Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus 2

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Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus-2.

Multisystem inflammatory syndrome in children (MIS-C) is a novel disease that is associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Until now, only one study has attempted to estimate the incidence of MIS-C among SARS-CoV-2 infected children and adolescents[2]. This study from the New York State has reported an incidence of MIS-C of 2 per 100,000 persons younger than 21 years of age between 1 March 1 and 10 May 2020. In the same period and population, the incidence of laboratory-confirmed SARS-CoV-2 infection was 322 per 100,000, equivalent to an incidence of MIS-C of one in 161 of SARS-CoV-2 infected individuals.[2] However, at this very early stage during the pandemic, access to SARS-CoV-2 PCR testing was very limited, particular among asymptomatic children and adolescents. Thus, the estimated incidence from the New York State may have been overestimated. Based on seropositive individuals in Denmark, we aimed to estimate the incidence of MIS-C among SARS-CoV-2 infected children and adolescents during the first year of the pandemic.

The study was a prospective nationwide cohort study of MIS-C using data from all 18 Danish paediatric departments, which serve 1,153,049 children and adolescents below 18 years of age. The study was carried out from 1 March 2020 to 28 February 2021. Each paediatric department had identified a principal investigator on 12 March 2020 as part of a nationwide paediatric COVID-19 research study. This study was approved by the Ethics Committee of Capital Region of Denmark (H-20028631) and the Danish Data Protection Agency (P-2019-29). Informed parental consent was provided before participation.

We found that 23 patients had been diagnosed with MIS-C, based on the criteria devised by the World Health Organization and American Centers for Disease Control and Prevention. This equated to a yearly incidence of two per 100,000 individuals under 18. The patients had a median age of eight (range 2-17) years, nine patients were aged 12-17 and median hospitalisation was eight (3-24) days. We found that 13/23 (57%) had hypotension, five (22%) received vasopressor support, 12 (52%) were admitted to intensive care units. Twenty-one (91%) received intravenous immunoglobulin, 17 (74%) had steroids and three (13%) were given anakinra while two cases were self-limiting. All the children survived. All cases had confirmed SARS-CoV-2 infection determined by either positive SARS-CoV-2 positive polymerase chain reaction prior to the diagnose of MIS-C (20 of 23 cases; 87%) (tested due exposure or symptoms) and/or positive SARS-CoV-2 serology (15 of 18 cases; 83%).

The cumulative incidence of Danish children with SARS-CoV-2 was estimated from a nationwide seroprevalence surveillance study by the Statens Serum Institute of randomly selected individuals in March 2021[3]. In this study, seroprevalence of SARS-CoV-2 in the Danish population was determined since August 2020 in the non-vaccinated population after personal invitation to persons above 12 years of age. These data were representative for all regions in Denmark with equal distribution. Detection of total antibodies to SARS-CoV-2 was determined an enzyme-linked immunosorbent assay in serum (WANTAI Ab ELISA®). The study found that 43/530 (8.1%) individuals aged 12-17 years had positive SARS-CoV-2 immunoglobulin G in March 2021 (personal communication Laura Espenhain) and 7.0% (CI 6.6-7.4) of 10,631 adolescents and adults[3].This suggests an incidence of MIS-C of one in 3,700 in paediatrics patient aged 12 years plus, based on nine MIS-C patients out of 33,183 positive for SARS-CoV-2. When we assumed the same seroprevalence for patients below 12 years of age, the overall incidence of MIS-C in children and adolescents was one in 4,100, based on 23 MIS-C patients out of 93,397 infected with SARS-CoV-2.

This study provides an estimate of the risk of MIS-C after SARS-CoV-2-infection. MIS-C cases were determined by prospective nationwide data from all Danish paediatric departments and we assume our case series was complete for several reasons. First, all cases underwent in-depth investigations for differential diagnoses. Second, all cases had either positive polymerase chain reaction (PCR) prior to MIS-C and/or positive SARS-CoV-2 serology. Third, children hospitalised with unexplained severe systemic inflammation in March and April 2020, before we became aware of MIS-C, were subsequently investigated with SARS-CoV-2 serology.

However, as no unequivocal diagnostic criteria exist, milder self-limiting cases could have gone undiagnosed. In addition, hyperinflammatory conditions unrelated to SARS-CoV-2, but occurring in patients with previous SARS-CoV-2 infection, could have been diagnosed as MIS-C. Another limitation of this study was the relatively few MIS-C cases which probably was due to the relatively low SARS-CoV-2 infection rate in Denmark.

With respect to Danish children and adolescents infected with SARS-CoV-2, we used nationwide seroprevalence data from children aged 12-17 years[3]. These surveillance data included relatively few individuals encumbering the total number of SARS-CoV-2 infected children and adolescents with some uncertainty. The data was extrapolated to children below 12 years, as a previous nationwide Danish study in the same settings showed that the SARS-CoV-2 seroprevalence was equal across all childhood age groups.[4] However, a Swiss population-based study found a lower seroprevalence in children below 10 years of age.[5] Thus, the one in 4,100 risk of MIS-C may have been underestimated in younger children. On the other hand, the risk could also have been overestimated as antibodies may wane. A strength of our study was the serology-based estimate of the SARS-CoV-2 incidence, as this was more reliable than using PCR-positive cases. The calculated number of infected individuals, determined by serology (93,397), was more than twice the number of PCR-positive children (38,877), according to national PCR-surveillance data from 1 March 2020 to 28 February 2021. Hence, the incidence was calculated to be as high as one of 1,700 individuals, versus one in 4,100, if counting to PCR-positive children only. This reflected the fact that PCR test capacity was limited in Denmark during the first wave and the possibility that a significant proportion of children were not tested due to no, or just mild, symptoms. Accordingly, the previous estimate of the incidence of MIS-C among SARS-CoV-2-infected individuals from the New York State in spring 2020 was based on PCR-positive cases and found a 25-fold higher incidence than the incidence estimated in our study (one in 161 versus one in 4,100 in our population)[2]. Thus, it may also reflect that asymptomatic children and adolescents may not have undergone PCR testing in The New York State at this early stage of the pandemic.

SARS-CoV-2 was initially regarded as a mild infection in children, but the emergence of MIS-C means that it is now recognised as an infection with a significant risk for serious complications.[1] We have previously reported that the risk of hospital admission due to acute COVID-19 was one in 1,250 SARS-CoV-2 infected children and that they were hospitalised for a median of only two days, without intensive care[6]. In contrast the children with MIS-C in this study were hospitalised for a median of eight days and more than half required intensive care.

In conclusion, despite this population-based prospective study is encumbered with several uncertainties, it confirms that MIS-C is a rare but serious complication of SARS-CoV-2 infection, which occurred in one in 4,100 infected children.

ABBREVIATIONS

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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