CASE REPORT

A Case of Severe Thrombocytopenia and Antiepileptic Hypersensitivity Syndrome

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Thrombocytopenia is a known complication of antiepileptic drug therapy. We present a case of a 3-year-old child who developed fever, rash, and severe thrombocytopenia within 10 days of initiating therapy with carbamazepine for new onset epilepsy. The patient's thrombocytopenia resolved following discontinuation of carbamazepine and introduction of valproic acid, however, his seizure disorder became poorly controlled. Phenobarbital was added to valproic acid therapy, which resulted in reoccurrence of fever, rash, and thrombocytopenia consistent with antiepileptic hypersensitivity syndrome. Discontinuation of phenobarbital, valproic acid and introduction of zonisamide resulted in resolution of his symptoms. The potential etiologies of thrombocytopenia in this case include carbamazepine-induced antiepileptic hypersensitivity syndrome, phenobarbital-induced antiepileptic hypersensitivity syndrome as a result of cross-reactivity with carbamazepine, and/or dose-dependent thrombocytopenia caused by valproic acid therapy. The pathogenesis and cases of aromatic anticonvulsant-induced immune-mediated thrombocytopenia are discussed. Alternative therapies for antiepileptic hypersensitivity syndrome with thrombocytopenia include gabapentin, levetiracetam, tiagabine, topiramate, and zonisamide.

Keywords: child, thrombocytopenia, carbamazepine, phenobarbital, valproic acid, antiepileptic hypersensitivity syndrome

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INTRODUCTION

Epilepsies are neurologic disorders that affect approximately 2.3 million people in the United States, with 100,000 new cases being diagnosed annually.[1] Broad spectrum older aromatic anticonvulsants (i.e., phenytoin, carbamazepine, phenobarbital) are considered the first line drug therapy for common seizure types despite their association with the antiepileptic hypersensitivity syndrome. This severe, idiosyncratic reaction was formerly known as phenytoin hypersensitivity syndrome.[2] It was first reported in 1930's when patients taking phenytoin developed rashes, fever, eosinophilia, lymphadenopathy, peripheral leukocytosis, and sometimes life-threatening hepatic necrosis.[2-3]

It was later discovered that other aromatic anticonvulsant medications, such as carbamazepine, phenobarbital and lamotrigine can also induce a similar syndrome.[4,5] The risk of developing an antiepileptic hypersensitivity syndrome within 60 days of the first prescription in new users of phenytoin or carbamazepine was estimated to be 2.3–4.5 per 10,000 and 1–4.1 per 10,000, respectively.[3] Antiepileptic hypersensitivity syndrome is manifested by a triad of fever, cutaneous eruption over the next one to two days and lymphadenopathy, which are often accompanied by internal organ involvement or hematologic abnormalities.[4-9] The most prominent organ manifestations are hepatitis, eosinophilia, blood dyscrasias and nephritis.[4-9] Additional clinical and laboratory findings may include facial

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Table. Laboratory values during hospital course

Laboratory Values	Admission 1		Admission 2			Admission 3						Admission 4		
Hospital days	1	2	1	2	3	1	2	3	4	5	6	1	2	5
WBC (x 1000 cells/mm^3)	3.2	2.6	2.6	5.2	6.5	3.6	4.2	3.9		3.6	3.2	4.6	2.8	7.2
Segs (%)	32	63	31	13	10		41					20		15
Bands (%)	3	2	11	2	0		7					21		8
Lymphocytes (%)	42	24	40	67	65		38					48		54
Eosinophils (%)	5	4	0	0	1		2					0		1
Atypical lymphocytes (%)	2	1	5	10	9		1					1		7
Platelets (x 1000 cells/mm^3)	10	24	416	357	433	161	102	73	66	58	68	84	160	366
AST (mg/dL)		54		37	29		30					101	81	33
ALT (mg/dL)		18		10	6		10					31	40	28
Total bilirubin (mg/dL)		0.13		0.18	0.13		0.13					0.11	0.21	0.12
VPA (μg/mL)			131	84	83	89	146			100		59		
PB (μg/mL)						22	24			31		35		

WBC=white blood cells; segs= segmented-form neutrophils; bands=band form neutrophils; AST= aspartate aminotransferase; ALT=alanine aminotransferase; VPA =valproic acid; PB=phenobarbital.
Reference range values are as follows: WBC 5,000–10,000/mm^3, segs 50–70%, bands 3–5%, eosinophils 0–5%, lymphocytes 20–40%, atyp lymph. 0–1%, platelets 50,000–350,000/mm^3, total bilirubin 0.2–1.3 mg/dL, AST 15–46 mg/dL, ALT 11–66 mg/dL, VPA 50–100 μg/mL, PB 15–45 μg/mL.

edema, strawberry tongue, hepatosplenomegaly, myopathy, disseminated intravascular coagulopathy, pneumonitis, and atypical lymphocytosis.[3-9] The presentation of antiepileptic hypersensitivity syndrome closely resembles other infectious, neoplastic, or collagen vascular conditions, thus early recognition and proper management of this potentially fatal reaction are essential.[10]

The incidence of antiepileptic hypersensitivity syndrome is approximately 1 in 3,000 exposures to aromatic anticonvulsants[10] and is of particular significance in pediatric patients due to the higher incidence of seizure disorder during the first decade of life.[11] This case report describes the clinical course and management of carbamazepine-induced antiepileptic hypersensitivity syndrome and thrombocytopenia in a 3-year-old child. The four admissions reported below occurred over a period of two months.

CASE REPORT

Admission 1

A three-year-old (16.2 kg) previously healthy white male was placed on carbamazepine (Carbatrol, Athena Neurosciences) 100 mg orally twice daily for the treatment of a new onset generalized tonic-clonic seizure. He presented 10 days later to the Emergency Department with a fever of 38°C and a maculopapular rash that began on his left cheek and progressed to his trunk and extremities. The rash was described as itchy and erythematous with scattered petechiae on trunk and extremities. Carbamazepine serum concentration on admission was 6.6 μg/mL (reference range: 4–12 μg/mL). Liver enzyme tests were within the reference range, with the exception of slightly elevated aspartate aminotransferase (AST) at 57 mg/dL (Table). Evaluation of complete blood count revealed leukopenia with an absolute neutrophil count of 1120/mm^3 and a platelet count of 10,000/mm^3. Bone marrow biopsy performed on the second day of hospitalization revealed increased numbers of megakaryocytes. The patient was diagnosed with CBZ-induced thrombocytopenia and CBZ was immediately discontinued. The child was placed on a prednisone taper to improve the rash progression and was discharged home the following day on valproic acid (Depakote sprinkles, Abbott) 250 mg orally in the morning and 375 mg at night for seizure control (38.5 mg/kg/day).

Admission 2

Seven days later, the patient returned to the Emergency Department because of breakthrough seizures on valproate monotherapy. The valproic acid serum concentration on admission was 131 μg/mL (reference range: 50-100 μg/mL). By the 5th day of hospitalization, his seizure disorder was well controlled on the same dose of valproate

he was previously receiving; however, the rash persisted. At this time, the rash was described as an erythematous maculopapular rash covering the right neck and shoulder, with no noticeable petechiae. Dermatology service was consulted and it was concluded that the patient probably had a contact dermatitis and was discharged on prednisone suspension 15 mg daily (1 mg/kg/day) in the morning for six days. During this admission, it was also noted that his thrombocytopenia completely resolved and the liver enzymes were within the normal reference range (Table).

Admission 3

One week later, the patient presented to the Emergency Department with poorly controlled seizures. The home valproate regimen was continued and the child was given a 15 mg/kg loading dose of phenobarbital, followed by a maintenance dose of 30 mg orally twice daily (3.7 mg/kg/day). The dermatology service was consulted again because of the persistent maculopapular rash that was covering his trunk and lower extremities. Contact dermatitis was again suspected and it was recommended that the child wear his own clothes while in the hospital, and use a hypoallergenic soap, hydrocortisone 2.5% ointment twice daily, ammonium lactate cream with his bath and hydroxyzine syrup as needed. The platelet count trended down from 161,000 cells/mm^3 on the day of admission (prior to phenobarbital) to 68,000 cells/mm^3 at discharge (Table).

Admission 4

Four days after being discharged, the patient returned to the Emergency Department with a three day history fever of 38.1°C, worsening maculopapular rash covering his entire body with petechiea on his trunk and palpable lymphadenopathy. Laboratory testing revealed a WBC of 4,600 cells/mm^3 with a significant bandemia, lymphocytosis, thrombocytopenia, and elevated AST. Admission valproic acid serum concentration was 59 μg/mL and the phenobarbital serum concentration was 35 μg/mL (Table). Drug-induced hypersensitivity reaction was suspected at this point. Valproic acid and phenobarbital were immediately discontinued, and the child was given intravenous lorazepam (Ativan, Wyeth-Ayerst) 0.7 mg every 6 hours for seizure control. The cutaneous reaction was controlled with 250 mg of intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn) once daily. Four days later, the child was afebrile, the rash had begun to resolve and the platelet count had returned to normal. It was suspected that the child had experienced severe thrombocytopenia in a setting of an antiepileptic hypersensitivity syndrome; and was switched to zonisamide (Zonegram, Athena Neurosciences) tablets 50 mg orally twice daily (6 mg/kg/day) and clonazepam (Klonopin, Roche Laboratories) 0.5 mg orally twice daily for seizure control. He was discharged after 9 days of hospitalization and the rash subsequently resolved.

DISCUSSION

We presented the case of a child experiencing severe thrombocytopenia potentially induced by multiple anticonvulsant agents (carbamazepine, phenobarbital, and valproic acid). The carbamazepine or phenobarbital -induced thrombocytopenia is usually a non-dose related immune-mediated reaction. In contrast, valproic acid is known to cause dose-dependent thrombocytopenia. The physical findings consistent with this diagnosis were rash, fever and lymphadenopathy. The laboratory data contributing to this conclusion were leukopenia, neutropenia, atypical lymphocytosis, elevation in liver enzymes, and a marked decline in platelet count. These adverse events resulted and continued to persist while the patient was exposed to aromatic anticonvulsants (carbamazepine and phenobarbital). Notably, the symptoms improved while the patient was on valproic acid monotherapy, a drug considered to be a safer alternative for patients with a history of antiepileptic hypersensitivity syndrome. The severe nature of this patient's skin reaction relating to anticonvulsant exposure was the predominant issue addressed during his four hospital admissions; however, the severity of decline in his platelet count while exposed to the aromatic anticonvulsants also helps to implicate this reaction as part of the antiepileptic hypersensitivity syndrome. Since many clinicians are still unfamiliar with this disorder, it is not surprising that it took several admissions before the correlation between the rash, fever and decline in platelet count was made.

A recent case-series identified fever and rash

as the two most common physical findings associated with childhood antiepileptic hypersensitivity syndrome.[4] The results were in agreement with previous literature reporting fever and rash in 100% and 87% of antiepileptic hypersensitivity syndrome cases, respectively.[9] Blood dyscrasias including leukopenia, thrombocytopenia, anemia and atypical lymphocytosis were reported in up to 50% of cases.[4,9] The proposed cause of the antiepileptic hypersensitivity syndrome is an immune reaction mediated by the toxic metabolites of the aromatic anticonvulsants leading to cell death, mutations, and tumors. The cytochrome P450 enzyme system is responsible for the metabolism of aromatic anticonvulsants to intermediate reactive metabolites (arene oxides), which in turn are detoxified by epoxide hydrolase. Susceptible individuals may have a diminished activity of epoxide hydrolase. There is some evidence to suggest that the diminished activity or deficiency of epoxide hydrolase is related to an autosomal co-dominant inheritance at the cellular level. Since a sensitization period is required for antiepileptic hypersensitivity syndrome to develop, it usually occurs 7–10 days after the first exposure, however, it may develop much sooner following a repeated exposure.

Aromatic anticonvulsant-induced thrombocytopenia can occur alone or in a setting of antiepileptic hypersensitivity syndrome. In a case report describing carbamazepine-induced antiepileptic hypersensitivity syndrome, a 17-year old female developed an isolated profound thrombocytopenia with a platelet count of 7,000/mm^3.[12] The decline in platelet count was found to develop within 2 weeks after the initiation of carbamazepine and returns to baseline within 1 week after its discontinuation.[12,14] In a review of 38 cases of phenytoin hypersensitivity, two patients had platelet counts of 70,000/mm^3 and 100,000/mm^3.[2] In another report, two of seven patients with hypersensitivity reactions to phenobarbital developed thrombocytopenia.[13] The temporal relationship in the above reports is similar with that of antiepileptic hypersensitivity syndrome, which usually occurs 1 week to 3 months after introduction of aromatic anticonvulsants.[4] Enlightened by the afore-mentioned cases, thrombocytopenia should be perceived as a clue of ongoing antiepileptic hypersensitivity syndrome, especially when it is accompanied by rash and fever in a patient recently initiated on an aromatic anticonvulsant.

Considering the severity of the reaction presented in this case and the high rate of cross sensitivity between aromatic anticonvulsants (40%-80%),[15] there is a need for a heightened awareness about the dangers of rechallenging patients with one of these agents. While valproic acid was described as an effective and safe alternative in patients with antiepileptic hypersensitivity syndrome, it should be avoided in those with impaired hepatic function due to its potential for hepatotoxicity. Clinicians should also keep in mind that valproic acid can cause dose-dependent thrombocytopenia. Newer anticonvulsants such as gabapentin, topiramate, tiagabine, levetiracetam and zonisamide may be considered as safe alternative for patients who experience an antiepileptic hypersensitivity syndrome.[16]

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