CASE REPORT

Case Report: A rare cause of multiple organ dysfunction syndrome: Human Herpes Virus 6 infection [version 1; referees: 1 approved, 1 approved with reservations]

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v1 **First published:** 16 Aug 2013, **2**:175 (doi: 10.12688/f1000research.2-175.v1)
Latest published: 16 Aug 2013, **2**:175 (doi: 10.12688/f1000research.2-175.v1)

Abstract

Human herpes virus 6 (HHV-6) is a member of the β-herpes virus subfamily which targets mainly CD4 T cells and is a well-known cause of roseola infantum. Fever without roseola, encephalitis and hepatitis however are not uncommon after HHV-6 infection. More severe clinical cases are commonly observed in immune compromised patients. Case: An 11-month old girl, after a 24-hour fever, and with poor appetite was admitted into the hospital. Oral antibiotic treatment was initiated and she was discharged from the state hospital's out-patient clinic two hours later. The following day, the patient continued to experience high fever, and hematemesis, and a tendency to sleep were added to her condition and she was once more admitted to the hospital. Lab results showed thrombocytopenia, alanine aminotransferase over 3000 U/L, INR was 2.5 and urea and creatinine were elevated at 75 mg/dl and 1.1 mg/dl, respectively. Due to persistent high fever and somnolence, a lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear of any cells; protein and glucose were within normal range. However, test results were positive for HHV-6 DNA in the CSF, serum, and lymphocytes. Four organ dysfunctions including the central nervous-, hematologic-, renal- and hepatic systems, developed because of HHV-6 infection. Organ functions were normalized within one week of supportive treatment. HHV-6 is a benign virus that very rarely causes severe infection and hardly ever leads to a fatal infection. However, in our case, a healthy child, with a HHV- viral infection led to multiple organ dysfunction without any predisposing reason.

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Referee Status: ✔ ?

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version 1 published 16 Aug 2013	✔ report	? report

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How to cite this article: Tekguc H, Galip N, Dalkan C *et al.* **Case Report: A rare cause of multiple organ dysfunction syndrome: Human Herpes Virus 6 infection [version 1; referees: 1 approved, 1 approved with reservations]** *F1000Research* 2013, **2**:175 (doi: 10.12688/f1000research.2-175.v1)

Grant information: The author(s) declared that no grants were involved in supporting this work.

Competing interests: No competing interests were disclosed.

First published: 16 Aug 2013, **2**:175 (doi: 10.12688/f1000research.2-175.v1)

Introduction

Human herpes virus 6 (HHV-6) is a member of the β-herpesvirus subfamily of herpesviruses and targets mainly CD4 T cells[1,2]; however, it can infect many other cells of the hematologic, neurologic and hepatobiliary systems. HHV-6 infection is a well-known cause of roseola infantum (sixth disease); however, fevers without roseola, encephalitis and hepatitis are not uncommon[1]. Usually, primary infection occurs between 6 and 15 months of age and seropositivity is almost 100% by age 3. HHV-6 establishes latency in mononuclear cells and probably in entire body systems. HHV-6 can reactivate in immunocompromised patients[3]. Multiple organ dysfunction syndromes (MODS) define two or more organ failures because of systemic inflammatory response (Table 1), infections and sepsis are the most common reasons for MODS[4].

Case

Written informed consent for publication of clinical details was obtained from the legal guardian of the 11-month-old girl. The patient was admitted to the state hospital, with a 24-hour fever and poor appetite, and subsequently treated with amoxicillin/clavulinic acid with 40 mg/kg at a private clinic. She was diagnosed with upper respiratory tract infections and otitis media. The patient returned to the hospital the following day as the fever continued. She was restless and had one-time hematemesis. Vital signs were noted as normal, although she had a tendency to sleep. Initial investigation showed thrombocytopenia (normal hemoglobin and leukocyte count), and aspartate levels, alanine aminotransferase activity, prothrombin time, urea- and creatinine levels were all elevated (Table 2). Serum electrolytes, blood glucose, and calcium levels were normal. Ceftriaxone treatment, 100 mg/kg, was started on the first day of admission. On the following day, a lumbar puncture was performed because of persistent high fever and somnolence. Acyclovir (10 mg/kg every 8 hours), and teicoplanin (10 mg/kg/day) treatment were given, even though the cerebrospinal fluid was clear of cells, and the protein- and glucose levels were within the normal range. It was noticed that urine output was progressively decreasing (less than 0.5 cc/kg/h) and creatinine values were rising (maximum; 1.09 mg/dl).

Table 1. Organ dysfunction criteria[4].

Organ system	Clinical observation
Cardio-Vascular	– Hypotension, or reliance on a vasoactive drug to maintain blood pressure, *or* two of the following: metabolic acidosis, elevated arterial lactate, oliguria, or prolonged capillary refill
Respiratory	– Arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) <300, arterial carbon dioxide tension ($PaCO_2$) >65 torr or 20 mmHg over baseline $PaCO_2$, need for >50 percent FiO_2 to maintain oxygen saturation ≥92 percent, *or* need for nonelective mechanical ventilation
Neurologic	– Glasgow coma score ≤11, *or acute* change in mental status
Hematologic	– Platelet count <80,000/microL or a decline of 50 percent from highest value recorded over the past three days
Renal	– Serum creatinine ≥2 times upper limit of normal for age *or twofold* increase in baseline creatinine
Hepatic	– Total bilirubin ≥4 mg/dl (not applicable to newborn) *or* alanine aminotransferase 2 times upper limit of normal for age

Table 2. Pathological laboratory findings showing organ failures.

Organ system	Variable	Count
Hematologic system	Thrombocytes	79,000 cells per mm^3
	Prothrombin time *(International normalized ratio)*	32.5sec *(2.5)*
Hepatic system	Alanine aminotranseferase	>3000 U/L
Renal system	Creatinine	1.09 mg/dl

On day four, the girl was transferred to the Near East University Pediatric Intensive Care Unit, due to dysfunction of four organ systems (the central nervous-, hematologic-, renal- and hepatic systems, Table 2)[4]. At her arrival, she was restless with a temperature of 36.4ºC, she had a tendency to sleep, her capillary refill time was prolonged, heart rate was 116/minute, and blood pressure was 100/55 mmHg. The patient had generalized edema but no hypotension, respiratory distress, hepatosplenomegaly, lymphadenopathy or rash was seen. Electroencephalography (EEG) was performed and showed bitemporal slow waves, but no electrical activity causing seizures was detected. During four nights of intensive care unit hospitalization, no fever was observed, but on the second day, a maculopapular rash started from the trunk and expanded to the whole body. The polymerase chain reaction test results on the first lumbar puncture were positive for HHV 6 DNA in the cerebrospinal fluid, serum and lymphocytes. Epstein Barr virus, cytomegalovirus, hepatitis A IgM results and bacterial cultures were all negative. The patient was diagnosed with HHV 6 infection and acyclovir treatment was continued for two weeks. Although ganciclovir or foscarnet would have been more appropriate for HHV 6 encephalitis and hepatitis treatment[3], we had to use acyclovir because these other drugs were not available at our hospital at that time. One week after admission to Near East University Hospital, creatinine levels became normal, and were still normal 15 days later (0.44 mg/dl). Immunoglobulin and lymphocyte subset analysis was normal. The patient was discharged from the hospital without any sequelae and at a check-up three months later her laboratory parameters and developmental status were completely normal. In the following two years, the patient showed no sign of immune deficiency or another severe infection.

Discussion

Roseola infantum is characterized by a sudden onset of fever, lasting for three to five days, followed by maculopapular rash, which may be transient or in fact may not appear at all[1]. HHV 6 usually causes roseola infantum but can also cause encephalitis and acute hepatitis[2,5]. In general, it is a benign virus that very rarely causes severe infection and hardly ever leads to a fatal infection[6]. However, our case showed MODS due to HHV 6 virus infection. The patient

had a Glasgow Coma Scale of 11 and EEG abnormalities, a more than twofold increase in baseline creatinine, the INR was over 2 and ALT was twice the normal upper limit for her age. Besides hepatitis and encephalitis, our patient displayed renal insufficiency, which can not be explained by prerenal or postrenal reasons. The patient did not display any hypotension or dehydration, and renal ultrasonography did not show any pathology. The patient was diagnosed with intrinsic renal failure. We were unable to find out whether the exact reason for intrinsic renal pathology was the HHV 6 infection. In the current literature there are no reports of renal insufficiency in an otherwise healthy child, although it has been shown that in renal-transplanted patients HHV 6 can cause re-infection[7] and allograft rejection[8].

We used a polymerase chain reaction technique to detect HHV 6 DNA in the CSF, serum and lymphocytes. We checked for other viruses which can cause hepatitis and encephalitis like enterovirus, herpes simplex type 1 and 2. The test results for all these were negative. For an 11-month-old girl without an predisposing immune deficiency, sepsis or transplantation, we diagnosed her with primary infection[9] after detecting HHV 6 DNA.

Conclusions

HHV 6 is usually a benign virus which causes no or negligible organ dysfunction in a healthy child. It is known that when the patient is immunocompromised HHV 6 can cause organ dysfunction and encephalitis[10,11]. In addition; HHV 6 infection can cause organ rejection problems in transplant patients[12,13]. In the current literature, there are no other studies that report renal and hepatic insufficiency proceeding to MODS due to HHV-6 virus infection in a healthy child without any predisposing factors.

Consent

Written informed consent for publication of clinical details was obtained from the legal guardian of the 11-month-old patient.

Author contributions

Hakan Tekguc was the primary doctor who followed the patient in the intensive care unit, and wrote the manuscript. Ceyhun Dalkan and Nilufer Galip were the other doctors following the patient at Near East University Hospital and helped writing the manuscript. Dr. Behceciler and Dr. Cobanoglu were two senior professors who supervised our team while following the patient in university hospital, also both reviewed the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgments

This article was based on a poster presented at 30th Annual Meeting of the European Society for Pediatric Infectious Diseases in Thessaloniki, Greece in 2012.

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Current Referee Status: ✔ ?

Version 1

Referee Report 04 March 2014

doi:10.5256/f1000research.1340.r3965

? **Peter Medveczky**
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Tekguc and colleagues describe an 11 month-old child hospitalized for high fever, thrombocytopenia, and possible multi-organ dysfunction. While it is possible that this is an unusual case of HHV-6 primary infection another obvious alternative is that the child has inherited or "*chromosomally integrated*" HHV-6 commonly referred to as ciHHV-6. Unfortunately this possibility was not considered in the differential diagnosis. The diagnosis of ciHHV-6 can be established by either quantitative PCR, or alternatively by PCR of hair follicles. Therefore the title "*A rare cause of multiple organ dysfunction syndrome: Human Herpes Virus 6 infection*" and the overall conclusions of the paper are not supported by the laboratory data.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 24 October 2013

doi:10.5256/f1000research.1340.r1655

✔ **Esra Şevketoğlu**
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Overall I 'Approve' of this paper but I have the following comments:

1. All the patient's laboratory values (normal-abnormal) should be displayed in table 2.
2. In the Case section the authors state that the capillary refill time was prolonged and that the patient had '*generalised edema*'; please state how these symptoms were treated.
3. In the Discussion section the authors state that '*The patient had a Glasgow Coma Scale of 11*'; this should probably also be mention in the Case section.
4. In the Discussion section the authors state that '*ALT was twice the normal upper limit for her age*' yet this measurement is recorded as being >3000 in table 2.

5. In the Discussion section the authors state that '*We checked for other viruses which can cause hepatitis and encephalitis like enterovirus, herpes simplex type 1 and 2*' yet in the Case section different viruses are mentioned: *'Epstein Barr virus, cytomegalovirus, hepatitis A IgM results and bacterial cultures were all negative.'*
6. Finally the authors state that '*The patient was diagnosed with intrinsic renal failure*.' but renal failure cannot be distinguished as intrinsic or extrinsic on the basis of this kind of laboratory data.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.