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# Hemophagocytic lymphohistiocytosis associated with sodium valproate

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### *Abstract*

Hemophagocytic lymphohistiocytosis(HLH) is known to have numerous causes, such as chronic inflammation, infection, malignancy, drug use, and primary or familial HLH. HLH triggered by valproate (VPA) has rarely been reported in the literature. Here we describe a pediatric patient with HLH induced by VPA. A 5-years-old girl presented to our center with recurrent fever accompanied by diffuse generalized rash after 2 weeks of taking oral VPA. Physical examination revealed hepatosplenomegaly; laboratory findings showed bicytopenia (hemoglobin and platelet), hemophagocytic cells on the bone marrow smear, hypofibrinogenaemia and hypertriglyceridaemia, and a high ferritin level. She was diagnosed to have HLH associated with VPA. She was treated with intravenous immunoglobulin, glucocorticoid and withdrawal of the sodium valproate, and she completely recovered. In conclusion, VPA can trigger HLH, a potentially fatal condition.

*Keywords:* Epilepsy, hemophagocytic lymphohistiocytosis, valproate.

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening immunological syndrome characterized by the uncontrolled activation of cytotoxic lymphocytes and macrophages, resulting in cytokine mediated tissue injury and multiorgan dysfunction.[1] If untreated, HLH is fatal; so early recognition and prompt treatment is critical. HLH has a variety of causes, such as chronic inflammation, infection, malignancy, drug use or primary/familial.[2] Identifying and addressing the triggering cause is thus critical. HLH caused by valproate (VPA) has rarely been reported. Here we describe the clinical course and management of a pediatric patient with HLH triggered by VPA.

## CASE REPORT

A 5-years-old girl presented to our clinic with a recurrent fever accompanied by diffuse generalized rash. The patient was diagnosed with children's absence epilepsy (CAE) one month ago due to recurrent absence seizures with an electroencephalogram (EEG) showing generalized 3Hz spike-and-slow waves. For the previous 3 weeks, she was given sodium VPA (Depakin), and the dose of sodium VPA had been increased from 10mg/kg.d to 20 mg/kg.d in the last 2 weeks. For 8 days, the patient had developed recurrent fever and a diffuse rash all over her body, so she was admitted to our hospital. Physical examination upon admission was normal except for hepatosplenomegaly, cervical lymph node enlargement and diffuse rash on the trunk, limbs, and face. The complete blood cell count showed that the white blood cells (WBC) were $19.93\times10^9$/L (reference value 4.03-11.09$\times10^9$/L), absolute neutrophil counts (ANC) were $6.7\times10^9$/L (reference value 0.86-6.03$\times10^9$/L), lymphocyte counts were $8\times10^9$/L (reference value 0.98-7.5$\times10^9$/L), eosinophils counts were 0.15 $\times10^9$/L(reference value 0-0.75$\times10^9$/L), hemoglobin (Hb) was 86g/l(reference value 108-144g/L), platelets (PLT) counts were 95 $\times10^9$/L(reference value 128-420$\times10^9$/L), c-reactive protein (CRP) was 99mg/l (reference value 0-10mg/L) and there were no atypical lymphocytes. Biochemical investigation showed that the triglyceride (TG) was 3.2mmol/L (reference value 0-2.3mmol/L), plasma fibrinogen was 0.68g/L (reference value 2-4g/L), serum ferritin was 1,468.4 ng/ml (reference value 10-291ng/ml), alanine aminotransferase (ALT) was 389.4u/L (reference value 14-44u/L), and aspartate aminotransferase (AST) was 559.3u/L (reference value 7-30u/L). Hemophagocytic cells were seen on the bone marrow smear (Figure 1).

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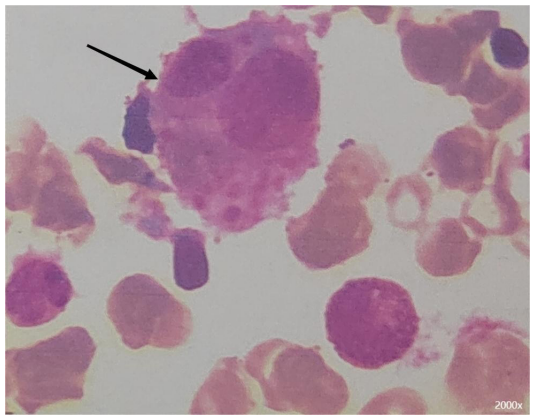


Figure 1. Hemophagocytic cells observed in the bone marrow (black arrow) with no malignancy

Serological testing for pathogens gave negative results for Epstein–Barr virus, hepatitis virus A, B, and C, herpes simplex virus (HSV), cytomegalovirus, rubella virus, tuberculosis, Toxoplasma gondii, human immunodeficiency virus, varicella-zoster virus, Treponema pallidum, respiratory syncytial virus, coxsackievirus, Legionella pneumophila, Mycoplasma pneumoniae, adenovirus, influenza virus A and B, and parainfluenza virus. Serological tests for parasites, glucan (G test) and galactomannan (GM test) were negative. Blood autoantibodies, rheumatoid factor (RF), erythrocyte sedimentation rate and antistreptolysin "O" were normal. Chest x-ray, ultrasonic cardiogram and electrocardiograph findings were normal. Abdominal ultrasonography revealed hepatomegaly (4.9cm subcostal) and splenomegaly (1.7cm subcostal), superficial lymph node ultrasonography revealed multiple lymphadenectasis (maximum 2.2×1.1cm).

Accordingly, she was diagnosed to have HLH triggered by sodium VPA. The sodium VPA was terminated on the 3th day of hospitalization, and the subsequent treatment consisted of IVIG (2 g/kg over 2 d) and glucocorticoid (intravenous injection of methylprednisolone at 15 mg/kg.d × 3 d, followed by oral prednisone at 1 mg/kg/d with tapering decrease in dose). On the 10th day of hospitalization she showed substantial recovery, repeat WBC were $12.03\times10^9$/L, Hb was 102g/l, PLT were $129\times10^9$/L, and CRP was 8mg/l. Repeat biomedical detection showed that the TG was 2.4mmol/L, plasma fibrinogen was 2.28g/L, serum ferritin was 203.5 ng/ml, ALT was 67.9u/L and AST was 43.1u/L. Repeat abdominal ultrasonography showed liver 2.3cm subcostal and spleen 0.6cm subcostal, repeat superficial lymph node ultrasonography revealed maximum cervical lymph node was 1×0.8cm, no hemophagocytic cells were seen on the bone marrow smear, and then she discharged to home. To date, the patient has been followed up for 2 months. She is currently receiving oral levetiracetam treatment, and has not experienced any absence seizures or the signs and symptoms associated with HLH. The blood routine, abdominal ultrasonography and transaminase were normal. Prednisone has been tapered off within 1 week of discharge.

## DISCUSSION

The diagnosis of HLH is based on the clinical, hematological, and bone marrow aspiration (Table 1).[3] Our patient had fulfilled six of the criteria, with a recurrent fever and hepatosplenomegaly, with laboratory findings of bicytopenia (Hb and PLT), hemophagocytic cells, hypofibrinogenaemia and hypertriglyceridaemia, and a high ferritin level. HLH is divided into a primary/familial form (F-HLH) and secondary/sporadic/reactive forms. F-HLH is a heritable disease from highly penetrant genetic mutations/variations impacting cytolytic functions, lymphocyte survival, or inflammasome activation. Secondary HLH is from acquired factors, such as chronic inflammation, infection, malignancy or drug use.[2] Our patient had no family history or previous history of HLH, so we hypothesized that she had secondary HLH. There was no evidence of chronic inflammation, infection, immunodeficiencies, Juvenile idiopathic arthritis or malignancy. As she had a recent history of oral VPA consumption, and rapidly recovery after the withdrawal of VPA, we concluded that her HLH was due to VPA. VPA is an anti-seizure medication (ASM) commonly used in the treatment of epileptic seizures, bipolar mood disorders, obsessive-compulsive disorders, and migraine. It is the first line drug used for CAE as well as being used for focal seizures. Increased bleeding time, thrombocytopenia, hives, tinnitus, rash, confusion, mood changes, tremor, erythema multiforme, hyperandrogenism, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are the known adverse effects of VPA.[4,5] Our patient had fever, rash, impaired liver function, blood count abnormalities, and the clinical picture with rapid resolution after medication cessation, IVIG and steroid which would be consistent with DRESS. But she also had hemophagocytic cells, hypofibrinogenaemia, hypertriglyceridaemia, and a high ferritin level which are supportive

**Table 1: Diagnostic criteria for HLH.**

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|---|---|
| 1 | Fever, more than 7 d |
| 2 | Splenomegaly |
| 3 | Cytopenia (at least two of the three cell lines)<br>Hemoglobin (Hb) <9 g/dl; Thrombocytes <100,000/mm3; Neutrophils <1,000/mm3 |
| 4 | Hypertriglyceridaemia or/and hypofibrinogenaemia<br>Fasting triglycerides >3mmol/L<br>Hypofibrinogenaemia <1.5 g/L |
| 5 | No or reduced NK activity |
| 6 | Ferritin ≥500 μg/L |
| 7 | Soluble CD25 ≥2400 U/ml |
| 8 | Hemophagocytosis observed in the bone marrow, lymph nodes, or spleen with no malignancy |

Note: The presence of five of these eight criteria is necessary

of the diagnosis of HLH. It s also known that HLH overlaps with DRESS.[6,7] A hypotheses holds that HLH may be a delayed reaction to untreated or persistent DRESS. While cytokine storm is central to HLH pathology, DRESS also features elevated inflammatory cytokines as both conditions result from immune dysregulation, although DRESS predominantly sees elevations in CD4/CD8 T cells, untreated cases may eventually cause proliferation and increased activity of macrophages because of continued elevations in inflammatory cytokines. Although HLH induced by VPA is rare, there are also cases of HLH associated with lamotrigine, oxcarbazepine and phenobarbital, also ASM.[8-10] The explanation of this is unclear. We hypothesized that some ASMs or their metabolites may activate cytotoxic CD4/$CD8^+$ T cells aberrantly that result in inflammatory cytokine release, the exact mechanism remains to be determined.

In conclusion, it is important to be aware that VPA may be the trigger for HLH, a potentially life-threatening syndrome.

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## DISCLOSURE

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Conflict of interest: None

Ethics: Written informed consent was obtained from the parents of the patients for publication of this case report and accompanying images.

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