

## Antiepileptic hypersensitivity and DRESS syndrome due to phenytoin in two pediatric cases

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Antiepileptic hypersensitivity syndrome (AHS) is a potentially life-threatening syndrome, especially in pediatric cases. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome reflects a serious hypersensitivity reaction to drugs.

We report here two children with AHS due to phenytoin. Both cases were under treatment with phenytoin: the first case was a seven-year-old boy who was referred with the classic form of AHS. The second patient was a five-year-old girl who manifested with DRESS. The manifestations in both cases improved after withholding the phenytoin.

Clinical presentations of adverse drug reactions are highly variable and must therefore be suspected in any patient who develops any unusual manifestation after taking antiepileptic drugs. Early recognition of AHS and withholding and/or changing the medication are necessary to prevent potentially fatal outcomes.

*Key words:* antiepileptic drug, hypersensitivity, pediatric, phenytoin, syndrome.

Antiepileptic hypersensitivity syndrome (AHS) is a rare but potentially life-threatening syndrome, which occurs after consumption of an anti-convulsant drug, most commonly the aromatic ones such as phenytoin, carbamazepine or phenobarbital<sup>1-6</sup>. Clinical features of this syndrome include cutaneous reactions, fever, lymphadenopathies, and eosinophilia. Different organs can be involved, such as liver, kidney, heart, lung, and the central nervous system<sup>1</sup>.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome reflects a serious hypersensitivity reaction to drugs. Its clinical manifestations include diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathies, fever, and multi-visceral involvement; it is associated with a high mortality rate<sup>7,8</sup>.

We report here two children with AHS due to phenytoin; the first patient had classic form of AHS and the second patient had symptoms of DRESS.

### Case Reports

#### Case 1

A seven-year-old boy with a history of renal tubular acidosis and chronic renal failure for four years was referred to Mofid Children's Hospital (Tehran, Iran) with fever and skin rash from one month before. On suspicion of adverse drug reactions to antibiotics, ceftriaxone and imipenem were stopped; however, fever and rash progressed and the patient's condition was complicated with cervical and inguinal lymphadenopathies and arthralgia. Laboratory workup showed mild anemia, leukopenia and elevated erythrocyte sedimentation rate. Chest X-ray showed parahilar reticular infiltrate. A detailed medical history revealed that the patient had been under treatment with phenytoin for two months. On the suspicion of AHS, phenytoin was discontinued. The rash and fever disappeared in one week. He was discharged from the hospital in good

condition; all symptoms had disappeared and hematological tests were approaching normal at the three-week follow-up.

### Case 2

A five-year-old girl was referred to our center with high fever, skin rash, and lymphadenopathies for two weeks. On the suspicion of Kawasaki disease, intravenous immunoglobulin therapy was started; however, the fever not only continued, she also manifested hepatosplenomegaly and severe respiratory distress. Moreover, exfoliative skin rash, cervical lymphadenopathies, and nonpitting edema of the extremity were detected in physical examination. Laboratory workup showed leukocytosis, eosinophilia, mild thrombocytopenia, mild increase in transaminase levels, and elevated erythrocyte sedimentation rate. Chest X-ray showed parahilar infiltrate. A detailed medical history revealed that the patient had been under phenytoin treatment for 1.5 months. A diagnosis of DRESS was suggested and consequently phenytoin was stopped and treatment with methylprednisolone was started. She had a good response to the treatment, and fever, dyspnea and rash disappeared in one week. She was discharged from the hospital in good condition.

### Discussion

Drug-induced hypersensitivity syndrome usually refers to severe cutaneous drug eruption associated with systemic involvement and potentially fatal outcome<sup>1-3</sup>. Clinical presentations of AHS are highly variable and include Stevens-Johnson syndrome, toxic epidermal necrolysis, cutaneous eruption associated with fever, lymphadenopathy, and a severe form of AHS such as DRESS<sup>6</sup>. The first patient in this report presented with rash, fever, lymphadenopathy, leukopenia, and elevated erythrocyte sedimentation rate, which showed good response after withdrawal of the culprit drug. Such manifestations have previously been reported in pediatric patients due to carbamazepine and phenobarbital<sup>4,5</sup>. Cross-sensitivity of carbamazepine and barbiturates with phenytoin has been observed. Gabapentin and valproic acid could be considered as alternative therapeutic options in such cases<sup>6</sup>.

The manifestations of the second patient in this study were compatible with DRESS syndrome. She responded immediately to high-dose intravenous methylprednisolone treatment. An acute severe hepatitis revealing an oxcarbazepine- and carbamazepine-induced DRESS syndrome has previously been reported in other studies<sup>7,8</sup>. It seems that steroid could resolve the manifestation in a short time<sup>8</sup>.

As clinical presentations of adverse antiepileptic drug reactions are highly variable, hypersensitivity must therefore be considered in any patient who develops any unusual manifestation. Early recognition of AHS and cessation of the suspect medications are required to prevent potentially fatal outcomes; systemic steroids are recommended in the cases with DRESS.

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