Chronic norovirus infection in immunodeficiency: A UK national case series

Alexandros Grammatikos, FRCPath[a,*], Anisha Mangtani, MBBS[b,*], Mark Ponsford, FRCPath[c], Stephen Jolles, FRCPath[c], Elizabeth McDermott, FRCPath[d], Sarah Johnston, FRCPath[a], Marina Frleta-Gilchrist, MRCP[e], Patrick Yong, FRCPath[f], Fiona Moghaddas, FRACP[a], Moira Thomas, FRCPath[g], Smita Patel, FRCPath[h], Caitlin Blundell, MBiochem[i], Phil Bright, FRCPath[a], Elizabeth Drewe, FRCPath[d], Suzanne Elcombe, FRCPath[j], Archana Herwadkar, FRCPath[k], Sai Murng, FRCPath[k], Da-In Kim, MRCP[l], Mark Gompels, FRCPath[a], and David Lowe, FRCPath[m]

Clinical Implications

Chronic norovirus infection can lead to significant diarrhea, malabsorption, and weight loss in immunodeficiency. The clinical and histologic picture in these patients is remarkably similar, suggesting that the virus is a main driver for the enteropathy.

Norovirus is a highly contagious virus that causes gastroenteritis. In healthy individuals, infection typically resolves in a few days, but certain populations are at higher risk of chronicity, including those with immunodeficiency. Chronic norovirus infection (CNI) can be debilitating in these patients, causing significant diarrhea, malabsorption, and weight loss. Infection control measures are usually required, resulting in a significant psychosocial impact. To gain more information on the clinical and laboratory picture of CNI in patients with immunodeficiency, we collated relevant cases from immunology centers across the United Kingdom.

We circulated a request via a mailing list, which included 41 UK clinical immunology centers. Immunodeficiency patients with two or more positive stool samples for norovirus, detected by polymerase chain reaction more than 4 weeks apart, were included in the study. A data capture form was circulated. Successful clearance was defined as two or more stool samples that were negative more than 2 weeks apart.

Forty-eight cases of CNI were reported from 11 UK centers (Table I). Patients were mainly male (65%) adults (96%). Common variable immunodeficiency (CVID) was the most common immunologic diagnosis (n = 27), followed by secondary immunodeficiency (n = 11). Twenty-seven patients underwent genetic testing, and a pathogenic mutation was detected in five: in BTK, XIAP, NFKB1, PTPN2, and TACI (heterozygous) genes. The total follow-up time for norovirus infection ranged from 3 to 190 months, mean 63 months. Ten patients also had another pathogen detected in their stool; in two patients this was chronic (*Campylobacter* and *Enterovirus*). All but one patient were receiving immunoglobulin replacement (intravenous in 35 and subcutaneous in 12) when CNI was diagnosed, and in 78% (35 of 45 patients) serum IgG trough level was 8 g/L or greater at the time. Patients who required higher doses (>0.4 g/kg per week; n = 9) had a lower mean level of serum albumin (23.9 vs 31.6 g/L), but not worse diarrhea.

Laboratory investigations revealed low pretreatment serum immunoglobulin levels in 87% of patients (41 of 47) for IgA (<0.22 g/L), 62% (36 of 47) for IgM (<0.21 g/L), 48% (15 of 31) for IgG (<1.34 g/L) where data were available, and 84% were panhypogammaglobulinemic (26 of 31) (Figure 1). B cells were reduced (<0.1 × 109 cells/L) in 78% of patients (36 of 46), and in those with normal levels, class-switched memory B cells were low (<2%) in half. In 46% of patients (22 of 48), T cells were also reduced (<0.67 × 109 cells/L); $CD4^+$ and $CD8^+$ T-cell subsets were equally affected (54% and 56%, respectively). Low natural killer cells (<0.1 × 109 cells/L) were seen in 67% of patients (31 of 46) (Figure 1).

Nearly all patients had diarrhea (94%), which was moderate to severe in 68% of them. Of the four patients who did not, one exhibited significant weight loss (>20 kg) and another experienced malabsorption. In most patients (79%), weight loss was present; it was severe in 60%. Serum albumin was low in 67%, and parenteral nutrition was required in 29%. In 94% of patients (44 of 47), there was evidence of malabsorption (≥1 serum nutrient was reduced). In 45% (21 of 47), four or more nutrients were low and zinc was most often found to be low in those patients (96%). Elevated fecal calprotectin was seen in 83% of patients (24 of 29). Stool α1-antitrypsin was measured in eight patients and was raised in half.

Villous atrophy and intraepithelial lymphocytosis were the two most common small bowel histologic findings, in 82% and 62%, respectively. In 35% of patients there was an inflammatory cell infiltrate, and in 24% plasma cells were absent or low. Twenty patients underwent a colon biopsy, and various forms of inflammation were reported in half (intraepithelial lymphocytosis, absent B cells, granulomatous inflammation, etc).

Treatment was given in 73% of patients, alone, in combination, or sequentially. Fifty-four percent of patients were given more than one treatment. Treatment led to viral clearance in only six (17%), who received favipiravir monotherapy, nitazoxanide monotherapy, ribavirin monotherapy, nitazoxanide with ribavirin, nitazoxanide with favipiravir, or hematopoietic stem cell transplantation (HSCT). No late recurrences were seen, and the follow-up for testing ranged from 4 months to 9 years. The primary diagnosis in those patients was CVID (n = 4), XLA (n = 1), and combined immunodeficiency(n = 1). One patient cleared the infection spontaneously, infected with genotype G1. In all patients for whom treatment was successful, this was associated with significant improvement in the clinical picture (diarrhea or weight loss) and/or normalization of absorption and gut mucosa. An improvement in the lymphocyte count was noted in two patients, and it was possible to halve the dose of immunoglobulin replacement in another two. Twelve patients died, six of whom had previously required parenteral nutrition. In two cases, the cause of death was deemed to be directly linked to CNI.

TABLE I. Baseline characteristics, immunologic profile, malabsorption parameters, histologic findings, and treatment of patients with chronic norovirus infection

Characteristics			
Age at diagnosis, years (median [range])	45 (6-70)	Nutrient deficiency (ratio [%])	
Male, n (%)	31 (65%)	Calcium	29/48 (60%)
Immunodeficiency type, n (%)		Copper	4/4 (100%)
Common variable immunodeficiency	27 (58%)	Iron	16/18 (89%)
Secondary*	11 (23%)	Ferritin	16/25 (64%)
Combined	7 (15%)	Folate	12/31 (39%)
Other primary†	3 (6%)	Magnesium	5/19 (26%)
Norovirus strain, n (%)		Phosphate	4/26 (15%)
Unknown	10 (21%)	Selenium	7/11 (64%)
1	1 (2%)	Zinc	24/25 (96%)
2	37 (77%)	Vitamin A	10/24 (42%)
Gastrointestinal coinfection (previous or current) (median [range])‡	10 (21%)	Vitamin D	14/24 (58%)
Laboratory parameters (pretreatment) (median [LQ-UQ])		Vitamin E	15/27 (56%)
B cells, $\times 10^9$ cells/L	0.02 (0.004-0.088)	Vitamin K	3/4 (75%)
T cells, $\times 10^9$ cells/L	0.75 (0.38-1.2)	Vitamin B12	8/33 (24%)
CD4 T cells, $\times 10^9$ cells/L	0.32 (0.2-0.49)	Small bowel histology (ratio [%])	
CD8 T cells, $\times 10^9$ cells/L	0.27 (0.12-0.52)	Villous atrophy	24/34 (82%)
Natural killer cells, $\times 10^9$ cells/L	0.07 (0.04-0.12)	Intraepithelial lymphocytes	21/34 (62%)
IgG, g/L	1.6 (0.62-3.2)	Inflammatory cell infiltrate	12/34 (35%)
IgM, g/L	0.1 (0.06-0.2)	Plasma cell depletion/absence	8/34 (24%)
IgA, g/L	0.1 (0.03-0.11)	Treatment (ratio [%])	35 (73%)
Immunoglobulin replacement dose per kg weight/wk (median [range])	0.31 (0.09-0.71)	Nitazoxanide	24 (50%)
Trough IgG, g/L (median [LQ-UQ])	9 (8-10.1)	Ribavirin	23 (48%)
Diarrhea (ratio [%])	44/47 (94%)	Corticosteroids	6 (13%)
Mild (stool frequency <5/d)	9/28 (32%)	Enteral immunoglobulin	2 (4%)
Moderate (stool frequency 5-10/d)	14/28 (50%)	Interferon	5 (10%)
Severe (stool frequency >10/d)	5/28 (18%)	Pentaglobin IV	3 (6%)
Weight loss (ratio [%])	35/44 (79%)	Favipiravir	13 (27%)
Mild to moderate (<20 kg)	14 (40%)	Other	2 (4%)
Severe (>20 kg)	21 (60%)	Outcome (ratio [%])	
Parenteral nutrition (ratio [%])	14/48 (29%)	Infection cleared	7 (15%)
Hypoalbuminemia (ratio [%])	32/48 (67%)	Infection ongoing	24 (51%)
Mild/moderate (serum albumin>25 g/L)	19 (59%)	Patient died	12 (26%)
Severe (serum albumin<25 g/L)	13 (41%)		

LQ-UQ, Lower quartile- upper quartile.
*Owing to hematologic malignancies (lymphoma, n = 3; leukemia, n = 2, monoclonal gammopathy of uncertain significance, n = 1), immunosuppressive treatment (n = 2), and Good syndrome (n = 2).
†X-linked agammaglobulinemia (n = 1), X-linked lymphoproliferative disease (n = 1), and other primary immunodeficiency (n = 1).
‡*Campylobacter*, n = 6; *Giardia*, n = 2, *Salmonella*, n = 1, *Clostridium difficile*, n = 1; echovirus E11, n = 1; Untypable enterovirus, n = 1; adenovirus, n = 1; sapovirus, n = 1.

To our knowledge this is the largest reported series of patients with CNI and immunodeficiency. In the seven previously published case series,[1-7] CVID was the most common diagnosis (47 of 99 cases), followed by combined immunodeficiency (20 of 99). Common variable immunodeficiency was the most common diagnosis in the current cohort, too, followed by secondary immunodeficiency, likely owing to different inclusion criteria. Case series in secondary immunodeficiency have also been published, including patients with cancer[8] and after transplantation.[9] There were no obvious differences between the presentation and histologic findings of CNI in the current series according to diagnosis, despite previous reports implicating norovirus in CVID enteropathy alone.

In the current cohort low baseline serum immunoglobulin and lymphocyte subsets were noted in most patients. For example, B cells were reduced in 73% of patients with CVID, although this is expected to affect only 10% to 20% of these patients. T cells were also frequently low, and HSCT studies have shown that these cells have an important role in the clearance of CNI. Other factors likely also contribute. For example, the only patient who spontaneously cleared CNI in the current cohort was infected with genogroup G1.

Diarrhea and malabsorption were the most common findings in the current cohort, and serum zinc and albumin were often low. Weight loss was also common, with parenteral nutrition required in a substantial proportion. Several patients required high-dose immunoglobulin replacement to maintain adequate IgG trough levels. Lower serum albumin levels were also seen in those patients, suggestive of a protein losing enteropathy state. The average immunoglobulin dose used, at around 1.3 g/kg per month, was

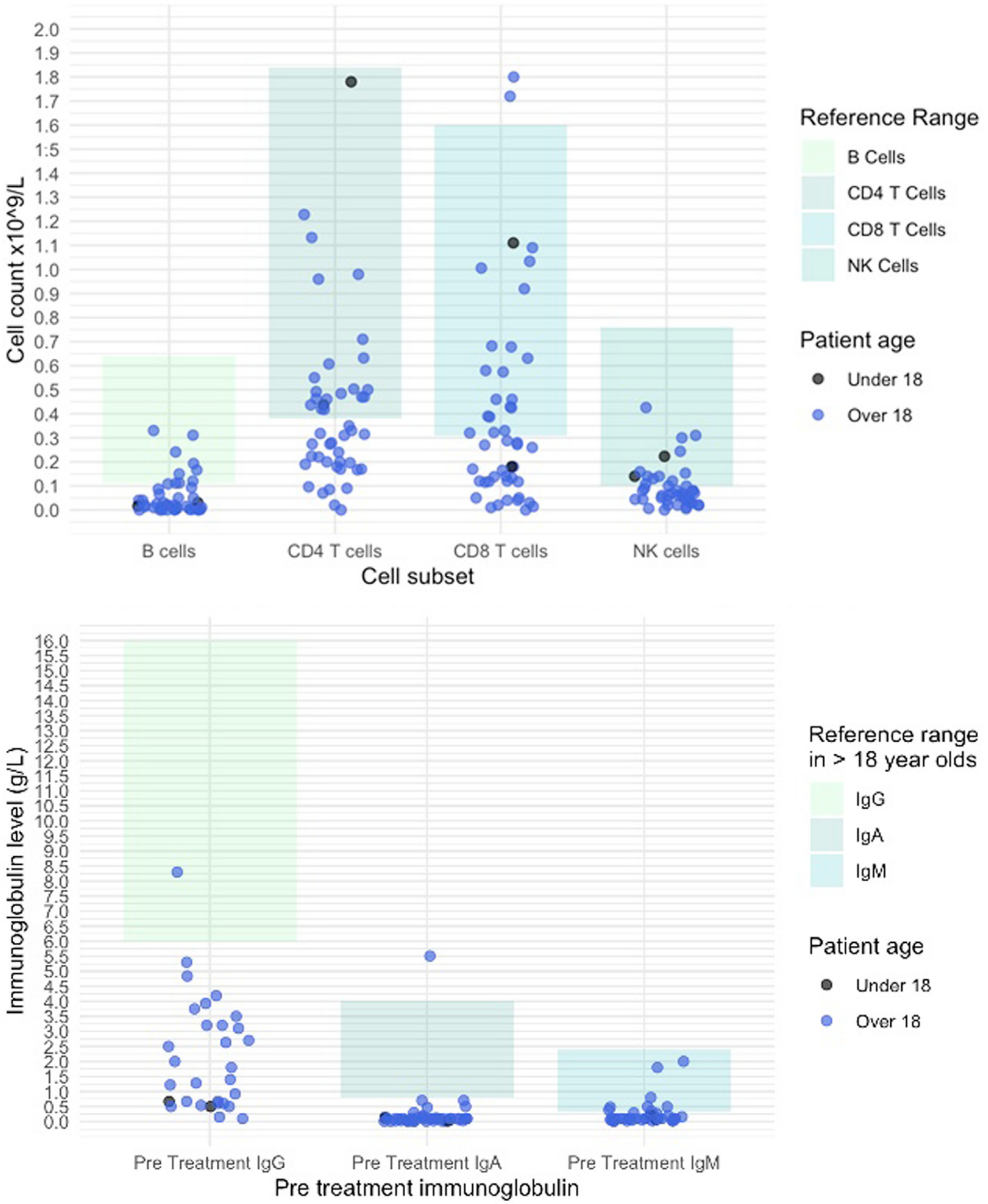

FIGURE 1. (*Top*) Pretreatment immunoglobulin levels and (*bottom*) lymphocyte subset absolute counts in patients with chronic norovirus infection. *NK*, natural killer.

much higher than the standard in antibody deficiency, emphasizing the high health care cost of this condition. Notably, the absence of diarrhea did not preclude the development of malabsorption or weight loss or the need for high-dose immunoglobulin therapy. As previously shown,[5,6] villous atrophy and intraepithelial lymphocytosis are common histologic findings in the small bowel of infected patients, likely underlying malabsorption. That the clinical and histologic picture is remarkably similar regardless of the immune deficiency suggests that the virus is a main driver for the enteropathy, rather than the underlying immune disorder.

Favipiravir, nitazoxanide, and ribavirin, used alone or in combination, are potential treatment options for these patients. However, a cure is often unachievable, and management has to focus on supportive measures. Hematopoietic stem cell transplantation should be considered in primary immunodeficiency.

This study was limited by its retrospective nature and the potential for reporting bias. Nevertheless, our survey identifies the burden of CNI and highlights clinical features that should prompt testing in patients with immunodeficiency, including diarrhea, weight loss, low serum nutrients or albumin, and the requirement for higher-dose immunoglobulin replacement. Further studies are required to elucidate the pathogenesis and guide therapy.

[a]Department of Clinical Immunology, Southmead Hospital, North Bristol NHS Trust, Bristol, UK
[b]Department of Clinical Immunology, University College London Hospitals NHS Foundation Trust, London, UK
[c]Department of Clinical Immunology, University Hospital of Wales, Cardiff, Wales, UK
[d]Department of Clinical Immunology, Nottingham University Hospitals NHS Trust, Nottingham, UK
[e]Department of Immunology, Queen Elizabeth University Hospital, Glasgow, UK
[f]Department of Clinical Immunology, Frimley Park Hospital, Frimley Health NHS Trust, Frimley, UK
[g]Department of Clinical Immunology, NHS Greater Glasgow and Clyde, Glasgow, UK
[h]Department of Clinical Immunology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[i]Synnovis, Guy's and St Thomas' NHS Foundation Trust, London, UK
[j]Department of Clinical Immunology, Royal Victoria Infirmary, Newcastle upon Tyne, UK
[k]Department of Clinical Immunology, Northern Care NHS Foundation Trust, Manchester, UK
[l]Department of Clinical Immunology, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK
[m]Department of Clinical Immunology, Royal Free NHS Foundation Trust, London, UK

*These authors contributed equally to the manuscript.
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Corresponding authors: Alexandros Grammatikos, FRCPath, Department of Immunology, Southmead Hospital, North Bristol NHS Trust, Southmead Road, BS10 5NB Bristol, UK. E-mail: alexandros.grammatikos@nbt.nhs.uk; Or: David Lowe, FRCPath, Department of Immunology, Royal Free NHS Foundation Trust, 10 Pond St, NW3 2PS London, UK. E-mail: david.lowe7@nhs.net
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