



# Chronic meningoencephalitis caused by Echo virus 6 in a patient with common variable immunodeficiency

## Successful treatment with pleconaril

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**Summary** Chronic enteroviral meningoencephalitis, most commonly caused by echoviruses, can particularly be seen in agammaglobulinemic patients. In spite of the fact that no specific treatment for enteroviral infections exists, pleconaril is an antiviral drug reported to be efficient against enteroviral infections in infants and adults. We present a case of a 42-year-old male, previously diagnosed with common variable immunodeficiency, who presented with severe chronic meningoencephalitis caused by Echo virus 6 and was successfully treated with pleconaril. Enteroviruses usually cause mild symptoms, but some strains can cause life-threatening conditions especially in immunocompromised patients. Although pleconaril production is unprofitable due to the rarity of severe disease, our effective treatment should encourage further availability of pleconaril.

**Keywords** Enterovirus · Echoviruses · Meningoencephalitis · Pleconaril · CVID

### Introduction

Immunodeficient patients are known to have a high susceptibility for the development of severe enteroviral (EV) infections of the central nervous system (CNS). Chronic EV meningoencephalitis can particularly be seen in agammaglobulinemic patients. It is most commonly caused by echoviruses, although some other cases have also been reported [1–4]. Common variable immunodeficiency (CVID) is a type of primary immunodeficiency characterized by a large heterogeneity in clinical presentation. It is diagnosed by reduced serum levels of IgG, IgA levels with more than two standard deviations from the normal values and without the presence of any other known cause of hypogammaglobulinemia (e.g. X-linked agammaglobulinemia) [5, 6]. Apart from chronic meningoencephalitis, other EV diseases in patients with CVID have also been reported, such as a recurrent case of hand, foot and mouth disease [7]. In spite of possible fatal outcome, there is no specific treatment for EV infections; however, pleconaril is a drug with reported antienteroviral effects. Pleconaril binds to a hydrophobic pocket in the viral capsid inducing conformational changes, which lead to altered receptor binding and virus uncoating. Furthermore, it achieves several fold higher concentrations within the CNS than in serum, which is highly desirable for the drug targeted toward viruses known to cause CNS infections [8]. Concomitant treatment with pleconaril and intravenous immunoglobulin (IVIG) is reported to be successful in solid organs of adult recipients [9]. There is also a report of in vitro but not in vivo efficacy of IVIG and pleconaril therapy in infants [10]. Monotherapy with pleconaril is reported

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**Table 1** Laboratory results obtained during treatment

Method/date	Cerebrospinal fluid	Serum	Stool
PCR—2/9/2016	Positive	Positive	–
Viral culture—2/9/2016	Echo virus 6	Not done	Echo virus 6
PCR—2/19/2016	Positive for enteroviruses	Positive for enteroviruses	–
Viral culture—2/19/2016	Not done	Not done	Not done
<i>14 day pleconaril started on 2/9/2016</i>			
PCR—3/7/2016	Negative	Negative	–
Viral culture—3/7/2016	Negative	Not done	Negative
PCR—6/9/2016	Negative	Negative	–
Viral culture—6/9/2016	Negative	Not done	Negative

to be beneficial in infants with severe EV infections [3, 11]. In order to provide evidence for the efficiency of pleconaril treatment in EV meningitis and sepsis in infants, two double-blinded randomized studies have been conducted. The self-limiting and benign nature of EV meningitis was a limiting factor in one study and the other one proved significant virologic but not clinical efficiency of pleconaril treatment [12, 13]. Reports of pleconaril therapy for EV infections in adults are scarce; however, several variably successful pleconaril treatments in patients with EV meningoencephalitis and hypogammaglobulinemia have been reported [14, 15].

We present a case of a 42-year-old male with previously diagnosed CVID who presented with severe chronic meningoencephalitis caused by Echo virus 6 and was successfully treated with pleconaril.

### Patient and methods

A 42-year-old patient was admitted due to chronic meningoencephalitis. The patient had been diagnosed with CVID since 1994 and treated with IVIG monthly ever since. The current illness started 5 weeks prior to admission with fever, headache, gait instability and intermittent dysphasia. At admission the vital signs were normal with jaundice and general malaise. Work-up revealed low white blood cell and low platelet counts of 2.7 and 71, respectively. The bilirubin was 120 (70 conjugated), aspartat aminotransferase 531 IU/L, alanin aminotransferase 662 IU/L, cerebrospinal fluid (CSF) analysis yielded an increased cell count of 105/mm<sup>3</sup> with 82% mononuclear cells and increased protein content of 1.8 g/l. Etiology quest revealed that PCR was positive for enteroviral RNA and viral culture detected Echo virus 6. Furthermore, enteroviral RNA could be detected by PCR in blood but the PCR target sequence was a 5'-noncoding region common to all enteroviruses. The patient's IVIG treatment was intensified with a weekly administration of the usual dose (0.4 g per kg body weight for 5 consecutive days) without any effect and with persistent detection of enteroviral RNA in serum and CSF. Approximately 1 month after admission, we were able to attain ple-

conaril (courtesy of Prof. Jacob Westman from Solna, Sweden) and the patient was started on oral treatment (3 × 400 mg daily). The drug provided was in powder form and it had to be prepared before administration.

### Results

After 14 days of pleconaril treatment, enteroviral RNA was not detected in CSF or serum by PCR (Table 1).

Hospitalization of the patient was complicated by the development of severe nosocomial pneumonia and influenza B infections. Due to this unfortunate turn of events, he required mechanical ventilation and tracheostomy. Fortunately, the pneumonia resolved with treatment and we were able to wean him from the ventilator. After 5 months, just prior to discharge from hospital, CSF and serum were analyzed for the presence of enteroviruses and the results of PCR and cultures remained negative and the bilirubin and liver enzymes normalized. At discharge the patient had a Karnofsky performance scale index score of 70% and was able to walk with assistance.

### Discussion

Enteroviral infections are usually known as mild diseases; however, certain enteroviral strains are more pathogenic and capable of causing severe illness in previously healthy children and adults as well as inducing severe illness in susceptible individuals, especially those with impaired humoral immunity [16]. Despite the fact that some enteroviral strains are resistant to pleconaril, it is most unfortunate that this potentially effective treatment option is not widely available for patients with the severe forms of any enteroviral disease.

Enterovirus 71 (EV 71) could be a life-threatening infection in children. In several well-known epidemics, many of the affected children succumbed to the disease [16, 17]. One of known epidemics was an outbreak of enteroviral infections in children in Kansas City, Missouri in 2014. It was caused by enterovirus D68 and the majority of patients presented with respiratory distress and severe bronchospasms. Pleconaril was not used as a therapy option in those

epidemics due to suspected resistance [18]; however, due to the effectiveness *in vitro*, it seems prudent to try pleconaril in all patients with severe enteroviral infections.

Chronic enteroviral meningoencephalitis is a known entity in patients with CVID or Bruton's disease. Untreated disease is usually progressive and often leads to a fatal outcome [19]. According to the literature and our own experience, this subgroup of patients might benefit from pleconaril treatment and should not be deprived of the treatment trial as it can save their lives. Our patient responded well to pleconaril treatment and was able to clear the Echo virus 6 from the blood and CSF. Furthermore, clinical progression of the disease was terminated and his condition improved substantially. Nowadays, the rarity of severe enteroviral disease has rendered the commercial production of pleconaril unprofitable and the drug is therefore unavailable, despite the fact that it has the potential to save lives in specific subgroup of patients; however, due to successful treatment in our patient, we believe that the medical community should endorse and assert the production and availability of pleconaril despite the unprofitable nature of such action.

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**Conflict of interest** I. Radanović, D. Rkman, P. Zekan, M. Kutleša, and B. Baršić declare that they have no competing interests.

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