Chronic norovirus infection in primary immune deficiency disorders: an international case series

M.C. Rolfsa, P. Sriaroonb, B.J. Dávila Saldaña c, C.C. Dvorak d, H. Chapdelaine e, R.M. Ferdman f, K. Chen g, S. Jolles h, N.C. Patel l, Y.J. Kim i, T.K. Tarrant b, T Martelius l, M. Seppanen l,m, A.Y. Joshi a,n,*

* Mayo Clinic School of Medicine, Rochester, MN
b USF/All Children’s Hospital Allergy/Immunology, St. Petersburg, FL
c Division of Blood and Marrow Transplantation, Children's National Health System, Washington, DC
d Division of Pediatric Allergy, Immunology, and Bone Marrow Transplantation, University of California, San Francisco, CA
Division of Allergy and Immunology, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada
f Division of Clinical Immunology and Allergy, Children’s Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA
Department of Pediatrics, Division of Allergy and Immunology, University of Utah School of Medicine, Salt Lake City, UT
m Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK
l Division of Pediatric Infectious Disease and Immunodeficiency, Levine Children's Hospital, Carolinas Medical Center, Charlotte, NC
 Division of Infectious Diseases and Immunodeficiency, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
 Division of Rheumatology and Immunology, Department of Medicine, Duke University, Durham, NC
i Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
l Rare Disease Center, Children’s Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
Division of Pediatric Allergy and Immunology, Department of Pediatric and Adolescent Medicine, Mayo Clinic Children’s Center, Rochester, MN

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A B S T R A C T

Objective: Predictive factors associated with clinical outcomes of chronic norovirus infection (CNI) in primary immunodeficiency diseases (PIDD) are lacking.

Method: We sought to characterize CNI using a multi-institutional cohort of patients with PIDD and CNI using the Clinical Immunology Society’s CIS-PIDD Listserv e-mail group.

Results: Thirty-four subjects (21 males and 13 females) were reported from centers across North America, Europe, and Asia. All subjects were receiving high doses (median IgG dose: 1200 mg/kg/month) of supplemental immunoglobulin therapy. Fifty-three percent had a complete absence of B cells (median B-cell count 0; range 0–139 cells/μL). Common Variable Immune Deficiency (CVID) subjects manifested a unique phenotype with B-cell lymphopenia, non O+ blood type, and villous atrophy (logistic regression model, P = 0.01). Five subjects died, all of whom had no evidence of villous atrophy.

Conclusion: While Norovirus (NoV) is thought to replicate in B cells, in this PIDD cohort of CNI, B-cell lymphopenia was common, indicating that the presence of B lymphocytes is not essential for CNI.

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1. Introduction

Norovirus (NoV) has recently emerged as the most common etiology of acute gastroenteritis in the United States. NoV infections are estimated to cause 19–21 million episodes of gastroenteritis and nearly 400,000 ED visits annually, leading to significant societal and economic burden (Hall et al., 2013). With the introduction of the rotavirus vaccine in 2006, NoV has become the leading cause of acute gastroenteritis in US children (Payne et al., 2013) and has emerged as a leading pathogen of gastroenteritis worldwide, with a global prevalence of nearly 20% in children with acute gastroenteritis (Ahmed et al., 2014). The virus is transmitted via the fecal–oral route, often through person-to-person contact or through contaminated food/water, and is highly infectious as few viral particles are capable of causing disease (Robilotti et al., 2015; Teunis et al., 2008). NoV infections in healthy individuals typically present with vomiting and abdominal cramps, followed by watery diarrhea for an average duration of 2 to 3 days (Glass et al., 2009), with median duration of viral shedding after experimental human infection of 28 days (range: 13–56 days).

While NoV infections are typically self-limiting in immunocompetent hosts, NoV is an emerging cause of chronic and life-threatening
gastroenteritis among vulnerable patient populations, especially in children, the elderly, and immunocompromised hosts (Glass et al., 2009). In particular, NoV has been shown to be one of the most common causes of chronic diarrhea in solid organ transplant patients (Angarone et al., 2016), especially in patients who undergo lung (Blando et al., 2010; Chagla et al., 2013; Gairard-Dory et al., 2014), kidney (Roos-Weil et al., 2011; Schorn et al., 2010; Westhoff et al., 2009), pancreas (Echenique et al., 2016), or heart transplants (Nilsson et al., 2003). Additional literature has shown chronic NoV infections to be prevalent in pediatric oncology patients (Ludwig et al., 2008; Munir et al., 2014; Simon et al., n.d.) and patients who have had chemotherapy or hematopoietic stem cell transplants (Robles et al., 2012; Roddie et al., 2009; Schwartz et al., 2011). The inability of immunocompromised hosts to adequately clear the virus leads to prolonged viral shedding that can result in months to years of persistent diarrhea, malabsorption, and weight loss (Green, 2014). Treatment of a persistent NoV infection has proven challenging in this subset of patients, contributing to prolonged hospital stay, chronic debilitation, and, in severe cases, mortality (Schwartz et al., 2011).

Despite increasing trends of NoV infections in immunocompromised patients, research investigating NoV infections in patients with immune deficiency, dysregulation, and increased risk for infections due to primary immunodeficiency disorders (PIDDs) is limited (Oksenhendler et al., 2008). In addition to sinopulmonary infections, many subsets of PIDD patients are particularly susceptible to gastrointestinal infections like Giardia lamblia, Cryptosporidium, Helicobacter pylori, cytomegalovirus, and Salmonella (Agarwal and Mayer, 2013; Daniels et al., 2014; Simon et al., n.d.) and patients who have had chemotherapy or hematopoietic stem cell transplants (Robles et al., 2012; Roddie et al., 2009; Schwartz et al., 2011). Several previous cohort studies have demonstrated NoV infection as the cause of prolonged gastroenteropathies in hospitalized children (Brown et al., 2016; Frange et al., 2012; Xerry et al., 2010) and in adults (Duraiasingham et al., 2015; Woodward et al., 2015) with immunodeficiencies. However, limitations exist in these studies, mainly due to the relatively small cohort sizes. A standard treatment approach is also lacking. Furthermore, very few studies to date have systematically assessed predictive factors associated with clinical outcomes in patients with PIDD and NoV. Therefore, in the context of increasing recognition of NoV gastroenteropathies in immunocompromised hosts and limited understanding of predictive factors associated with clinical outcome, we sought to characterize a large multi-institutional cohort of patients with PIDD and CNI.

2. Methods

We performed a retrospective review of CNI in PIDD by recruiting centers through the Clinical Immunology Society’s CIS-PIDD Listserv e-mail service. Data collected included patient initials, date of birth, sex, weight, height, body mass index as well as white blood cell, absolute lymphocyte, CD3⁺, CD4⁺, CD8⁺, CD16⁺56⁺ and CD19⁺ cell counts, and blood type, primary diagnosis, date of diagnosis, IgG therapy, IgG trough, date of first NoV infection, symptoms, hospitalization and duration, treatment given, date of symptom onset, date of symptom resolution, date of NoV shedding resolution, NoV genotype, endoscopy findings, pathology, coexistent infections, presence of NoV in other sites, coexistent CMV, enterovirus or adenovirus replication, outcomes, and date of last follow-up.

3. Results

1. Overall cohort

Thirty-four subjects (21 males) were reported from centers across North America, Europe, and Asia (Fig. 1) with median duration of CNI of 1.6 years (range 0.95–2.35 years). Fifty percent of subjects had common variable immunodeficiency (CVID), 23% had severe combined immunodeficiency disease (SCID), 12% had combined immunodeficiency (CID), and 12% had Wiskott–Aldrich syndrome (WAS). All subjects were on supplemental immunoglobulin therapy, needing high doses (median IgG dose: 1200 mg/kg/month). Sixty-five percent were hospitalized with CNI (median stay: 47 days; range 7–88 days), and 53% had a complete absence of B cells (median B-cell count: 0; range 0–139 cells/μL). T-cell lymphopenia was also seen with a median T-cell count of 650 cells/μL (range 212–1360 cells/μL).

NoV genotype data were available for 28 out of 34 patients (82%); genogroup GI was present in 22 subjects (79%), while GI/GII was identified in 6 patients (21%). There was a higher likelihood of resolution of CNI with GI (likelihood ratio: 4.6, P = 0.03).

2. CVID vs. non-CVID

Table 1 shows the comparison in the baseline characteristics of CVID patients vs. non-CVID patients. CVID patients developed NoV infection at a later age (31.23 years vs. 4.5 years, P < 0.001). CVID patients also had a higher BMI (20.2 kg/m² vs. 16.09 kg/m², P < 0.001) and were less likely to be blood type O+ (3% vs. 76%, OR: 0.15, CI: 0.04–0.72, P = 0.01). All patients were on high-dose supplemental IgG therapies. However, CVID patients received relatively lower doses of IgG (1275 mg/kg/month vs. 2666 mg/kg/month, P = 0.03) and were less likely to be NoV genotype GI (62% vs. 93%, OR: 0.11, CI: 0.01–0.98, P = 0.045). CVID patients also had a longer time of observation with multiple follow-up visits (Fig. 2).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVID (n = 17)</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Non-CVID (n = 17)</td>
<td>11 (65%)</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.70</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age of NoV Dx (years)</th>
<th>Mean</th>
<th>25–75 percentile</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVID</td>
<td>31.23</td>
<td>17.2–49.1</td>
<td>26.5</td>
</tr>
<tr>
<td>Non-CVID</td>
<td>4.5</td>
<td>0.6–8.8</td>
<td>1.53</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Mean</th>
<th>25–75 percentile</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVID</td>
<td>20.2</td>
<td>18.1–21.6</td>
<td>16.09</td>
</tr>
<tr>
<td>Non-CVID</td>
<td>16.1</td>
<td>15.03–18.1</td>
<td>16.09</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Blood type: O+       | 3 (23%) | 10 (76%) |
| Supplemental IgG     | 1275  | 2666    |
| Dosing (mg/kg/month) |       |         |

| Hospitalization      | 9 (56%) | 12 (71%) |
| NoV Genotype (GI)    | 8 (62%) | 14 (93%) |
| Villous atrophy      | 8 (47%) | 4 (23%)  |
| C. difficile Infection| 5 (30%)| 6 (40%)  |

Table 1: Basic demographics in CVID and non-CVID CNI cohort.
Table 2 shows the immune parameters of the cohort. CVID patients vs. non-CVID patients had different immunology profiles. Most notably, patients with CVID had higher total white blood cell counts, absolute lymphocytic counts, CD4+ T-cell counts (median 380 cells/μL vs. 159 cells/μL, \( P = 0.03 \)), and CD8+ T-cell counts (median 350 cells/μL vs. 109 cells/μL, \( P = 0.04 \)). CVID patients also had lower CD16+56+ NK cell counts (median 40 cells/μL vs 205 cells/μL, \( P = 0.01 \)). Villous atrophy was seen commonly in CVID patients (Fig. 3) together with increased intraepithelial lymphocytes and absence of plasma cells. Absence of B cells was common in both the CVID and non-CVID subjects, with no significant difference between the 2 subgroups (\( P = 0.15 \)). Concurrent *Clostridium difficile* infection was reported in 30% and 40% of the CVID and non-CVID cohort, respectively.

Resolution of CNI was experienced by 8 (24%) patients; only 1 of these had CVID. The odds of persistence of CNI in CVID were 11 times higher as compared to non-CVID subjects (\( P = 0.01 \)).

Five subjects died, resulting in a 2-year postdiagnosis survival of ~60% (95% CI: 55–99%) (Fig. 4). The causes of death included chronic lung disease, disseminated mycobacterial avium infection, unresolved diarrhea, and acute aspiration pneumonia. Of these 5 patients, 4 were non-CVID; the odds of survival for CVID subjects were thus nearly 5-fold higher (\( P = 0.13 \), NS) as compared to the non-CVID subjects. The absence of villous atrophy decreased the chances of survival by nearly 5-fold (\( P = 0.03 \)) and was a predictor of mortality, but with the current study design, it was difficult to ascertain causality.

**Table 2**

<table>
<thead>
<tr>
<th>Immune assessment</th>
<th>CVID (( n = 17 ))</th>
<th>Non-CVID (( n = 17 ))</th>
<th>Odds ratio</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC count (median) (( \times 10^9/\mu L ))</td>
<td>5.9</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>3.3–9.9</td>
<td>2.8–5.5</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Absolute lymphocyte count (ALC) median (( \times 10^6/\mu L ))</td>
<td>1218</td>
<td>820</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>500–1936</td>
<td>310–1550</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CD3+ T-cell counts median (cells/μL)</td>
<td>883</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>224–1894</td>
<td>70–1097</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>CD4+ T-cell counts median (cells/μL)</td>
<td>380</td>
<td>159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>227–700</td>
<td>38–797</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>CD8+ T-cell counts median (cells/μL)</td>
<td>350</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>194–1087</td>
<td>10–655</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>CD16+56+NK cell counts median (cells/μL)</td>
<td>40</td>
<td>205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>17–118</td>
<td>93–448</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>CD19+ cell counts median (cells/μL)</td>
<td>0</td>
<td>0</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>25–75 percentile</td>
<td>0–51</td>
<td>0–691</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Time to follow-up is shorter in non-CVID patients. Patients with CVID as referenced as 1 above had a longer time to follow-up as compared to non-CVID patients (referenced as 2 above).

Fig. 3. Histopathology of CNI. a. Low power (20×): CVID with CNI showing villous atrophy and increased intraepithelial lymphocytes. b. High power (40×): CVID with CNI showing rare plasma cells in the lamina propria.
of fecal samples still positive after a median of 9.5 months of follow-up (Frangé et al., 2012). Brown et al. (2016) supported these results, demonstrating the presence of NoV in fecal samples in 11 of 18 children hospitalized with SCID. Finally, in a study monitoring for contamination in a pediatric immunodeficiency unit in London, UK, Xerry et al. (2010) found 80% of environmental swabs to be positive for NoV, with subsequent transmission to 2 patients who consequently suffered prolonged gastroenteritis.

Taken together, the above studies demonstrate the presence of CNI in patients with PIDD. However, evidence regarding clinical predictors of outcome is lacking. It is clear that there is a wide spectrum of disease course and outcomes. Some immunocompromised patients have a self-limited disease, while others suffer from prolonged excretion of NoV, leading to debilitation and, in worse cases, mortality. In a previous cohort study of 12 patients with CNI following HSCT, 2 patients died: 1 from unrelated complications and 1 from malnutrition (Roddie et al., 2009). In an additional study of 10 patients with CNI after HSCT, 5 patients died: 3 died due to disease progression without gastrointestinal symptoms, and 2 died due to graft-versus-host–related complications (Ueda et al., 2015). Yet additional investigations are lacking in terms of more specific predictors of disease progression and long-term outcomes in patients with PIDDs. In addition to limited evidence of disease course among immunocompromised patients with CNI, previous literature also fails to establish a standard treatment approach for chronic NoV in immunocompromised patients. The genetic diversity and rapid antigenic variation of NoV and complex interactions with variable host environments appear to contribute to the ongoing therapeutic challenge (Robiliotti et al., 2015). There is currently no routine antiviral therapy or vaccine available, and treatment regimens are mainly anecdotal (Green, 2014). Adjustments in immunosuppressant medications have been shown to reduce symptoms and facilitate clearance of NoV in some groups of transplant patients (Roddie et al., 2009; Schorn et al., 2010). Oral immunoglobulins have also shown some promise in immunocompromised patients, with 1 study reporting successful treatment of 11 of 12 lung transplant patients and another study reporting a reduction in diarrhea but not a reduction in time-to-symptom resolution (Florescu et al., 2011; Gairard-Dory et al., 2014). Furthermore, Chagla et al. (2013) demonstrated success with enteral immunoglobulin in a single case report of a transplant recipient. All of our patients received supplemental parenteral IgG, needing high doses (median IgG dose: 1200 mg/kg/month), but impact on CNI progression was unclear.

Additional medication trials have shown variable effectiveness. In a small, double-blinded placebo-controlled trial in immunocompetent patients, nitazoxanide was shown to be an effective option for enteric viruses including NoV, and 1 case study further reported successful treatment in an immunocompromised patient (Rossignol and El-Gohary, 2006; Siddiq et al., 2011). Ribavirin may also be an option, potentially facilitating clearance of NoV infection in some children with PIDD, although other children with NoV have been refractory (Frangé et al., 2012; Woodward et al., 2015). Chen et al. (Siddiq et al., 2011) described the novel development and therapeutic potential of NoV specific monoclonal antibodies, though this approach has not yet been implemented in clinical practice. A NoV vaccine is currently under development and has shown proof of efficacy in human challenge studies; however, it will likely be several more years before it will be available (Riddle and Walker, 2016). Furthermore, use of this vaccine will likely have limitations in immunocompromised hosts. In spite of ongoing efforts, there is clear variability in approaches and outcomes, and treatment in this group of patients continues to pose a challenge. More research in terms of treatment and outcomes of CNI is warranted. Extended-release enteric-coated budesonide has shown variable effects in patients with autoimmune enteropathy (Gentile et al., 2012).

Our study has several limitations. First, as a majority of the data was from multiple institutions, we were unable to obtain longitudinal and
follow-up data. Secondly, this was a heterogeneous group of PIDD patients, and the medical practices may not have been uniform across the different institutions, which may have the potential to affect the overall outcomes of the patients.

Despite these limitations, our study highlights the increasing need for better recognition and clinical management of CNI in patients with PIDD. We have demonstrated that the clinical course of patients with CVID versus those with other PIDD may differ, mainly in terms of age of onset, average time to follow-up, and BMI. However, despite the specific PIDD, the majority of the patients in our cohort had need for higher dosing of supplemental IgG therapy and had severe weight loss with prolonged hospitalizations, leading to chronic debilitation and decreased quality of life, with 5 cases resulting in mortality. It is therefore increasingly important for physicians and other health care providers to be aware of increasing rates of NoV infections, particularly in immunocompromised patients. NoV can be detected in a patient’s stool or vomit through real-time polymerase chain reaction (RT-qPCR), a test that is widely available. The currently available PCR is qualitative, and there is a greater need for quantitative PCR to track CNI disease progression and burden. In this regard, physicians should have a lower threshold for NoV screening in patients who present with prolonged symptoms of gastroenteritis. Furthermore, as RT-PCR analysis also allows for genetic characterization of NoV strains, there is potential to conduct more expansive epidemiological studies.

5. Conclusion

This is one of the first international multi-institutional studies of CNI in PIDD patients. While NoV is thought to replicate in B cells, in this PIDD cohort of CNI, B-cell lymphopenia was common, indicating that the presence of peripheral B lymphocytes is not essential for CNI. It was also interesting to note that death from CNI was not associated with villous atrophy. Furthermore, the clinical course of CNI in patients with CVID versus other PIDDs may differ. CNI in PIDD patients is severely debilitating, yet predictive factors for outcomes and effective treatment strategies are still unknown. This case series gives insights into the types of PIDD affected by CNI infection, their immunological phenotypes, and the significant therapeutic challenges which remain for this severely debilitating and costly infection in PIDD.

References