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Commentary

Understanding Asymptomatic Norovirus Infections

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In this issue of EClinical Medicine, Qi and colleagues estimate the global prevalence of asymptomatic norovirus infection is to 7% (95% CI: 6%–9%) with higher prevalence in Africa (15%), Meso America (14%) and South America (11%) [1]. While some of the reviewed studies reported that up to 36% of asymptomatic individuals had norovirus other studies did not find any. Several factors might contribute to this remarkable difference in prevalence including: i) Study design, ii) Inclusion criteria to define an asymptomatic case, iii) the sensitivity of the detection method, iv) the sanitary conditions of the study site, v) age group studied, vi) the study time frame, vii) level of exposure, viii) virus diversity, ix) immunity, and x) host genetic.

Immune-competent individuals can excrete norovirus in stool for up to 4 weeks, therefore norovirus detection in the convalescent phase might indicate long term excretion rather than asymptomatic infection [2–4]. Thus, long term excretion is an important issue to be considered in studies aiming to identify authentic asymptomatic norovirus infections.

The use of highly sensitive methods, like real time RT-PCR (qRT-PCR), may also contribute to increased detection rates of asymptomatic norovirus infections. A most dramatic example was that the detection rate of asymptomatic norovirus infections increased from 0.3% (6/2205) to 16% (358/2205) after re-examination by PCR of archived stool samples previously examined by electron microscopy [5]. Currently, qRT-PCR is more widely used for norovirus research due to limited sensitivity of the available ELISA assays [6]. The use of these quantitative and sensitive methods might be also useful to discriminate between symptomatic and asymptomatic infection. Shioda and colleagues assessed how the cycle threshold (Ct) values of qRT-PCR from human clinical specimens were associated with symptomatic norovirus infections and reported that Ct values were lower (i.e., higher viral loads) among symptomatic cases (25.3 ± 1.2) compared with asymptomatic controls (28.5 ± 1.4) [7].

The high genetic variability of norovirus might be another factor contributing to higher rates of asymptomatic infections. Possibly, some genetic variants have less capacity to develop disease, but are readily transmitted in populations with insufficient sanitary conditions. In Nicaragua, for instance, we have previously observed that while the majority of symptomatic norovirus infections were associated with genotype GII.4 (53%), genotype diversity was higher in asymptomatic children with GII.4 representing only 1.4% [8]. Qi and colleagues did not explore genetic variability at genotype level, but, reported that 80% of the asymptomatic infections were associated with genogroup II, which is similar to the percentage of genogroup II reported for symptomatic disease [9]. Altogether, these observations suggest that further studies are needs to understand the role of different genotypes in asymptomatic norovirus infections.

It is unlikely that a pre-existing adaptive immune response prevent the development of clinical symptoms in all asymptomatic individuals as challenge studies have shown illness development after re-infection with the same strain [10]. Moreover, asymptomatic norovirus infections have been commonly found in children younger than 6 months, probably experiencing their first norovirus infection [4,11]. Of note, recent studies of natural norovirus infections have suggested that acquired immunity follows natural infections, with genogroup II noroviruses, although it may be genotype specific [4,12]. Birth cohort studies are still needed to understand genotype specific immunity and their role in asymptomatic infections.

If host genetic play any role in asymptomatic norovirus infections, remain to be seen. It is however known, that host genetic factors such as the secretor status is associated with susceptibility to both symptomatic or asymptomatic norovirus infection [8,13]. In particular the globally dominant GII.4 norovirus, which appears to be more virulent, exhibit a strong secretor specificity in vivo [13]. In contrast, higher rates of non-GII.4 infections have been reported in secretor-negative individuals [14]. The proportion of secretor and non-secretors individuals is strongly dependent on ethnicity. Thus, a high proportion of secretors individuals susceptible to GII.4 viruses might lead to higher disease rates. The observation by Qi and colleagues that asymptomatic norovirus prevalence was higher in Africa (15%), Meso America (14%) and South America (11%) warrant more investigation alongside host genetic [1].

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