Case Report
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# On Seizures and Knives: Perampanel-Induced Psychosis: A Case Report and Literature Review

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Managing epilepsy in the context of intellectual disability can be complicated as this population is known to have higher rates of drug resistance and sensitivity to side effects of antiseizure medications (ASMs). Perampanel is a novel ASM recently approved as an adjunctive treatment for drug resistant focal seizures. It carries a black-box warning for serious psychiatric and behavioral adverse reactions of aggression, irritability, et cetera. However, psychosis is a seldom reported side effect of perampanel. We herein describe a case of a 15-year-old girl with moderate intellectual disability who presented with refractory seizures managed successfully after using perampanel. Around 2 months later, she developed psychosis and aggression. The patient's history lacked any significant family or personal history of mental illness. Managing psychotic symptoms was difficult in this case; as perampanel was needed for proper seizure control, and both psychosis and seizures were severe and significantly endangering the patient and people around her. Thus, symptoms were addressed by adding a low-dose risperidone, an atypical antipsychotic. This paper highlights the importance of pre-treatment counselling and monitoring for the emergence of psychiatric side effects including the rarely occurring psychosis while using perampanel, particularly in highly sensitive patients, e.g., those with intellectual disability. We also emphasize on the importance of accurate weighing of risks and benefits while managing psychosis as an adverse event to ASMs in the background of drug-resistant epilepsy. **(2024;14:37-41)**

**Key words:** Perampanel, Psychosis, Epilepsy, Intellectual disability

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## Introduction

Behavioral and psychiatric symptoms are commonly encountered in patients with epilepsy; especially those with comorbid intellectual disability. This can be related to epilepsy itself, or as side effects to antiepileptic drugs (ASMs), which are more pronounced in patients with intellectual disability as well.[1-3] Perampanel is a recently approved adjunctive treatment for drug-resistant focal seizures.[4] Psychosis is a rarely reported side effect of perampanel,[4] and when it occurs, it can constitute a diagnostic and management dilemma. Both seizures and psychosis may have significant and disabling effects on patients and people around them. It can be challenging to attribute psychosis to perampanel versus other contaminant ASMs, epilepsy, or a primary psychotic disorder. Furthermore, it is usually difficult to manage these effects as it usually requires weighing risks and benefits of either stopping perampanel, which is needed for adequate seizure control, or adding antipsychotic agents, which themselves may carry a risk of inducing seizures.

## Case Report

We report a case of a 15 years old girl, with a background of moderate intellectual disability and acute lymphocytic leukemia who underwent bone marrow transplantation (BMT) at 10 years of age after two relapses. Her first seizure was at the age of 13 years and her semiology was a generalized tonic-clonic seizure. She was started initially on levetiracetam, and her seizures were uncontrolled despite reaching maximum dosing (60 mg/kg/day). She developed another semiology, drop attacks, and was started on topiramate until she reached 8 mg/kg/day. Her seizures were very difficult to control, and within a year of her first seizure, she reached maximum dosing of levetiracetam, topiramate (discontinued and replaced with clobazam), and valproic acid. She was admitted to our epilepsy monitoring unit, and her long-term electroencephalogram (EEG) showed a slow back-

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ground for her age and frequent generalized frontally dominant inter-ictal discharges and captured many of her seizures. She underwent magnetic resonance imaging (MRI)/magnetic resonance spectroscopy which was unremarkable, and a basic metabolic work-up was unrevealing (including serum and urine acylcarnitines, serum amino acids, and urine organic acids). Given her past history of BMT and her refractory seizures, the possibility of autoimmune epilepsy was entertained, and she underwent treatment with intravenous immunoglobulins and 2 weeks of steroids, despite the fact that her serum and cerebrospinal fluid autoimmune epilepsy panel were negative; as it does not entirely exclude it. These interventions had no benefit, and then she was started on perampanel and reached a dose of 4 mg per day. She had a dramatic response to the medication, and within a few days, she became seizure-free for the first time since her seizures started. After 3 months of starting perampanel, she presented to our hospital's emergency department with acute behavioral change and was admitted. Three weeks prior to admission, the patient became increasingly irritable, verbally and physically aggressive towards her family. She once had held a knife threatening to harm her family. She was accusing people surrounding her of doing things they did not do, such as killing her father, revealing her secrets to unknown strangers, and stealing her toys. She was constantly self-talking while no one was around; stating that she sees and hears things that others cannot perceive. These changes were associated with a significant decrease in sleep and were ongoing daily, throughout the day. The patient's past history was unremarkable of any aggression, mood, or psychotic symptoms. Her family history was unremarkable for mental illnesses as well.

There was no negative change in her physical health in the last few months, and no new medications (apart from perampanel) or illicit substances were used. Her mental state examination revealed marked irritability, psychomotor agitation, disorganized speech, persecutory delusions, and auditory and visual hallucinations with hallucinatory gestures. She was conscious, alert, and oriented. No other delusions, hallucinations, self-harm, or suicidal ideas expressed or attempted.

Upon presentation to the hospital, vital signs, neurological examination, and a repeated head MRI were all unremarkable. She underwent EEG upon admission but was of little value as it showed similar findings to her baseline EEG. Her plasma ammonia level was 32.43 μmol/L, and pre-dose valproic acid level was 88.2 μg/mL.

She was admitted to the ward with constant nursing observation, which confirmed the above-mentioned findings. The impression of Perampanel-induced psychotic disorder was established. Risperidone 0.5 mg per day was added, on which she showed an initial response, evidenced by decreased irritability and aggression and improved sleep. She was discharged after a few days and maintained on Risperidone 1.5 mg daily, resulting in almost a full resolution of her psychotic symptoms. The patient was back to her previous baseline.

On outpatient follow-ups over the next 6 months, improvement was maintained on the same dose. However, the patient developed pill-rolling tremors and bradykinesia, attributed to Parkinsonian symptoms of extrapyramidal side effects (EPSE). Wilson's disease workup was done and was unremarkable. Risperidone dose was gradually reduced to 0.25 mg daily, which resulted in improvement of the EPSE and maintenance of the effects of the drug. She was followed in the neurology clinic as well, and she continued to be seizure-free since starting Perampanel.

## Discussion

Epilepsy is a common diagnosis among patients with intellectual disability, with a 16-30% prevalence; which is around 15-30 times higher than that of the general population.[1] The prevalence of epilepsy is directly proportional to the severity of intellectual disability; being higher in those with more severe disabilities.[1] In this population of patients, seizure control can be more difficult, leading to therapy failure, and sometimes mandating the use of multiple ASMs.[2] Various ASMs have different side effect profiles, and some of them carry a risk of causing psychiatric side effects. In our case, the patient developed psychotic symptoms following the introduction of perampanel as an add-on drug to her previous ASMs. Perampanel is a selective non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, which is US Food and Drug Administration (FDA) approved for adjunctive treatment in drug-resistant focal seizures in 2012. Its most common side effects include dizziness, somnolence, fatigue, and irritability. However, psychiatric effects of irritability, aggression, anxiety, and anger were reported as well. Moreover, serious psychiatric and behavioral reactions were mentioned by the FDA in a black box warning letter, mentioning "serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats" reported among patients taking perampanel.[4] An analysis of the pooled safety data from three phase III trials on patients with focal-onset seizures was published in Epilepsia[5] and found that the overall rate of psychiatric treatment-emergent adverse events (TEAE) events was higher in higher doses of

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**Table 1.** A comparison of the two reported cases to our currently reported case

| Study | Date published | Sex | Age | Diagnoses | Perampanel dose at which psychotic symptoms evolved | Symptoms experienced | Timing of psychosis onset | Concomitant ASMs used | Management |
|---|---|---|---|---|---|---|---|---|---|
| Pujal Rodríguez et al.[11] | 2021 | Female | 29-year-old | Generalized tonic-clonic seizures | -1st episode: 12 mg (prescribed dose was 4 mg, patient tripled dose to compensate for skipped doses)<br>-2nd episode: 8 mg | -1st episode: disorganized behavior, agitation, and confusion<br>-2nd episode: aggression, disorganized behavior, confusion, and persecutory delusions | -1st episode: the day after tripling dosage<br>-2nd episode: during 2 days of reintroducing perampanel at 8 mg/day | Non (switched to perampanel from lamotrigine 200 mg/day) | -1st episode: olanzapine 30 mg/day, diazepam 15 mg/day, and perampanel discontinuation. Discharged on olanzapine 5 mg/day<br>-2nd episode: olanzapine 30 mg/day, perampanel discontinuation. Discharged on olanzapine 10 mg/day with gradual tapering, gradual reintroduction of lamotrigine up to 200 mg/day |
| Leite et al.[12] | 2021 | Female | 57-year-old | Drug-resistant temporal and left front-opercular epilepsy | 12 mg | Disorganized thoughts, Persecutory, and reference delusions, auditory and olfactory hallucinations | 2 weeks after increasing perampanel dose to 12 mg | Topiramate 100 mg twice daily, clonazepam 2 mg twice daily, and lacosamide 100 mg twice daily | -Acute management: reducing perampanel to 6 mg/day, risperidone 2 mg/day, lorazepam 2.5 mg/day<br>-Risperidone was later switched to quetiapine 200 mg/day due to extrapyramidal side effects |
| Currently reported case | 2022 | Female | 15-year-old | -Drug-resistant generalized tonic-clonic seizures<br>-Moderate intellectual disability | 4 mg | Insomnia, Irritability, aggression, homicidal threats, persecutory delusions, auditory, and visual hallucinations, and disorganized speech | Around 2 months after taking perampanel at 4 mg/day | -Levetiracetam 800 mg twice daily (48 mg/kg/day)<br>-Valproic acid 650 mg twice daily (39 mg/kg/day)<br>-Perampanel 4 mg QHS (her weight on admission was 33 kg) | Risperidone 1.5 mg/day |

ASMs, antiseizure medications; QHS, at bedtime every night.

perampanel (8 mg and 12 mg). The most common events reported were irritability (4% at 4 mg, 7% at 8 mg, and 12% at 12 mg) and aggression (1% at 4 mg, 2% at 8 mg, and 3% at 12 mg). This analysis has also shown that these symptoms generally appeared in the first 6 weeks of treatment, consistent with an earlier observation that incidence is higher during drug titration.[5] A proposed mechanism to explain these undesired effects was thought to be polypharmacy and treatment with concomitant ASMs. However, Glauser et al.[6] published a *post hoc* analysis of the same three trials and found that the incidence TEAEs was similar with regard to the number of ASMs at baseline.[6] A study by Juhl and Rubboli[7] examined the association between perampanel as an add-on drug and aggressive behavior in severe drug-resistant epilepsy. A group of 12 out of 49 patients from the sample experienced aggressiveness with perampanel. One-third of this group had intellectual disability, and five patients took levetiracetam as a concomitant ASM. Another retrospective study of 895 patients by Yamamoto et al.[8] evaluated the risk factors for psychiatric adverse events associated with perampanel. Intellectual disability and psychiatric comorbidity were identified as risk factors; while younger age (less than 16 years) and concomitant use of lamotrigine and inducer drugs were associated with a decreased risk of psychiatric adverse events. Andres et al.[9] reported similar findings in regard to the risk factors in a retrospective evaluation of 27 patients with intellectual disability and drug-resistant epilepsy. Aggression was the most commonly observed event, appearing at all doses (2-10 mg), but more often at higher doses. Andres et al.[9] found no significant influence for sex, severity of the intellectual disability, seizure frequency, therapeutic effect of perampanel or the number of concomitant medications taken on the risk for developing these effects. Another 62-patient retrospective study by Snoeijen-Schouwenaars et al.[10] reported 40% behavioral adverse events to perampanel, confined with the previously mentioned findings regarding age, severity of the intellectual disability, epilepsy, and seizure reduction. Nonetheless, it elaborated to mention an inverse relationship between the number of concomitant anticonvulsants and risk of behavioral adverse effects.

Although aggression and irritability were commonly reported in literature, psychosis was seldom mentioned. Up to the current time, only two recently published cases[11,12] reported psychosis induced by perampanel. In both of them, patients were females, lacking previous psychiatric history and presenting with acute psychosis mandating hospital admission. In the Table 1, we compare the two reported cases with our currently reported case.

In the light of the above-mentioned information, in addition to the temporal association of perampanel to the severe and suddenly emerging aggression and psychosis, we highly considered perampanel as the culprit for the symptoms encountered in our patient. Additionally, the fact that she had moderate intellectual disability increased her susceptibility to these particular adverse events. The course of symptoms, the lack of recent significant changes in the patient's objective measures (EEG and MRI) or doses of other ASMs, the lack of change in seizure activity, the lack of family or past history of aggression and psychosis all made other differential diagnoses less likely to explain her presentation. Those differentials include a primary psychotic disorder, psychotic disorder secondary to epilepsy -which is not uncommon, particularly in those with comorbid intellectual disability, where the prevalence can be as high as 24%,[3] forced EEG normalization, and a psychotic disorder secondary to another ASM.

The management of our patient was complicated. Initially, we considered gradually tapering perampanel as a step to confirm diagnosis and treat symptoms. However, this option was difficult to resort to, as seizure control was hardly achieved after adding perampanel. Before that, the frequency and severity of seizures were disabling and put the patient at risk of trauma and falls. On the other hand, side effects of perampanel were severe and life-threatening to the patient and people around her. So, adding an antipsychotic agent was an identified solution, choosing low-dose risperidone as a potent agent with a relatively low seizure risk. Resolution of symptoms with a maintained antiepileptic effect were achieved and sustained.

Patients treated with ASMs should be generally monitored for behavioral side effects. Psychosis has rarely been reported in the context of perampanel treatment; however, when it develops, it can be serious and life-threatening. Thus, we recommend close monitoring for patients taking perampanel, especially at the initial few wakes of treatment, during drug titration, and at higher doses. Patients and families should be counseled about these effects in advance. This is particularly relevant in patients with heightened sensitivity to these effects, e.g., those with intellectual disability and pre-existing psychiatric conditions. Management of these side effects requires a delicate balance of the risks and benefits of continuing perampanel therapy and\or adding antipsychotic agents.

## Conflict of Interest

All the listed authors have no conflicts of interests to declare.

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