MIS-C Associated with COVID-19

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This study aimed to achieve a better understanding of the epidemiological and clinical characteristics of multisystem inflammatory syndrome in children (MIS-C) following coronavirus disease 2019 (COVID-19).

Keywords: multisystem inflammatory syndrome ; COVID-19 ; SARS-CoV-2 ; meta-analysis ; conjunctivitis

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induced more than 129 million confirmed cases and 2.8 million deaths globally until the end of March 2021. The affected adults may experience fever, diarrhoea, respiratory failure, and heart/renal failure [1]. Children are less infected and present milder symptoms/signs (s/s) compared to adult patients [2][3][4].

However, the United Kingdom's National Health Service alerted paediatricians regarding a new outbreak of a Kawasaki-like disease, which was temporally associated with COVID-19 and revealed clinical evidence of SARS-CoV-2 infection [5][6]. Affected children appear to have severe illness, including fever and multi-organ inflammation (shock, cardiac, respiratory, renal, gastrointestinal, or neurological symptoms) similar to the cytokine storm in Kawasaki disease (KD) [7][8][9]. The novel disease is defined as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) [10][11][12].

The ocular manifestation (conjunctivitis) is common in MIS-C associated with COVID-19 [7][8]. Retinal manifestations and SARS-Cov-2 detection in retina have also been reported [13][14][15]. Whether conjunctivitis is due to virus attack or related to an inflammatory response remains unknown. Previous studies on adult COVID-19 have detected the presence of SARS-CoV-2 in conjunctiva/tear swab by reverse transcription polymerase chain reaction (RT-PCR), suggesting that the conjunctiva is a transmission route of COVID-19 in adults [1]. Therefore, it is crucial to investigate the relationship between ocular manifestation (conjunctivitis) and COVID-19 in children. Since paediatric cases comprise only 0.8–2.2% of all confirmed cases [3][16], we conducted a meta-analysis to enrol more paediatric patients and increase the statistical power.

The underlying mechanism of MIS-C remains unknown. MIS-C exhibits Kawasaki-like symptoms; hence, it is important to describe its systemic manifestations. Furthermore, exploring the proportion of complete KD among MIS-C patients helps us understand the similarities/differences between MIS-C and KD. Assessing the exposure history to suspected/confirmed cases and analysing the positive rate of virus detection through nasopharyngeal PCR and serology can provide a better explanation of the pathogenesis.

2. Research on systemic manifestations in paediatric MIS-C patients associated with COVID-19

This meta-analysis focused on the ocular and systemic manifestations in paediatric MIS-C patients associated with COVID-19, based on 32 studies derived from the database search. Among the 1458 patients, 48.4% had conjunctivitis. The five most prevalent systemic manifestations were fever (96.4%), gastrointestinal s/s (76.7%), shock (61.5%), rash (57.1%), and neurological s/s (36.8%). Around one-third of the patients had presentations of complete KD and nearly half had exposure history to suspected/confirmed cases. The PCR positive rate of nasopharyngeal PCR was almost 40%, while serum antibody revealed a higher rate of about 80%.

Since the COVID-19 pandemic has spread worldwide, many researchers have noticed the importance of MIS-C, which is a severe complication following SARS-CoV-2 infection in children. Several studies have proposed that SARS-CoV-2 triggers MIS-C [8][17][18][19][20]. The evidence includes the timing of the MIS-C that occurred in several countries related to the SARS-CoV-2 epidemic, the geographical areas matched with SARS-CoV-2 infection, and the positive finding of

SARS-CoV-2 or exposure history in MIS-C patients. Furthermore, MIS-C usually occurs one month after SARS-CoV-2, implying that post-infectious inflammation might be the underlying mechanism of MIS-C [21].

MIS-C was first reported as a novel disease that had presentations of multi-organ dysfunction and manifestations resembling KD. KD is among the most prevalent vasculitis in childhood, which classically presented with fever (more than 5 days) and at least four out of five clinical s/s, including conjunctivitis, oropharyngeal mucosa changes, peripheral extremities changes, skin rash, and cervical lymphadenopathy [22]. The mechanisms of KD have long been studied, and several factors have supported the hypothesis that previous infections, mainly those from respiratory viruses, may trigger KD. Although MIS-C and KD have similar clinical manifestations, they still have some differences in several aspects. MIS-C occurs more often in children over 5 years old; however, KD often affects children younger than 5 years old [23][24]. MIS-C is reported more in Western countries, whereas KD is more common in Asian/Pacific regions such as Japan [24]. The frequencies of gastrointestinal symptoms and shock in MIS-C are higher than that in KD [6][25]. In contrast, conjunctivitis and rash are less prevalent in MIS-C compared to KD [6][25]. Furthermore, lab data show that MIS-C usually has more lymphopenia, lower platelet count, higher ferritin level, and higher cardiac biomarkers than KD [20]. Therefore, MIS-C and KD are now regarded as two distinct clinical entities [6][19][20][23][24].

Previous review articles written by Jiang, Kiss, Esposito, and Kabeerdoss et al. have provided a panoramic view of MIS-C [8][18][19][20]. However, they are lacking in precise calculation of the proportion of each s/s, presentation of complete KD, positivity of nasopharyngeal PCR/serum antibody, and exposure history. For a comprehensive understanding of MIS-C, we analysed the data of 1458 patients from 32 studies. To the best of our knowledge, our meta-analysis has included a larger number of studies than previous meta-analyses or reviews.

Our study revealed that 48.4% of MIS-C patients had conjunctivitis, comparable to a previous meta-analysis conducted by Baradaran, Hoste, Sood, and Aronoff [6][7][26][27]. The prevalence of conjunctivitis in our MIS-C patients was much higher than that in Lofredo's study of adult COVID-19 patients (around 1.1%) [28]. The fact that the proportion of conjunctivitis is higher in MIS-C than that in adult COVID-19 patients may imply the different pathogenesis of the two diseases. Conjunctivitis in MIS-C might be induced more by systemic immunological reaction than by a local virus attack [20]. Because immunological reaction can last longer, conjunctivitis may have more chances to be detected.

The five most prevalent systemic manifestations in our MIS-C patients were fever (96.4%), gastrointestinal s/s (76.7%), shock (61.5%), rash (57.1%), and neurological s/s (36.8%). Several meta-analyses supported our findings, with similar prevalence [6][7][8][19][26][27][29]. It is worth noting that the frequencies of gastrointestinal s/s and rash in MIS-C were higher than those in typical adult COVID-19 [19][30][31], demonstrating possible differences in the underlying mechanism between MIS-C and adult COVID-19.

In our meta-analysis, 30.7% of MIS-C patients had complete KD. A previous study by Jiang et al. found the rate of complete KD to be around 41.1% [8]. It is worth noting that we have only calculated the ratio of complete KD. If we added incomplete KD into the analysis, the proportion should be higher than 30.7%. Furthermore, we found that MIS-C was slightly more prevalent in males than in females, which was consistent with previous meta-analyses or population-based studies [6][7][17][19][26][32]. Kabeerdoss et al., in their review article, demonstrated that there is no significant male predominance in MIS-C [20]. However, previous studies found a stronger male-predominant pattern in KD [33][34]. At present, we do not fully understand why the proportion of males in KD is higher than that in MIS-C. Further genetic, immunological, or epidemiological studies are warranted to investigate this issue.

Our study, as well as several previous studies, found that MIS-C patients had a less positive rate of SARS-CoV-2 in PCR than in serology (mostly IgG), suggesting that this inflammatory syndrome is not mediated by direct viral invasion but coincides with the development of acquired immune responses to SARS-CoV-2 [6][7][8][17][26][35].

Our study revealed that 47.4% of MIS-C patients had a history of contact with COVID-19 cases. The included studies showed that the exposure history ranges from 10.3% to 99.3%, which might be affected by lifestyle. Due to the full-blown and worldwide spread of SARS-CoV-2, the CDC recommends wearing masks and maintaining social distancing when in public. Moreover, hand hygiene and staying at home were introduced as effective ways of infection prevention.

Current treatment of MIS-C mimics the treatment of KD. Guidelines published by the American College of Rheumatology suggested an IVIG dosage of 2 gm/kg and adding methylprednisolone IV 1–2 mg/kg/day for hemodynamic unstable MIS-C or refractory MIS-C. Aspirin should be considered based on clinical condition and risk–benefit evaluation [19][36]. The limitation of this meta-analysis is that we have only focused on the part of epidemiological and clinical characteristics, but did not analyse the part of lab data, treatment, and prognosis.

All the main outcomes of our study did not show significant public bias. However, outcomes regarding conjunctivitis, exposure history, and complete KD demonstrated moderate to high heterogeneities. The high heterogeneities can be explained by the fact that the current inclusion criteria of MIS-C are too broad and might overlap children with different diseases such as KD, toxic shock syndrome (TSS), and macrophage-activation syndrome (MAS). Or it may result from differences in ethnicity, pre-existing health conditions, socioeconomic factors, and access to healthcare. In addition, different timings of laboratory tests and discrepancies in thresholds for defining abnormal values increase the heterogeneity between studies. Another limitation of our analyses is that data for a few variables were not reported in every included study, making direct comparisons between studies difficult. In addition, we did not investigate the genetic variants of SARS-CoV-2 in our analyses. We have tried to add the keywords United Kingdom variant (20I/501Y) and South African variant (20H/501Y.V2) into our previous searching term. However, there have been no studies regarding these genetic variants in children associated with COVID-19. More studies with complete data are warranted to derive a profound knowledge of MIS-C in COVID-19.

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