

Approach to infection in immunosuppressed patients

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Norovirus infection as a model of chronic or recurrent infection in common variable immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency (PID) in general population. PID are genetic diseases that share a dysfunction in the immune system entailing a greater risk of both chronic and recurrent infections. These patients can also develop chronic gastrointestinal infections caused by norovirus with persistent viral dissemination, which can be detected months after primoinfection. Additionally, a proportion of CVID patients show a typical severe enteropathy presenting with recurrent diarrhoea, intestinal malabsorption, inflammatory lesions, and villous atrophy. Some studies have related this enteropathy with chronic intestinal infection caused by norovirus.

Keywords: common variable immunodeficiency, Norovirus, enteropathy

INTRODUCTION

Primary immunodeficiencies constitute an heterogeneous group of more than 450 genetic diseases that share a deficient production in the components of innate and/or adaptative immune system. These disorders entail a higher susceptibility of developing infections which can sometimes be severe, chronic, recurrent, and may be caused by opportunistic agents. Nevertheless, in the last two decades, genomic, biochemical, and cellular analysis have demonstrated that the clinical characteristics of PID are wider than initially thought, and are not only restricted to infections. The immune system dysregulation has been described in many PID and can cause multiple autoim-

mune disorders, lymphoproliferative diseases, and neoplasms which, when not promptly suspected and diagnosed, will negatively impact the patient prognosis [1,2].

CVID is the most common symptomatic PID, with an estimated prevalence of 1:25.000 to 1:50.000 individuals. It is characterised by decreased blood levels of at least two immunoglobulin (Ig) isotypes (IgG, IgA and/or IgM) together with decreased or absent production of specific antibodies. Diagnosis is made when excluding secondary causes of hypogammaglobulinemia and other well-defined PID, including combined immunodeficiencies with decreased number of CD4 T-cells. CVID patients share a central alteration in the B-cell differentiation to plasmatic Ig secretory cells, and, despite the fact that CVID is classified as a PID with B-cell defect, in the last years a large number of other cellular defects have been discovered. Although the clinical spectrum of CVID is wide, two main phenotypes can be found: a first group of CVID patients that show recurrent infections, and a second group which develops autoimmune/inflammatory manifestations [3]. Within this second phenotype, a small proportion of patients (5-15%) may develop a typical severe enteropathy (called CVID-related enteropathy) of unknown cause. It might present as recurrent diarrhoea, intestinal malabsorption, inflammatory lesions, and villous atrophy in the patients' intestinal mucosa.

The most common infectious manifestations in CVID patients are recurrent airway infections, especially acute bronchitis, sinusitis, and pneumonias. Infections may also less frequently affect the CNS, gastrointestinal tract, and skin and soft tissue. In a subsection of CVID patients, chronic diarrhoea can be the main symptom of disease. Some parasites such as *Giardia intestinalis* can be responsible for the recurrent diarrhoea, but the villous atrophy or the intestinal inflammatory lesions that are seen in these patients have been related to the chronic or recurrent intestinal infection caused by norovirus [4].

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NOROVIRUS INFECTION AND CVID-RELATED ENTEROPATHY

Norovirus is the most common agent of gastroenteritis described both in isolated cases and in outbreaks all along the world. It is a non-enveloped RNA virus of the *Caliciviridae* family. Although it is a unique species, norovirus is divided into six genogroups (GI–GVI) that are subdivided into more than 40 genotypes. Among them, only GI, GII, and GIV can infect humans, being the strain GII.4 the most frequent one, causing more than 80% of intestinal infections worldwide. This virus has faecal-oral transmission, but it can also be transmitted by direct contact or by contaminated water or food. It is highly infectious as very few viral particles are able to cause the disease. Norovirus infection in immunocompetent patients is characterized by intense vomiting, followed by at least 4 days of diarrhoea, reaching the peak of viral excretion in 1 to 3 days after the disease onset. Up to 32% of the infected patients will develop an asymptomatic infection [5]. PID patients infected by norovirus may present the same initial symptoms. Nevertheless, 5 to 20% of these patients can develop severe and prolonged diarrhoea which can last for more than 4 months due to their diminished viral clearance. In addition, the disease can worsen, entailing a higher mortality rate [6]. It is not clear whether the prolonged symptoms are owed to a chronic norovirus infection or to a repeated series of infections, as the incomplete immune response of PID patients imply a higher susceptibility to recurrent infections in all age groups. Despite the cause of the disease, CVID patients develop viral persistent dissemination which can be detected between 9 months to 1 year after the primoinfection. Furthermore, there is no evidence that specific strains are responsible for this persistent infection in human hosts, as the most common genotype in immunosuppressed patients is the strain G-II which is also the predominant genotype in general population [7].

The histopathological findings of the CVID-related enteropathy are similar to those found in coeliac disease: increased number of intraepithelial lymphocytes, severe villous atrophy, crypt hyperplasia and lymphocyte infiltration of the lamina propria. Nevertheless, plasmatic cells may be absent, and, in some severe cases, enterocytes can show important degeneration and vacuolization. In fact, gluten abstinence is rarely beneficial, and most of the patients do not show class II HLA variants (DQ2 or DQ8). It has been recently demonstrated that norovirus infection provokes pathological changes in the duodenal mucosa of immunocompetent patients that resemble those pathological findings of coeliac disease, including villous atrophy, increase of intraepithelial lymphocytes, and permeability increase [8].

In a well-known patient series with CVID-related enteropathy, Woodward et al. [9] proposed that chronic norovirus infection could play an important role in the aetiology of this severe enteropathy. The 8 identified patients of this retrospective series

were positive for norovirus in faecal samples, and, interestingly, 3 patients showed clinical resolution and an improvement of villous duodenal atrophy after achieving viral clearance when treated with ribavirin for several months. On the contrary, many patients with this chronic enteropathy seemed to symptomatically respond to immunosuppressor treatment, which included steroids and anti-TNF antibodies, despite the fact no significant histological changes were observed in the intestinal biopsies after this therapy. These findings support a possible role of cytotoxic aberrant immune response to the chronic infection caused by norovirus, and maybe to other enteric infections, in the aetiology of the CVID-related enteropathy.

IMMUNE RESPONSE TO NOROVIRUS IN IMMUNODEFICIENT PATIENTS

When talking about the immune response in CVID patients to norovirus infection and the presence of chronic enteropathy, it is essential to understand two main facts: which the mechanisms that eliminate norovirus from the host are, and which the pathogenicity of the villous atrophy and the inflammation of the intestinal mucosa is. According to the established hypothesis based on experimental animal and human models, norovirus mainly infects antigen-presenting cells (APCs), B-lymphocytes and epithelial cells, where it can produce direct toxicity. The infected cells release type I and type III interferon (IFN). The norovirus antigen is then presented by the infected cells through type I major histocompatibility complex to CD8 T-lymphocytes, or through type II major histocompatibility complex in B-cells and in APCs to CD4 T-lymphocytes. The expression of IL-15, specially in epithelial cells can increase the activation of T-cells. CD8 T-lymphocytes exert their cytotoxic role as intraepithelial lymphocytes, inducing apoptosis of mucosal epithelial cells through the release of granzyme and perforin, union of Fas/Fas ligand, and through the interaction with group 2D natural killer cells. CD4 T-lymphocytes proliferate and release cytokines which improve the activity of APCs, the cytotoxicity induced by CD8 T-lymphocytes, and the antibody production exerted by B-cells and plasmatic cells. This coordinated immune response is able to eliminate norovirus in immunocompetent hosts. Contrarily, in immunodeficiencies such as CVID, B-cell differentiation to plasmatic cells is compromised, and thus, the production of neutralizing antibodies, the interaction among T-cells and B-cells, and the release of cytokines from CD4 T-lymphocytes are impaired. As a result, norovirus clearance is altered, and a persistent and uncontrolled CD8 T-cell response produces epithelial damage and, in the end, causes the typical villous mucosal atrophy [5] (Figure 1).

DIAGNOSIS AND TREATMENT OF NOROVIRUS IN IMMUNODEFICIENT PATIENTS

In the majority of cases, norovirus infection is diagnosed by detecting the presence of viral RNA though PCR in faecal

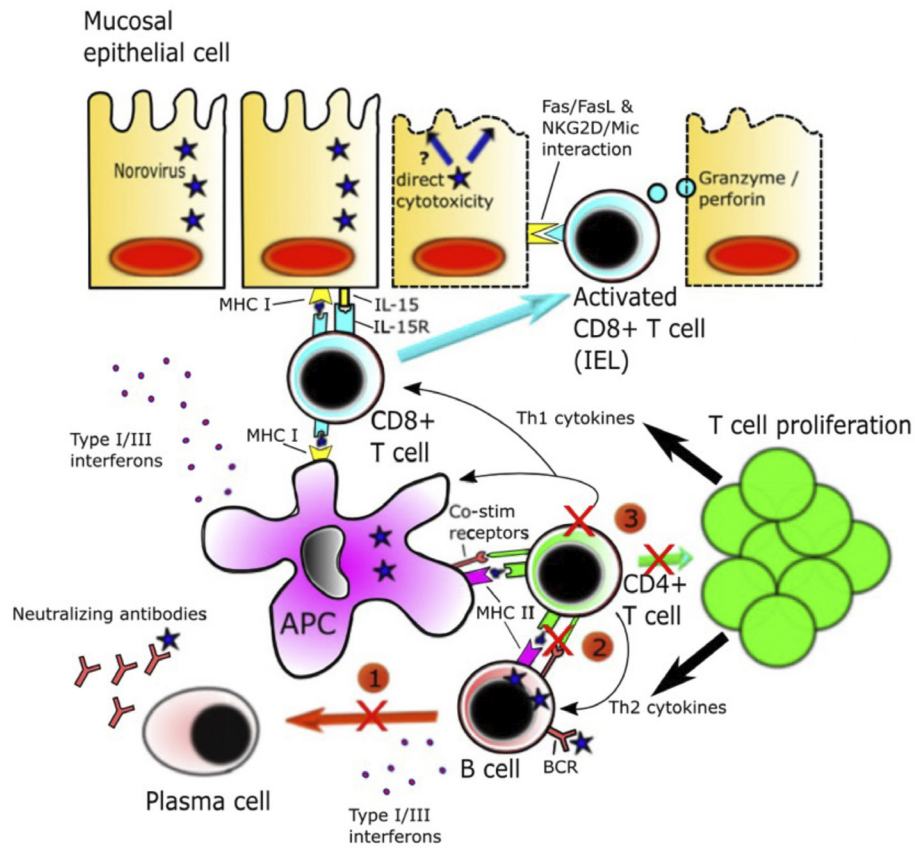


Figure 1 Pathogenesis of chronic intestinal infection by norovirus [5]

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samples. The sample must be processed within the first 48 to 72h after the beginning of the symptoms. Nevertheless, the PCR can still detect viral RNA in faeces during weeks or months after the resolution of the symptoms, especially in patients with PID. This PCR analysis can also genetically classify norovirus strains, which is helpful for epidemiological research.

Nowadays, there is an active debate on whether the presence of norovirus itself implies the need of treatment, whether it is just an innocent spectator, or whether the treatment of norovirus infection should be restricted to the use of immunomodulator agents. Treatment of acute norovirus infection is mainly addressed to the patients' symptoms, and is focussed on fluid therapy for dehydration. To the moment, there are no available vaccines or antiviral targeted therapy. Treatment for patients with chronic infection caused by norovirus remains a therapeutical challenge. There are cases where the use of antivirals, specifically ribavirin and favipiravir, have achieved viral clearance measured through faecal PCR, together with clinical

resolution, and improved histopathologic findings [8]. Immunomodulation with oral Ig [10] and breastmilk [11] have also shown some benefits. In addition, several antiparasitic agents such as nitazoxanide have demonstrated antiviral properties with transient benefit [12]. Finally, the use of immunomodulators such as mTOR inhibitors (sirolimus or everolimus) have proved a significant increase in the antiviral properties of the host that should be furtherly and deeply studied [13].

Recently, a unique association *Clostridioides difficile* coinfection has been observed in patients with chronic norovirus infection [14]. This fact has shed light on the role that microbiome modification may play in facilitating enteric replication of the virus and its establishment as a chronic infection. Some works in experimental animal models suggest that commensal bacteria, which are reduced as a consequence of antibiotic treatment, can counter the innate immune response to norovirus, which limits their efficacy in preventing new infections. Another hypothesis is that commensal bacteria may help norovirus in infecting specific cells of the intestinal mucosa [15].

CONCLUSIONS

CVID is the most frequent symptomatic PID in the population, and it is characterized by a dysfunction of the humoral component of the adaptive immune system which leads to a higher risk of repeated, chronic and/or recurrent infections. CVID patients may occasionally develop chronic intestinal norovirus infections with persistent viral shedding that can be detected months after the initial infection. This chronic infection has been related with the presence of a specific enteropathy characterized by an increase in intraepithelial lymphocytes, villous atrophy, crypt hyperplasia, and lymphocytic infiltration of the lamina propria, together with an absence of plasma cells, which poses a differential diagnosis with celiac disease. To date, no effective medical treatment has been described to treat this type of chronic infection.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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