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Molecular and epidemiologic analysis of enterovirus B neurological infection in Argentine children

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Abstract

Background: Human enteroviruses are one of the major causes of central nervous system (CNS) infections in pediatrics.

Study design: We have studied 1242 children under 15 years old with suspicion of CNS infection from January 1998 to December 2003. CSF was obtained and molecular typing of human enterovirus B serotypes was performed by RT-PCR and sequencing of the N-terminal part of VP1 gene.

Results: According to the clinical syndromes, patients were grouped as aseptic meningitis ($n = 654$, 52.6%), encephalitis ($n = 239$, 19.2%), febrile seizures ($n = 153$, 12.3%), febrile infant ($n = 84$, 6.7%), neonatal disease ($n = 70$, 5.6%),), acute flaccid paralysis ($n = 31$, 2.4%) and acute disseminated encephalomyelitis ($n = 11$, 0.9%).

HEV was detected in 335/1242 CSF samples (26.97%) and was associated to aseptic meningitis ($n = 243$, 72.5%); febrile infant ($n = 31$, 9.2%); neonatal infection ($n = 26$, 7.7%); encephalitis ($n = 25$, 7.5%), febrile seizures ($n = 9$, 2.68%); acute flaccid paralysis ($n = 1$, 0.3%). Seasonal incidence of HEV-B species was analyzed showing that in Buenos Aires infections occur mainly during late spring and summer. Molecular serotyping was completed in 60/335 samples. Echovirus 30, Echovirus 9, Coxsackie B3 to B5 and Echovirus 33 were the most frequently identified.

Conclusions: We showed that HEV are responsible for a considerable proportion of hospitalizations in children with central nervous system compromise reaching 27% of overall etiology.

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Keywords: Aseptic meningitis; Molecular typing; Echovirus; Coxsackievirus

1. Introduction

Human enteroviruses (HEV) are ubiquitous, enterically transmitted agents that cause a wide spectrum of both common and uncommon illnesses among infants and children, varying from nonspecific viral syndromes with mild clinical symptoms to severe and even fatal diseases, such as neonatal sepsis, aseptic meningitis, encephalitis, myocarditis, or polio-like illness (Rotbart et al., 1994; Ahmed et al., 1997; Sawyer, 1999, 2001). The clinical presentation is strongly influenced by age. Among neonates and young children, clinical features can overlap those of systemic bacterial infection (Dagan, 1996; Verboon-Maciolek et al., 2003). The most common of the potentially severe enteroviral diseases is aseptic meningitis, reported to occur mainly in summer and autumn. Less commonly, enteroviral infections of the central nervous system can appear as encephalitis or acute flaccid paralysis (Trallero et al., 2000; Chang et al., 2004).

The HEV are small, single-stranded RNA viruses, belonging to the large genus *Enterovirus* within the Picornaviridae

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family. Based on molecular and biological properties they have been recently classified into five species: polioviruses (PV) including types 1, 2 and 3; HEV-A, including 11 Coxsackie A viruses (CAV) and EV 71; HEV-B, including all Coxsackie B viruses (CBV)s, all echoviruses, EV 69 and CAV9. HEV-C encompasses the other 11 CAVs; and HEV-D includes EV 68 to EV 70 (Hyypiä et al., 1997). HEV-B is the most clinically relevant species as well as the most frequently associated with aseptic meningitis and neonatal disease (Thoelen et al., 2003). Identification of serotype is essential for epidemiological surveillance, for the study of the association between subtypes and disease, and for the identification of new types. VP1 is the major surface protein in the mature picornavirus virion, bearing important serotype-specific neutralization epitopes (Mateu, 1995). Molecular serotyping by direct use of clinical specimens without cell culture can be applied for the rapid identification of the causative agent of an epidemic. Currently, laboratory diagnosis of enterovirus infections is based on amplification of the highly conserved 5′ noncoding region (5′NCR), followed by typing through amplification and sequencing of the VP1 capsid protein gene. Results are consistent with those of serum typing and have been successfully used to detect the most frequent enteroviruses (Thoelen et al., 2003, 2004; Caro et al., 2001; Casas et al., 2001; Oberste et al., 1999, 2000). The purpose of this study was to analyze the role of HEV and HEV B species as CNS pathogens with these methods applied to cerebrospinal fluid (CSF) samples from children hospitalized from 1998 to 2003 in Buenos Aires.

2. Material and methods

2.1. Patients and clinical samples

CSF samples were referred to the Virology Laboratory of the Ricardo Gutiérrez Children's Hospital from children under 15 years of age admitted to the neonatology and pediatric wards of Public Hospitals in Buenos Aires city and environs, based on clinical suspicion of enteroviral central nervous system infection.

An epidemiological record for each sample including clinical diagnosis and laboratory parameters was filed by the physician. Patients were grouped in the following clinical syndromes.

2.1.1. Aseptic meningitis

Acute onset of meningeal symptoms, fever, and CSF pleocytosis (>5 cells/mm^3).

2.1.2. Encephalitis

Depressed or altered level of consciousness lasting more than 24 h, lethargy, or change in personality, with one or more of the following symptoms: fever, seizures, CSF pleocytosis, with electroencephalography or focal neuroimaging abnormal findings indicating parenchymal involvement.

2.1.3. Febrile seizures

Convulsive events secondary to a rapid increase in body temperature occurring between 6 months and 2 years of age that consists of a rhythmic jerking of the extremities, eye rolling, unresponsiveness, sometimes cyanosis, followed by 30 min of drowsiness and confusion.

2.1.4. Neonatal enteroviral disease

Fever, irritability, poor feeding, emesis, or diarrhea, jaundice, seizures, or lethargy in children <30 days. Patients with diagnosis of non-HEV pathogen that can produce the constellation of presenting symptoms were excluded.

2.1.5. Febrile infant

As above, in children >30 days and <1 year old.

2.1.6. Acute disseminated encephalomyelitis (ADEM)

Brief but intense attack of inflammation in the brain and spinal cord with neurological symptoms related to myelin damage usually having a monophasic course. Encephalitis-like symptoms such as fever, fatigue, headache, nausea and vomiting, and in severe cases, seizures and coma can also be present. MRI imaging shows focal or multifocal neurologic dysfunction with perivascular inflammation and demyelination. Lessions are large and symmetric with basal ganglia and thalamic involvement.

2.1.7. Acute flaccid paralysis

Acute onset of flaccid paralysis in one or more limbs or acute onset of bulbar paralysis. Patients with neuropathies associated to other causes were excluded.

Other common viral neurological infections such as those caused by herpes simplex or varicella-zoster viruses or bacterial infections were discarded. The study period was January 1998–December 2003.

2.2. Reverse transcription PCR assay

Viral RNA was purified from 100 μl of CSF by the guanidine-isothiocyanate-phenol acid method (Chomczynski and Sacchi, 1987) and CSF aliquots were stored frozen at −20 °C. HEV diagnosis was performed by RT-nested PCR of a conserved 127-bp fragment of the 5′NTR region (Read and Kurtz, 1999). All positive samples were additionally tested before sequencing by a one-step RT-PCR (Qiagen) amplifying a 231-bp gene fragment in the second half of the 5′NTR with two 5′NCR-specific primers, E4KB-F and E1-R (Thoelen et al., 2003). Samples that were positive for both 5′PCR assays were considered an HEV-positive case. The analytical sensitivity of the assays was 0.1 $TCID_{50}$ for Read and Kurtz (1999) and 0.01 $TCID_{50}$ for Thoelen et al. (2003).

Cases were defined as sporadic when a unique case in a short period of time was reported or epidemic when numerous cases per epidemiological week were recorded. All the

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