be most consistent with cycloserine toxicity. Cycloserine was immediately discontinued and the other anti-tuberculous medications were maintained. During the patient's admission, no additional seizure or new neurologic abnormalities were noted.

The follow-up MRI performed on a 1.5T MR system 2 weeks after the discontinuation of cycloserine showed the resolution of the high signal intensity in the dentate nuclei (Figure 2a-c). Thereafter, there were no further neurological events during the follow-up of 3 months and she has been receiving anti-tuberculous medications except cycloserine.

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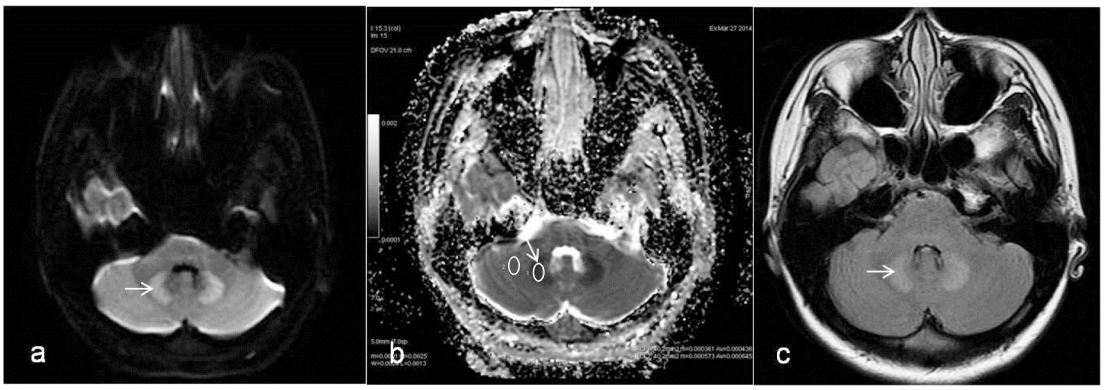

Figure 1. Initial MRI performed on 3T system shows high signal intensity on diffusion-weighted imaging (a), reduced apparent diffusion coefficient (b) and high signal intensity on FLAIR (c) within the dentate nuclei (arrow). Quantitative ADC measurement demonstrates a reduced ADC value of 0.44 x 10^{-3} mm^2/s within the right dentate nucleus. ADC value of normal appearing ipsilateral white matter is 0.65 x 10^{-3} mm^2/s.

DISCUSSION

Cycloserine is an analog of the amino acid D-alanine and indicated for the treatment of tuberculosis if the causative organisms are susceptible to this drug and if the treatment with the primary medications has proved to be inadequate. The frequencies of any adverse drug reaction from cycloserine was 9.1%; it was 5.7% for psychiatric adverse drug reactions, and 1.1% for CNS related adverse drug reactions.[3] Side effects of cycloserine, particularly CNS toxicity, may be dose-related and more commonly seen with daily doses greater than 500 mg.[4,5] Convulsions occur in about 10 percent of all patients receiving large doses of cycloserine.[6] These symptoms generally disappear after discontinuation of the drug. Also the daily administration of pyridoxine may help to prevent the cycloserine-related neurotoxicity.[7] In our case, the patient was taking 500 mg of cycloserine daily without pyridoxine. Associated imaging manifestations of cycloserine toxicity have been reported only rarely. A review of the literature demonstrates one case report documenting MR imaging findings.[2] In this case, imaging findings of cycloserine toxicity were reported in a 69-year-old woman who developed hypersomnolence and asterixis whilst on anti-tuberculous medication. MR imaging of the brain showed bilateral symmetric thalamic hyperintensities on DWI with isosignal intensity on ADC imaging, suggesting a vasogenic, not a cytotoxic edema. After discontinuation of cycloserine, the patient's symptoms resolved and the follow-up MR imaging of the brain demonstrated nearly normal findings.

In our case, the brain MRI showed a reversible

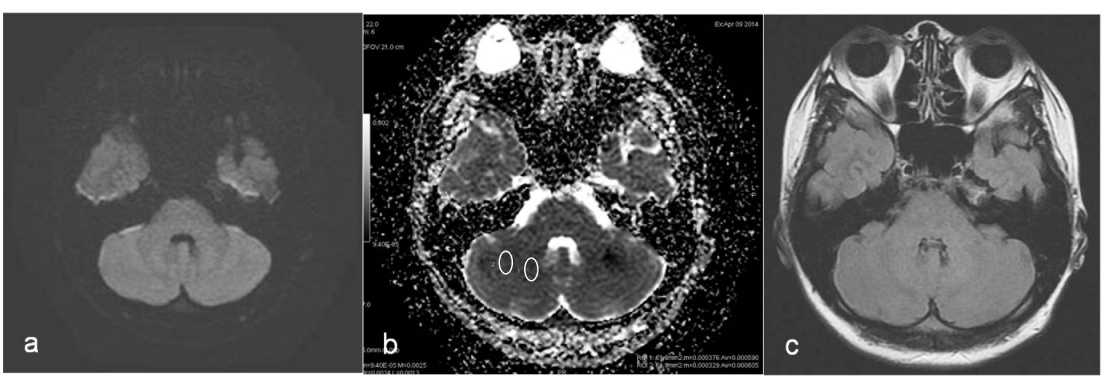

Figure 2. Follow-up MRI performed on 1.5T system 2 weeks after discontinuation of cycloserine. DWI (a) and corresponding FLAIR (c) demonstrate the resolution of previously noted areas of high signal intensity. Quantitative ADC measurement (b) demonstrates an ADC value of 0.59 x 10^{-3} mm^2/s. ADC value of normal appearing ipsilateral white matter is 0.61 x 10^{-3} mm^2/s.

cytotoxic edema limited to the dentate nuclei. The DWI demonstrated increased signal intensity on the isotropic DWI obtained with DW gradients applied in three orthogonal axes with a b-value of 1000 s/mm^2. ADC maps demonstrated a decrease in the ADCs corresponding to the areas of abnormal DWI signal intensity. The follow-up MRI showed the resolution of the previously noted areas on DWI and an ADC imaging.

In general, lesions with reduced ADC maps, representing a cytotoxic edema might be related to a poor prognosis and are more likely to be irreversible.[8,9] However, it may be reversible in some cases such as migraine, status epilepticus and toxic or metabolic leukoencephalopathy.[10] This reversibility in the cytotoxic edema may be due to intramyelinic edema located in the intramyelinic cleft or resulting from edema of the reactive astrocytes in the acute phase.[11] Thus, low ADC lesions on the initial MRI are not always associated with poor clinical outcome.

The differential diagnosis of our patient includes ischemia, demyelinating diseases, metabolic, infectious and inflammatory diseases. The bilateral symmetric involvement of the dentate nuclei and the normal brain MR angiogram rendered an ischemic diagnosis very unlikely. Multiple sclerosis and acute disseminated encephalomyelitis may be present with encephalopathy, seizures and various neurological deficits. But an involvement of the gray matter, a normal CSF and the resolution of the MRI changes make those possibilities unlikely. Wernicke's encephalopathy is primarily associated with chronic alcoholism and predominantly involves the midbrain and diencephalon.[11] In our case, there was no risk factors to thiamine deficiency and Wernicke's encephalitis.

In conclusion, reversible cytotoxic edema in the dentate nuclei may be considered as one of the MRI findings associated with cycloserine toxicity. Early diagnosis by using brain MRI and prompt cessation of the medication may facilitate reversibility of the brain lesions.

DISCLOSURE

Conflict of Interest: None

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