CLINICAL VIGNETTE

Levetiracetam Induced Acute Psychosis

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A 70-year-old female with a history of metastatic lung cancer with brain involvement was sent to the Emergency Department from a skilled nursing facility with an acute encephalopathy and increased drowsiness. She also has a history of systolic congestive heart failure, atrial fibrillation with episodes of rapid ventricular rate, heart block with permanent pacemaker implantation, thyroid cancer treated with thyroidectomy and radioactive iodine treatment, hypertension, anxiety and depresssion. Given high Programmed death-ligand one (PDL1) expression of the tumor, the patient had been receiving pembrolizumab and pemetrexed with appropriate response and a steady decrease of tumor burden. Cycle eleven of treatment was administered one month prior to admission. She had also received stereotactic body radiation therapy to several brain lesions six months prior to admission and was noted on her most recent MRI (2 weeks prior to admission) to have decreasing enhancing masses particularly in the right occipital lobe with improved cerebral edema. Her other medications included, metoprolol XL 100 mg daily, furosemide 40 mg BID, apixaban 5 mg BID, levothyroxine 200 mcg daily, dexamethasone 4 mg BID, bupropion 200 mg BID, and alprazolam as needed. The patient's family later clarified that furosemide had been held by her physician at the skilled nursing facility prior to admission due to acute kidney injury (AKI). Given reduced vasogenic edema noted on her most recent outpatient MRI, the patient has been started on a steroid taper and had been reduced from dexamethasone 4 mg TID to BID with the plan to taper to daily dosing. Her sister who was also diagnosed with lung cancer and is a former smoker with a twenty-five pack year history.

On physical exam, she was drowsy but able to answer simple questions. She was afebrile, normotensive and noted to have an irregularly irregular heart rate without tachycardia. The rest of her exam was unremarkable. Her labs were remarkable for a mild leukocytosis to 14.1 K/uL, lactic acid of 1.6 mmol/L, B-natriuretic peptide (BNP) of 2521 pg/mL, and a troponin of 0.09 ng/mL (unchanged on subsequent checks). She also had an elevated blood urea nitrogen (BUN) and creatinine of 108 mg/dL and 1.70 mg/dL respectively as well as mild elevated liver enzymes with AST and ALT levels of 264 U/L and 408 U/L. Antibiotics were started given concern for infectious etiologies causing acute encephalopathy. Intravenous diuretics were started and cardiology was consulted given concern for cardiorenal syndrome with uremia. The patient's case was discussed with her outpatient medical oncologist who recommended continuing steroid taper and decreasing dexamethasone to 4 mg a day. Bupropion and alprazolam were held due to somnolence on admission. Patient's mental status improved modestly with improvement in volume status, BUN improved to 36 mg/dL and BNP improved to 490 pg/mL by hospital day three. She continued to have waxing and waning of her mental status. Infectious work-up was negative and antibiotics were stopped. Common metabolic causes were ruled out as well. On hospital day four, she was observed by nursing to have facial twitching and droop along with upper extremity muscle twitching, with normal vital signs during the episode. A rapid response team activation was called given concern for stroke versus seizure activity. A CT head and MRI brain ruled out hemorrhagic or ischemic stroke. The peripherally enhancing mass in the right medial occipital lobe showed improved surrounding vasogenic edema. Neurology was consulted, a bedside EEG did not capture any seizure like activity, and levetiracetam was started prophylactically to prevent further episodes. Dexamethasone was also increased back to 4 mg BID.

Levetiracetam was increase after the patient had two additional seizure like episodes with improved control. Each episode was similar with facial twitching and upper extremity decerebrate posturing with a post ictal period. She was awake during her episodes and was able to even follow simple commands but then would not remember the episode after her post-ictal period resolved. Neurology indicated these were likely partial motor only seizures and she continued with the increased dose of levetiracetam. However, the patient started to exhibit signs of acute agitation and psychosis. She started pulling at IVs and had to be placed on two-point soft restraints. She also had worsening confusion, including incoherent speech and agitation. While she had been previously conversant, she started repeating one word or short phrases over and over again and was unable to participate in intelligible conversation though continued to be alert. Given levetiracetam can cause acute agitation and even acute psychosis, she was switched from levetiracetam to lacosamide with complete resolution of agitation and psychosis. The patient was stable for discharge after being on lacosamide without any additional seizure episodes, agitation or encephalopathy.

Discussion

Seizures are commonly seen in oncologic patients. When all types of neurological problems were analyzed at a specialty cancer center, seizure was found in 13% of cases.[1] Half of the seizures were attributed to intracranial metastasis, and most of the remainder to metabolic disturbances.[1] Lung cancer, both

non-small cell and small cell is the most common cancer associated with metastasis presenting with seizures. Seizures are usually a manifestation of parenchymal metastasis but can also be a feature of leptomeningeal metastasis.[1] In those with primary brain tumors, surgical resection is often a highly effective treatment for both recurrence free survival and seizure control. In patients with primary brain tumors, not amenable to surgery, or metastatic tumors, the standard of care for patients who present with seizures is the administration of anti-epileptic drugs (AEDs).[2] There is no consensus guideline for the administration of prophylactic AEDs. Several studies have evaluated the usefulness of AEDs for brain tumor patients with no history of seizures and produced conflicting results.[2] In clinical practice, many radiation oncologists, oncologists, neurologists and neurosurgeons reported administering prophylactic AEDs

Levetiracetam is one of the most common AEDs used and it is known to be effective with few drug-drug interactions.[2] In one multicenter, open label follow up study, seizure frequency per week was generally stable and remained low. Most adverse effects were mild or moderate and unrelated to the study drug, leading investigators to indicate that levetiracetam was well-tolerated and provided stable seizure control during long-term treatment.[3] Though generally well-tolerated, adverse effects have been described in numerous studies. Some of the side effects described included somnolence, headache, asthenia, dizziness, and infection. A meta-analysis, which included ten trials, assessed common adverse effects, usual AED adverse effects (ataxia, dizziness, fatigue, nausea), and behavioral adverse effects. Trials tended to publish an adverse effect if greater than 5% or 10% had been affected. Only "somnolence" and "infection" were statistically significant adverse effects. However, when broadening the infection category to also include a variety of words/phrases to describe infections including pharyngitis, rhinitis, flu syndrome, the results were no longer significant. While no single behavioral effect was significant, when combined to include words/phrases like hostility, personality disorder, agitation to name a few, significance was noted.[4]

The combined psychiatric side effects in the previous study was noted to be 7.6% of the participants on levetiracetam compared to 4.6% of participants on placebo. In another long-term follow-up study of levetiracetam, psychiatric side effects were seen in up to 13.3% of adults with the most common psychiatric side effect being depression (7.4%). Severe symptoms, including agitation, hostility and psychotic behavior was noted in only 0.7% of patients.[5] There have been several case reports that describe acute agitation or psychosis like that seen in our patient. In these cases, patients were started on levetiracetam due to new onset seizures or breakthrough seizures and subsequently developed symptoms of acute psychosis, agitation or aggression. Within 48-72 hours of levetiracetam being withheld, all the patients had resolution of their symptoms.[6-8] Lacosamide is an alternative to levetiracetam as it shares many of the same properties including a low adverse effect profile and does not require blood level monitoring. In one review as an adjunctive therapy or as monotherapy, lacosamide was effective in the treatment of focal seizures in adults and adolescent patients.[9]

Levetiracetam is known to have a higher association with psychiatric and behavioral side effects than other AEDs.[10] Another review evaluated 4085 adult patients from the Columbia and Yale Antiepileptic Drug (AED) Database, found that levetiracetam had the greatest psychiatric and behavioral side effects rates (22.1%) when compared to other AEDs while controlling for potential non AED related factors.[10] Psychiatric and behavioral side effects included depressive mood, psychosis, increased irritability and aggressive behavior. This study also demonstrated that a prior history of psychiatric condition was a strong predictor of psychiatric and behavioral side effects with AED in adult patients.[11,12] This correlation has been demonstrated in other studies as well.

While less common in the general population, it is important to recognize severe adverse effects of levetiracetam, including psychiatric symptoms like agitation, psychosis, aggression especially in patient populations that are more susceptible to developing these adverse effects, particularly those already with a psychiatric disorder. Quick identification of the offending agent and switching to effective and similarly low risk alternatives can reverse adverse effects while still maintaining seizure control.

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