Valproate-Induced Pancytopenia and Phenytoin Toxicity in a Young Adult With Intellectual Disability and Mesial Temporal Lobe Sclerosis

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The prevalence of epilepsy in patients with intellectual developmental disorder is higher than in the general population and is known to increase with the severity.[1–3] Evaluation and management of such patients pose multiple challenges. One of the major challenges is to monitor the side effect profile of the antiepileptic drugs and prevent toxicity. There are few case reports from India reporting toxicities of antiepileptic drugs, especially valproate or phenytoin.[4–6] Here, we present a case of a young adult with intellectual disability and seizures, who developed toxicity to both these antiepileptic drugs prescribed for seizure control.

Case Report

Mr A, a 20-year-old male patient, was admitted to the long-term care ward in our department after having been found abandoned on the roadside with unusual behavior. On examination, he was oriented and had minor physical anomalies (facial dysmorphism, low-set ears, and high-arched palate). He could speak a few words of his native language and obey simple commands. The systemic examination was normal. The mental status examination revealed no features of psychosis or mood disorder. Mr A was able to carry out only basic activities of daily living. After an IQ assessment, he was diagnosed with severe intellectual developmental disorder. Soon after admission, the patient had an episode of focal seizure. Neuroimaging was suggestive of left mesial temporal sclerosis (results of his computed tomography, electroencephalography, magnetic resonance imaging, and positron emission tomography scans are provided in Table 1). He was started on phenytoin up to 250 mg after a neurology consultation. Antipsychotics were given on an as-needed basis for agitation. Vitamin B_{12} and folate supplements were also added. Due to inadequate control of seizures, valproate 1 g/d was added. Mr A had no further seizure episodes. After 3 months of taking these antiepileptic drugs, he suddenly developed ataxia and multiple falls and was diagnosed with phenytoin toxicity (serum phenytoin levels = 38.1 µg/mL at 250 mg/d). A neurology consultation was conducted, and phenytoin was stopped. Valproate was increased to 1.5 g/d, and clobazam 15 mg/d was added (Table 1).

Complete blood counts at 6, 10, and 15 weeks after increasing valproate showed decreasing platelet counts from 1.28 L/uL to 38,000/uL along with a white blood cell count of 4,000/uL and hemoglobin of 12.2 g/dL. Mr A had bilateral fine tremors but no clinical signs of valproate toxicity or bleeding manifestations (serum valproate of 133 µg/mL, ammonia of 52 µg/mL). There was no history of fever, joint pain, rashes, or gastrointestinal symptoms. Tests for chikungunya IgM and dengue IgM were negative. After detection of reduction in cell counts, an immediate neurology referral was made, and valproate was planned to be tapered and stopped (Table 1).

Mr A was thereafter maintained on levetiracetam 1,000 mg/d and clobazam 20 mg/d and subsequently did not have seizures. Blood investigations were monitored regularly (Table 1). From the 11th day after stopping valproate, his platelet count started to noticeably increase. His platelet count, hemoglobin, and total white blood cell counts stably normalized from the 28th day, 47th day, and 15th day onward, respectively. At 3 months, a full investigation panel including complete blood count; renal, liver, and thyroid function tests; serum electrolytes; fasting glucose level; and lipid profile was noted to be within normal limits.

Discussion

The thrombocytopenia induced by valproate has been reported; however, other hematologic toxicities like macrocytosis, neutropenia, and pure red cell aplasia have rarely been reported.[4–7] Although the prevalence of thrombocytopenia ranged from 12% to 18% in some studies,[3,6–10] there is currently a lack of research regarding its clinical implications. The thrombocytopenia induced by valproate is assumed to be a dose-dependent side effect; however, the exact mechanism of this adverse effect is unclear as is its timeline of appearance. Adjustment of dosage has been shown to partially reverse the thrombocytopenia.[8] Shifting to other antiepileptics like phenytoin helps when

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Prim Care Companion CNS Disord 2021;23(6):20cr02897

To cite: Lhamu T, Sadh K, Dahale AB, et al. Valproate-induced pancytopenia and phenytoin toxicity in a young adult with intellectual disability and mesial temporal lobe sclerosis. *Prim Care Companion CNS Disord*. 2021;23(6):20cr02897.

To share: https://doi.org/10.4088/PCC.20cr02897

Table 1. Mr A's Drug Doses and Levels and Blood Parameters[a]

Day of Blood Test	Phenytoin Dose (mg)[b]	Phenytoin Level (µg/mL)	Valproate Dose (mg)[c]	Valproate Level (µg/mL)	Ammonia Level (µg/mL)	Hemoglobin (g/dL)	Red Blood Cell Count (million/µL)	Total Leukocyte Count (per µL)	Platelets (per µL)
1 (baseline)	…	…	…	…	…	13	…	6,500	162,000
18	250	…	…	…	…	13	…	6,500	162,000
30	250	24.5	…	…	…	…	…	…	…
36	250	23.34	…	…	…	…	…	…	…
144	250	…	1,000	32	…	…	…	…	…
170	250	20.2	1,000	…	…	…	…	…	…
171	250	…	1,000	45	…	…	…	…	…
209	250	…	1,000	…	…	12.4	4.40	5,100	129,000
234	Stopped at 250	38.1	1,000	62	54	13.5	4.76	6,700	142,000
247	…	…	1,500	…	…	12.5	4.31	6,200	202,000
262	…	…	1,500	83	…	…	…	…	
281	…	…	1,500	…	…	12.5	4.34	5,200	128,000
300	…	…	1,500	116	…		…	…	…
311	…	…	1,500	…	…	13.0	4.45	4,500	89,000
333	…	…	1,500	116	…	…	…	…	…
352	…	…	1,500	133	…	12.2	4.04	4,000	38,000
354	…	…	1,250	…	…	10.4	3.66	4,000	45,000
356	…	…	1,000	…	…	…	…	…	…
357	…	…	1,000	…	…	11.1	3.75	3,500	43,000
360	…	…	750	…	…	12.3	4.04	4,800	56,000
362	…	…	750	…	…	10.9	3.51	4,300	45,000
363	…	…	750	…	…	10.5	3.62	3,900	50,000
364	…	…	500	…	…	9.8	3.36	3,700	57,000
365	…	…	500	…	…	10.9	3.60	3,600	56,000
367	…	…	250	…	…	10.6	3.56	4,400	75,000
371	…	…	…	…	…	9.9	3.28	4,500	90,000
376	…	…	…	…	…	10.7	3.53	4,600	113,000
399	…	…	…	…	…	13.0	4.26	8,400	161,000
412	…	…	…	…	…	13.1	4.06	6,200	139,000
441	…	…	…	…	…	13.2	4.33	6,300	138,000
567	…	…	…	…	…	15.1	5.30	7,600	149,000

[a]Baseline investigations included renal function test: within normal limits; liver function test: within normal limits; serum electrolytes: within normal limits; hepatitis B surface antigen: nonreactive; hepatitis C antibodies: nonreactive; serum folate: 4.25 ng/mL; serum vitamin B_{12}: 180 pg/mL; venereal disease research laboratory test for syphilis: nonreactive; screening for inborn errors of metabolism: no abnormality detected; computed tomography scan of the brain: normal; electroencephalogram: left temporal intermittent rhythmic delta and α waves (temporal intermittent rhythmic delta activity) with occasional spikes; and magnetic resonance imaging and positron emission tomography scan of the brain: left mesial temporal sclerosis.
[b]Phenytoin started on day 18. Phenytoin stopped on day 234.
[c]Valproate started on day 108 at 1 g/d and increased to 1.5 g/d on day 235. Valproate taper started on day 353; valproate was stopped on day 369.

cost is a major limiting factor for prescribing the newer antiepileptic drugs. Phenytoin can rarely cause hematologic side effects.[9]

Notably, our patient developed neurotoxicity on phenytoin 250 mg after 2 months of initiation of treatment and later developed hematologic toxicity on valproate. Hematologic parameters started worsening a few weeks after increasing the dose of valproate and started improving within 11 days of stopping the drug.

Conclusion

There is a need for vigilant and regular monitoring for toxicity of antiepileptic drugs like valproate and phenytoin, especially in individuals with intellectual developmental disorder. Close monitoring is required even when the patient is stable. Monitoring is needed more frequently in the initial year, probably monthly.[10] Exploring newer antiepileptic drugs for efficacy, affordability, and a safer side effect profile would be beneficial.

Published online: December 23, 2021.
Potential conflicts of interest: None.
Funding/support: None.

Patient consent: As the patient was diagnosed to have intellectual disability and the family members could not be traced despite multiple efforts, consent was obtained from 2 independent psychiatrists not related to the treating team. All information has been de-identified to protect anonymity.

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