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Systemic features of rotavirus infection

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Summary A growing body of evidence warrants a revision of the received/conventional wisdom of rotavirus infection as synonymous with acute gastroenteritis. Rotavirus vaccines have boosted our interest and knowledge of this virus, but also importantly, they may have changed the landscape of the disease. Extraintestinal spread of rotavirus is well documented, and the clinical spectrum of the disease is widening. Furthermore, the positive impact of current rotavirus vaccines in reducing seizure hospitalization rates should prompt a reassessment of the actual burden of extraintestinal manifestations of rotavirus diseases. This article discusses current knowledge of the systemic extraintestinal manifestations of rotavirus infection and their underlying mechanisms, and aims to pave the way for future clinical, public health and research questions.

Introduction

Rotavirus vaccines have significantly changed the landscape of rotavirus infection: a) directly, through impact on the disease itself; and b) indirectly, by boosting our knowledge on the disease, as it is usually the case with infectious diseases once a vaccine becomes available. The driving force that has fostered rotavirus vaccine development and implementation is obvious: every 50 s, one child under 5 years of age dies of rotavirus infection[1—3] even after vaccine implementation in selected countries. However, if we consider everything we have learned in the last decade, common perceptions of rotavirus diseases might seem too narrow. The available rotavirus vaccines have shown an outstanding effectiveness and impact against rotavirus gastroenteritis.[4,5] In those countries where rotavirus vaccines are part of the national immunization program, not only a dramatic decrease in the number of cases has been achieved, but the threshold to declare the annual epidemics has no longer been reached.[1,5] Even with moderate coverage, marked reductions in both rotavirus and all-cause acute gastroenteritis hospital admissions have been reported.[5—7] Unexpectedly, we have observed that rotavirus vaccines may also reduce the risk of seizures in

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vaccinated children as well as the rate of childhood hospitalization due to any kind of seizures.[8,9] This positive but also unexpected finding raises questions about the mechanisms behind this effect and warrants a reassessment of the rotavirus infection beyond the gastrointestinal tract. As a matter of fact, we may be witnessing a "Rotavolution", i.e., a revolution in the very concept and clinical perception of rotavirus infection.

This "Rotavolution" has widened the scope of our interest in this infection, as new practical questions may arise: Might we be missing rotavirus cases because we do not clinically suspect the infection? Should we think about rotavirus infection in children without diarrhea? How do rotavirus vaccines affect the non-diarrheal clinical spectrum of rotavirus disease? Should we expect any role for rotavirus vaccines beyond the scenario of acute gastroenteritis? The present article aims to improve our understanding of this expanded view of rotavirus infection, to provide an updated rationale for these questions, and to pave the way for further studies of the "Rotavolution".

Extraintestinal clinical spectrum of rotavirus infection

Rotavirus is a major diarrheal pathogen in humans and animals. The classic understanding of rotavirus infection considers the gastrointestinal tract as the niche where the infection is confined.[10,11] Increasing evidence indicates that rotavirus infection is systemic and the involvement of rotavirus reaches beyond the intestinal lumen. Several systemic manifestations have been reported related to rotavirus infection in children with or without diarrhea.[12–36] Furthermore, the role of rotavirus infection as a trigger of autoimmune disease in susceptible subjects has been also described.[37–40] The main non-intestinal manifestations of rotavirus infection described in the literature are summarized in Table 1. The precise burden of each of these extraintestinal clinical syndromes is relatively unknown, particularly for those cases without accompanying diarrhea, or occurring out of the typical age ranges expected for rotavirus infection.

Acute extraintestinal manifestations

There is an increasing body of evidence supporting the role of rotavirus infection as the cause or trigger of clinical neurological illness, however it is difficult to estimate the actual proportion of seizure cases that are explained by this entity.[15,22,32,41] Rotavirus is usually underestimated as a pathogen in children without diarrhea and it does not constitute part of the routine diagnostic work-up of children with seizures.[42] Seizures constitute the most frequent extraintestinal manifestation of rotavirus infection. Particularly, benign seizures following gastroenteritis are the most common extraintestinal and neurologic symptom of rotavirus infection reported in the literature, occurring in 4–8% of patients infected with rotavirus.[8,9,22,34,43] These seizures triggered by rotavirus are usually characterized by clusters of brief focal seizures over 24–48 h, have a good prognosis and have no associated alterations in the neuroimaging exams.[32] No specific antiepileptic therapy is necessary and thus prompt recognition can avoid unnecessary therapies.

Rotavirus (RV) might act as a trigger in susceptible children or get directly involved in the pathogenesis of the convulsions.[8–10,15,22,35,36,41,44,45] Several mechanisms have been suggested to explain the relationship between rotavirus infection and seizures, from direct neurotoxicity to specific neurotransmitter interferences at calcium channel level.[46,47] The theory of direct action rather than an antibody-mediated process is supported by some researchers, given the lack of delayed response evident for example in acute disseminated encephalomyelitis.[48] In this regard, the viral nonstructural protein 4 — NSP4 — was demonstrated to act as an enterotoxin that may induce an inflammatory response, either as a free toxin or as part of the viral particle.[48] At the same time, it has also been suggested that elevation of nitric oxide metabolites during rotavirus infection might be the neurotoxic mechanism.[46] In some patients, the inflammatory cytokine interleukin-6 was associated with nitric oxide levels.[46] Nevertheless, the presence of RV nucleic acid has been demonstrated in cerebrospinal fluid in previously reported cases of acute cerebellitis in children.[44,48–50] Kobayashi et al. reported two cases, one of them with viral RNA detected in cerebrospinal fluid, which also demonstrated cerebellar foci on diffusion-weighted magnetic resonance imaging and residual cerebellar atrophy.[49] Both patients exhibited ataxia and expressive dysphasia or mutism, with neurological sequelae that persisted up to several months after the acute illness.[49] Other reports have presented suspected cases with cerebellar signs, although viral RNA could not be isolated from the cerebrospinal fluid.[20,30] Alternatively, the changes in blood-brain barrier permeability of children during seizures might explain the presence of rotavirus in the cerebrospinal fluid without being the actual trigger of those convulsions. In any case, most reported seizures related to rotavirus infection correspond to afebrile children with diarrheal disease, without (or with only minor) electrolyte or metabolic disturbances, and with a benign and self-limited course.

Other acute extraintestinal symptoms listed in Table 1 are mainly based on isolated clinical reports or case series. It is therefore even more difficult to try to ascertain the concrete burden of pancreatitis, acute hemorrhagic infantile edema, or acute encephalopathy, among others. However, we should bear in mind that it is not uncommon for rotavirus to provoke serious complications different from diarrhea related dehydration, and even long-term morbidity.

Autoimmune diseases that might be triggered by rotavirus

Celiac disease, an autoimmune disorder of the small intestine triggered by environmental factors in genetically predisposed individuals, has been related with rotavirus infection. In particular, it has been suggested that rotavirus is involved in the pathogenesis of celiac diseases by means of a mechanism of molecular mimicry.[51] It has been shown that rotavirus VP7 can be recognized by certain anti-transglutaminase IgA antibodies, and that the presence of anti-rotavirus VP7 antibodies may precede the detection