

Review

Chronic sequelae and severe complications of norovirus infection: A systematic review of literature

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ABSTRACT

Norovirus causes an estimated 18% of all cases of acute gastroenteritis worldwide and is found to be associated with mortality. To create a first overview of severe complications and chronic sequelae of norovirus infections, a systematic review of literature was performed. Of 3928 individual hits, 176 publications remained for data extraction. Study periods varied between 1974 and 2017, though strongly skewed towards the last decade ($n = 122$, 70%). Countries of studies were worldwide, though Africa, and Caribbean, Central and South America were underrepresented. Strong evidence was found for chronic diarrhea in immunocompromised patients, affecting 9%–100% of investigated cohorts. The duration of chronic diarrhea varied from four weeks up to nine years, leading to either wasting, weight loss or failure to thrive in a third of the reported cases (224). Other complications with significant evidence were necrotizing enterocolitis (NEC) in preterm infants associated with norovirus infection (8 papers), and benign infantile convulsions with gastroenteritis (BICG; 19 papers). Studies on norovirus infection and inflammatory bowel disease (IBD) mostly concluded against this association (5 of 7). The remaining papers mentioned a large variety of possible sequelae or complications. Based on the available literature, chronic norovirus diarrhea is the major sequela of norovirus infection in primary immune deficient, oncologic and transplant patients. Norovirus infection – like other gastrointestinal pathogens – can cause a range of sequelae and complications, and should be considered in the differential diagnosis of these manifestations.

1. Background

Worldwide, norovirus has been estimated to cause 18% of all acute gastroenteritis cases [1], ranging from mild to severe (hospitalized). Norovirus infection is generally seen as a mild and self-limiting acute gastroenteritis. However, less well understood are potentially severe or long-term effects after a norovirus infection. Norovirus is found to be associated with mortality in studies using outbreak data, syndromic surveillance, or case-based death certificates [2–6]. In addition to mortality, norovirus illness has been reported in relation to several severe or life-threatening complications as well as chronic sequelae, such as necrotizing enterocolitis (NEC) [7], benign infantile seizures with gastroenteritis (BICG) [8], or chronic diarrhea [9]. There is a lack of knowledge on the pathogenic mechanism of norovirus infection in humans, and the mechanisms causing sequelae. Assessing the occurrence of sequelae could help prioritize research into these mechanisms.

2. Objective

Here, we review literature to provide a complete overview of severe or chronic sequelae and complications that have been reported in the context of norovirus infection.

3. Study design

3.1. Search strategy

A keyword search was performed on the 19th of January 2018 using Embase, Medline (ovidSP), Web-of-science, Cinahl (EBSCO), Cochrane and Google scholar to identify information on severe or chronic sequelae reported together with norovirus infection. Based on a preliminary literature scan and expert opinions, possible complications or sequelae mentioned in association with norovirus infection were added

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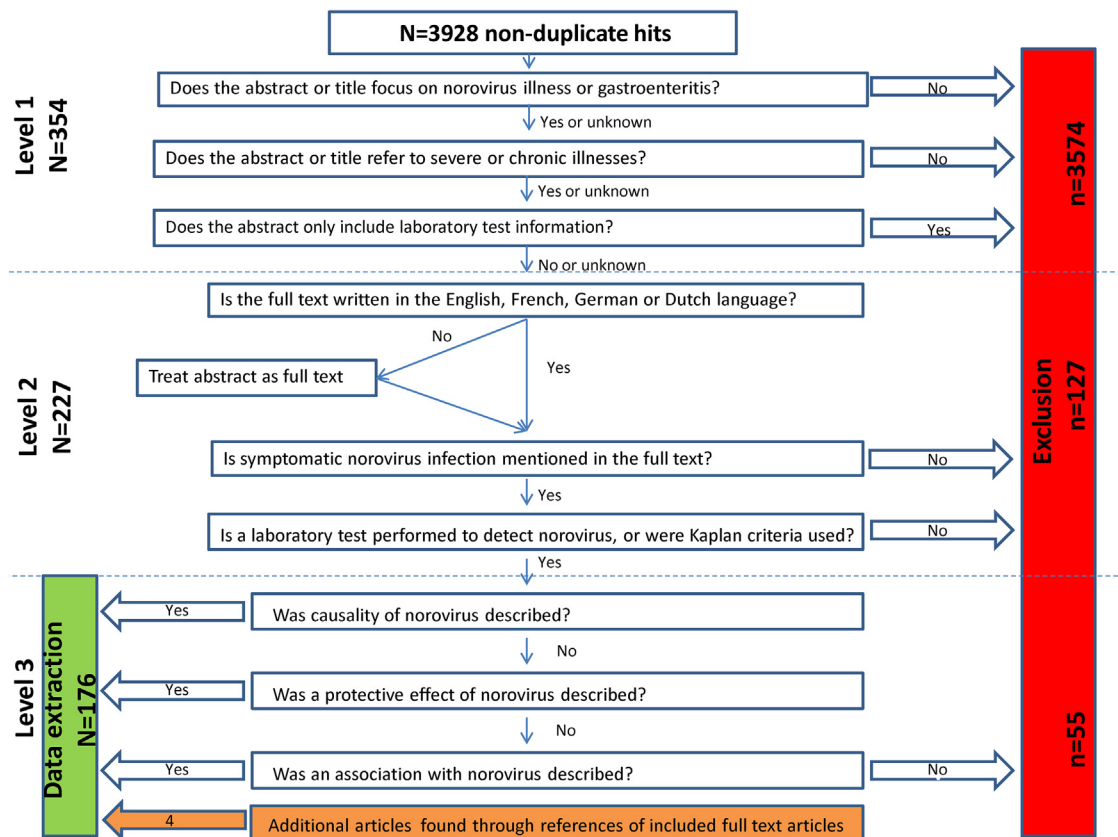


Fig. 1. Scheme for inclusion of papers for data extraction.

to the search string to be able to narrow down the search. Also, a scan of a more sensitive search was performed to detect possibly missed keywords. No limitations on country of publication or language were used. All articles published between January 1979 and the search date were included. The search strategy is provided in Appendix S1. All references were imported into Endnote where duplicates were removed.

3.2. Inclusion and exclusion criteria

Screening was performed by two reviewers for publications until the 31st of October 2012 [MP, LV], publications found through an update search until the 30th of March 2015 were screened by a single reviewer [MP], and a final update until the 19th of Jan 2018 by three reviewers [MP, LV, MdG]. Screening was performed at three levels, aiming to be sensitive rather than specific. Conference abstracts, letters and reviews were included, whereas editorials were excluded from the review. If both an abstract for conference and a full text publication was available, only the full text publication was included. If an abstract was not available and the full text could not be obtained, the publication was excluded.

3.3. Data extraction

Data extraction was conducted using a standardized form created in Microsoft Excel (Version 2010). Information on population (dates for data collection, country, age range of norovirus cases, and gender distribution of norovirus cases), sequela or severe complication, disease status (related to the sequela) prior to the study, outbreak source (where applicable), study design, study directionality, source or confirmation of data (categories describing both norovirus diagnosis and sequela), genotype, the interval between norovirus infection and occurrence of sequela, the follow-up time, and outcomes (number of participants with norovirus, number of participants who developed

chronic sequelae) were extracted (Appendix S2: data extraction file). The studies were categorized as cohort study, case-control study, or case-report (for both norovirus and sequela population groups, cases or case series). The population group was classified based on the starting point of inclusion criterion for cases as 'norovirus cases', 'general population', 'comorbidity patient group', 'patient with sequela'. The study directionality was classified as either prospective (diagnosis of norovirus or sequela occurred during the study period) or retrospective (identification as a case of norovirus and of sequela had already occurred). Age was categorized as < 5 and ≥ 5 years old. Norovirus diagnosis was classified as confirmed (through one of the following laboratory tests: PCR, EM, ELISA, EIA, IDEIA, radioimmunoassay blocking test, IgG/IgA detection), probable (based on Kaplan criteria), or possible (method not reported). Diagnosis of sequela referred to the method by which the sequela were diagnosed and categorized as taken from medical records/diagnosed by physician, self-reported (based on responses from questionnaire), indexed criteria used by medical trained person, or not reported.

The level of proof for norovirus as a cause of a complication or sequela was determined per study as follows with increasing level of proof:

1. Co-existence: for case studies, descriptive reports or cohorts of norovirus positive patients without comparison to norovirus negative cases, irrespective of the starting point for case selection and proposing a hypothesis without further medical clarification on the pathogenesis.
2. Prevalence of norovirus (for studies where the sequela were the inclusion criteria) compared to literature evidence. For this, a positive association was assumed if the prevalence of norovirus infection in the study population was more than 5% for community cases [10] or higher than 20% for Health Care settings [11]. These background prevalence rates were derived from the studies cited,

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