A Pediatric Case of Intrathecal Methotrexate Toxicity

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Background

- Intrathecal Methotrexate (IT-MTX) is the standard treatment of pediatric acute lymphoblastic leukemia (ALL), the most common malignancy in childhood[1]
- MTX is a potent penetrator of the blood-brain barrier; cases of IT-MTX neurotoxicities have been documented. Findings include focal-neurologic defects, transient encephalitis, and psychiatric manifestations including emotional lability and heightened anxiety[3]

Objectives

- Present a case of atypical IT-MTX toxicity
- A comparison between neuropsychiatric implications in classic presentations of IT-MTX toxicity and Hashimoto's Thyroiditis will be highlighted (Table 1)

Case

- 11-year-old female with no psychiatric history and B-Cell ALL presented with acute anxiety, headache, difficulty with ambulation, and disorientation five days post IT-MTX treatment
- Vital signs included tachycardia and fever; neurological exam was non-focal
- Selective mutism, labile mood and affect, and visual hallucinations prompted a psychiatric consultation and low-dose olanzapine was initiated
- Symptoms progressed with concern for catatonia (prominent mutism, echopraxia, echolalia, mannerisms, and perseveration present), with a BFCS score of 9; resulting in antipsychotic discontinuation and use of lorazepam with minimal benefit
- Urine drug screen, COVID test, ammonia levels were negative. CFS Meningitis and autoimmuneencephalitis panel was negative
- TSH returned normal with low T4; Thyroid antibodies were within normal limits
- EEG with very slight background slowing and rare generalized polyspike wave discharges, considered by the neurology team to be of little clinical significance
- Brain MRI demonstrated restricted diffusion of the periventricular white matter (Figure 1)
- Treatment with dextromethorphan for presumed IT-MTX led to improvement of both encephalopathy and catatonia in serial MoCA and BFCS evaluations; however, patient experienced abrupt onset of paranoia followed by a seizure for which levetiracetam was initiated
- Mental status changes had resolved completely by discharge, paranoia persisted for several weeks subsequently resolving without recurrence

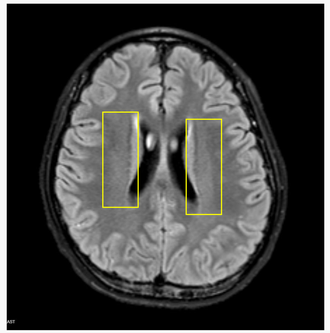

Figure 1. Hyperintensity of the periventricular white matter

	IT-MTX toxicity	Hashimoto's Encephalopathy[6]	
		Subtype A	Subtype B
Onset	Subacute (2-14 days)	Subacute	Insidious
Course	Fluctuating	Fluctuating	Progressive
Neurological sign	Focal, stroke like deficits	Seizure and myoclonus	
Delirium	Present	Present	Not present (dementia)
MRI Findings	Restricted diffusion in the centrum semiovale "*Panda eye sign*" and periventricular white matter	Non-specific	
Catatonia	Not typically present	Cases reported	
Psychosis	Not typically present	Paranoia, hallucinations, delusions common	

Table 1. Comparison of typical neuropsychiatric presentations of Hashimoto's Thyroiditis and IT-MTX toxicity

Discussion

- IT-MTX toxicity typically presents with focal neurologic deficits which were not found in this case[3]
- Given additional findings of paranoia and seizure, differential diagnosis included Hashimoto's thyroiditis (Table 1). Based on the temporal association of symptoms and treatment response, IT-MTX toxicity was the most fitting diagnosis
- IT-MTX MRI findings have been described in literature and supported the diagnosis [4,5]
- Seizure was thought to be idiopathic, contributed to by sleep deprivation
- Abrupt onset of paranoia is consistent with peri-ictal psychosis[2]

Conclusions

- Common chemotherapeutics, including IT-MTX, have a narrow therapeutic index and can present with a wide range of neuropsychiatric implications
- Current literature depicts majority of documented cases of IT-MTX neurotoxicity are transient, supporting the safety of IT-MTX rechallenge for continued ALL treatment
- Cases of persistent neuropsychiatric sequela and/or recurrence of symptoms with subsequent IT-MTX use have been described, however
- Risk factors for prolonged course of IT-MTX toxicity or susceptibility with future treatment remains unknown although hypothesized to be polygenetic in origin
- IT-MTX toxicity should be suspected in children with altered mental status who are undergoing treatment for ALL

References

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