HHV-6 infection in immunocompetent children, is it really benign infectious disease?

A case series and systematic review from literature.

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Background: HHV-6 is commonly responsible for a mild childhood infectious disease, known as exantema subitum. Severe clinical manifestations have been reported in immunocompromised patients which in some cases can be fatal. Rarely, the infection can be clinically relevant in immunocompetent children. The correct diagnostic and therapeutic approach in these cases has never been clarified.

Methods: We performed a systematic review on clinical cases of HHV-6 complicated infection in immunocompetent children from 1945 up today. We further reported our clinical experience on complicated cases occurring in immunocompetent children followed at “Bambino Gesù” Children’s Hospital in the last 10 years.

Results: We identified in the literature 222 cases of HHV-6 primary infection with complicated clinical manifestations (Figure 1). Antiviral therapy was the preferred therapeutic option: 13 (5.8%) cases were treated with intravenous ganciclovir, while 25 and 2 cases were treated with acyclovir and foscarnet respectively. Alternative treatments included corticosteroids and iv Ig, in 7.2% and 3.6% of the cases respectively. An equal percentage (37.8%) of patients with favourable or poor outcome was observed (Figure 2). No significant correlation between antiviral treatment and outcome was found. We also identified 16 complicated cases admitted to Bambino Gesù Children’s Hospital of Rome from 2007 up to now (Table 1) and described the clinical management of these patients.

Conclusions: HHV-6 infection can be fatal or lead to several morbidities both in immunocompromised and immunocompetent patients. Our review highlights the wide spectrum of clinical presentation of HHV6 in pediatrics and the variability in the diagnostic and therapeutic management of complications. Multicenter trials are needed in order to clarify all these aspects.

Clinical Trial Registration:

N/A

Figure 1

Figure 2

Table 1.. The figure reports the case series of HHV-6 complicated infections in immunocompetent children admitted to Bambino Gesù Children’s Hospital

Sex	Age	N. days of Hospitalization	Diagnosis	Cause	Clinical presentation	Antiviral treatment	Other drugs	Antiviral treatment duration (days)	PCR HHV-6 blood	PCR HHV-6 CNS	Diagnostic tools	Outcome
F	1,91	10	Encephalitis	HHV6	Stiff neck	Aciclovir	Cephalosporin	9	Yes	Yes	CT	Good
M	1,54	8	Cerebellitis	HHV6	Stiff neck	Aciclovir	Cephalosporin	NA	Yes	Yes	EEG, CT, MRI	Good
M	0,68	16	meningoencephalitis	HHV6	Respiratory distress and complexive seizures	—	—	—	NA	NA	NA	Good
M	2,45	17	Encephalitis	HHV6	Complexive seizures and stiff neck	Aciclovir	Amoxicillin and clavulanate Amikacin	11	Yes	Yes	EEG, CT, MRI	Good
M	0,09	42	Encephalitis	HHV6	Respiratory insufficiency and sepsis	Aciclovir	—	41	Yes	Yes	RMI/CT	Hypotone for few months
F	0,16	15	Encephalitis	HHV6	Sepsis	Aciclovir	Cephalosporin	7	Yes	Yes	—	—
M	1,24	22	Meningoencephalitis	HHV6	Complex seizures	Aciclovir	Ig iv Cephalosporin	18	Yes	Yes	EEG, CT, MRI	Good
M	0,95	61	Meningitis	HHV6	Complex seizures	Aciclovir	Cephalosporin	24	Yes	Yes	EEG, CT, MRI	Emiparesis, Status epilepticus
F	0,05	28	Meningoencephalitis	HHV6, enterovirus	Fever	Ganciclovir Valganciclovir	Netilmidn Ampicillin	25+7	Yes	Yes	RMI/EEG	Cognitive impairment Hypotone for few months
F	3,04	32	Meningoencephalitis	HHV6	Lethargy	—	Cephalosporin, Ig iv, Dexamethason	NA	Yes	Yes	RMI/EEG	Cognitive neurologic impairment
M	0,07	17	Meningoencephalitis	HHV6	Respiratory distress	Aciclovir	Amoxicillin and clavulanate	14	Yes	Yes	RMI, EEG	Complex seizures
M	0,16	8	Cytopenia	HHV-6	Fever	—	—	—	Yes	No	None	Good
M	0,66	5	Neutropenia	HHV-6	Fever and diarrhea	—	—	—	Yes	No	None	Good
F	1,41	6	Cytopenia	HHV-6	Rash, fever, legs pain	Ganciclovir Valganciclovir	—	10+6	Yes	Yes	US, RMN	Good
M	0,08	17	Meningitis and sepsis	HHV-6	Vomiting and poor feeding	Ganciclovir, Valganciclovir	Ig iv	10+6	Yes	Yes	US	Good
M	0,5	13	Anemia	HHV-6	Vomiting and diarrhea	—	Ig iv	—	Yes	NA	NA	Good