Prepublication Release

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Intussusception and COVID-19 in Infants: Evidence for an Etiopathologic Correlation

Federico Scottoni, Giovanni Giuseppe Giobbe, Elisa Zambaiti, Sahira Khalaf, Neil J Sebire, Joe Curry, Paolo De Coppi, Fabrizio Gennari

DOI: 10.1542/peds.2021-054644

Journal: *Pediatrics*

Article Type: Case Report

Citation: Scottoni F, Giobbe GG, Zambaiti E, et al. Intussusception and COVID-19 in infants: evidence for an etiopathologic correlation. *Pediatrics.* 2022; doi: 10.1542/peds.2021-054644

Intussusception and COVID-19 in Infants: Evidence for an Etiopathologic Correlation

Federico Scottoni[1,&], Giovanni Giuseppe Giobbe[2,&], Elisa Zambaiti[1], Sahira Khalaf[2], Neil J Sebire[3], Joe Curry[4], Paolo De Coppi[2,4,*], Fabrizio Gennari[1,*]

[1] Department of Pediatric General Surgery, Regina Margherita Children's Hospital, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, Turin, Italy.

[2] Stem Cell and Regenerative Medicine Section, GOSICH Zayed Centre for Research into Rare Disease in Children, University College London, London, UK

[3]Department of Histopathology, NIHR Great Ormond Street Hospital BRC, London, UK

[4] Dept. of Specialist Neonatal and Paediatric Surgery, NIHR Great Ormond Street Hospital BRC, London, UK

[&]: Federico Scottoni and Giovanni Giuseppe Giobbe contributed equally as Co-first authors

*: Paolo De Coppi and Fabrizio Gennari contributed equally as co-senior authors.

Correspondence should be address to: fscottoni@msn.com

Corresponding Author.
Federico Scottoni
Email: fscottoni@msn.com
Tel: 00443274412549
Address: UOC Chirurgia Pediatrica, Ospedale Infantile Regina Margherita, Piazza Polonia 94, 10126 Torino (To) ,Italy.

Conflict of Interest Disclosures
The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support
OAK Foundation Award W1095/OCAY-14-191 and the Horizon 2020 grant INTENS 668294 support Stem Cell and Regenerative Medicine Section, GOSICH Zayed Centre for Research into Rare Disease in Children, however there are not specific role for this paper to declare.

GGG is supported by the BRC COVID-19 fund without specific role for this paper.

PDC is supported by NIHR Professorship and the GOSH Children's Charity without specific role for this paper.

This research was supported by the NIHR GOSH BRC as main funder for Stem Cell and Regenerative Medicine Section, GOSICH Zayed Centre for Research into Rare Disease in Children without any role.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Abbreviations
COVID-19 = coronavirus disease 2019
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Article Summary
This report presents data to support an etiopathologic correlations between COVID-19 infection and intussusception in children.

Contributors' Statement Page
Drs Federico Scottoni and Giovanni Giuseppe Giobbe conceptualized and designed the study, drafted the initial manuscript and contributed to subsequent revisions.

Dr Elisa Zambaiti collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Mrs Sahira Khalaf conducted the laboratory analyses, provided initial interpretation of the results, participated in conceptualizing and designing the paper, assisted with the initial draft and subsequent revisions.

Prof Neil J Sebire partcipated in conceptualizing and designing the study, coordinated and supervised the laboratory analyses, finalised the interpretation of the results, and critically reviewed and revised the final manuscript.

Mr Joe Curry, Prof Paolo De Coppi and Dr Fabrizio Genneri conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Non-respiratory conditions related to SARS-CoV-2 infections have been largely described. Ileocolic intussusception has been reported in association with SARS-CoV-2 infection in ten children, raising the possibility of an etiopathologic role for the virus, but none of these cases documented tissue pathology that would have supported SARS-CoV-2 intestinal inflammation. We report two cases of intussusception in patients with SARS-CoV-2 infection who were treated at different pediatric tertiary centers in Europe and provide evidence of the presence of the virus in mesenteric and intestinal tissues of the patients.

Introduction

As SARS-CoV-2 infections continues to spread worldwide, investigators have reported many non-respiratory manifestations of infection. In the pediatric population, a multisystem inflammatory syndrome develops in a small percentage of children weeks after the acute infection. (1) Furthermore, children infected by SARS-CoV-2 may also exhibit gastrointestinal (GI) symptoms. (2)

An association between adenovirus and intussusception has been documented (3). It has been hypothesized that hyperplasia of gut-associated lymphoid tissue, secondary to infection, may act as the lead point for intussusception. (4)

At present, ileocolic intussusception has been reported in association with SARS-CoV-2 infection in 10 children, raising the possibility of an etiopathological role for the virus, (5,10) but none of these cases documented direct tissue involvement.

We report two cases of intussusception in SARS-CoV-2 positive patients treated at different pediatric tertiary centers in Europe.

Patients:

A 1-month-old female infant infected by SARS-CoV-2 presented to the emergency department after a 5-day history of constipation and several episodes of postprandial milky emesis for the

previous 24 hours. On admission the patient was moderately lethargic and dehydrated and developed rectal bleeding after a digital rectal examination. Abdominal ultrasound scan demonstrated ileocecal intussusception that extended to the sigmoid colon in the left iliac fossa. Prior to any intervention, a fast antigenic rhino-pharyngeal test for SARS-CoV-2 was positive. Due to a deterioration in clinical condition that did not allow an attempt at fluoroscopy guided hydrostatic reduction, the infant was transferred to the operating theatre for urgent vascular access and laparotomy. Laparotomy confirmed an ileo-caecal intussusception that was manually reduced. A large lymph node measuring 1.5 cm diameter was noted within the mesentery, in proximity to the ileo-caecal valve. The lymph node was excised for histological evaluation. (**Supplementary Figure 1**)

On post-operative day one, oral feeding was started, and the patient achieved full enteral feedings by the end of day two. The patient remained hospitalized for 5 more days for isolation and monitoring. At one month follow-up the patient demonstrated full resolution of all gastro-intestinal signs.

A five and half month-old male infant presented with a history of lethargy, poor feeding and non-bilious vomiting. His medical history was notable for hyperinsulinism that required diazoxide treatment. He had been feeding orally and his blood sugars had been stable. On admission, he tested positive for SARS-CoV-2 but had no signs of respiratory illness. After two days he was transferred to a tertiary center for evaluation of new findings of bilious vomiting and fresh blood in his stool. At that stage an abdominal x-ray showed a prominent loop of dilated bowel in the right iliac fossa.

He underwent an abdominal ultrasound scan which demonstrated ileocolic intussusception. Pneumatic reduction was attempted but was complicated by intestinal perforation that required emergent laparotomy. The perforation was identified in the colon adjacent to the ileocecal

intussusception and intestinal necrosis was present from the terminal ileum to the splenic flexure. An extended right hemicolectomy and ileo-colic anastomosis were performed. The resected sample underwent histological examination. Post-operatively he was admitted to the intensive care unit (ITU) where he required high frequency ventilation and low dose noradrenaline support for significant respiratory disease. He was extubated on day 9 after surgery and was discharged from ITU to the surgical ward on postoperative day 11.

After the admission to the surgical ward the patient progressed to full oral feeds and was discharged in good condition on post-operative day 26.

Both the lymph node from patient 1 and the intestine from patient 2 demonstrated non-specific findings on routine histopathologic examination (**Supplementary Figure 1**). In order to confirm the role of SARS-CoV-2 as directly contributory, immunofluorescence staining for ACE2 (human angiotensin-converting enzyme 2, a transmembrane enzyme serving as cell entry point for SARS-CoV-2), NP CoV (SARS-CoV-2 nuclear protein) and dsRNA (viral *double-stranded RNA)* was performed on both samples. Immunofluorescence staining demonstrated the presence of SARS-CoV-2 in both the mesenteric lymph node from patient 1 and in the ileum from patient 2 (**Figure 1, Supplementary Figure 1**).

Discussion

The association between virus and intussusception in children is well known from previous studies (4). Furthermore, ileocolic intussusception has been reported in association with SARS-CoV-2 infection in 10 children, raising the possibility of a correlation between these conditions. (5-10) However, these reports did not directly implicate SARS-CoV-2 in intestinal pathology.

In literature, the accepted hypothesis regarding the etiopathology of intussusception and its correlation with viral infection is based on Peyer's patch swelling and lymph node hypertrophy

acting as lead points. (4,11) Theoretically any virus capable of triggering an enteric inflammatory response could produce an intussusception in a vulnerable host. Notably, ACE2, the most important receptor that mediates intracellular SARS-CoV-2 entry in humans, is densely present in the membranes by small intestine enterocytes. (12) It is reasonable to hypothesize that inflammation of the small intestine and associated lymphatic hyperplasia from SARS-CoV-2 infection may result in intussusception.

In summary, we have provided histopathologic evidence that supports a role for SARS-CoV-2-mediated intestinal inflammation and lymphoid hypertrophy in the etiopathogenesis of ileocolic intussusception.

Acknowledgments

This research was funded by the OAK Foundation Award W1095/OCAY-14-191 and the Horizon 2020 grant INTENS 668294. GGG is supported by the BRC COVID-19 fund. PDC is supported by NIHR Professorship and the GOSH Children's Charity. This research was supported by the NIHR GOSH BRC. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. We thank Alessandra Linari and prof. Mauro Giulio Papotti from the "Città della salute e della scienza di Torino" Histopathology Facility, for providing the tissue slides of patient no.1. We would also like to thank Olumide K Ogunbiyi and Talisa Mistry from the GOSH Histopathology Facility, for providing the tissue slides of patient no.2.

References

1. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, Klein JD, Bhutta ZA. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020 Nov;20(11):e276-e288. doi: 10.1016/S1473-3099(20)30651-4. Epub 2020 Aug 17.

2. Pedro A. Pousa, Tamires S.C. Mendonça, Eduardo A. Oliveira and Ana Cristina Simões-e-Silva. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations J Pediatr (Rio J). 2021 March-April; 97(2): 116–139. Published online 2020 Sep 22.

3. Bhisitkul DM, Todd KM, Listernick R. Adenovirus infection and childhood intussusception. Am J Dis Child. 1992;146(11):1331-3.

4. Lee YW, Yang SI, Kim JM, Kim JY Clinical Features and Role of Viral Isolates from Stool Samples of Intussuception in Children. Pediatr Gastroenterol Hepatol Nutr. 2013 Sep;16(3):162-70. doi: 10.5223/pghn.2013.16.3.162. Epub 2013 Sep 30.

5. Moazzam Z, Salim A, Ashraf A, Jehan F, Arshad M. Intussusception in a child with COVID-19 in the USA. J Pediatr Surg Case Rep. 2020;59:101533–101533. doi: 10.1016/j.epsc.2020.101533.

6. Cai X, Ma Y, Li S, Chen Y, Rong Z, Li W. Clinical characteristics of 5 COVID-19 cases with non-respiratory symptoms as the first manifestation in children. Front Pediatr. 2020;8:258. doi: 10.3389/fped.2020.00258.

7. Martínez-Castaño I, Calabuig-Barbero E, Gonzálvez-Piñera J, López-Ayala JM. COVID-19 infection is a diagnostic challenge in infants with ileocecal intussusception. Pediatr Emerg Care. 2020;6:e368. doi: 10.1097/PEC.0000000000002155.

8. Khan S, Hartman L, Navarro YJS, Rossini CJ, Burdett C, Pennell C. Pediatric Covid-19 mesenteric lymphoid hyperplasia associated intussusception: A case report and literature review. J Pediatr Surg Case Rep. 2021;73:101988. doi:10.1016/j.epsc.2021.101988

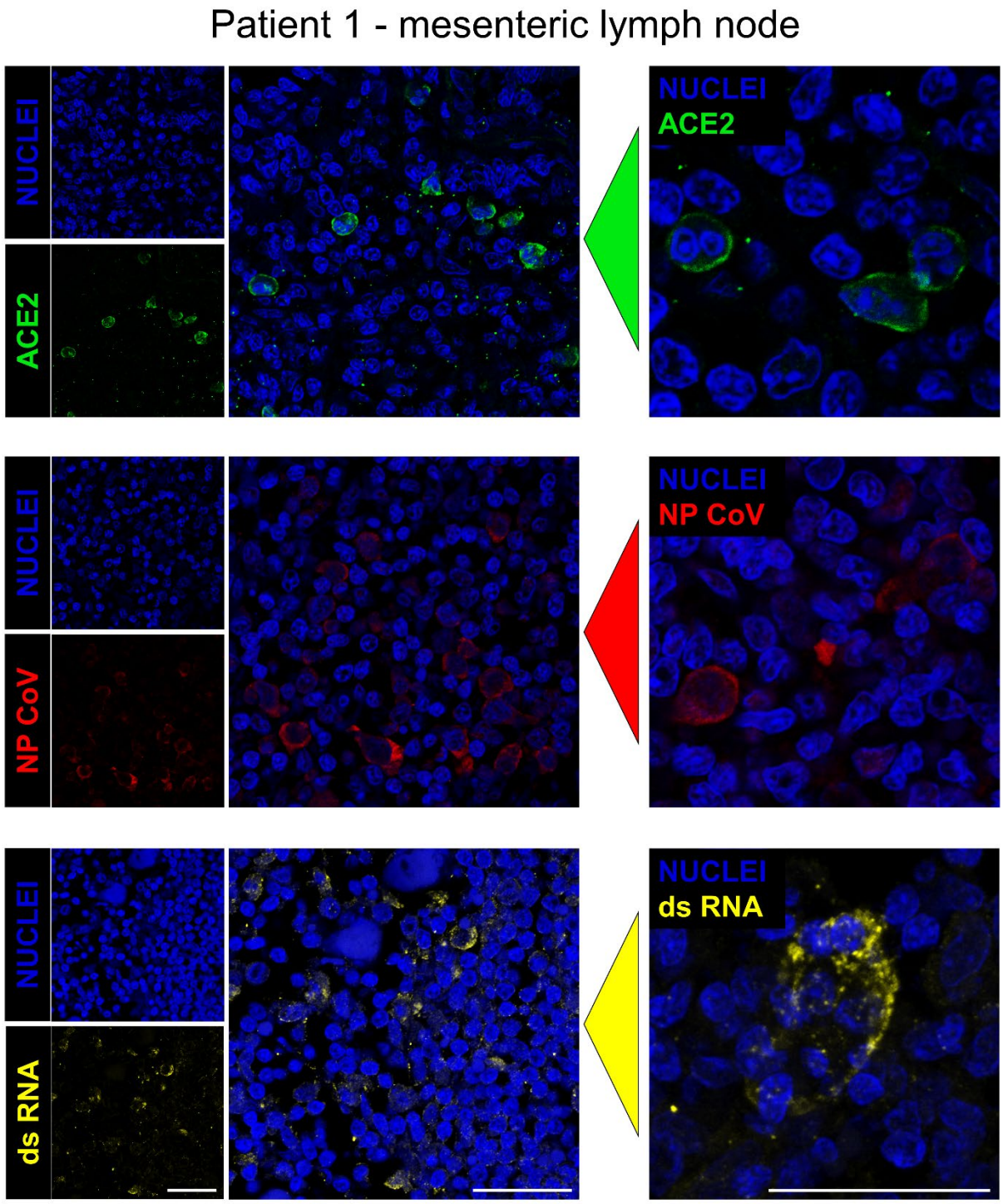
9. Yi HJ, Ahern BJ. A lethargic child with COVID-19 infection. JAAPA. 2022 Jan 1;35(1):34-36. doi: 10.1097/01.JAA.0000800240.20418.41. PMID: 34939588.

10. Noviello C, Bollettini T, Mercedes R, Papparella A, Nobile S, Cobellis G. COVID-19 Can Cause Severe Intussusception in Infants: Case Report and Literature Review. Pediatr Infect Dis J. 2021;40(11):e437-e438. doi:10.1097/INF.0000000000003257

11. Kombo LA, Gerber MA, Pickering LK, Atreya CD, Breiman RF. Intussusception, infection, and immunization: summary of a workshop on rotavirus. Pediatrics. 2001 Aug;108(2):E37. doi: 10.1542/peds.108.2.e37. PMID: 11483847.

12. Zhang H, Li HB, Lyu JR, et al. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. Int J Infect Dis. 2020;96:19-24. doi:10.1016/j.ijid.2020.04.027

Figure 1. Immunofluorescence panels of paraffin-embedded 7 µm tissue sections, following antigen retrieval in mesenteric lymph node isolated from patient 1. Angiotensin-converting enzyme 2 (ACE2) (R&D Systems AF933) shown in green; SARS-CoV-2 nucleocapsid (NP CoV) (Sino Biological 40143-MM05) shown in red; SARS-CoV-2 Double Strand RNA (dsRNA) (Scicons J2) shown in yellow; all nuclei are stained in blue (Hoechst 33342) (Thermo Fisher 62249). All scale bars in main images and enlargement panels are 30 µm.



Supplementary Figure 1. a) Photomicrograph of paraffin-embedded 7 µm tissue section. Haematoxylin and eosin staining showing reactive lymph node with non-specific, likely arti factual, capsule dissociation only (indicated by the black asterisk) of mesenteric lymph node isolated from patient 1. Scale bar 250 µm. **b)** Immunofluorescence panels of paraffin-embedded 7 µm tissue sections, following antigen retrieval in ileum adjacent to intussusception isolated from patient 2. Angiotensin-converting enzyme 2 (ACE2) (R&D Systems AF933) shown in green; SARS-CoV-2 nucleocapsid (NP CoV) (Sino Biological 40143-MM05) shown in red; SARS-CoV-2 Double Strand RNA (dsRNA) (Scicons J2) shown in yellow; all nuclei are stained in blue (Hoechst 33342) (Thermo Fisher 62249). All scale bars in main images and enlargement panels are 30 µm.