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(REVIEW ARTICLE)

COVID-19 and intracranial hypertension in the paediatric population: A systematic review

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Abstract

The purpose of this systematic review is to explore the published evidence pertaining to reports of raised intracranial pressures following a COVID infection in those under the age of 18, to establish whether there is a link between COVID-19 and intracranial hypertension in the paediatric population. A systematic search of published reports was conducted on PubMed and Google Scholar, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. 7 papers met the eligibility criteria, involving a total of 10 patients. Patients were aged between 6-15, and all showed objective features of raised intracranial pressure and had evidence of current or recent COVID-19 infection. Raised intracranial pressure was demonstrated through objective measures such as raised opening pressures on lumbar puncture or papilloedema on ophthalmoscopy, and the presence of COVID-19 infection was evidenced through PCR or serology results. Raised intracranial pressure was not attributable to another cause, suggesting a link between raised intracranial pressure and concurrent COVID-19 infection in the paediatric population.

Keywords: COVID-19; Intracranial hypertension; Paediatrics; MIS-C

1. Introduction

While intracranial hypertension is becoming recognised as a neurological feature of the post-COVID period [1], evidence of this in the paediatric population is limited and has largely been confined to case reports.

Intracranial hypertension is defined as a CSF pressure above 250mm H2O in adults and 200mm H2O in children. The cause of intracranial hypertension is commonly split into two categories: primary (or intracranial) causes, and secondary (or extracranial) causes. Primary causes include trauma, space occupying lesions, meningitis, and hydrocephalus. Secondary causes included hypoventilation, hypertension, metabolic and seizures [2].

Adult studies have demonstrated a link between COVID-19 infection and raised intracanal pressures. Silva et al. [3] demonstrated that a significant proportion of COVID-19 patients had raised pressures on lumbar puncture. Thakur et al. [4] describe a case of a 49-year-old who developed intracranial hypertension and associated acute vision loss, which resolved following endoscopic optic nerve fenestration. However, literature demonstrating this link in the paediatric population has so far been relatively limited. This review presents reports from the literature of intracranial hypertension in patients aged under 18 with current or recent COVID-19 infection.

2. Methods

A literature search was carried out on Google Scholar and PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [5]. Search keywords used were "raised intracranial

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pressure", "intracranial hypertension", "paediatric", "pediatric", "COVID-19", "SARS-CoV2". There was no publication date restriction.

The inclusion criteria were 1) patients under the age of 18; 2) evidence of intracranial hypertension; 3) evidence of current or recent COVID-19 infection.

The search strategy and selection process are detailed in Figure 1. 4,400 records were identified from the literature search, of which 3,160 were excluded prior to screening for reasons including: duplication, non-English language, and article non-availability. The 1,240 articles remaining were screened, and 1,233 were excluded for not meeting the inclusion criteria. The remaining 7 publications were included, and these were a combination of case reports and case series.

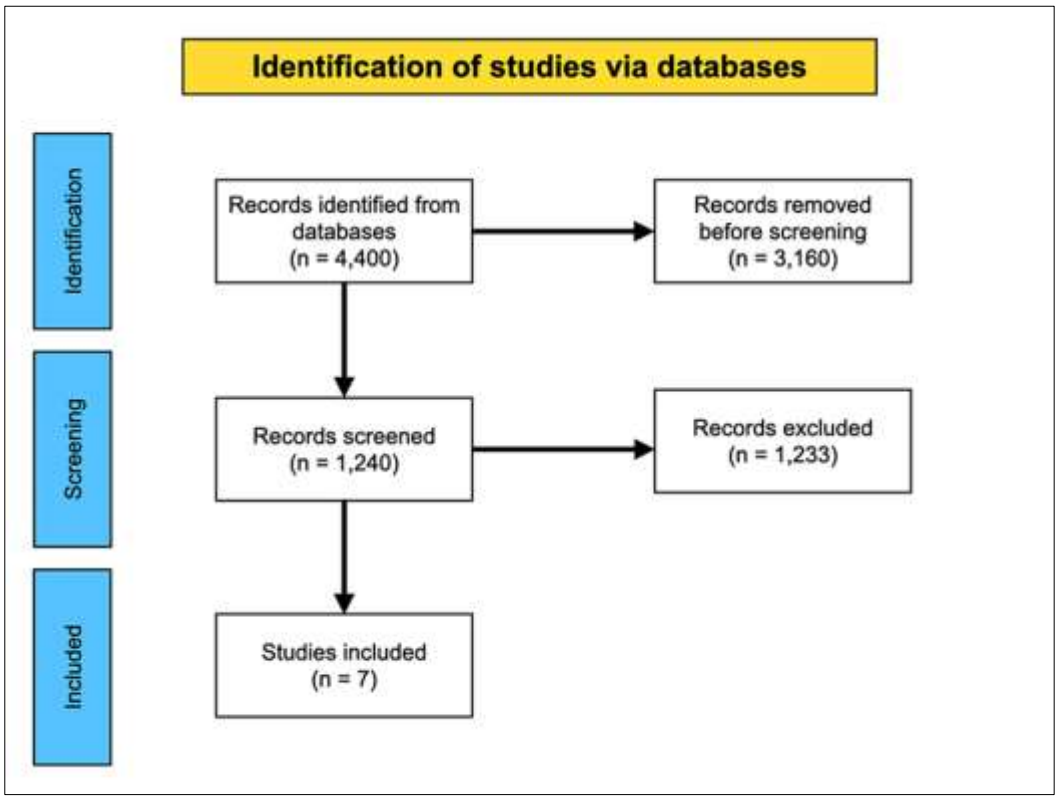

Figure 1 PRISMA flowchart of study selection process

Both Verkuil et al. [6] and Becket et al. [7] reported cases of 14-year-old girls that attended the Children's Hospital of Philadelphia, US. The values of CRP (3.43), opening pressure (36) and certain features of the cases (e.g. discharged after 14 days of admission) were identical in both reports. The likelihood that these are two distinct cases is low, and for the sake of this review, they have been deemed as one single case.

3. Results

7 publications were included, with a total patient number of 10. Table 1 provides a brief summary of the publications selected, including the ages, opening pressures and main features reported.

Rajabi et al. [8] reported a 13-year-old girl that presented with headache and diplopia, as well as anorexia, nausea, vomiting, fever and flank pain. The patient had no relevant past medical history, but was noted to have a BMI of 23. She had a normal MRI brain and CT orbit, and was started on acetazolamide following a diagnosis of raised ICP. The patient's diplopia worsened, and on examination there was a bilateral abducens nerve palsy, with bilaterally papilloedema on fundoscopy. The patient had a normal MRV scan, with no evidence of venous thrombosis. Lumbar puncture (LP) demonstrated a CSF opening pressure of 40 cm H2O. The patient tested positive for SARS-CoV2 from PCR analysis of a nasopharyngeal swab. The patient made a full recovery 1 month after the LP.

Table 1 Brief summary of studies, including ages, opening pressures and main features reported

Authors	Number of patients	Age(s)	Opening pressure(s) / cm H2O	Main features
Rajabi et al. [8]	1	13	40	Headache, diplopia, anorexia, nausea, vomiting, fever, flank pain
Jack & Kannappan [9]	1	15	>34	Headaches, reduced visual acuity
Talebian et al. [10]	1	10	56	Headache, diplopia, bilateral abducens nerve palsy
Verkuil et al. [6]	1	10	56	Fever, headache, vomiting, diarrhoea, dyspnoea, blurred vision
Becker et al. [7]	3	6, 13, 12	31, >38, 34	(1) Fever, irritability; (2) fever, headache, neck pain; (3) fever, vomiting, diarrhoea
Baccarella et al. [11]	2	9, 6	34, 14	(1) Diplopia, headache; (2) diplopia, abducens palsy
Bilen et al. [12]	1	8	12	Fever, fatigue, headache, vomiting

Jack & Kannappan [9] presented a 15-year-old girl who attended a Children's Emergency Department with headaches and reduced visual acuity following a COVID-19 infection 1 month prior. She was noted to have no relevant past medical history, but had an increased BMI. Her right eye had worsening visual acuity on comparison with her left, and bilateral papilloedema and haemorrhages were noted on examination. The patient developed monochromacy and a relative afferent pupillary defect in her right eye. Lumbar puncture demonstrated raised intracranial pressures on two separate occasions, with pressures above 34 cm H2O (due to the limit of the manometer used). The patient was treated with acetazolamide and intravenous methylprednisolone, and went on to have a lumboperitoneal shunt inserted. Following surgery, the patient made a significant improvement, with resolving fundoscopic examination findings, and resolution of colour vision and the afferent pupillary reflex defect.

A 10-year-old girl reported by Talebian et al. [10] presented with headache, diplopia, bilateral abducens nerve palsy and papilloedema following a 2-week history of fever. The patient had no prior medical history of note, but had a BMI of 21. Lumbar puncture demonstrated an opening pressure of 56 cm H2O. PCR analysis from a nasopharyngeal swab was positive for COVID-19. The patient was treated with acetazolamide, and after three weeks of treatment, fundoscopy demonstrated a significant improvement of papilloedema and the abducens nerve palsy was significantly subsided.

A 14-year-old girl reported by both Verkuil et al. [6] and Becker et al. [7] presented with dyspnoea following 4 days of fever, headache, vomiting and diarrhoea. Her past medical history was notable for oppositional defiant disorder. On examination she was hypotensive and tachycardic, with increased work of breathing and a diffuse erythematous rash. Following admission, the patient was noted to have blurry vision and was found to have an abducens nerve palsy as well as bilateral papilloedema on fundoscopy. MRI Brain findings of optic nerve sheath diffusion restriction, posterior sclera flattening, and optic disc eversion were consistent with papilloedema. Lumbar puncture demonstrated an opening pressure of >36 cm H2O. Following initiation of acetazolamide, the patient's abducens nerve palsy improved. At 2 month follow up, the patient had no clinically evident neurological deficits.

3 cases described by Becker et al. [7] have been outlined below:

A 6-year-old girl presented with a 4-day history of fever and irritability, with systemic symptoms of rash, conjunctivitis, crackled lips, vomiting and diarrhoea. On examination she appeared shocked, with nuchal rigidity present. The patient was systemically unwell, with metabolic acidosis, pancytopaenia, electrolyte abnormalities and elevated cardiac markers. A SARS-CoV-2 PCR test on the second day of admission was positive, and serology was positive for IgG antibodies. Lumbar puncture demonstrated an opening pressure of 31 cm H2O, and CT Head showed evidence of cerebral oedema. Based on the clinical features and positive COVID PCR, a diagnosis of Multisystem Inflammatory Syndrome in Children (MIS-C) was made. The patient was managed with epinephrine and milrinone due to left ventricular dysfunction, and treated with IVIG, aspirin and anakinra. At discharge, the patient had returned to her normal neurology, with no obvious deficits [7].

A previously healthy 13-year-old girl presented with 5 days of fever, headache, neck pain. On examination she was shocked, with nuchal rigidity, neck tenderness and a fluctuating mental status. She had metabolic acidosis, elevated inflammatory markers, leukocytosis, with anaemia and thrombocytopaenia. SARS-CoV-2 serology was positive for IgG antibodies, and a lumbar puncture demonstrated an opening pressure of >38 cm H2O. The patient was treated with antibiotics for possible meningitis, and vasopressors due to progressive biventricular dysfunction. The patient also received IVIG, IVMP and aspirin, and on discharge was noted to have no neurological deficits [7].

A 12-year-old boy presented with a 2-day history of fever and vomiting, following 3 more days of diarrhoea. The boy was hypotensive and tachycardic on examination, and had fluctuation of mental status, as well as conjunctivitis, cracked lips, nuchal rigidity and a heart murmur. The patient had leukocytosis, raised inflammatory markers, with raised cardiac markers and an acute kidney injury. SARS-CoV-2 serology was positive for IgG antibodies. CT Head was normal, and lumbar puncture demonstrated an opening pressure of 34 cm H2O. The patient was commenced on milrinone and epinephrine due to biventricular dysfunction. He was treated with IVIG and IVMP, as well as aspirin. Following normalisation of cardiac function, the patient was discharged home at his neurologic baseline [7].

Baccarella et al. [11] described 2 cases:

A 9-year-old boy presented with diplopia and worsening headache following a 7-day febrile illness. The patient was previously healthy, and was noted to have a right abducens nerve palsy with no papilloedema. SARS-CoV-2 antibody testing was positive. MRI and MRV Head were normal. Lumbar puncture demonstrated an opening pressure of 34 cm H2O, and following the lumbar puncture the patient's headache improved. 2 days later, the abducens palsy and diplopia resolved. He was treated with acetazolamide, and at 2 month follow up had no symptoms [11].

A 6-year-old boy presented with diplopia and was found to have right abducens palsy with bilateral papilloedema. He had recently been discharged from hospital following an admission for MIS-C, during which he had tested positive for SARS-CoV-2 (both PCR and serology). MRI head demonstrated kinking and distention of both optic nerve sheaths, with protrusion of the optic discs consistent with increased intracranial pressure. Interestingly, lumbar puncture demonstrated a normal opening pressure of 14 cm H2O. However, the authors note that the lumbar puncture was performed one week after the onset of symptoms. The next day, the diplopia had resolved, and at 5 month follow up, the papilloedema had resolved and the patient was symptom free [11].

Bilen et al. [12] described the case of an 8-year-old boy that presented with a 7-day history of fever and fatigue. He was managed initially as an upper respiratory tract infection, but re-presented 3 days later following persistence of his symptoms and the development of headache, vomiting, as well as redness and swelling in both eyes. It was noted that his father had tested positive for SARS-CoV-2 infection one month prior. On examination he was pyrexial and tachycardic, and had bilateral conjunctivitis, with bilateral papilloedema on fundoscopy. SARS-CoV-2 serology was positive for IgG and IgM antibodies. MRI Head had findings consistent with intracranial hypertension, with flattening of the posterior sclera, enlargement of the peri-optic nerve subarachnoid cerebrospinal fluid space and tortuosity of the optic nerve. However, lumbar puncture revealed a normal opening pressure of 12 cm H2O. The patient was managed as MIS-C, and treated with IVIG and acetazolamide. 45 days after presentation, the papilloedema had resolved.

4. Discussion

Of the 10 patients included, 7 were managed as MIS-C. These patients were systemically unwell, and as per the definition of MIS-C, had symptoms not limited to the nervous system.

It is unclear whether the mechanisms causing intracranial hypertension in these cases, where there was marked systemic inflammation, are the same mechanisms mediating the raised pressures seen in the less severe cases. Indeed, the former are reported as manifestations of Idiopathic Intracranial Hypertension (IIH). For the sake of this review, the MIS-C cases will be discussed separately to the IIH cases.

4.1. MIS-C

While rare, neurological manifestations of MIS-C have been reported. Baccarella et al. [10] and Bilen et al. [12] hypothesised that the neurological symptoms associated with MIS-C are caused by increased intracranial pressure.

Becker et al. [7] note that there is no clear aetiology for the neurological features of MIS-C, especially with respect to intercranial hypertension, and that the cause is likely multifactorial.

Baccarella et al. [10] note that raised intracranial pressure has been documented as an initial feature of some autoimmune conditions, such as Systemic Lupus Erythematosus, Kawasaki disease and Sjögren syndrome. The authors therefore suggest that the intercranial hypertension seen in MIS-C is mediated by similar mechanisms, and due to the otherwise normal CSF studies that the raised opening pressures were more likely from a systemic cause and not due to direct CSF infiltration and central nervous system infection of SARS-CoV-2.

In contrast to the other MIS-C cases, the patient described by Bilen et al. [12] was haemodynamically stable, and not as severely systemically unwell. The authors also note that angiotensin-converting enzyme 2 (ACE2), which is understood to be the target of SARS-CoV-2, is expressed in the brain. They suggest this might be a mechanism through which the virus itself may contribute to raised intracranial pressures.

4.2. IIH

Not all patients were systemically unwell, and were therefore not managed as MIS-C.

Rajabi et al. [8] suggest that SARS-CoV2 infection may contribute to a hypercoagulable state due to increase in von Willebrand factor, systematic inflammation and impaired endothelial function; this state could lead to clot formation, resulting in CSF outflow obstruction. In this way, the authors hypothesise a mechanism in which SARS-CoV-2 could lead to the development of 'Idiopathic' Intracranial Hypertension, although they concede that MRV and MRI in their report of the 13-year-old girl did not demonstrate a clot formation.

Talebian et al. [10] similarly suggest that SARS-CoV-2 may affect the neurological system in three ways: 1) via increased systematic inflammation; 2) hypercoagulation and activation of the coagulation system leading to thrombosis; 3) direct attack to cells causing cell injury. The authors state that these same mechanisms might contribute to Idiopathic Intracranial Hypertension, as although the mechanisms underlying IIH are not fully understood, they are thought to include abnormalities of venous outflow, impaired production and absorption of CSF, as well as low-grade inflammation and intracranial clotting. Indeed, the authors highlight the commonalities between these mechanisms and those associated with SARS-CoV-2.

Jack & Kannappan [9] note that the lockdowns during the COVID-19 pandemic have been associated with increased weight gain. Obesity is a well-documented risk factor for IIH [13], and therefore an increase in obesity could lead to a theoretical increase in the incidence of IIH.

5. Conclusion

The established link between COVID-19 and intracranial hypertension in adults is also demonstrated in the paediatric population. The underlying mechanisms that explain this connection are unclear, and in some patients the intracranial hypertension is part of a more severe MIS-C response, while in others it is more consistent with an idiopathic intracranial hypertension picture.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflicts of interest to declare.

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