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BRIEF REPORT

Persistent infection with a rotavirus vaccine strain in a child suffering from Severe Combined Immunodeficiency in Argentina

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Abstract Due to the high burden of disease associated with rotavirus, the massive vaccination in children before six months of age has been encouraged. Currently licensed oral live vaccines have shown low risk of associated adverse events in the general population. Noteworthy, post-marketing reports of severe gastroenteritis with persistent vaccine viral shedding in children with severe combined immunodeficiency (SCID) have led companies to include this inborn error of immunity as an additional contraindication. SCID is not usually screened in newborns from developing countries. Therefore, the administration of live attenuated vaccines represents the first contact of these patients with life-threatening pathogens. We describe a clinical case of an infant with SCID who suffered from persistent rotavirus symptomatic diarrhea after receiving the rotavirus oral vaccine and was found to be infected with the vaccine strain. This case attempts to contribute to the discussion of those diseases that need to be incorporated into a screening program since an early diagnosis permits clinicians to withhold live attenuated immunization.

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Infección persistente por cepa vacunal de rotavirus en un niño con inmunodeficiencia combinada severa en Argentina

Resumen Debido a la elevada carga de enfermedad asociada con rotavirus, se ha aconsejado incorporar la vacunación masiva en los menores de seis meses. Las vacunas vivas orales que se encuentran actualmente licenciadas han mostrado un bajo riesgo de eventos adversos en la población general. Sin embargo, algunos años después del comienzo de su comercialización, la publicación de reportes de gastroenteritis grave con excreción viral persistente de la cepa vacunal en niños con inmunodeficiencia combinada severa (IDCS) llevaron a las compañías productoras de estas vacunas a sumar esta alteración congénita de la inmunidad a la lista de contraindicaciones. La IDSC generalmente no se tamiza en los recién nacidos de países en desarrollo. Por lo tanto, la administración de vacunas vivas atenuadas representa el primer contacto de estos pacientes con agentes patógenos potencialmente mortales. Describimos el caso de un niño con IDSC que presentó diarrea sintomática persistente por rotavirus luego de recibir la vacuna oral y que estaba infectado con la cepa vacunal. Este caso intenta contribuir a la discusión de aquellas enfermedades que deberían incorporarse a un programa de tamizaje debido a que su diagnóstico temprano permite a los médicos evitar la inmunización con virus vivos atenuados.

Rotavirus represents one of the leading causes of acute diarrhea in children worldwide[6]. Because of the high burden of disease associated with this virus, the World Health Organization (WHO) recommends all countries to introduce rotavirus vaccines into their national childhood immunization programs as a part of a comprehensive strategy to control diarrheal diseases among other interventions as improvements in hygiene and sanitation, and overall improvements in case management[18]. Since 2006, two licensed live oral vaccines are available worldwide: monovalent GSK Rotarix™ (RV1, live attenuated G1P[8] strain) and pentavalent Merck RotaTeq™ (RV5, live oral attenuated, G1-4 and P[8] human components in a bovine genetic backbone) and both have demonstrated to be broadly effective and safe[14,17]. In Argentina, the monovalent vaccine has been included for massive administration since 2015 after an extensive cost-effectiveness analysis and its first impact study has shown evidence of successful results[5,16].

As in other live attenuated oral vaccines (e.g. polio, OPV), vaccine virus shedding in feces occurs after administration and can last for several weeks depending on the doses received and the infants' clinical aspects[4]. Rotavirus vaccines have shown low risk of associated adverse events not only in the general population but also in hospitalized, preterm and HIV-infected or HIV-exposed infants[4]. Conversely, their administration is contraindicated in children with previous allergic reactions to them or any of their ingredients, severe infections with high temperature, diarrhea or vomiting, a previous intussusception event or birth defects of the gastrointestinal system. Noteworthy, between 2009 and 2010, due to postmarketing reports of severe gastroenteritis with persistent vaccine viral shedding in children suffering from severe combined immunodeficiency, both companies later included this disease as an additional contraindication in their product information[3].

Severe combined immunodeficiency (SCID) is a group of inborn errors of immunity (IEIs) that affects cellular and humoral immunity and is defined by T-cell lymphopenia (CD3+ T cells less than 300/μl)[1]. Its global incidence remains unknown but in the United States has been estimated in 1 of 50 000 to 100 000 live births with fatal prognosis due to severe recurring infections and failure to thrive if no hematopoietic cell transplantation is conducted within the first year of life[12]. As an early diagnosis is unusual when there is no family history of immunodeficiency, the first contact of SCID patients with life-threatening pathogens is set because of the administration of live attenuated vaccines, such as BCG, OPV and rotavirus[9]. We describe a case of an infant with SCID who suffered from persistent rotavirus symptomatic diarrhea after receiving the oral vaccine and was found to be infected with a rotavirus vaccine strain.

A pre-term (36 weeks) 5 month-old male infant was admitted to a referential children's hospital due to acute diarrhea, oral intolerance, bronchiolitis, oral thrush and failure to thrive. He presented no complications at birth after an uneventful pregnancy. He had received BCG and the first dose of hepatitis B vaccine at birth, and completed polio, pneumococcal, rotavirus, *Haemophilus influenzae* type b (Hib), and diphtheria, tetanus and pertussis (DTP) schemes (first doses at 2 months of age and second doses at 4.5 months of age). Blood, urine, cerebral-spine fluid (CSF), stool, and nasopharyngeal and gastric aspirate samples were drawn for biochemical and culture studies.

Considering his faltering growth, persistent thrush and a white cell count of 4100/mm^3 (lymphocytes count 984/mm^3, 24%), further immunological tests were conducted. Nearly undetected levels of IgG were found (1.38 mg/dl; range: 650–1600 mg/dl), IgA (0.16 mg/dl; range: 40–350 mg/dl) and IgM (0.88 mg/dl; range: 54–300 mg/dl). Furthermore, the analysis of lymphocytic populations showed 98.6% of

CD19, 1.0% of CD56 and 0.1% of CD3. There was no pathogen recovery from any of the blood, urine, nasopharyngeal aspirate and CSF samples. However, rotavirus was detected by ELISA in the initial stool sample (day +1) and symptomatic diarrhea did not end up after 7 days as expected. Subsequent samples (from days +10, +24, +35 and +50) were also positive for rotavirus. Thus, blood, CSF and stool samples were sent to the National Reference Laboratory of Rotavirus and Norovirus for further studies. Amplification and sequencing of VP7, VP4 and NSP4 genes from the stool sample revealed a G1P[8] strain with high identity at nucleotide level (>99.5%) with the Rotarix™ vaccine strain. No detection of the rotavirus genome was found in blood or CSF samples. On the other hand, acid-fast bacilli were found in the gastric aspirate which led to the diagnosis of BCGitis with meningeal compromise and antimycobacterial drugs were administered.

Final diagnosis of x-linked severe combined immune deficiency (x-SCID) was assessed by confirmation of the presence of the c.63_66delG (p.Gly22fsX2) mutation in the exon 1 of *IL2RG* gene (heterozygous mutation carrier mother). Thus, a haploidentical hematopoietic cell transplant could be performed once the rotavirus infection cleared (day +72, at 7.5 months of age). Despite the transplant, the patient died 2 months later without immune reconstitution and with evidence of disseminated BCG infection.

To our very best knowledge, this is the first report of a chronic diarrhea case with a rotavirus vaccine strain in an infant suffering from severe combined immunodeficiency in Argentina. Although rotavirus vaccines have been clearly contraindicated for over a decade in children with this particular IEI, this case highlights the need for improvements in earlier diagnosis to permit clinicians to withhold live attenuated immunization. In most countries, newborns are only screened for metabolic and endocrine disorders to rapidly allow to know what kind of nutrition has to be avoided or to implement an early treatment to reduce potential permanent damages. However, primary immune deficiencies are yet still far from being widely screened considering that administration of live attenuated vaccines, such as BCG, OPV and rotavirus occurs within the first weeks of birth and represents the first contact of life-threating pathogens causing severe infections in patients with IEIs. Since SCID is the most severe IEI, several developed countries have already included its screening, using dried blood spot specimens of the newborns' heel, by detecting T-cell receptor excision circles (TRECs)[2]. As TRECs are present when T-cells are being produced, infants with few or no T-cells have low levels or absence of them. Nonetheless, a complete blood count with lymphocytic populations' analysis by flow-cytometry is further needed for confirmatory purposes[7].

In general, the assessment of SCID diagnosis is set after a severe infection with chronic diarrhea and failure to thrive has already occurred. This delay limits the possibilities of an early and proper treatment and impacts directly on the child prognosis. Thus, until SCID could be included in the newborn screening core panel it is important to reflect on some alternative and feasible strategies for the early detection of this IEI before immunization with live attenuated vaccines in infants with no family backgrounds of genetical disorders.

Oral rotavirus vaccines have been broadly described to be safe and effective in the general population. However, in some particular settings (low and middle-low income countries) its effectiveness is far from expected[15]. Therefore, efforts are made to analyze if parenteral immunization with an inactivated rotavirus vaccine will show overcoming results[8,13]. Considering that adaptive immunity plays a central role in this disorder, only SCID has been associated with persistent symptomatic infection in rotavirus-vaccinated children, mostly after the second or third dose administration[10,11]. Thus, the future administration of these inactivated vaccines currently in development will represent a valuable tool not only for those children living in areas with documented lower effectiveness but also for children with immunodeficiencies, since even if the response could be suboptimal or even null for them, at least will not represent a threat in terms of severe infection development.

This case attempts to contribute to the discussion of those pathologies that need to be incorporated into a screening program. All things considered, better newborn screening approaches and alternative strategies replacing immunization with live attenuated vaccines are needed for infants with SCID and other immunity disorders to prevent severe infections and to provide prompt treatment so they can achieve healthier lives.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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