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Commonly circulating human coronaviruses do not have a significant role in the etiology of gastrointestinal infections in hospitalized children

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ABSTRACT

Background: Human coronaviruses (HCoVs) OC43, 229E, NL63 and HKU1 are common causes of respiratory infections. Over the years, it has been proposed that HCoVs play a possible role in gastrointestinal infections.
Objectives: To assess the role of HCoVs in acute gastroenteritis (AGE) in children.
Study design: Study was conducted at Tampere University Hospital over 2 years. Both stool and nasal swab samples were collected from 172 children with AGE, 545 with acute respiratory tract infection (ARTI) and 238 with symptoms of both. The samples were tested for HCoVs by RT-PCR.
Results: HCoVs were detected in 52 (5.4%) children: in 6.4% of those with AGE, 4.4% with ARTI and 7.1% with symptoms of both. HCoVs OC43, HKU1, 229E and NL63 were encountered in 13, 11, 13 and 15 cases, respectively. HCoVs were detected simultaneously in stool and nasal swab samples in 17 children, in nasal swabs alone in 33 children, and in the stools alone in two children. HCoVs were present in the stools of eight (4.7%) of the 172 children with AGE; in six of these cases, the nasal swab sample was also positive for the respective HCoV. Additionally, in six of the eight cases, the stool sample contained either rotavirus or calicivirus.
Conclusions: HCoVs can be detected in the stools of children with AGE, but usually together with well-known gastroenteritis viruses, and concomitantly in the respiratory tract. It appears that commonly circulating HCoVs do not have a significant role in the AGE of children admitted to hospital.
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1. Background and objectives

Human coronaviruses (HCoV) cause respiratory infections of varying severity. OC43 and 229E, the “common cold viruses”, have been known since the 1960s [1–4], and they have been found in 1.9% of children hospitalized for respiratory tract infection [5]. A more recently discovered coronavirus, NL63 [6], has been detected in 1.7–3.2% of respiratory tract samples of children hospitalized with acute respiratory tract infection (ARTI) [5,7–9], including acute laryngitis [5,7,9]. Another recently discovered human coronavirus, HKU1 [10], was detected in 2.95% of children hospitalized for upper or lower respiratory tract infections [11]. It seems that all of these HCoVs may cause respiratory tract infections in children that are severe enough to lead to hospitalization, but none of them seems to be more pathogenic than any other [12].

HCoVs can also cause serious disease, as shown by SARS-CoV experience [13–16] and the recently discovered MERS-CoV, which causes severe respiratory infection and renal dysfunction [17]. Both of these coronaviruses are of animal origin and are not well established in humans.

Electron microscope (EM) studies in the 1970s detected coronavirus-like particles in the stools of children with acute gastroenteritis (AGE), and the existence of enteric coronaviruses was proposed [18]. The possibility that HCoVs could have a role in gastrointestinal infections is supported by findings that some animal coronaviruses are “pneumoenteric” and capable of causing both gastrointestinal and respiratory tract infections [19]. When SARS-CoV was discovered in 2003, it was noted that 23.6–73% of SARS patients had diarrhea [16,20,21], SARS-CoV RNA could be detected in the patient’s stools [14,16,21], and SARS-CoV could be isolated by culture in the intestinal tissues [21].

Gastrointestinal symptoms may also occur in patients with non-SARS-CoVs, but usually HCoVs have been studied only from respiratory samples [22] or, if found in stool samples, the

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Table 1
Characteristics of the study groups.

	N	Male (%)	Age (median)	Number of children in the different age groups				Number of cases per season	
				<6 months	6–24 months	2–5 years	>5 years	2009–2010	2010–2011
All patients studied	955	62.3	14 months	224 (23.5%)	481 (50.4%)	178 (18.6%)	72 (7.5%)	559 (58.5%)	396 (41.5%)
AGE[a] group	172	61.6	20 months	31 (18.0%)	63 (36.6%)	48 (27.9%)	30 (17.4%)	92 (53.5%)	80 (46.5%)
ARTI[b] group	545	62.9	13 months	156 (28.6%)	275 (50.5%)	93 (17.1%)	21 (3.9%)	352 (64.6%)	193 (35.4%)
AGE/ARTI[c] group	238	61.3	13 months	37 (15.5%)	143 (60.1%)	37 (15.5%)	21 (8.8%)	115 (48.3%)	123 (51.7%)

[a] Acute gastroenteritis.
[b] Acute respiratory tract infection.
[c] Symptoms of both AGE and ARTI.

simultaneous presence of gastrointestinal and respiratory symptoms has made the interpretation of the results difficult [23,24]. In our previous study, we found all four commonly circulating HCoVs in the stool samples of children with AGE [23]. However, half of these children also had respiratory symptoms, and some of the stool samples of the control children without gastrointestinal symptoms also harbored HCoVs.

In this prospective study, we simultaneously collected stool and nasal swab samples from children with AGE and an ARTI in order to clarify whether HCoV findings in stools are actually associated with AGE.

2. Study design

2.1. Patients and samples

This study was approved by the Ethics Committee of Pirkanmaa Hospital District and conducted at Tampere University Hospital's Department of Pediatrics from September 2009 to August 2011.

Children under 16 years of age with AGE who were admitted as outpatients or inpatients, or who came down with AGE during a stay in hospital, were eligible for the study. Of children with ARTI, those admitted as inpatients were eligible. Informed consent was obtained from the parents of all children enrolled. For the analysis of the study results, the patients were divided into three groups: the AGE group (children with symptoms of gastrointestinal infection only), the ARTI group (children with symptoms of respiratory tract infection only), and the AGE/ARTI group (children with different combinations of symptoms of both AGE and ARTI). Some children were admitted to the hospital more than once during the study period, and these admissions were considered to represent separate episodes if the child had been healthy for at least 2 weeks between the admissions.

Altogether, 1610 patients were eligible for the study, but in only 955 cases were both stool and nasal swab samples available and tested for HCoVs. These 955 cases included 172 children with AGE, 545 with ARTI and 238 with symptoms of both AGE and ARTI (Table 1). Moreover, 288 acute phase serum samples were available from these 955 children.

In addition to HCoVs, all stool and nasal swab samples were examined for human bocaviruses [25], all stool samples were examined for rotaviruses [26], and the stool specimens of the patients in the AGE and AGE/ARTI groups were examined for caliciviruses (including noroviruses and sapoviruses) [26,27]. HCoV-positive stool samples were additionally tested for adenoviruses and astroviruses.

2.2. Methods

Stool specimens were diluted in phosphate-buffered saline to create 10% suspensions. Nasal swab specimens were collected in UTM-RT Mini tubes (Copan Italia, Brescia, Italy), blended, centrifuged, and used for extraction.

A QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany) was employed to extract viral nucleic acid from stool suspensions, nasal swabs and sera. The nucleic acid was amplified by a two-step RT-PCR method as described previously [23]. Primers covered a part of the conserved polymerase gene region and were designed to recognize all HCoVs in the first PCR step, and more specifically group 1B (229E and NL63, now classified as alphacoronaviruses), group 2A (OC43 and HKU1, now lineage A of betacoronaviruses) and SARS-CoV in the second step. PCR products were recognized in agarose gel electrophoresis and the HCoV types were finally determined by sequencing.

For the other viruses studied, RT-PCR was used for rotaviruses and caliciviruses [26,27], PCR was used for human bocaviruses [28] and ProSpecT enzyme immunoassay kits (Oxoid, Basingstoke, UK) were used for adenoviruses and astroviruses. In addition, samples that tested positive for the adenovirus antigen were also tested using the PCR method based on Allard et al. [29] to distinguish enteric adenoviruses from non-enteric types.

IBM SPSS Statistics 20 (IBM Corp., Armonk, USA) was utilized for statistical analysis. Fisher's exact test or χ^2 test were used according to the criteria for the tests, and p values below 0.05 were considered statistically significant.

3. Results

Of the 955 children studied, 595 (62.3%) were male. The median age was 14 months, with a range from 6 days to 15 years; the age distribution is shown in Table 1.

HCoVs OC43, HKU1, 229E and NL63 were detected in 19 stool samples (2.0%) and 50 nasal swab samples (5.2%). As expected, no SARS-CoV or SARS-like CoV was detected. In all but two cases of an HCoV RNA-positive stool sample, the same coronavirus was concomitantly detected in the nasal swab sample. HCoV RNA was not detected in any of the 20 available serum samples from the HCoV-positive children.

The seasonality of the HCoV findings is shown in Fig. 1. HCoV 229E and HKU1 circulated mainly during the first season, from September 2009 to August 2010, and OC43 and NL63 during the second season, from September 2010 to August 2011.

HCoV OC43 was detected in the ARTI and AGE/ARTI groups but not in the AGE group (difference between the groups was statistically significant, $p = 0.036$; Table 2), whereas HKU1, 229E and NL63 were all found in each of the three study groups, with no significant differences between the AGE, ARTI and AGE/ARTI groups ($p = 0.486$ for HKU1, $p = 0.079$ for 229E and $p = 0.362$ for NL63; Table 2). The most commonly detected virus was HCoV NL63 (15 cases), followed by OC43 (13 cases), 229E (13 cases) and HKU1 (11 cases). HCoV NL63 was detected concomitantly in stool and nasal swab samples in seven (47%) of the positive cases, and OC43 in six (46%) of the positive cases. HKU1 and 229E were mainly detected in the nasal swab samples only.

HCoVs were detected in eight (4.7%) stool samples of children in the AGE group, and in six of the eight cases, both stool and nasal

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