

DR SEBASTIAN VOIGT (Orcid ID : 0000-0003-1544-9903)

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Life-threatening systemic rotavirus infection after vaccination in Severe Combined Immunodeficiency (SCID)

Leonard Rosenfeld, MD¹, Andreas Mas Marques, PhD², Sandra Niendorf, PhD², Jörg Hofmann, PhD^{3,4},
Alexander Gratopp, MD¹, Jörn-Sven Kühl, MD⁵, Johannes H. Schulte, MD⁵, Horst von Bernuth, MD, PhD^{1,6,7,8}
and Sebastian Voigt, MD^{5,9}

Author Affiliations:

¹Department of Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin, Germany

²Unit for Gastroenteritis and Hepatitis Pathogens and Enteroviruses, Robert Koch Institute, Berlin, Germany

³Institute of Medical Virology, Helmut-Ruska-Haus, Charité-Universitätsmedizin Berlin, Germany

⁴Department of Virology, Labor Berlin Charité-Vivantes GmbH, Germany

⁵Department of Pediatric Oncology/Hematology/Stem Cell Transplantation, Charité-Universitätsmedizin Berlin, Germany

⁶Department of Immunology, Labor Berlin Charité-Vivantes GmbH, Berlin, Germany

⁷Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany

⁸Center for Chronically Sick Children, Charité-Universitätsmedizin, Berlin, Germany

⁹Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany

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Contact information:

Sebastian Voigt, MD

Department of Infectious Diseases, Robert Koch Institute, Seestr. 10, 13353 Berlin, Germany

Tel. +49 30 18 754 2271

Fax +49 30 18 10 754 2271

Email: sebastian.voigt@charite.de

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To the Editor:

Rotavirus (RV) infections are the major cause of severe gastroenteritis in children under five years of age, causing 215,000 deaths per year worldwide mainly due to dehydration in countries with weak economic resources (1). In the immunocompetent host RV infections are self-limiting and mortality is low in high-income countries. Notifications of RV cases have declined from 49,000 in season 2012/2013 to 25,000 in season

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2015/2016 (2) since RV vaccination has been recommended by the Standing Committee on Vaccination (STIKO) in Germany in 2013. The recommendation was based on systematic reviews and meta-analyses of studies showing efficacy and safety of RV vaccination (3). Live vaccines are generally contraindicated in immunodeficiency and RV vaccination is specifically contraindicated in severe combined immunodeficiency (SCID) due to potentially severe sustained RV infections caused by vaccine strains (4, 5). To date, newborn screening for immune deficiencies has not been implemented in Germany and many other countries. Hence, the recommendation to vaccinate young infants against RV puts non-diagnosed patients with SCID at increased risk of developing untreatable diarrhea if not fatal infection.

An 8 ½ month-old-boy born to non-consanguineous parents had been vaccinated twice with Rotarix® (RV1; GlaxoSmithKline) according to national guidelines at the age of three and four months. His body weight as well as his body length had been stagnant since the age of five months and he was transferred to our hospital for diagnostic workup for failure to thrive. Shortly after admission, he developed pneumonia with progressive respiratory failure and was transferred to the intensive care unit for mechanical ventilation. Molecular analyses of tracheal specimens revealed bocavirus and rhinovirus infection (Figure 1). With persistent impaired oxygenation a trial of iNO was started that had to be extended by high frequency oscillation ventilation. Respiratory support lasted for 30 days altogether. Stool specimens taken to investigate ongoing diarrhea were positive for RV RNA and later also for norovirus RNA. These multiple viral infections prompted immunodeficiency diagnostics that revealed a T⁺B⁺NK⁻ SCID phenotype and a mutation in the common gamma chain of the interleukin IL-2-receptor gene (X-linked *IL2RG* mutation; exon 3: hemizygous c343T>G pCys115). Therefore, the patient underwent allogeneic hematopoietic stem cell transplantation (HSCT) without conditioning as fast as possible (Figure 1).

RV genome was detected at high amounts in stool samples for several weeks. Genome concentrations were fluctuating between 8.2×10^3 and 1.7×10^{11} genome equivalents per ml (GE/ml) stool suspension until day 118 after HSCT (median 1.1×10^9 GE/ml). In this period, several serum samples and white blood cells also contained RV genomes with peak values of 4.6×10^5 GE/ml serum and 5.8×10^2 GE/ml blood, respectively. By sequencing and phylogenetic analysis (Figure 2), the RV strain from the patient proved to be a RV1 vaccine-related strain

the patient was inoculated with according to national guidelines, thus confirming systemic RV infection in a SCID patient after vaccination. Six months after HSCT, RV RNA concentration in stool samples decreased and virus shedding ceased. The overall decline of RV genome in stool samples correlated with progressive reconstitution of the immune system (Figure 1).

Post transplantation, the boy developed severe brain atrophy with hypophyseal insufficiency including secondary Addison's disease as well as cholestatic hepatopathy with gamma-glutamyltransferase values up to 8,000 U/l and bilirubin values up to 6 mg/dl. Liver biopsy revealed intrahepatic bile duct destruction and papillary stenosis not typical of graft-versus-host disease. Instead, both extensive brain damage and hepatopathy may suggest prolonged hypoxia associated with initial respiratory failure. After multiple endoscopies with intermittent placement of bile duct stents, cholestasis partly resolved and the boy was discharged on day +141 after HSCT.

Few chronic RV infections with vaccine strains have been described in children with SCID after vaccination with live virus (4, 6-8). Vaccine-acquired RV infections have been associated with the Rota-Teq® vaccine (6, 8-10) and with RV1 in children with previously undiagnosed SCID (4, 11). RV viremia was reported in natural RV infection and may be associated with increased disease severity (12). In natural infection, antigenemia and RNAemia appear to be particularly common in genotype G1P[8] infection (12). To date, most reported patients with infections after RV vaccination presented shortly after vaccination with gastrointestinal symptoms between 3 and 5 months of age (4, 6, 8, 11). Although frequently observed in SCID patients, successful clearance of RV infection after HSCT is rarely published (13). Klinkenberg et al. reported a patient with *IL2RG* defect and persistent RV shedding in stool presenting at the age of 21 months (5); this patient died due to his compromised clinical status. Our SCID patient with the same genetic defect was similarly sick as highlighted by detailed data on RV1 shedding and duration of viremia after HSCT. However, as liver fibrosis progresses, the boy is likely to experience organ failure.

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It is indisputable that RV vaccinations are useful and prevent healthy infants and young children from complications caused by RV infection. Even in cases of undetected SCID, RV vaccination rarely causes severe systemic infections. However, our case clearly demonstrates that RV vaccination in SCID children can be disastrous. Therefore, the growing number of reported cases with fatal or near-fatal RV infections after vaccination strongly argues for SCID newborn screenings using, e.g., assays detecting levels of T-cell recombination excision circles (TREC) and kappa-deleting element recombination circle (KREC). These screenings for SCID might be extended to all infants with lymphopenia.

Leonard Rosenfeld, MD^a

Andreas Mas Marques, PhD^b

Sandra Niendorf, PhD^b

Jörg Hofmann, PhD^{c,d}

Alexander Gratopp, MD^a

Jörn-Sven Kühl, MD^e

Johannes H. Schulte, MD^e

Horst von Bernuth, MD, PhD^{a,f,g,h}

Sebastian Voigt, MD^{e,i}

From ^athe Department of Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin; ^bthe Unit for Gastroenteritis and Hepatitis Pathogens and Enteroviruses, Robert Koch Institute; ^cthe Institute of Medical Virology, Helmut-Ruska-Haus, Charité-Universitätsmedizin Berlin; ^dthe Department of Virology, Labor Berlin Charité-Vivantes GmbH; ^ethe Department of Pediatric Oncology/Hematology/Stem Cell Transplantation, Charité-Universitätsmedizin Berlin; ^fthe Department of Immunology, Labor Berlin Charité-Vivantes GmbH; ^gthe Berlin-Brandenburg Center for Regenerative Therapies; ^hthe Center for Chronically Sick Children, Charité-

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Universitätsmedizin Berlin; and the Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany.

E-Mail: sebastian.voigt@charite.de.

Abbreviations

B: B-lymphocyte; HSCT: Hematopoietic stem cell transplantation; IL2R: Interleukin 2 receptor; iNO: inhaled nitric oxide; NK: Natural killer cell; RV: Rotavirus; SCID: Severe combined immunodeficiency; T: T-lymphocyte

Disclosure of potential conflict of interest

The authors declare that they have no conflict of interest.

Legends to figures

Figure 1. Time course of virus detection, diarrhea, respiratory support and lymphocyte reconstitution. Bars denote length of respiratory support as well as duration of diarrhea. Rotavirus antigen was detected in stool samples by enzyme-immunoassay. Rhinovirus and bocavirus genomes were detected in nasal swab samples by PCR. Stool samples became positive for norovirus RNA on day 103 after transplantation. **Top graph:** CD3⁺ cell counts are shown as open rhombs, CD8⁺ as triangles, and CD4⁺ as reverse triangles. **Bottom graph:** RV genome concentrations are displayed as filled circles (stool, GE per ml stool suspension), triangles (serum, GE per ml serum), and squares (leukocytes, GE per ml blood). RV RNA extracted from stool suspension (10% stool in PBS), serum and leukocytes was quantified by reverse-transcription real-time PCR. MS2 RNA phage was used as an internal control.

Figure 2. Phylogenetic tree of the complete coding sequence of VP7. Neighbour-joining tree using the Kimura-2 parameter method with 500 replicates (scale bar: nucleotide substitutions per site). Sequences from patient samples are marked with a triangle. Sequences from samples collected from 9 days before HSCT to 104 days after HSCT have 99.5% identity with the reference sequence of the vaccine strain due to point mutations and single nucleotide polymorphisms.

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