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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

EDITORIAL

More research is needed on the long-term effects of COVID-19 on children and adolescents

COVID-19 continues to present us with new clinical challenges in all medical specialities. Signs and symptoms in infected patients have been highly variable, and some were not evident in the early phase of the pandemic. As paediatricians, the foremost finding early on was the fundamental age-dependent difference in the risk of becoming severely ill, or even modestly ill, from COVID-19. Early Chinese, Italian and US studies implied that low numbers of children were being diagnosed and that the mortality in both children and adolescents were very low.[1,2] The reason for this age difference is not yet fully understood, but it is the focus of many on-going research initiatives.[3] As a result of the early epidemiology reports, few paediatricians had spent much time worrying about the late effects that this novel virus would have on children. That is something we must reconsider now.

This edition of *Acta Paediatrica* contains reports on two of these late conditions affecting children and adolescents. These are multisystem inflammatory syndrome in children (MIS-C) and long-term signs and symptoms in children and adolescents after COVID-19. The latter has been unofficially termed long COVID in adult medicine.

A Kawasaki-like inflammatory condition was reported early during the pandemic in areas with high circulation of the virus that causes COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] About four weeks after becoming infected and displaying mild symptoms or even being asymptomatic, children presented with a range of symptoms. These included a high fever, lethargy, conjunctivitis, exanthema, decreased cardiac function or even cardiogenic shock, respiratory problems and abdominal or thoracic pain. Initial comparisons were made with Kawasaki disease, but children with MIS-C were generally older and coronary involvement was less frequent. The termed MIS-C was coined by the American Centers for Disease Control and the World Health Organization (WHO), while the Royal College of Paediatrics and Child Health used the term paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) to describe cases seen in the UK.[5] The terminology used reflects the hyperinflammatory state that the children suffer from and the effect this has on multiple organs. The immune profile of children with MIS-C shares some similarities with Kawasaki disease but also differs from it in other ways, suggesting different modes of immune activation.[6]

The paper by Carbajal et al in this issue of *Acta Paediatrica* describes some important epidemiological and clinical findings in children with COVID-19, who were diagnosed and treated in Paris.[7] Although only a modest number of patients were included in the analysis, the temporal relationship between becoming infected with SARS-CoV-2 and MIS-C was strong. All the MIS-C cases studied by the authors were clustered around one month after the peak of new reported cases of COVID-19 in France, whereas Kawasaki disease cases are evenly distributed over time. Whether this implies that the rate of classic Kawasaki disease is unaffected by the COVID-19 pandemic is too early to say. Interestingly, two of the patients in this study fulfilled the classic Kawasaki disease criteria, but both of them were included in the MIS-C group. In contrast, a joint European and American study carried out earlier in 2020 found that the MIS-C subgroup, who met the diagnostic criteria for classic Kawasaki disease, tended to be older and have higher neutrophil, C-reactive protein, ferritin, fibrinogen and troponin levels, but lower lymphocyte counts.[8] The clinical signs and symptoms reported by Carbajal et al were similar to those reported in a systematic review from September 2020, which reported that fever and gastrointestinal-related symptoms, like abdominal pain, diarrhoea and vomiting, were the most common clinical presentations.[9] The major differences between the children with MIS-C and Kawasaki disease were that the MIS-C patients were older, all of them needed of intensive care support and inotropes, they had myocardial dysfunction and displayed low lymphocytes and higher C-reactive protein levels than those with Kawasaki disease.

One current problem that needs to be addressed in studies of MIS-C is the different case definitions provided by the UK Royal College of Paediatrics and Child Health and the US Centers for Disease Control and the WHO. They only vary slightly, but the most noticeable difference is that the UK definition does not require a temporal association with clinical COVID-19 disease. It is important to note that Carbajal et al's findings were consistent, regardless of which definition they applied to their data. The scientific community needs to agree case definitions and inclusion criteria for MIS-C, to enable comparisons between different studies in the future,

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

In another paper in this issue of *Acta Paediatrica*, Ludvigsson describes five Swedish children and adolescents with long-term symptoms after they were presumably infected with SARS-CoV-2.[5] The same paper also contains a systematic review on paediatric long COVID, using the established MEDLINE, EMBASE and Web of Science databases, as well as a search of medical papers filed in the medRxiv/bioRxiv preprint database. One of the most interesting findings in this paper is that the search failed to identify any previous reports on long COVID in children, probably indicating how late in the pandemic paediatric long COVID occurred and how new this phenomenon is to the paediatric community. Alternatively, this may be a much rarer condition than we have seen in adults. Only time will tell. All five had symptoms lasting for at least six months, and the main symptom was fatigue, dyspnoea and either heart palpitations or chest pain. Interestingly, the children had not tested positive for SARS-CoV-2, using reverse transcription polymerase chain reaction, or for antibodies using serology. However, it is important to point out that there was sparse, or close to non-existent testing at the beginning of the pandemic in Sweden, especially for children. Having said that, the lack of serological proof of infection is still interesting. Do long COVID patients have lower antibody titres than others who are infected with SARS-CoV-2? Ludvigsson calls for follow-up programmes to be established for children who appear to demonstrate long COVID. At the time of writing this editorial, in late 2020, we had seen around 30 children and adolescents with suspected long-term consequences from COVID-19 at our clinic in the Karolinska University Hospital in Stockholm. This is a first, and important, step in understanding the long COVID pathophsiology in relation to other post-infectious syndromes, like chronic fatigue syndrome in children. In contrast to chronic fatigue syndrome, we do not understand the epidemiology, clinical presentations and treatment of long COVID yet.[10] Despite the differences between these conditions, important lessons can hopefully be learned from chronic fatigue syndrome on how to support the children, adolescents and families affected by long COVID.

Advances have been made on managing the acute phase of severe COVID-19. However, we still need high-quality studies to help us to find better ways to help children and adolescents who have been infected with SARS-CoV-2 and are now experiencing severe or long-term complications.

CONFLICT OF INTEREST

None.

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