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Neurological Manifestations of COVID-19 Associated Multi-system Inflammatory Syndrome in Children: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Children comprise only 1–5% of COVID-19 cases. Recent studies have shown that COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) can present with neurological signs and symptoms. In this systematic review and meta-analysis, we have reviewed neurological involvement in these patients.

Methods: A comprehensive electronic literature search was done on PubMed, Google Scholar, Embase, Cochrane database, and SCOPUS for the published English language articles from December 1, 2019, to February 28, 2021. A meta-analysis of the proportion was expressed as a pooled proportion with a 95% confidence interval (CI). Representative forest plots showing individual studies and the combined effect size were generated to provide an overview of the results.

Results: This systematic review and meta-analysis analyzed 15 published MIS-C studies with a total of 785 patients. Neurological manifestations in patients with MIS-C was found in 27.1%. We found that 27% developed headaches, 17.1% developed meningism/meningitis and 7.6 % developed encephalopathy. Other uncommon neurological manifestations of MIS-C includes anosmia, seizures, cerebellar ataxia, global proximal muscle weakness and bulbar palsy. In MIS-C patients with neurological feature, neuroimaging showed signal changes in the splenium of the corpus callosum. Electroencephalography showed slow wave pattern and nerve conduction studies and electromyography showed mild myopathic and neuropathic changes.

Conclusions: Our study revealed that neurological manifestations are not uncommon in patients with MIS-C. Further large prospective studies are needed to better explore the disease spectrum and to unravel the underlying pathophysiology.

Keywords: Children; COVID-19; kawasaki disease; MIS-C, neurology

INTRODUCTION

The Coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a defining global health crisis of our time and the biggest challenge we have faced since the World War II.[1] Since its emergence in China at the end of 2019, the virus has spread to every corner of the world, and cases have increased exponentially. The rise in the index of global cases and mortality led to a global public health crisis, which was subsequently declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.[2] Known to predominantly cause respiratory illness, the spectrum of COVID-19 ranges from mild, self-limiting respiratory illness to severe

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progressive pneumonia, multiple organ failure, and death.[3] Unlike adults, who usually have the severe form of the disease, COVID-19 usually causes mild respiratory symptoms in children and adolescents.[4] However, recently, among children infected with COVID-19, increasing cases of Kawasaki disease mimicking multi-system inflammatory disorder have been reported. These cases with hyperinflammatory syndrome and multiorgan involvement were later provisionally named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the United States.[5] So far, several papers have been published in the medical literature about the epidemiology, clinical manifestations, treatment, and outcome of MIS-C.[6-20] Although the syndrome mainly involves the cardiovascular system and the gastrointestinal system, neurological manifestations have been described. Therefore, we aimed to conduct a systematic review and meta-analysis of the literatures to elucidate the neurological manifestations of MIS-C related to COVID-19.

METHODS

Our meta-analysis explored the prevalence of neurological manifestation in children with COVID-19 associated multisystem inflammatory syndrome according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement in conjugation with the PRISMA flow diagram and MOOSE checklist for meta-analyses of observational studies.[21, 22]

Literature search and selection

A comprehensive electronic literature search was performed on PubMed, Google Scholar, Embase, Cochrane database, and SCOPUS for the published English language articles from December 1, 2019, to February 28, 2021. Boolean logic was used for conducting database search and Boolean search operators "AND" and "OR" were used to link search terms. The search terms used were COVID-19, SARS-CoV-2, pediatric inflammatory multisystem syndrome, multisystem inflammatory syndrome in children, PIMS-TS, Kawasaki-like disease, and MIS-C. Detailed search strategy for PubMed search is mentioned in supplementary file, appendix 1. For each study shortlisted through this process, the reference section of the paper was checked to identify further studies not found in previous database searches. Furthermore, repositories of grey literature and preprint servers were also searched. All the studies obtained from the above-mentioned methods were imported to Mendeley library. Check for duplicates was run on Mendeley, which displayed a list of duplicate references, which were then removed. Although reference management software use algorithms to remove duplicates, this is only partially successful and necessitates removing the remaining duplicates manually. Therefore, studies were screened for duplicates by two independent reviewers (GN and JHR). The titles and abstracts of the studies remaining after duplicates removal were screened independently by GN and JHR. Potentially relevant full-texts were then screened according to our inclusion and exclusion criteria by GN and JHR. Any discrepancies were resolved through discussion with GSS. For multiple publications of the same data, the most inclusive, comprehensive, and the publication with larger sample size and the most recent one was considered.

We included all prospective or retrospective studies and case series published in the English language, which enrolled children and adolescents of any gender, ethnicity, or nationality diagnosed with COVID-19 associated MIS-C. We included the studies that had defined the neurological manifestations in patients with COVID-19 associated MIS-C. We excluded case reports, case series involving 2 or less cases, review articles, studies published in language other than English and the manuscripts that did not report neurological manifestations in patients with COVID-19 associated MIS-C.

Data extraction

The finally included studies were collated, and the two reviewers (GN and JHR) used standardized data extraction formats to extract the data. After extraction, both reviewers matched their data with each other and revisited papers where disagreements arose. Any discrepancies were resolved through discussion with the third reviewer (GSS). The extracted data included the following: first author, study design, site of study, year of publication, the total number of patients with COVID-19 associated MIS-C, mean age, the gender of patients, and number of patients with various neurological manifestations. If the required data were missing, not reported in the paper, or reported in an unusual form, the corresponding author of the very papers was approached via email or researchgate for clarification. Supplementary material associated with the main paper was also explored for further clarifications.

Quality assessment

To evaluate the quality of the studies included in this review, the Newcastle-Ottawa Scale for cross-sectional studies and case-control studies was used (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Using the tool as a checklist, the qualities of each of the original articles were evaluated independently by the authors (GN and GSS). Interrater reliability (Cohen's kappa) was calculated to assess the level of agreement between two authors for the quality assessment of the studies. The mean score of two authors was used for the final decision making, and articles with score ≥5 were included in the analysis. The detailed quality assessment of the articles is shown in the supplementary file, appendix 2.

Statistical analysis

The goal of our analysis was to determine the proportion of COVID-19 patients associated with MIS-C and having neurological manifestation. The heterogeneity across each effect size was evaluated with the I^2 statistics. When I^2 was ≤ 50%, a fixed-effect model was used for meta-analysis. When I^2 was > 50%, DerSimonian, and Laird random-effects model was used for meta-analysis. A meta-analysis of the proportion was expressed as a pooled proportion with a 95% confidence interval (CI). Representative forest plots showing individual studies and the combined effect size were generated to provide an overview of the results. Publication bias was evaluated by visual inspection of the funnel plot, Begg's test, and Egger's test. We also performed a sensitivity analysis by removing a single study at a time, and the impact on the effect size estimate was examined. For all analyses, a p value <0.05 indicated statistical significance. All statistical analysis was performed in Comprehensive Meta-Analysis software (CMA 3.3, Biostat, Englewood, NJ, 2014).

RESULTS

Study Characteristics

Our literature search yielded a total of 87 articles. After excluding duplicates and those not meeting inclusion criteria, 15 papers were included in our systematic review with a total of 785 MIS-C patients. Figure 1 displays the results of our literature search and selection. The characteristics of each study are summarized in Table 1. Two studies were from the UK,[6,7] 2 from France,[10,11] 1 from Italy,[18] 1 from France/Switzerland,[9] 1 from Pakistan[8] and 7 from the USA.[1217,20] One study was a multicenter study involving 13 European, Asian and American countries.[19] Two studies had the prospective design, one had mixed prospective/retrospective design, and 10 had the retrospective design. Most of the studies used real time-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab and detection of serum SARS-CoV-2 IgG for the diagnosis of COVID-19. For the diagnosis of COVID-19 associated multisystem inflammatory syndrome in children, the majority of the studies used diagnostic criteria set by CDC. Among the included studies, the total number of MIS-C patients ranged from 8 to 186.

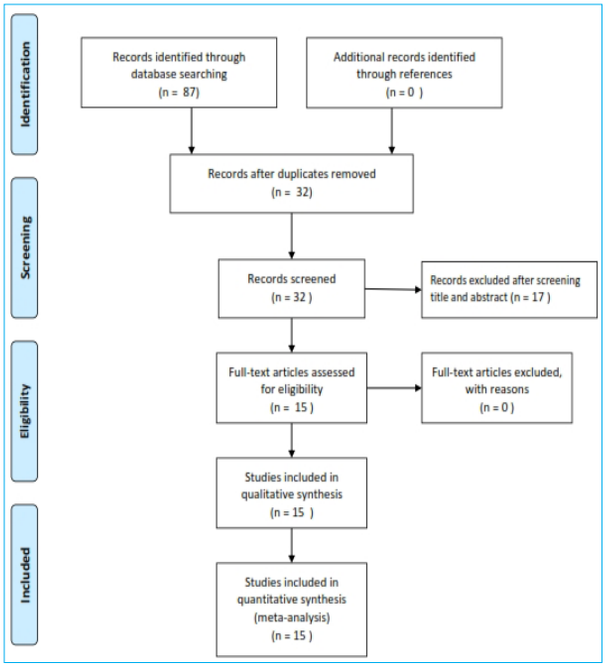

Table 1. Key methodological characteristics of studies included in this systematic review and meta-analysis.

Authors	Study year	Study site	Study design	Covid-19 diagnosis	MIS-C diagnostic criteria	Total MIS-C patients	Median (range) of Age	Female n (%)	Race n (%)
Abdel-Mannan et al[6]	2020	UK	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	Not available	27	12 (8-15) years	2 (50)	• South Asian: 2(50) • Afro-Caribbean: 2(50)
Whittaker et al[7]	2020	UK	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	RCPCH, CDC, or WHO	58	9 (0.25-17) years	33 (57)	• African American: 22 (38) • Asian:18 (31) • White :12 (21) • Others:6 (10)

Pouletty et al[10]	2020	France	Retrospective study	RT-PCR assay of NP swab or documented recent contact with PCR positive individual	Not available	16	10 (4.7-12.5) years	8 (50)	• Afro-Caribbean: 10 (62) • Middle East: 2 (12) • European: 4 (25)
Toubiana et al[11]	2020	France	Prospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	Not available	21	7.9 (3.7-16.6) years	12 (57)	• Afro-Caribbean: 24 (57) • Asian: 4 (10) • European: 12 (29) • Middle Eastern: 2 (5)
Riollano-Cruz et al[12]	2020	USA	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	CDC	15	Mean: 12 years	4(27)	• Hispanic/Latino: 10(71) Unknown: 1(6.6) • African American: 2 (13) • White: 2 (13)
Miller et al[13]	2020	USA	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	CDC	44	7.3 (0.58-20) years	24 (55)	• White: 9 (20.5) • African-American: 9 (20.5) • Hispanic: 15 (34) • Unknown: 11 (25)
Capone et al[14]	2020	USA	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	CDC	33	8.6 (5.5-12.6) years	13 (39)	• White: 3 (9) • African American: 8 (24) • Asian: 3 (9) • Others: 15 (45) • Unknown: 4 (12)
Feldstein et al[15]	2020	USA	Prospective and retrospective	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	CDC	186	8.3 (3.3-12.5) years	71(38)	• White: 35 (19) • African American: 46 (25) • Hispanic/ Latino: 57 (31) • Others: 9 (5) • Unknown: 41 (22)
Dufort et al[16]	2020	USA	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	NYSDOH	99	• 0 to 5 years: 31 (31%) • 6 to 12 years: 42 (42%) • 13 to 20 years: 26 (26%)	46(46)	Of 78 patients with data on race: • White: 29 (37) • African American: 31 (40) • Asian: 4 (5) • Others: 14 (18)
Kaushik et al[17]	2020	USA	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	CDC	33	10 (6-13) years	13(39)	• Hispanic or Latino: 15 (45) • African American: 13 (39) • White: 3 (9) • Asian: 1 (3) • Others: 1 (3)
Sadiq et al[8]	2020	Pakistan	Prospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	WHO	8	9.5 (5-15) years	1(12.5)	All South Asian
Belhadjer et al[9]	2020	Switzerland and France	Retrospective study	RT-PCR assay of NP swab, feces, tracheal swab and serology	Not available	35	10 years	17 (49)	Not available
Verdoni et al[18]	2020	Italy	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	Not available	10	Mean: 7.5 years	3 (30)	Not available
Cheung et al[20]	2020	USA	Case series	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	Not available	17	8 (1.8-16) years	9 (53)	• Ashkenazi Jewish: 6 (35) • White: 6 (36) • Black: 4 (24) • Asian: 1 (6)
Bautista-Rodriguez et al[19]	2021	13 European, Asian, and American countries	Retrospective study	RT-PCR assay of NP swab or Serum SARS-CoV-2 IgG test	Not available	183	Mean: 7 years	74(40.4)	• Black: 56 (30.6) • Asian: 22 (12.0) • Other: 105 (57.4)

Figure 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review.

Overall Neurological manifestations

Fifteen studies reported neurological manifestations in MIS-C patients. Heterogeneity between studies was high (I^2= 82 %). We thus used the DerSimonian and Laird random-effects model for meta-analysis. Our analysis showed that overall neurological manifestation in MIS-C patients was 27.1% (95% CI: 19 % to 37.1 %) (Figure 2). The overall effect size was stable after sensitivity testing. Funnel plot examination, Begg's test (P=0.76), and Egger's test (P = 0.72) showed no publication bias (Figure 3A).

Headache

Six studies reported headaches in MIS-C patients. Heterogeneity in between studies was absent (I^2= 0 %). We thus used a fixed-effect model for meta-analysis. Our analysis showed that headache in MIS-C patients was 27%

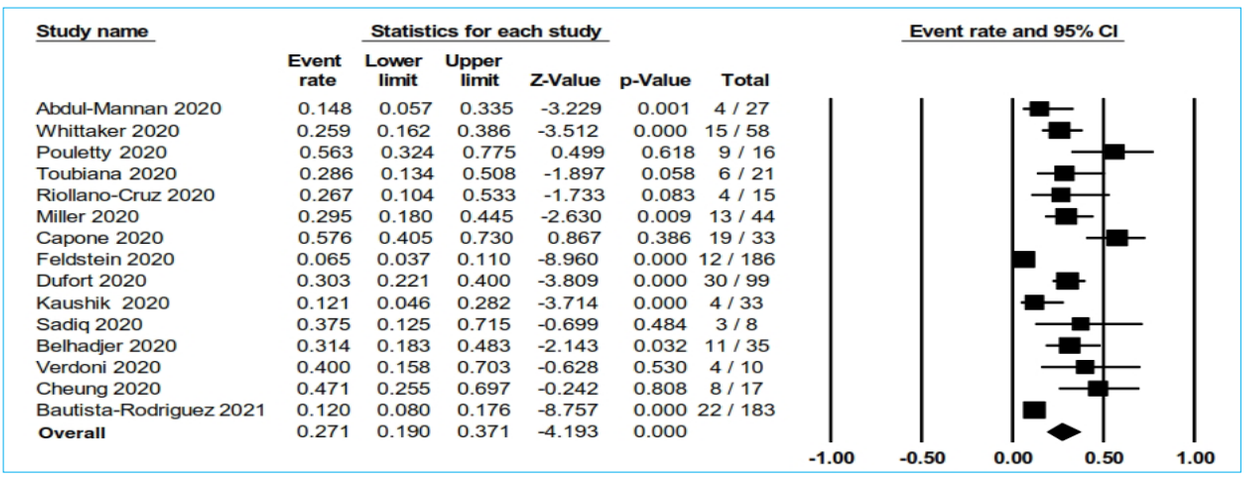

Figure 2. Forest plot with 95% CI for meta-analysis of proportion of children with COVID-19 associated multisystem inflammatory syndrome developing neurological manifestations (overall). The area of each square is proportional to the study's weight in the meta-analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

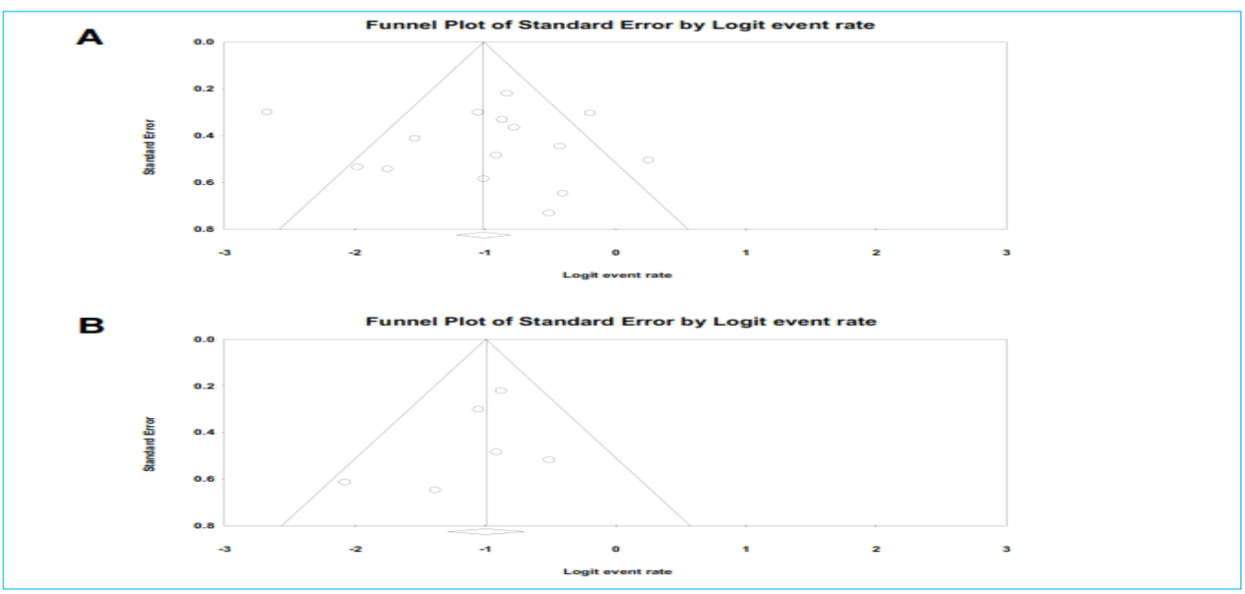

Figure 3. Funnel plot for detection of publication bias in meta-analysis of proportion of children with COVID-19 associated multisystem inflammatory syndrome developing neurological manifestations. A: for overall neurological manifestations; B: for headache.

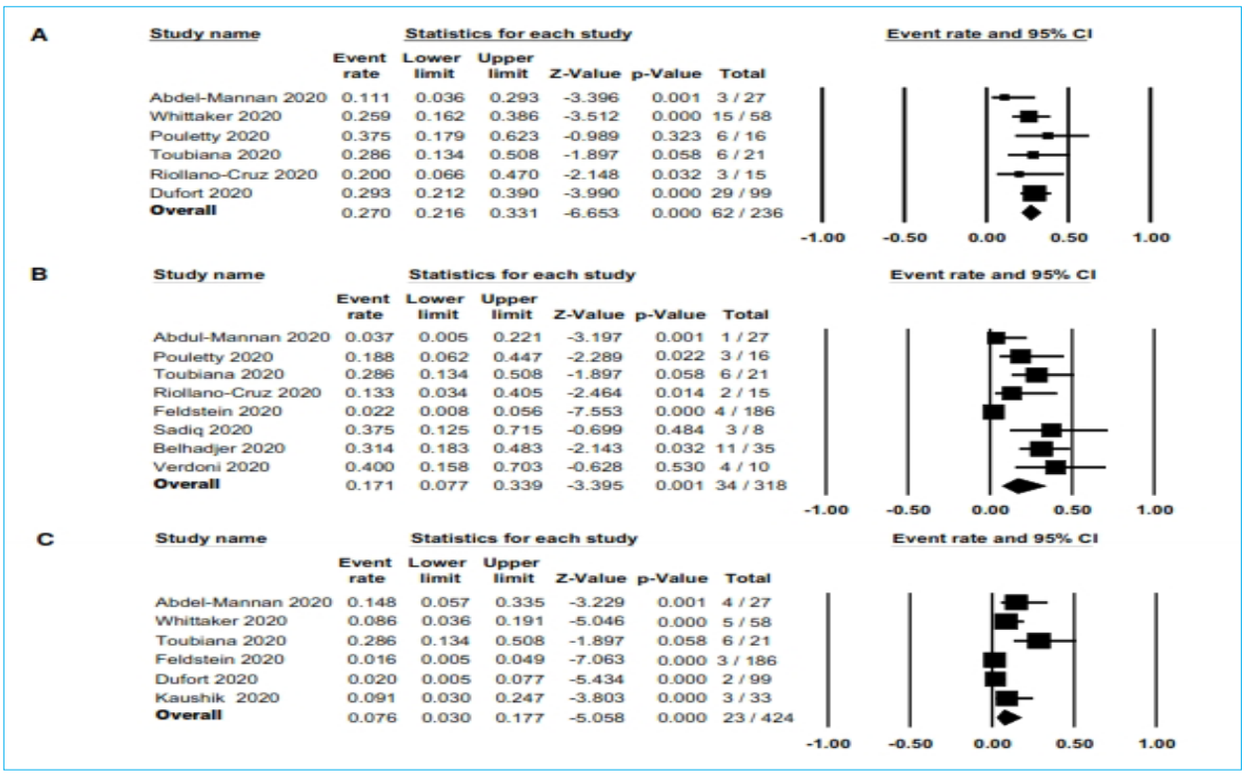

Figure 4. Forest plot with 95% CI for meta-analysis of proportion of children with COVID-19 associated multisystem inflammatory syndrome developing neurological manifestations. A: Forest plot for headache; B: Forest plot for meningism/meningitis; C: Forest plot for encephalopathy.

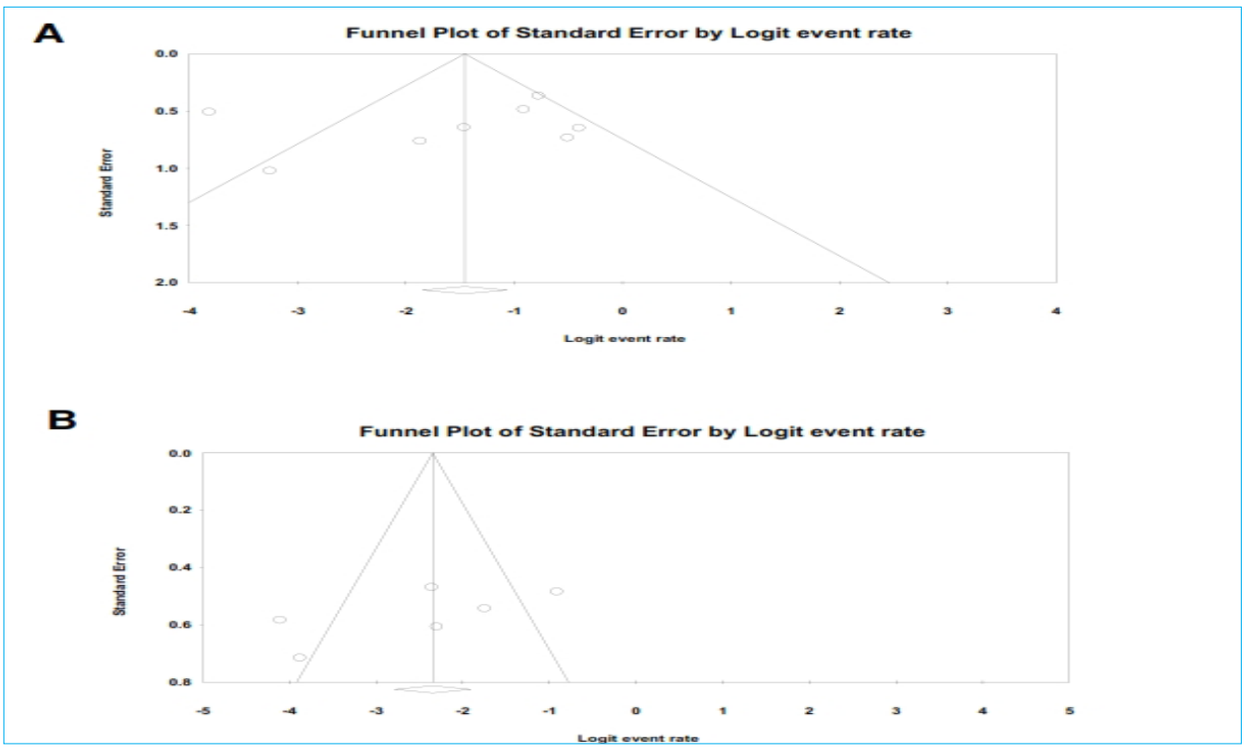

Figure 5. Funnel plot for detection of publication bias in meta-analysis of proportion of children with COVID-19 associated multisystem inflammatory syndrome developing neurological manifestations. A: for meningism/meningitis; B: for encephalopathy.

(95% CI: 26.1% to 33.1 %) (Figure 4A). The overall effect size was stable after sensitivity testing. Funnel plot examination, Begg's test (P=0.45), and Egger's test (P = 0.36) showed no publication bias (Figure 3B).

Meningism/meningitis

Eight studies reported meningism or meningitis in MIS-C patients. For statistical analysis, we took both entities the same. Heterogeneity between studies was high (I^2= 79.57 %). We thus used the DerSimonian and Laird random-effects model for meta-analysis. Our analysis showed that meningism or meningitis in MIS-C patients was 17.1% (95% CI: 7.7 % to 33.9 %) (Figure 4B). The overall effect size was stable after sensitivity testing. Funnel plot examination, Begg's test (P=0.26), and Egger's test (P = 0.58) showed no publication bias (Figure 5A).

Encephalopathy

Six studies reported confusion, altered sensorium, or coma in COVID-19 associated MIS-C patients. For statistical analysis, we grouped above presentation as encephalopathy. Heterogeneity between studies was high (I^2= 78.98 %). We thus used the DerSimonian and Laird random-effects model for meta-analysis. Our analysis showed that encephalopathy in MIS-C patients was 7.6 % (95% CI: 3 % to 17.7 %) (Figure 4C). The overall effect size was stable after sensitivity testing. Funnel plot examination, Begg's test (P=0.45), and Egger's test (P = 0.16) showed no publication bias (Figure 5B).

Other neurological manifestations

In the study by Abdel-Mannan et al., 4 out of 27 patients with MIS-C had neurological involvement. Apart from headache, meningism, and encephalopathy, one patient had cerebellar ataxia, all 4 had global proximal muscle weakness and 2 had bulbar palsy. Neuroimaging showed signal changes in the splenium of the corpus callosum in all 4 patients. Electroencephalography (EEG) showed excess of slow activity in all 3 patients. Nerve conduction studies and electromyography showed mild myopathic and neuropathic changes in all 3 patients tested.[6] Similarly, in the study by Verdoni et al., EEG was performed in two out of 4 patients with neurological manifestation, which showed a slow wave pattern.[18] Furthermore, Feldstein et al. reported 3 cases of seizure among 186 MIS-C patients.[15] Paulette et al. and Toubiana et al. reported one case of anosmia among 16 and 27 MIS-C patients respectively.[10,11]

DISCUSSION

It is known that children comprise only 1-5% of COVID-19 cases. Also, unlike adults, who usually have a severe form of the disease, COVID-19 in children causes mild respiratory illness, and the majority of them are asymptomatic.[4,23] Studies have shown that a substantial number of adult COVID-19 patients develop neurological manifestations.[24,25] However, neurological involvement in children and adolescents with COVID-19 is rare. Although, direct neurological involvement of COVID-19 in the pediatric age group is rare, surprisingly, recent studies have shown that children with COVID-19 associated MIS-C can develop neurological signs and symptoms. In our systematic review and meta-analysis, we quantified to what extent MIS-C patients have neurological involvement. Our analysis showed that overall neurological manifestation in MIS-C patients was 27.7%. We found that 27% of MIS-C patients develop headaches, 17.1% develop meningism/ meningitis and 7.6 % develop encephalopathy.

MIS-C is clinically identical to Kawasaki disease, a common primary vasculitis of children, affecting medium-sized vessels.[26] The viral trigger is thought to be one of the causes of Kawasaki disease and various viruses including enterovirus, adenovirus, rhinovirus, and coronavirus are associated with Kawasaki disease.[27] The prevalence of neurological complications in Kawasaki disease is estimated to range from 1.1 to 3.7% and can include strokes, meningoencephalitis, cranial nerves palsy, hearing loss, behavioral disorders as well as the syndrome of inappropriate antidiuretic hormone secretion.[28] The underlying mechanisms can primarily be attributed to systemic vasculitis, widespread endothelial dysfunction, and generalized inflammatory process associated with the disease.[29] In line with Kawasaki disease, MIS-C also characterizes itself as hyperinflammatory syndrome evidenced by a rise in C-reactive protein, procalcitonin, erythrocyte sedimentation rate, ferritin, and interleukin-6.[6-18] However, the high incidence of neurological involvement in MIS-C remains unclear.

Although the various neurological manifestation of COVID-19 has been established, neurotropism of SARS-CoV-2 is not well established. None of the studies have directly demonstrated SARS-CoV-2 activity in the nervous system. Also, in adults, neurological involvement has been considered secondary to endothelitis and immune-mediated destruction of the nervous system.[25] The reason for neurological complications in MIS-C remains unclear. Also, since the disease is emerging, we still do not know the spectrum of neurological involvement. Although most common manifestations like headache, meningism/meningitis, and encephalopathy can be explained by viral meningoencephalitis, none of the

included studies have demonstrated the SARS-CoV-2 virus in CSF. Another possible cause can be cytokine-mediated neuronal damage. Viruses can activate an immune response that damage neuronal tissue. SARS-CoV-2 has been reported to cause a massive release of cytokines, a syndrome known as "cytokine storm".[24] Another possible route of entry is through the olfactory nerve. Retrograde transfer into the axon, whether through synapses, endocytosis, or exocytosis, could explain viral migration into the brain.[24,30,31] Pouletty et al. and Toubiana et al. had reported one case of anosmia each in their study, which might be due to the involvement of olfactory nerve.[10,11] However, the prevalence of anosmia is quite low compared to adults where the prevalence is very high.[24]

Our study quantified the neurological involvement of COVID-19 associated MIS-C and highlight a need for further investigation into this syndrome. Through brain imaging, lumbar puncture and CSF study, auto-antibody test and electrophysiological studies are required to decipher this emerging neurological complication. While we continue to learn more, efforts to facilitate the identification of children with neurologic complications may allow targeted interventions to improve outcomes. We aimed at quantifying data regarding neurological involvement of MIS-C to aid treating physicians to remain updated about evolving literature on neurological manifestations of COVID-19 associated MIS-C.

Our study has several limitations. Both COVID-19 and its associated MIS-C are emerging diseases, where unknown predominates the known, making this premature investigation subject to false prediction. The majority of included studies have a retrospective design with a small sample size. Of 15 included studies, only one has extensively investigated neurological complications of MIS-C, including neuroimaging, CSF studies, EEG, and autoantibodies test. Remaining studies either presented an overall clinical picture of MIS-C patients or focused on non-nervous system manifestations. However, despite the aforementioned limitations, we hope this study will aid clinicians in the timely identification and treatment of neurological complications of COVID-19 associated MIS-C.

CONCLUSIONS

MIS-C, a mimicker of Kawasaki disease, can present with neurological manifestations in COVID-19 pediatric patients like headache, meningism, and encephalopathy, along with other atypical presentations. Neurological manifestations in COVID-19 pediatric patients could be due to MIS-C or neurotrophic effects of the viral invasion. Further prospective studies with a large number of patients are needed to be familiarized with the disease spectrum.

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