

ARTICLE



A prospective long-term evaluation of the ocular findings of children followed with the diagnosis of multisystem inflammatory syndrome (long-term evaluation of ocular findings following MIS-C)

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BACKGROUND/OBJECTIVES: The most frequently reported ocular finding in the acute phase of the multisystem inflammatory syndrome in children (MIS-C), is conjunctivitis. More rarely, punctuate epitheliopathy, anterior uveitis and optic disc oedema can be seen. We aimed to investigate the acute and long-term ocular effects of MIS-C.

SUBJECTS/METHODS: Cases aged 1 month to 18 years who were diagnosed with MIS-C between January 2022 and June 2022 in the Department of Pediatric Infectious Diseases in our hospital were included in the study. Ophthalmological examinations were performed immediately after diagnosis, at one month, three months, and six months.

RESULTS: Males consisted of 64.7% of the 34 cases included in the study and the mean age was 8.68 ± 4.32 years (min-max:2–17). In the first examination, conjunctivitis was observed in 6 (17.6%), punctuate epitheliopathy in 4 (11.7%), and subconjunctival haemorrhage in 3 (8.8%) patients. Two patients (5.8%) had optic disc oedema. No pathological anterior or posterior segment findings were observed in the sixth-month examination. The relationship between subconjunctival haemorrhage and intensive care hospitalisation was statistically significant ($p = 0.014$). Also, all patients with subconjunctival haemorrhage were clinically classified as severe MIS-C ($p = 0.002$).

CONCLUSION: Although pathological ocular findings were observed in the acute phase of the disease, all of them were found to be improved at the sixth-month follow-up. The most striking finding of our study is that cases with subconjunctival haemorrhage were clinically more severe, and all patients needed intensive care. This study may be informative in establishing ocular follow-up protocols that are expected to be carried out in the acute period and in the follow-up of these patients.

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INTRODUCTION

The multisystem inflammatory syndrome in children (MIS-C) was first described in the second half of April 2020 as a new syndrome possibly associated with SARS-CoV-2 infection in children and adolescents [1, 2]. Features of this syndrome are similar to those of Kawasaki Disease, toxic shock syndrome, and hyperinflammatory conditions such as secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome [3]. The exact pathogenesis of MIS-C is unclear. Given that many patients with MIS-C are found to be positive for SARS-CoV-2 antibodies, it has been suggested that an abnormal immune response to SARS-CoV-2 plays a key role [4]. The fact that MIS-C usually occurs one month after SARS CoV-2 infection also supports that the underlying mechanism may be post-infectious inflammation [5]. Clinically, fever (96.4%), gastrointestinal symptoms (76.7%), shock (61.5%), rash (57.1%), and neurological findings (36.8%) are observed most frequently [6].

In the literature, the most frequently reported ocular finding in the acute phase in patients undergoing MIS-C is conjunctivitis, similar to Kawasaki disease, and less commonly punctuate epitheliopathy, anterior uveitis and papilledema [7–12]. Studies in the literature generally include the findings of MIS-C in the acute period. Our study is the first prospective observational study as far as we know in which the ocular findings in MIS-C were evaluated both in the acute period and in which the patients were followed up for six months.

Since MIS-C is a newly defined clinical condition and causes an exaggerated immune response, the damage it causes to the organs is not yet known. Therefore, our study aimed to investigate the acute and long-term ocular effects of MIS-C.

MATERIAL AND METHODS

Cases aged 1 month to 18 years who were diagnosed with MIS-C according to the diagnostic criteria of the Center for Disease Control and

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Prevention (CDC) between January 2022 and June 2022 in the Pediatric Infectious Diseases Clinic in our hospital were included in the study. Cases with a history of serious eye problems (such as cataract, active uveitis, glaucoma, and previous intraocular surgery) and cases who refused to participate in the study were excluded.

Detailed ophthalmological examinations of the cases were performed immediately after diagnosis, at one month, three months, and six months. The best corrected visual acuities, anterior and posterior segment examinations, and Schirmer 2 tests were performed, and the findings were recorded. Since patients were examined immediately after diagnosis, some patients were examined in the ward at the bedside or in the intensive care unit. In some cases, the Schirmer 2 test could not be applied healthily because they were very young and agitated. Since the follow-up of the patients was planned as a six-month follow-up, the same applicable methods were preferred for standardisation. At each examination, the ocular surface was examined by staining with fluorescein papers. All examinations were performed by the same ophthalmologist. Bedside examination was performed with an indirect ophthalmoscope and 20/28 D lenses. In the age group who cannot express their vision reliably, amblyopia and all risk factors that may reduce vision were screened in detail, and refraction examinations with cycloplegia were performed. In addition, the medical records of the cases were examined and their demographic data, MIS-C clinical classification, and previous treatments were noted. The severity of cardiac findings, echocardiogram findings, and laboratory results were evaluated together for the MIS-C clinical classification [13].

Ethics committee approval was obtained from the Health Sciences University Izmir Tepecik Training and Research Hospital Ethics Committee for this prospective observational study (Decision no: 2021/12-18). Informed consent was obtained from the parents of all patients participating in the study.

Statistical analysis was performed using SPSS version 24.0 using the obtained data (IBM Corp., Armonk, New York, USA). Descriptive analyses are given as mean \pm standard deviation [minimum-maximum (min-max)] or median [Interquartile range (IQR)] values according to the normal distribution for numerical variables. Normally distributed numerical variables were compared with the t-test, while non-normally distributed variables were compared with the Mann-Whitney U test. Categorical data are given numerically and as a percentage. Pearson and chi-square tests were used to compare categorical data. A *p* value below 0.05 was considered statistically significant.

RESULTS

During the study period, a total of 38 patients were diagnosed with MIS-C. A total of four patients were excluded from the study because one of them died and three patients did not accept to participate in the study. Schirmer 2 test could not be applied to seven cases out of 34 cases.

A total of 34 cases, 12 (35.3%) females and 22 (64.7%) males, diagnosed with MIS-C were included in the study and their ophthalmological examinations were performed. The mean age of the cases was 8.68 ± 4.32 years (min-max:2–17). According to the clinical classification, 17 (50%) of the cases were followed up with a diagnosis of mild, 10 (29.4%) with moderate, and 7 (20.6%) with severe MIS-C. Nine of the patients (26.4%) were admitted to the intensive care unit.

No loss of vision was observed in any of the cases during their follow-up. In the first examination of the patients, follicular conjunctivitis was observed in 6 (17.6%), subconjunctival haemorrhage in 3 (8.8%), and punctate epitheliopathy in 4 (11.7%) patients. Almost all patients with follicular conjunctivitis had a superficial hyperaemia with preservation of the limbus, but no discharge was observed in any of them. Conjunctivitis symptoms regressed in all cases the day after systemic treatment started. Therefore, none of the cases needed topical treatment. The median Schirmer values were 18 mm (IQR:15–22) in the right eye and 20 mm (IQR:15–25) in the left eye. The anterior segment findings of the other 21 patients (61.7%) were normal. Optic disc oedema was observed in two patients (5.8%). There was no neurological defect in 2 of our cases, but when optic disc oedema was detected during our examination, detailed neurological

examination and imaging were performed. Oral carbonic anhydrase treatment was given in one of our cases with high cerebrospinal pressure, while no additional treatment was given in the other case.

In the first month's examination, punctate epitheliopathy was observed in only two (5.8%) patients, while anterior segment examinations of all the others were normal. Fundus examination was normal in all cases. The findings completely regressed in two cases with optic disc oedema. Systemic therapy was also discontinued of the patient who received oral carbonic anhydrase treatment. The median Schirmer values were 24.5 mm (IQR:17.7–30) in the right eye and 25.5 mm (IQR: 18–30) in the left eye.

In the three-month examination, punctate epitheliopathy was observed in only one (2.9%) of the patients, while the anterior segment examinations of the others were normal. Fundus examination was normal in all cases. The median Schirmer values were 25 mm (IQR:22–30) in the right eye and 25 mm (IQR:20–30) in the left eye.

In the sixth-month examination of the patients, pathological anterior or posterior segment findings were not observed in any of the cases. The median Schirmer values were 25 mm (IQR:24–30) in the right eye and 26.5 mm (IQR:25–30) in the left eye. Topical artificial tear treatment was given to patients with punctate epitheliopathy and low schirmer until the symptoms improve. No corneal involvement was observed during the entire follow-up. In cases with optic disc oedema, the findings did not recur in the 6-month follow-up.

There was no statistically significant relationship between pathological ocular examination findings and age and gender ($p = 0.180$, $p = 0.089$, respectively). Also, there was no statistically significant relationship between pathological ocular examination findings and the treatment administered (IVIG, steroid, anakinra, or plasmapheresis) ($p = 0.374$, $p = 0.115$, $p = 0.054$, $p = 0.392$, respectively). However, there was a statistically significant correlation between hospitalisation in the intensive care and the development of pathological ocular findings ($p = 0.034$). While no statistically significant relationship was found between other pathological findings and hospitalisation in the intensive care, the relationship between subconjunctival haemorrhage and hospitalisation in the intensive care was statistically significant ($p = 0.014$) (Table 1). Both patients with optic disc oedema had a history of

Table 1. Comparison of clinical features in patients with or without subconjunctival haemorrhage.

	Patients with sc haemorrhage <i>n</i> (%)	Patients without sc haemorrhage <i>n</i> (%)	<i>p</i> value
Clinical classification			
Mild	0 (0)	17 (54.8)	0.002
Moderate	0 (0)	10 (32.2)	
Severe	3 (100)	4 (13)	
Cardiac involvement			
None	0 (0)	14 (45.2)	<0.001
Mild	0 (0)	6 (19.4)	
Moderate	0 (0)	9 (29)	
Severe	3 (100)	2 (6.4)	
Intensive care			
Existing	3 (100)	6 (19.4)	0.014
None	0 (0)	25 (80.6)	

Sc subconjunctival.

p value below 0.05 was statistically significant.

intensive care admission, but no statistically significant relationship was found ($p = 0.056$).

While no statistically significant relationship was observed between other pathological ocular examination findings and MIS-C clinical classification ($p = 0.314$), a statistically significant correlation was observed between subconjunctival haemorrhage ($p = 0.002$) (Table 1). All patients with subconjunctival haemorrhage were followed up with a diagnosis of severe MIS-C. No statistically significant correlation was found between the presence of conjunctivitis at the first examination and the development of pathological ocular examination findings ($p = 0.416$). When the change in Schirmer 2 tests was analysed in the sixth-month follow-up, a statistically significant increase was observed in both eyes between the first and the sixth months ($p = 0.019$ for the right eye, $p = 0.009$ for the left eye). In the sixth-month examination of the patients, no pathological findings were observed in the anterior and posterior segments, and improvement was found in all patients with pathological ocular findings.

DISCUSSION

The most common ocular finding in children in the acute period of MIS-C is conjunctivitis [7, 14, 15]. In a study that included 1458 cases in which systemic and ocular findings were evaluated by a meta-analysis, conjunctivitis was reported with a rate of 48.4% [6]. Although the rate was lower in our study, the most common finding in the first examination was conjunctivitis (17.6%). Conjunctivitis is the swelling and inflammation of the conjunctival tissue with the occlusion of the vessels [16]. It can cause epiphora, chemosis, pain, a reaction in tarsal follicles, and regional lymphadenopathy. Conjunctivitis in MIS-C may be induced due to a systemic immunological reaction rather than a local virus attack [17, 18].

Angurama et al. reported haemorrhagic nonpurulent conjunctivitis in three cases with MIS-C [19]. This finding has been described for the first time. It took two to three weeks for the haemorrhage to recede. The authors thought that haemorrhagic nonpurulent conjunctivitis may have been due to SARS-CoV-2-induced endothelial cell damage and necrosis or vasculitis in conjunctival vessels. The described setting was stated as subconjunctival haemorrhage in our study. In our study, subconjunctival haemorrhage was observed during the initial examination of the patients with a rate of 8.8% and similarly, it was not observed in any case in the first month examinations. In our study, there was a relationship between intensive care admission and MIS-C clinical classification and subconjunctival haemorrhage. The correlation between the severity of the disease and subconjunctival haemorrhage in our study is an important finding. Subconjunctival haemorrhage can be an important examination finding that can inform us about the course of the disease. However, there is not enough information on this subject in the literature yet.

In our study, punctate epitheliopathy was observed in the first examination of the patients with a rate of 11.7%, while it was observed only with a rate of 5.8% in the first-month examinations and 2.9% in the third-month examinations. At the sixth-month examination, this finding was not observed in any of the cases. Ozturk et al. reported non-granulomatous anterior uveitis and three severe corneal punctate epitheliopathies in five acute MIS-C patients [8]. In our study, anterior uveitis was not observed in any of our patients in the acute period or during follow-up. However, there was a case in which we still observed punctate epitheliopathy in the third month. The dry eye may be the cause of corneal punctate epitheliopathy. Although there is no information in the literature regarding dry eye in MIS-C cases, in a study involving 535 COVID-19 patients in China, the rate of the dry eye without conjunctival congestion was found to be 20.1% [20]. Since the first examination of our patients was usually done

at the bedside in our study, we could only use the Schirmer 2 test to objectively evaluate the dry eye. While values below 10 mm were observed in only two (7.4%) of 27 patients for whom the Schirmer 2 test was performed, values below 5 mm were not observed in any of the cases. No Schirmer value below 10 mm was observed in any of the patients in the examinations from the first month. However, when the change in Schirmer 2 tests was analysed in the sixth-month follow up, a statistically significant increase was observed in both eyes between the first and the sixth months. Dry eye is a common finding in autoimmune diseases [21]. For this reason, it is expected that MIS-C, whose underlying pathogenesis is thought to be an abnormal immune response, also causes dry eye [4]. In our study, although there was no finding other than punctate epitheliopathy to support severe dry eye at the time of the first examination, the increase in Schirmer values in the sixth-month follow-up supports this.

In our study, bilateral optic disc oedema was observed in the first examination of two patients. There was no complaint of low vision in either of these two cases, and it was thought that it was detected incidentally within the study. There are case reports of papilledema in MIS-C patients in the literature, albeit in a small number. Similar to the cases in our study, in the case report published by Divya et al, in the examination of an 11-year-old patient, the visual acuity was 20/20, and colour vision was complete in both eyes [9]. Similar to the one patient in our study, this patient was diagnosed with pseudotumor cerebri and received systemic acetazolamide therapy. After treatment, optic disc oedema resolved. Bilen et al. also reported a case of bilateral papilledema with low vision [10]. Baccarella et al. reported two cases with increased intracranial pressure and papilledema [11]. Becker et al. also reported four cases with increased intracranial pressure, but only one of these cases had papilledema [12]. Papilledema is swelling of the optic nerve due to increased intracranial pressure, and if left untreated, it can cause optic nerve damage and vision loss [22]. Since it can be seen without causing any complaints as in our study, although there are still a small number of cases, it shows us the importance of fundus examination in these cases in terms of rapid diagnosis and treatment.

MIS-C is a rare complication of SARS-CoV-2 infection [23]. For this reason, the fact that our study was conducted with a small number of cases is a limitation. In addition, the necessity of performing the first examination of the patients in the intensive care unit or the ward and the poor cooperation in the paediatric age group constitute other limitations. However, the study provided valuable data in terms of monitoring the patients for six months and monitoring the improvement of the findings in cases with pathological findings.

CONCLUSION

In our study, a relationship was found between subconjunctival haemorrhage and hospitalisation in the intensive care and the severity of the disease. Subconjunctival haemorrhage may be an examination finding that can give us information about the course of the disease. However, there is not enough information on this subject in the literature yet.

Moreover, a significant increase was observed in Schirmer 2 tests between the first and the sixth months in our study. Additionally, no pathological findings were observed in the anterior and posterior segments at the sixth-month examination of the patients, and improvement was found in all patients with pathological ocular findings. It was seen that two cases with optic disc oedema also returned to normal in the first-month examination.

MIS-C is a newly defined disease and information about the disease is very limited. It is not known what changes occur in the eye in patients who have undergone MIS-C. This study is important in terms of establishing ocular follow-up protocols that

are foreseen to be carried out both in the acute period and in the follow-up of the patients. More publications are needed to elucidate the MIS-C ophthalmologic examination findings in the acute and chronic stages.

Summary

What was known before

- The most frequently reported ocular finding in the acute phase of the multisystem inflammatory syndrome in children is conjunctivitis.

What this study adds

- The most striking finding of our study is that cases with subconjunctival haemorrhage were clinically more severe, and all patients needed intensive care.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

EKG and EKO designed the study and the computational framework and analysed the data. EKG and AS carried out the implementation. AKA performed the calculations. EKG wrote the manuscript with input from all authors. DY and YEK conceived the study and were in charge of overall direction and planning.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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