Catatonia as a post-liver transplant complication in a pediatric patient

Alexander Palffy DO, Neera Ghaziuddin MD MRCPsych
University of Michigan Department of Psychiatry

Background

Catatonia

- Psychomotor disorder with a wide range of symptoms[1] :
  - Motor disturbance (posturing, stereotypies, grimace, rigidity)
  - Speech changes (mutism, perseveration, verbigeration)
  - Changes in behavior (developmental regression, disorganization, worsened anxiety, mood or psychotic episodes)
- Occurs in neurodevelopmental disorders, psychotic disorders, bipolar disorder, and major depressive disorder
- Can also occur secondary to medical conditions such as encephalitis (autoimmune, hepatic), metabolic derangements, malignancy
- Mechanism is unclear, but thought to include reduced GABA-A function, glutamate hyperactivity, and dopamine hypoactivity[2]

Neurologic complications post-liver transplant

- About 1/3 of liver recipients have neurologic complications[2], 23% in recent pediatric study[3]
- GABAergic dysfunction
  - Chronic liver failure has been linked with upregulation of GABA signaling, which is thought to be secondary to poor metabolism of neurotransmitters involved in the GABA system
  - Transplant with a functioning liver leads to rapid increase in metabolic rates of the GABAergic neurotransmitters, leading to a relative GABA deficiency
  - Immunosuppressants such as tacrolimus are thought to inhibit GABA activity
- Ammonia shown to modulate GABA activity[2]

Posterior reversible encephalopathy syndrome (PRES)

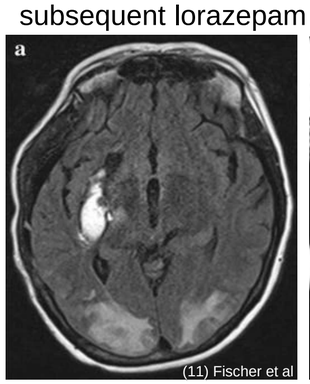
- Headache, confusion, visual symptoms, and/or seizures, with MRI showing vasogenic edema typically in posterior cerebral hemispheres
- Most commonly etiologies are hypertensive crisis, preeclampsia, and immunosuppressants
- Not always posterior, not always reversible
- Three case reports describing catatonia as a complication of PRES
- Calcineurin inhibitors are used for rejection prophylaxis, often implicated in PRES. 7/10 patients with catatonia post-liver or kidney transplant were on tacrolimus[4]

Typical findings of PRES
- Vasogenic edema in occipital or parietal regions
- This image also shows a R insular hemorrhage

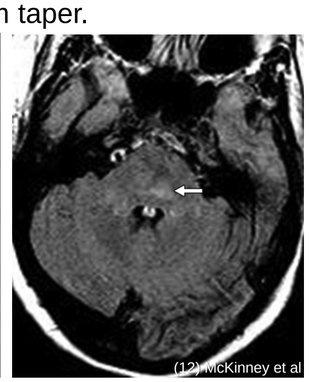
Case

A 12-year-old male with Budd-Chiari syndrome admitted for hyponatremia and acute liver failure, no past psychiatric history other than delirium during a previous hospitalization for ascites/liver failure. Shortly after hospitalization, a donor match was found and on day 4 he underwent liver transplant.

- Day 6 – CL consulted for delirium. At that time patient was agitated, making bizarre statements, grabbing at lines with a waxing and waning frequency. Started on clonidine PRN and gabapentin BID.
- Day 9 – Neuro consulted, concern for seizures. At one point was given versed which seemed to improve the seizure like activity. Started on Keppra.
- Day 10 – MRI showed findings consistent with PRES. Around this time, he was switched from one calcineurin inhibitor (tacrolimus) to another (cyclosporin).
- Day 11 – CL reconsulted. Showed verbigeration, perseveration, echolalia, posturing, motor rigidity, and labile mood. Positive Ativan challenge 10 minutes after 1 mg administered IV.
- From here, his course became significantly more complicated. Seizure like activity resumed, ultimately being captured by EEG. His seizures were not able to be controlled with multiple antiepileptics - at one point was on topiramate, levetiracetam, lacosamide, phenobarbital, and lorazepam while still having breakthrough seizures. MRI showed worsening signs of PRES. Developed status epilepticus, pseudobulbar affect, and fluctuating visual deficits.
- On day 45 of the hospitalization, a multidisciplinary team meeting was held where the role of immunosuppressants impacting his presentation was discussed. Ultimately this led to a switch from cyclosporin to everolimus (mTOR inhibitor)
- Seen as an outpatient one month after discharge, at that time was not showing any signs of catatonia and has tolerated the subsequent lorazepam taper.



(11) Fischer et al


(12) McKinney et al

Central variant of PRES
- FLAIR image showing mild edema within pons(arrow), caudate, and PLIC
- Taken from a patient on cyclosporine presenting with seizure

Discussion

- At their core catatonia, delirium, and PRES are all syndromes of brain dysfunction. In our patient, all three syndromes resolved with cessation of the cyclosporin inhibitor.
- While the mechanism is not known, it has been suggested that cyclosporin can induce endothelial cell injury and disrupt the blood-brain barrier[5,6]
- This patient had an “atypical” form of PRES, in that there was brain involvement beyond the regions supplied by the posterior cerebral artery – ie. basal ganglia and pons
- Recent systematic review of neuroimaging studies in catatonia found a majority of cases in literature showing diffuse lesions consistent with hypoperfusion typically in the frontal and temporal lobes, and basal ganglia[8]
- It has been suggested that GABA-A receptors are involved in regulation of cerebral blood flow [9, 10]
- Further research is needed; however, we hypothesize that failure of cerebral blood flow autoregulation is a pathophysiologic mechanism that is implicated in catatonia.

Practical Considerations

- Likely to be underrecognized or diagnosed as delirium. Recent study of critically ill adults identified 23% of patients meeting criteria for catatonia[7]
- May lead to prolonged hospitalizations, polypharmacy

Key Points

- Catatonia presents in a wide range of medical conditions, even in those without a primary psychiatric disturbance
- Addressing the underlying cause may ultimately resolve catatonia and associated neurologic symptoms
- Further education around identification of catatonia is need, especially in specialized patient populations where psychiatry is not typically involved

References

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596
2. Brown GD, Muzyk AJ, Preud'homme XA. Prolonged Delirium With Catatonia Following Orthotopic Liver Transplant Responsive to Memantine. J Psychiatr Pract. 2016 Mar;22(2):128-32. doi: 10.1097/PRA.0000000000000133. PMID: 27138082.
3. Ide K, Uchida H, Sakamoto S, Nishimura N, Nakagawa S, Kobayashi T, Ito S, Kasahara M. Neurological impairment in children with acute liver failure following liver transplantation-A single-center experience. Pediatr Transplant. 2022 Feb 7:e14240. doi: 10.1111/petr.14240. Epub ahead of print. PMID: 35132740.
4. Tatreau JR, Laughon SL, Kozlowski T. Catatonia After Liver Transplantation. Ann Transplant. 2018 Aug 28;23:608-614. doi: 10.12659/AOT.910298. PMID: 30150606; PMCID: PMC6248284.
5. Sloane JP, Lwin KY, Gore ME, Powles RL, Smith JF. Disturbance of blood brain barrier after bone-marrow transplantation. Lancet 1985;2:280–281
6. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. Cyclosporin-induced endothelial cell injury. Lab Invest 1986;55: 455–462
7. Connell J, Kim A, Brummel NE, Patel MB, Vandekar SN, Pandharipande P, Dittus RS, Heckers S, Ely EW, Wilson JE. Advanced Age Is Associated With Catatonia in Critical Illness: Results From the Delirium and Catatonia Prospective Cohort Investigation. Front Psychiatry. 2021 Nov 19;12:673166. doi: 10.3389/fpsyt.2021.673166. PMID: 34867501; PMCID: PMC8639534.
8. Haroche A, Rogers J, Plaze M, Gaillard R, Williams SC, Thomas P, Amad A. Brain imaging in catatonia: systematic review and directions for future research. Psychol Med. 2020 Jul;50(10):1585-1597. doi: 10.1017/S0033291720001853. Epub 2020 Jun 16. PMID: 32539902.
9. Krause BW, Wijtenburg SA, Holcomb HH, Kochunov P, Wang DJ, Hong LE, Rowland LM. Anterior cingulate GABA levels predict whole-brain cerebral blood flow. Neurosci Lett. 2014 Feb 21;561:188-91. doi: 10.1016/j.neulet.2013.12.062. Epub 2014 Jan 4. PMID: 24397910; PMCID: PMC3963135.
10. Chi OZ, Hunter C, Liu X, Chi Y, Weiss HR. Effects of GABA(A) receptor blockade on regional cerebral blood flow and blood-brain barrier disruption in focal cerebral ischemia. J Neurol Sci. 2011 Feb 15;301(1-2):66-70. doi: 10.1016/j.jns.2010.10.024. Epub 2010 Nov 20. PMID: 21094956.
11. Fischer, M., Schmutzhard, E. Posterior reversible encephalopathy syndrome. J Neurol 264, 1608–1616 (2017). https://doi.org/10.1007/s00415-016-8377-8
12. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. AJR Am J Roentgenol. 2013 Sep;201(3):631-8. doi: 10.2214/AJR.12.9677. PMID: 23971457.