Mamczur et al.
Medical Journal of Cell Biology 2022
DOI: 10.2478/acb-2022-0010
Received: 2.05.22
Accepted: 13.06.22

Ocular manifestations of Pediatric Inflammatory Multisystem Syndrome

Joanna Mamczur[1], Manuela Pajdowska[1*], Aleksandra Krasińska[1*], Agata Brązert[1]

Abstract

This article aims to present up-to-date information on ocular symptoms of pediatric multi-system inflammatory syndrome. The reviewers obtained the results based on a search of an electronic database. The pediatric multi-system inflammatory syndrome appears a few weeks after COVID-19 in children. The exact etiology remains unclear. It is diagnosed based on clinical and laboratory criteria. The most prevalent manifestation of the syndrome is non-purulent conjunctivitis (observed in around 50% of cases). The other ocular findings in the pediatric multi-system inflammatory syndrome can be; eyelid swelling, bilateral uveitis or vitreous hyperreflective dots in the posterior vitreous. The treatment of the ophthalmic symptoms is systemic and topical, targeting the enhanced inflammatory response of the organism and the presence of the given ocular findings.

Running title: Ocular manifestations of PIMS

Keywords: PIMS, multisystem inflammatory syndrome, MIS-C, COVID-19, ocular manifestations, conjunctivitis

[1]Department of Ophthalmology, Poznan University of Medical Sciences, Poznań, Poland
Correspondence: joanna.mamczur96@gmail.com
*equally contributed
Full list of author information is available at the end of article

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Introduction

Lately, the world's rate of COVID-19 has slowly decreased. Despite this, the recently reported global numbers of confirmed cases (500 million) and deaths (over 6 million) are still enormous [1]. Children with COVID-19 are asymptomatic or have mild symptoms [2]. However, the "after-COVID-19 syndrome" - the pediatric multi-system inflammatory syndrome (PIMS) might be severe and the majority of patients need intensive care treatment [2,3]. The first cases of PIMS occurred in April 2020 [4]. The condition is observed in children a few weeks after having SARS CoV-2 infection [5,6]. The other terms used to define PIMS are; multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), pediatric hyperinflammatory syndrome or Kawasaki-like disease [7]. The World Human Organization (WHO) has defined diagnostic criteria for PIMS [8]. The only ophthalmic symptom mentioned is bilateral non-purulent conjunctivitis. Nevertheless, there have been reported numerous cases of PIMS with various ocular symptoms. In this article, we aim to focus on the etiology, diagnosis, manifestation, and treatment of ocular manifestation in PIMS.

Methodology

Two reviewers have independently searched electronic databases using search terms: "ocular manifestations, pediatric multi-system inflammatory syndrome, multisystem inflammatory syndrome in children and adolescents, MIS-C, PIMS", to obtain information on etiology, diagnosis, manifestation, and treatment of ocular symptoms of PIMS.

PIMS - etiology

PIMS affects mostly children with no history of chronic illnesses [9,10]. There are many hypotheses explaining the pathogenesis of PIMS. The first one is that SARS CoV-2 can block some types of interferon responses leading to delayed cytokine storm. This can happen especially in patients with difficulties in controlling viral replication or with high viral load [9,11]. The second hypothesis says that the IgG antibody-dependent enhancement (ADE) of the disease can lead to the greater activation of monocytes, CD8+ T-cells, and cytopenia [9,11–13]. Furthermore, the condition may be associated with uncontrolled inflammation caused by delayed clearance of the virus [11]. According to a study conducted by Abrams, in a group of patients with PIMS, the positivity of SARS-CoV-2 serology tests was greater than the positivity of SARS-CoV-2 RT-PCR tests. This data suggests that PIMS is caused by immune-mediated post-infectious inflammation [14]. In terms of ocular manifestations, the etiology of conjunctivitis in PIMS tends to be more immunological than viral. The hypothesis is based on the fact that the occurrence of conjunctivitis in PIMS (48,4% Tzu-Chen Lo study) is much higher than in adults with COVID-19 (1,1% Loffredo's study) [15,16].

Diagnosis

PIMS diagnostic criteria vary in different countries. The Polish Paediatric Society Expert Group proposed 6 criteria for the diagnosis. Criteria 1-5 have to be fulfilled to diagnose the syndrome. Criterion 6 is not required if the clinical picture indicates this condition.

The criteria are listed below:

- Age (0-18 years of age)
- Fever ≥ 3 days
- High inflammatory markers
- Multisystem (≥ 2) organ involvement
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection [6].

By WHO definition, PIMS-TS is diagnosed in patients between 0-19 years with fever for at least 3 days, elevated inflammatory markers (CRP, PCT, ESR), excluded alternative microbial cause of infection, evidence of COVID-19 infection (RT-PCR, antigen test or serology positive) or exposure to COVID-19 and symptoms (at least 2 of the following): skin rash or bilateral conjunctivitis or stigmata of inflammation on mucosa or skin, hypotension or shock, myocardial dysfunction, valvulitis, pericarditis, or coronary abnormalities, coagulopathy, acute gastrointestinal problems [17].

Ocular symptoms of PIMS

The most common ocular manifestation of PIMS is non-purulent conjunctivitis. According to a systematic review conducted by Hoste et al. the prevalence was 49.8 % (423 out of 849 patients), Lo et al. noted that among the 1458 patients 48,4 % had conjunctivitis and Tang et al. in the review of twenty-four studies observed the prevalence between 30-94%. In the study conducted on 48 patients, by Mandal et al. 37.5 % (18 patients) presented with conjunctivitis [2,7,15,18]. Eyelid swelling was the second most common ocular manifestation with a prevalence of 8,3 % [18]. The other observed ocular finding in PIMS is bilateral uveitis. Karthika et al. reported a case of a 14-year-old girl with bilateral non-granulomatous anterior uveitis associated with bilateral disc edema. [19]. Öztürk et al. described a series

of five cases of bilateral acute anterior uveitis (AU) in children diagnosed with MIS-C, three of them had also a corneal punctate epitheliopathy [20]. Wong et al. published a case report of a 12-year-old boy with bilateral AU secondary to SARS-CoV-2 infection. [21]. In the recent reports, one can also find cases of PIMS involving the posterior segment of the eye. Arkan et al. reported two cases; the first of an 8-year-old with optic disc hemorrhage and several vitreous hyperreflective dots in the posterior vitreous of the right eye. The left eye was clear. The second case was a 10-year-old girl with conjunctival hyperemia, periorbital rash, dilatation, and minimal tortuous increase in the retinal arteries and vitritis-like hyperreflective spots in the posterior vitreous [22]. Less common symptoms found in PIMS are subconjunctival hemorrhages, episcleritis, papilledema, or bilateral optic neuritis [18,23].

Treatment

Ocular symptoms of PIMS should be treated with topical, eye-directed medications. It has been observed that the intensity of ocular symptoms positively correlates with blood C-reactive protein (CRP) level [18]. This explains the significance of systemic treatment. The treatment should be initiated with immunomodulatory therapy. In multisystem inflammatory syndrome in children (MIS-C) the first line of treatment is based on intravenous immunoglobulin (IVIg) at a dose of 2 g/kg, calculated using ideal body weight. The second line of therapy is intravenous glucocorticosteroids (GCs) such as methylprednisolone (10-30 mg/kg). The third-line therapy uses biological agents like an inhibitor of the IL-6 receptor (tocilizumab), an inhibitor of the IL-1 receptor (anakira) or an inhibitor of the TNF-α (infliximab) [6,24,25]. In reported cases of ocular symptoms in PIMS, the time from diagnosis to full recovery lasts from 1 to 4 weeks [6]. Patients with conjunctivitis were provided with topical non-steroidal anti-inflammatory drugs (NSAIDs) (Ketorolac) and topical antibiotics to prevent secondary bacterial infection. Topical steroids (prednisolone acetate 1% or dexamethasone) with cycloplegic (atropine or homatropine) were used in uveitis. For subconjunctival hemorrhage, topical NSAIDs and sodium hyaluronate / artificial tear drops were given [18,20]. For eyelid swelling or retinitis there was not any specific topical treatment [18]. Disc oedema was managed only by systemic treatment (IVIg and GCs) or in combination with neuroprotector (Methylcobalamin in tablets) and intracranial pressure-lowering drugs (intravenous mannitol or Diamox in tablets) [18,23].

Conclusions

The etiology of PIMS is associated with the enhanced inflammatory response. The exact pathomechanism is still unclear. The most prevalent ophthalmic manifestation of PIMS is non-purulent conjunctivitis (observed in around 50% of cases of PIMS). The other, rarely appearing, ocular symptoms are; eyelid swelling, bilateral uveitis or vitreous hyperreflective dots in the posterior vitreous or bilateral. The treatment is both topical and systemic. The choice of medications depends on the symptoms and the treatment response of the patient.

Ethical approval

The conducted research is not related to either human or animal use.

Acknowledgments

Not applicable.

Corresponding author

Joanna Mamczur, Department of Ophthalmology, Poznań University of Medical Sciences, 84 Szamarzewskiego St., 60-569 Poznań, Poland, email: joanna.mamczur96@gmail.com.

Conflict of interest

The authors declare they have no conflict of interest

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