

## Mini Review

## Extraintestinal Involvement of Rotavirus Infection in Children

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### Abstract

Rotaviruses (RVs), a member of Reoviridae family, are a major cause of severe diarrhea in children < 5 years of age worldwide, infecting mainly the gastrointestinal tract although recent findings have shown extraintestinal spread of RV infections. The RV is known to cause systemic infection in children with acute gastroenteritis (AGE). The systemic RV infection may lead to the virus reaching extraintestinal organs, therefore developing clinical symptoms. RV RNA, antigen, and infectious particles have been found in serum, cerebrospinal fluid (CSF) and extraintestinal tissues in children with AGE. According to previous studies on molecular genotyping of RV, no specific association has been yet found between antigenemia and RV G genotype. However, nucleotide changes and genotype discordance in RVs have been detected in paired stool and serum samples. In children, who show the evidence of antigenemia, RV genome is detectable in extraintestinal organs. Although, clinical significance of the laboratory findings remains to be determined.

**Keyword:** Antigenemia, extraintestinal sites, rotavirus, viremia

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### Introduction

Acute gastroenteritis (AGE), an important symptom of most enteric infections, is mostly frequent in children < 5 years of age. Several viruses are supposed to cause AGE, including rotaviruses (RVs), noroviruses (NoVs), sapoviruses (SaVs), enteric adenoviruses (EAdVs) serotypes 40 and 41, astroviruses (AstVs), human parechoviruses (HPeVs), Aichiviruses (AiVs), picobirnaviruses, as well as less frequently toroviruses (ToVs) and coronaviruses (CoVs).<sup>1-3</sup> Among these viruses, RVs are responsible for around 6% of AGE episodes and 20% of AGE related deaths among children in developing countries.<sup>4</sup> Moreover, RV-associated AGE represents a huge economic burden in developed countries.<sup>5</sup> Over the last 30 years there has been lots of efforts towards RV vaccine development. Rotashield™, (Wyeth Lederle Vaccines, Philadelphia, PA), was the first licensed RV vaccine, however it was withdrawn due to its epidemiological association with intussusceptions in vaccinated children.<sup>6,7</sup> More recently, RotaTeq™ and Rotarix™ were developed as live attenuated vaccines, and shown to protect efficiently against severe diarrhea.<sup>8-10</sup> Among candidate vaccines, replication-defective RV vaccines such as virus-like particle (VLP)-based constructs or inactivated virus particles have offered promising results.<sup>11-15</sup>

RVs initially infect the mature and differentiated enterocytes of the small intestine, although some reports indicated that RVs are able to spread beyond the gastrointestinal tract and become systemic. According to the available data, there are increasing reports about extraintestinal manifestations of RV infection.<sup>16-18</sup> This

study aimed to review the articles that studied RV antigen or RNA detection in serum, CSF, and other extraintestinal sites in children < 5 years of age. To identify relevant articles, we searched the MEDLINE and PubMed databases, as well as references from relevant articles. We applied several searches using the following keywords: RV gastroenteritis, RV antigenemia, RV viremia, RV RNA detection, RV and CSF, RV and encephalitis, RV and encephalopathy, RV and convulsions, RV and seizures.

#### RV and extraintestinal infections

Detection of RV antigen was initially reported in serum of three immunodeficient patients with chronic RV infection.<sup>19</sup> Indeed, the presence of RV antigen and/or RNA in sera of immunocompetent children with RV infection first documented by Blutt, et al.<sup>20</sup> To support these findings, studies carried out on experimental animal models and demonstrated the infectious RV at extraintestinal sites.<sup>21,22</sup> The mean frequency of RV antigen and RNA in serum of patients with RV-associated AGE was reported to be around 63.2% (range, 33.3% – 90%) and 74.7% (range, 64.3% – 93%), respectively.<sup>20,23-31</sup> However, in a study conducted on serum, RNA was only detected in 5% of the cases.<sup>31</sup> In this regard, variations in disease duration prior to sample collection, diversity of study populations, and differences in the sensitivity of methods may be behind the observed discrepancies.

The detection rate and concentrations of RV antigen in serum are shown to be significantly higher in the acute phase than the convalescent phase.<sup>24</sup> The presence of RV antigen and RNA in serum has been associated with high fever, although no significant difference was found with regard to seizures and convulsions.<sup>32</sup> Furthermore, passaging of the sera taken from children with RV antigenemia in cell culture has confirmed the presence of infectious RV particles.<sup>27</sup>

Closer investigation of RV genotypes in paired stool and PBMC/serum samples indicated the nucleotide changes and the genotype discordance, although no specific association has been reported between RV G type with antigenemia.<sup>23</sup> These findings led to the

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speculation that RV replication may occur in extraintestinal sites perhaps due to variations in tissue tropism. Detection of RV antigen and/or RNA from different sites including CSF, heart, testes, kidneys, lung, liver, and bladder<sup>33</sup> suggests that a systemic RV infection may allow the virus to escape from the gastrointestinal tract and access the extraintestinal sites. However, rather than extra intestinal virus spread, other factors are required to cause severe disease.

In association with RV infections, several neurological complications have been reported, including acute encephalitis or encephalopathy, convulsions, and seizures. In this regard, the frequency of neurological manifestations of patients with RV gastroenteritis was reported to be approximately 2% – 6%. In addition, the detection of RV in CSF of patients with neurological manifestations has been reported by several case reports.<sup>34</sup> However, analyzing the sequences of RV genes no significant changes have been observed between samples taken from CSF and stools.<sup>23</sup> Although any causal relationship between RV and CNS disorders remains unclear, the frequency of CNS complications in patients with RV gastroenteritis is substantial.

In summary, although considered as an enteric virus, the mysterious role of RV infection in extra intestinal sites, and the global imprint that RV infection can have on tissue tropism and clinical complications in children with AGE yet to be examined.

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