CASE REPORT
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Antiepileptic Hypersensitivity Syndrome to Phenobarbital: A Case Report

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ABSTRACT

Phenobarbital is still one of the most commonly used medical treatments for different types of seizures. It has numerous different side-effects. Antiepileptic hypersensitivity syndrome (AHS) is a rare and potentially life-threatening adverse reaction to aromatic anticonvulsants such as phenobarbital. Its characteristic features are fever, rash, and lymphadenopathy with different severity of hematologic abnormalities. This case report presents a 26-month-old girl that developed fever, disseminated maculopapular rash, petechiae and thrombocytopenia two weeks after the initiation of phenobarbital prescribed for febrile seizure prophylaxis. The patient was admitted in our center with the impression of hypersensitivity syndrome, so phenobarbital was discontinued and her treatment was resumed with methylprednisolone and intravenous immunoglobulin. After a few days, all symptoms improved and the platelet count was normalized. Thrombocytopenia is a rare complication of hypersensitivity syndrome to phenobarbital in children. Paying attention to this point can prevent the life-threatening adverse effects of this highly consumed medicine.

Keywords: Child; Hypersensitivity syndrome; Phenobarbital; Thrombocytopenia

INTRODUCTION

Hypersensitivity syndrome is an almost perceived disorder characterized by a serious drug reaction usually occurring 2-8 weeks after exposure to antiepileptic drugs, sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and allopurinol.[1] This disorder usually presents with fever, rash, lymphadenopathy, hepatitis, eosinophilia, and atypical lymphocytes.

Other clinical presentations are edema, myalgia, nephritis, and leukocytosis.[2,3] The incidence of antiepileptic hypersensitivity syndrome is approximately 1 in 1000-10000 patients exposed to aromatic anticonvulsants. However, its true incidence is unknown due to varying presentations.[4] This incident is more frequent in the pediatric group because of the higher incidence of seizure disorder in the first decade of life.[5] Both pharmacokinetic and immunologic mechanisms are involved in developing antiepileptic hypersensitivity syndrome.[6] Phenobarbital (PB) is a highly-consumed medication indicated for epilepsy and

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other chronic global conditions such as anxiety, insomnia, addiction to barbiturates, etc.[7] The most important side-effects of phenobarbital are behavioral and cognitive changes. In developing countries, despite its undesirable effects, phenobarbital is widely used due to its cost-effectiveness. Phenobarbital-induced hypersensitivity syndrome is uncommonly seen and hematological abnormalities may occur as part of PB hypersensitivity.[8] This case report describes the clinical presentation and management of phenobarbital-induced antiepileptic hypersensitivity syndrome in a twenty-six month-old girl.

CASE REPORTS

A 26- month-old girl was brought to our pediatric emergency unit with a history of three days of fever that began two weeks after taking phenobarbital tablet (15 mg twice daily) and onset of itchy maculopapular rash that started from the face and spread to the trunk and extremities then followed by scattered petechial and purpuric rashes since two days prior to hospital admission (Figure1). The patient had a history of two episodes of simple febrile seizure at 12 and 14 months of age. Phenobarbital was started by a physician to prevent febrile seizure, a week before recent symptoms. In the past medical history, her vaccination was complete. Her development and growth indices were normal. There was no history of taking another medication and contact with a person with fever and rash recently. On physical examination, vital sign measurements were: temperature 38.8°C (axillary), blood pressure 100/70 mmHg, pulse rate110 bpm, and breaths/minute and respiratory rate 30 breaths /minute. There were generalized itchy maculopapular rashes and numerous petechiae on the face, trunk, and extremities. Lymphadenopathy and hepatosplenomegaly were not detected. In laboratory data, thrombocytopenia was detected. Other blood parameters were within normal limits (WNL) (Table 1).

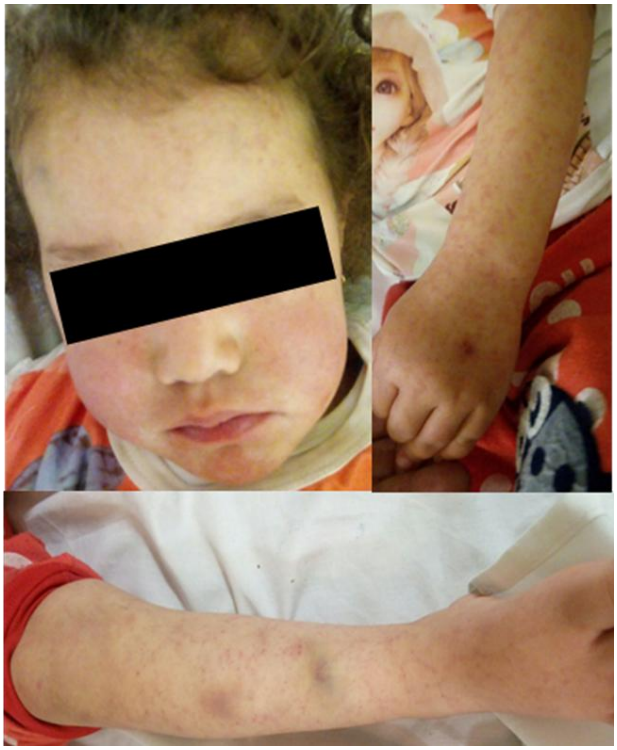

Figure 1. A 26- month-old girl with diffuse itchy maculopapular rash accompanied by petechiae and purpura two weeks after taking phenobarbital

Table 1. Laboratory Data of a 26-month-old girl with diffuse pruritic maculopapular rash, petechiae and purpura two weeks after phenobarbital administration

Hematologic investigations	Admission time	Reference values
White Cell Count, $\times 10^3$ /mm^3	6.2	5-15
Neutrophils, (%)	37	54-62
Lymphocytes, (%)	60	25-33
Eosinophils, (%)	3	1-3
Hemoglobin level, g/dL	11	11.5-14.5
Platelet, $\times 10^3$ /mm^3	9	150-400
Erythrocyte sedimentation rate mm/hr	22	3-13
C Reactive Protein mg/L	25	0.8-7.9
Blast cells	Not seen	_
Atypical lymphocytes	Not seen	_
Liver function test		
Alanine aminotransferase U/L	22	5–45
Aspartate aminotransferase, U/L	32	20-60

Although ITP was one of the differential diagnosis, presence of fever and itchy maculopapular rashes was against. Regarding the good general condition, normal WBC count and ESR, negative blood culture, and no local infection on the physical exam, the bacterial infection was also ruled-out and the presence of itchy maculopapular rash was against viral infection. So, with the impression of hypersensitivity syndrome and phenobarbital-induced thrombocytopenia, phenobarbital was discontinued, intravenous immunoglobulin therapy (1 g/kg) and prednisolone (1 mg/kg/day) were started. One day after treatment, the fever was gone and skin lesions began to improve. The platelet count reached 15,000/mm^3. Three days later, the platelet count was 50,000/mm^3. The patient was discharged with a prednisolone tapering course for 10 days. Since simple febrile seizure is benign and there was not any risk factor in patient's past medical history, anticonvulsant was not prescribed at the time of discharge. In follow up for two weeks, skin rashes were completely improved and platelet count was normalized (346000/mm^3). An informed consent was obtained from the patient's parents for reporting the case.

DISCUSSION

We introduced a child with thrombocytopenia and maculopapular rashes due to phenobarbital consumption. Although some cases of thrombocytopenia to AHS induced by anticonvulsants such as phenytoin, lamotrigine, and carbamazepine has been reported, we did not find any reports on thrombocytopenia as part of AHS following phenobarbital alone in humans.[4,9,10] Secondary thrombocytopenia following phenobarbital treatment has also been reported in some animal studies.[11] Antiepileptic drugs can induce hypersensitivity reactions in children.[12] Hypersensitivity syndrome is a rare and potentially life-threatening adverse reaction to aromatic anticonvulsants such as phenytoin, phenobarbital, carbamazepine, primidone, and lamotrigine. This complication usually develops 2 to 8 weeks after initiation of therapy with one of the above agents and is characterized by the classic triad of fever, rash (a maculopapular erythematous eruption is the most common), and internal organ involvement. It was reported for the first time in 1934.[2,13] The skin involvement is seen in about 90% of antiepileptic hypersensitivity syndrome cases and ranges from a mild pruritic rash to severe exfoliating dermatitis.[14] Multiple organ involvement (50% liver and 11% kidney) is usually present in the first few weeks after the administration of anticonvulsant treatment.[2] In one study, fever and skin rashes were manifested in all children by definition of antiepileptic hypersensitivity syndrome.[15] In the study by Karimzadeh et al in Iran, cutaneous eruptions were seen in all of the patients with antiepileptic hypersensitivity syndrome, the skin

reactions began as maculopapular rash, and the most common medication was Phenobarbital.[16] Hepatic and hematological systems involvement is common. Hematological abnormalities including lymphocytosis, lymphopenia, eosinophilia, atypical lymphocytosis, and thrombocytopenia were encountered.[17,18] Signs and symptoms of hypersensitivity syndrome ranked by frequency included fever (90-100%), rash (90%), lymphadenopathy (with or without systemic or cutaneous pseudolymphoma) (70%), multiorgan involvement (60%), hepatitis (with or without hepatosplenomegaly) (50-60%), hematologic abnormalities (e.g., eosinophilia. anemia, thrombocytopenia) (50%), periorbital or facial edema (25%) myalgia, arthralgia (20 %), interstitial nephritis (10%) and pharyngitis (10%).[19] Tichy E et al reported a 3-year-old child that developed fever, rash, and severe thrombocytopenia after initiation of carbamazepine for new onset epilepsy. The patient's thrombocytopenia resolved after discontinuation of carbamazepine and introduction of valproic acid, but due to poorly controlled seizure, they added phenobarbital to valproic acid therapy, which resulted in the reoccurrence of fever, rash, and thrombocytopenia consistent with antiepileptic hypersensitivity syndrome. Discontinuation of phenobarbital, valproic acid and introduction of zonisamide led to resolving of his symptoms. Thrombocytopenia after initiation of carbamazepine or phenobarbital is usually a non-dose-related immune-mediated reaction that can occur alone or in combination with antiepileptic hypersensitivity syndrome, .[9] AHS is a synonym for DRESS in many articles characterized as type IVb hypersensitivity reactions.[4,20,21] The mechanism of AHS is associated with the accumulation of aromatic anticonvulsant drugs (ACDs) oxidizing metabolites (i.e., phenytoin, carbamazepine, and phenobarbital). The epoxide hydrolase enzyme detoxifies reactive intermediates produced by cytochrome P450 enzymes from ACDs. Ineffective detoxification may result in the formation of an antigen that causes an immune response. In vitro, lymphocytes show cytotoxicity in patients with a history of allergy to ACDs.[22] Current studies show that some viral infections such as EB virus, HHV-6, HHV-7 and CMV, especially HHV-6, have a role in the pathogenesis of hypersensitivity syndrome to anticonvulsants. Some researchers assert that hypersensitivity syndrome should be regarded as a reaction induced by a complex interplay among herpes viruses, antiviral immune responses, and drug-specific immune responses.[4,10] Supportive care and close observation are the most important steps in the management of patients and include hydration and electrolyte balance. Improvement after withdrawal is usually complete, but the rash and hepatitis may persist for several weeks. The use of systemic corticosteroids, especially in cases of internal organs involvement, has been accompanied by dramatic improvement.[23]

Given the wide range of symptoms associated with AHS, early detection in patients receiving anticonvulsant medication can be effective in improving symptoms and preventing severe disorders. Although thrombocytopenia is a rare complication in patients being treated with anticonvulsants, especially aromatic ones, the criticality of this problem demands special attention.

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