Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublisher.com/sjams/

OPEN ACCESS

Ophthalmology

Ocular Manifestations in Kawasaki Disease: A Literature Review

Shinji Makino[1*], Nobuko Makino[2]

[1]Department of Ophthalmology, Jichi Medical University Shimotsuke, Japan
[2]Department of Public Health, Jichi Medical University Shimotsuke, Tochigi, Japan

***Corresponding author:** Shinji Makino
| **Received:** 02.04.2019 | **Accepted:** 12.04.2019 | **Published:** 30.04.2019
DOI: 10.21276/sjams.2019.7.4.18

Abstract **Original Research Article**

The number of studies on ocular manifestations in Kawasaki disease (KD) is limited. We conducted a literature review and extracted data from the case reports about ocular manifestations in KD. A wide spectrum of ocular complications in KD had been reported. There are few reports of ocular manifestations under 5 years of age. Although ocular fundus changes are not uncommon, severe lesions are presumed to be rare. It seems difficult to evaluate the findings of ophthalmologic examination in the acute period in young children; however, retinal vascular changes may be useful in predicting the future cardiovascular sequelae of KD. We believe that ocular manifestations in the acute phase might be useful in determining the etiology of KD, and ocular signs manifested later might be useful in predicting cardiovascular events associated with KD.
Keywords: Kawasaki disease, Ocular manifestation.

INTRODUCTION

Kawasaki disease (KD), characterized by vasculitis, is an acute febrile multisystem syndrome of unknown etiology affecting most frequently infants and children under 5 years of age [1-7]. According to Diagnostic Guidelines for KD, principal symptoms are as follows; 1) Fever persisting for 5 days or more, 2) Bilateral conjunctival congestion, 3) Changes of the lips and the oral cavity, 4) Polymorphous exanthema, 5) Changes of peripheral extremities, and 6) Acute non-purulent cervical lymphadenopathy.

In Japan, nationwide surveys were conducted every two years culminating in the 24th nationwide survey [1-4]. The cumulative count of patients with KD in Japan was greater than 360 thousand. According to the most recent nationwide survey [1], the prevalence of KD was 16,323 (9,385 males, and 6,938 females) in 2015, 15,272 (8,675 males, and 6,597 females) in 2016, the total number of patients in 2 years was 31,595, and the sex ratio (male: female) was 1.34. The incidence rate (/100,000 children aged 0-4 years/year) was 330.2 (371.2 in male, 287.3 in female) in 2015, and 309.0 (343.2 in male, 273.2 in female) in 2016. The age-specific incidence rate according to sex was highest in children between 9 and 11 months of age, after which the incidence rate gradually decreased with advancing age.

A serious concern in KD is cardiac sequelae, including coronary aneurysms, coronary stenosis, and valvular lesions [5-7]. In addition, vasculitis—the main characteristic of KD—could potentially lead to rapid progression of atherosclerosis in children, as their cardiovascular system is immature. However, evidence for this hypothesis is inconsistent. Follow-up of patients with a history of KD is important in preventing chronic diseases in adulthood. Rapid progression of atherosclerosis among those with a history of KD would suggest that such a history is a risk factor for cardiovascular and cerebrovascular diseases. Therefore, if a history of KD is found to be an additional risk factor, patients with such a history may need more intensive control of other risk factors, such as blood pressure, serum lipids, and smoking habit. To determine the outcomes of patients with a history of KD, Nakamura *et al*. [7] evaluated the results (until the end of 2009) of the eighth follow-up examination of the cohort, which comprised patients who visited any of the 52 hospitals between July 1982 and December 1992. This study was highly significant in that the follow-up rate was extremely high at 99.5%. According to this cohort, of the 6,576 patients enrolled, 46 (35 males and 11 females) died (Standardized Mortality Ratio (SMR): 1.00; 95% CI: 0.73–1.34). Among persons without cardiac sequelae, SMR was not high after the acute phase of KD (SMR: 0.65; 95% CI: 0.41–0.96). Among persons with cardiac sequelae, 13 males and 1 female died during the observation period (SMR: 1.86; 95%

CI: 1.02–3.13). In this cohort, the mortality rate among Japanese patients with cardiac sequelae due to KD was significantly higher than that of the general population. In contrast, the rates for males and females without sequelae were not increased.

It is unclear whether all children with KD have increased risk of cardiovascular disease later in life. It is well known that the retinal microvasculature reflects changes in the systemic microcirculation and is associated with traditional cardiovascular risk factors and events [8]. In 2007, Chen *et al*. [9] investigated retinal microvascular parameters in two populations of patients with previous KD and control participants. They performed case-control studies of 116 (57 patients and 59 controls) Australian and 156 (78 patients and 78 control) Singaporean individuals, for at least two years since their acute illness. Standardized retinal photographs were graded, which quantifies the retinal microvasculature (caliber, branching angle, fractal dimensions, and tortuosity). Retinal venules of Singaporean KD patients were 9.67 μm larger than control participants following correction for traditional cardiovascular risk factors. An increment in the size of retinal venules in those with coronary artery abnormalities was observed. Differences in retinal microvasculature were particularly evident in Singaporean KD patients. Larger retinal venules may reflect chronic inflammation and endothelial dysfunction, and are associated with coronary artery disease in adults.

From the viewpoint of ocular manifestations in KD, they are commonly limited to the anterior segment and are characterized by bilateral bulbar conjunctivitis without exudate, superficial punctate keratitis, uveitis, or vitreous opacities. However, a wide spectrum of ocular complications in KD has been reported. Therefore, we conducted a literature review and extracted data from the case reports on ocular manifestations in KD.

Subjects and Methods

We searched the MEDLINE (December, 2018, via PubMed) electronic database for articles in English (1975-present) using the following combinations of terms: Kawasaki disease AND eye, lid, conjunctiva, cornea, iris, lens, retina. In addition, we also searched Ichushi Service, for articles in Japanese (1983-present) using the same search terms. When full text articles were not available, we extracted all available data from the abstracts.

Results

A wide spectrum of ocular manifestations in KD has been reported (Table 1) [10-40]. However, there were few prospective and retrospective studies [10-12, 14, 15, 25, 31].

In 1981, Rennebohm *et al*. [10] evaluated the anterior segment of the eye in six patients with KD prospectively. They reported that five had anterior uveitis during the acute phase of the illness. In 1982, Ohno *et al*. [11] evaluated 18 Japanese patients (11 boys and 7 girls, ranging in age from 5 months to 9 years) with KD prospectively. They reported bilateral non-exudative conjunctivitis in 16 children, bilateral iridocyclitis in 14, and superficial punctate keratitis in four, vitreous opacities in two, papilledema in two, and subconjunctival hemorrhage in one. Jacob *et al*. [12] evaluated nine patients (4 boys and 5 girls, ranging in age from 4 months to 7 years) with KD. They reported anterior uveitis in eight patients, and retinochoroidal change with unilateral vitritis in one.

Taking the ocular fundus, Nanri *et al*. [14] evaluated fundus changes in 100 patients (60 boys and 40 girls, ranging in age from 3 months to 10 years) with KD prospectively. They reported mild changes (retinal vascular dilation and tortuosity) in 62 (62%), optic disc swelling in 4 (4%), and retinal ischemia in one (1%). Fujimoto *et al.* [15] evaluated ocular findings from the acute phase in 44 patients (26 boys and 18 girls, ranging in age from 3 months to 6 years) with KD prospectively. They reported conjunctival congestion in all cases (100%), and iridocyclitis in 32 (73%).There was no abnormality on fundus examination.

On examination of the anterior segment of the eye, Kaiya *et al*. [25] found manifestations of ocular surface disorders in 15 patients (8 boys and 7 girls, ranging in age from 3 months to 9 years) with KD retrospectively. Bilateral injection of the bulbar conjunctiva was found in 15 cases (100%) and 11 of them showed other ocular disorders, such as discharge in 4 cases (27%), itching in 3 cases (20%), lid swelling in 2 cases (13%), acute conjunctivitis in 6 cases (40%), superficial punctate keratopathy in 4 cases (27%), and corneal stromal opacity in 2 cases (13%).

According to the most recent prospective study of KD complications, Alves *et al*. [31] reported that 15 patients (13.2%) had ophthalmologic complications out of 155 cases; 13 had anterior uveitis, one had papilledema and another had a conjunctival hemorrhage. Of these, 40% occurred in the acute phase, the others in the subacute phase, and these complications were not present at the second ophthalmologic assessment 30 days later.

Table-1: Manifestations found in the literature

References	design	Number of cases	Age/sex	Manifestations
Rennebohm et al. 1981 [10]	Prospective study	6	16yF/8yM/6yF/3yM/2yF/1yM	anterior uveitis
Ohno et al. 1982 [11]	Prospective study	18	5m-9y, M/F:11/7	iridocyclitis, superficial punctate keratitis, vitreous opacities, papilledema, subconjunctival hemorrhage
Jacob et al. 1982 [12]	Prospective study	9	4m-7y, M/F:4/5	uveitis, choroidal, retinal and vitreous changes
Font et al. 1983 [13]	Case report/ post mortem findings	1	4mM	inner retinal ischemia
Nanri et al. 1983 [14]	Prospective study	100	3m-10y, M/F:60/40	retinal vascular dilation and tortuosity, optic disc swelling, retinal ischemia
Fujimoto 1987 [15]	Prospective study	44	3m-6y, M/F:26/18	iridocyclitis
Mizuno and Kabe 1983 [16]	Case report	1	1yF	corneal stromal opacity
Okuyama 1985 [17]	Case report	1	1yF	corneal stromal opacity
Yamagisawa et al. 1989 [18]	Case report	3	6yM/8yF/11yF	retinochoroidal lesions
Kawasaki et al. 1990 [19]	Case report	1	8yF	acute retinal pigment epitheliopathy
Kunito et al. 1990 [20]	Case report	1	15yF	optic disc vasculitis, central retinal vein occlusion
Mizuno et al. 1993 [21]	Case report	1	5mM	corneal stromal opacity
Takamura et al. 1994 [22]	Case report	1	8yM	iridocyclitis, optic disc edema, choroidal circulation disturbance
Kurosawa et al. 1994 [23]	Case report	1	11yM	corneal stromal opacity
Iwano et al. 1998	Case report	1	5yF	retinal aneurysmal vein, retinal arterio-venous anastomosis
Kaiya et al. 2000 [25]	Retrospective study	15	3m-9y, M/F:8/7	lid swelling, superficial punctate keratopathy, corneal stromal opacity
Tomatsu et al. 2001 [26]	Case report	1	7yM	branch retinal artery occlusion after cardiac catheterizaion
Anand and Yang 2004 [27]	Case report	1	8yF	optic disc swelling, anterior uveitis
Kadyan et al. 2006 [28]	Case report	1	11yM	disciform keratitis, optic disc swelling
Murakami et al. 2006 [29]	Case report	1	5yM	uveitis
Farvardin et al. 2007 [30]	Case report	1	9yF	optic disc swelling, ophthaimic artery obstruction
Alves et al. 2011 [31]	Prospective study	155	2m-11y, M/F:77/38	anterior uveitis, papilledema、conjunctival hemorrhage
Grouteau et al. 2011 [32]	Case report	1	12yF	anterior uveitis, vitritis, optic disc swelling
Garweg et al. 2012 [33]	Case report	1	6yM	epithelial keratitis, anterior uveitis, retinal vasculitis, optic disc involvement
Cerman et al. 2013 [34]	Case report	1	6yM	orbital cellulitis
Erdem et al. 2013 [35]	Case report	1	7yF	crystalline-like keratopathy after intravenous immunoglobulin
Nakada 2016 [36]	Case report	1	12yF	blindness
Viswanathan et al. 2016 [37]	Case report	1	12yF	crystalline-like keratopathy after intravenous immunoglobulin
Tsumura et al. 2017 [38]	Case report	1	2yF	optic disc swelling
Hameed et al. 2017 [39]	Case report	1	3yM	ptosis after intravenous immunoglobulin
Gao et al. 2018 [40]	Case report	1	11yF	retinitis, retinal detachment

DISCUSSION

We emphasize the following four points from this review. Firstly, as mentioned above, there are several reports in the acute phase, but those in the late phase are extremely rare [20, 26]. Kunito *et al*. [20] reported on a 15-year-old girl with a history of KD 10 years ago who developed central retinal vein occlusion due to optic disc vasculitis. Tomatsu *et al*. [26] reported on a 7-year-old boy with a history of KD 3 years ago who developed branch retinal artery occlusion after cardiac catheterization. Secondly, although the age-specific incidence rate is highest in children between 9 and 11 months of age, there are few reports of ocular manifestations under 5 years of age. This apparent discrepancy might be explained by the known difficulty of ophthalmologic diagnosis. Thirdly, although ocular fundus changes are not uncommon, severe lesions are presumed to be rare. Lastly, corneal involvement may not only be due to KD itself but can also be iatrogenic due to intravenous immunoglobulin administered as a treatment [35, 37]. This ocular side effect comprises crystalline-like keratopathy that might be caused by subepithelial deposition of immunoglobulin. Fortunately, this corneal lesion resolves spontaneously.

From the epidemiological point of view, infection and host factors are considered to be causes of KD [1-4]. The following seven different epidemiological factors are highly suggestive of an infectious etiology: 1) three instances of nationwide epidemics, 2) geographic spread of the epidemics, 3) age-specific incidence rate with a peak in late infancy, 4) chronologic and geographic clustering, 5) seasonal variations, 6) involvement of siblings, and 7) clustering of the disease in small areas. In addition, the following four epidemiological factors are suspected to be host-related; 1) lower incidence rate than measles and chicken pox in areas with no access to vaccination facilities, 2) different incidence rates between ethnic groups; Japanese > Asians outside Japan > African-Americans > White Americans, 3) existence of parent-child cases, and 4) existence of sibling cases. Therefore, several infectious agents are thought to serve as triggers of the disease in susceptible children.

We believe that ocular manifestations in the acute phase might be useful in considering an infectious etiology of KD, and ocular manifestations in late and remote periods might be useful in predicting cardiovascular events associated with KD.

CONCLUSIONS

Monitoring the eye and the fundus routinely, while treating KD systemically benefits patients with retinal lesions, and potentially prevents the ocular inflammation from progressing to loss of vision. Although it seems difficult to evaluate ophthalmologic examination in the acute phase at a young age, retinal vascular changes may be useful findings in pre-empting the future cardiovascular sequelae of this disease.

Disclosure

No conflicts of interest were declared in relation to this paper.

REFERENCES

1. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, Aoyama Y, Yanagawa H. The nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. Pediatrics International. 2019 Feb 20.
2. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H. Epidemiological observations of Kawasaki disease in Japan, 2013–2014. Pediatrics International. 2018 Jun;60(6):581-7.
3. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, Kojo T, Uehara R, Kotani K, Yanagawa H. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. Journal of epidemiology. 2015 Mar 5:JE20140089.
4. Nakamura Y, Yashiro M, Yamashita M, Aoyama N, Otaki U, Ozeki Y, Sano T, Kojo T, Ae R, Aoyama Y, Makino N. Cumulative incidence of Kawasaki disease in Japan. Pediatrics International. 2018 Jan;60(1):19-22.
5. Kibata T, Suzuki Y, Hasegawa S, Matsushige T, Kusuda T, Hoshide M, Takahashi K, Okada S, Wakiguchi H, Moriwake T, Uchida M. Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin. International journal of cardiology. 2016 Jul 1;214:209-15.
6. Abrams JY, Belay ED, Uehara R, Maddox RA, Schonberger LB, Nakamura Y. Cardiac complications, earlier treatment, and initial disease severity in Kawasaki disease. The Journal of pediatrics. 2017 Sep 1;188:64-9.
7. Nakamura Y, Aso E, Yashiro M, Tsuboi S, Kojo T, Aoyama Y, Kotani K, Uehara R, Yanagawa H. Mortality among Japanese with a history of Kawasaki disease: results at the end of 2009. Journal of epidemiology. 2013 Nov 5;23(6):429-34.
8. Al-Fiadh AH, Farouque O, Kawasaki R, Nguyen TT, Uddin N, Freeman M, Patel SK, Burrell LM, Wong TY. Retinal microvascular structure and function in patients with risk factors of atherosclerosis and coronary artery disease. Atherosclerosis. 2014 Apr 1;233(2):478-84.
9. Chen KY, Burgner DP, Wong TY, Saw SM, Quek SC, Pang AY, Leo SW, Wong IB, Zannino D, Curtis N, Cheung M. Evidence of microvascular changes in the retina following Kawasaki disease. Scientific reports. 2017 Jan 17;7:40513.
10. Rennebohm RM, Burke MJ, Crowe W, Levinson JE. Anterior uveitis in Kawasaki's disease.

American journal of ophthalmology. 1981 Apr 1;91(4):535-7.
11. Ohno S, Miyajima T, Higuchi M, Yoshida A, Matsuda H, Saheki Y, Nagamatsu I, Togashi T, Matsumoto S. Ocular manifestations of Kawasaki's disease (mucocutaneous lymph node syndrome). American journal of ophthalmology. 1982 Jun 1;93(6):713-7.
12. Jacob JL, Polomeno RC, Chad Z, Lapointe N. Ocular manifestations of Kawasaki disease (mucocutaneous lymph node syndrome). Canadian journal of ophthalmology. Journal canadien d'ophtalmologie. 1982 Oct;17(5):199-202.
13. Font RL, Mehta RS, Streusand SB, O'Boyle TE, Kretzer FL. Bilateral retinal ischemia in Kawasaki disease: postmortem findings and electron microscopic observations. Ophthalmology. 1983 May 1;90(5):569-77.
14. Nanri T, Fukuda H, Komiyama R, Oshima K. *Ocular fundus changes of 100 cases with Kawasaki disease. A total of 279 examinations for 5 years*. Shonika. 1983; 24: 375-379. *Japanese.*
15. Fujimoto T. Course of ocular manifestations of Kawasaki disease. Rinsho Ganka. 1987; 41: 337-341. *Japanese.*
16. Mizuno K, Kabe S. *A case of transient corneal stromal opacity in Kawasaki disease*. Ganka. 1983; 25:265-268. *Japanese.*
17. Okuyama S. *A case of Kawasaki disease with corneal stromal opacity*. Ganka. 1985; 27:83-86. *Japanese.*
18. Yamagisawa Y, Gomibuchi M, Kato K, Ohara K. Retinochoroidal lesions in Kawasaki disease. Rinsho Ganka. 1989; 43: 331-334. *Japanese.*
19. Kawasaki M, Yoshida G, Kurihara H. A case of acute retinal pigment epitheliopathy in Kawasaki disease. Nihon Ganka Kiyo. 1990; 41: 365-369. *Japanese.*
20. Kunito N, Funada M, Okamoto I, Tamai A, Nishigori T. Optic disc vasculitis in a girl with past history of Kawasaki disease. Ganka Rinsho Iho. 1990; 84: 1765-1769. *Japanese.*
21. Mizuno T, Kitagawa K, Katsura S. A case of Kawasaki disease with transient corneal opacity]. Rinsho Ganka. 1993; 47:1355-1359. *Japanese.*
22. Takamura H, Yamaguchi K, Satoh T, Takahashi S. Indocyanine green angiographic findings in uveitis in Kawasaki disease. Nihon Ganka Kiyo. 1994; 45: 1035-1040. *Japanese.*
23. Kurosawa J, Hayamizu F, Shoji J, Harada K. A case of corneal stromal lesion in Kawasaki disease. Ganka. 1994; 36:921-925. *Japanese.*
24. Iwano M, Isomura Y, Itou Y. Retinal aneurysmal veins in a case of Kawasaki disease. Ganka Rinsho Iho. 1998; 92: 60-63. *Japanese.*
25. Kaiya R, Shoji J, Inada N, Sawa M. Ocular surface disorders complicated with Kawasaki disease. Ganka. 2000; 42:1037-1042. *Japanese.*
26. Tomatsu A, Ishibashi T, Fujisawa M, Inoeu J, Yoshizawa T, Ueno S. Branched retinal artery occlusion in a child with Kawasaki disease after cardiac catheterization. Ganka. 2001; 43: 1845-1848. *Japanese.*
27. Anand S, Yang YC. Optic disc changes in Kawasaki disease. J Pediatr Ophthalmol Strabismus. 2004; 41: 177-179.
28. Kadyan A, Choi J, Headon MP. Disciform keratitis and optic disc swelling in Kawasaki disease: an unusual presentation. Eye (Lond). 2006; 20:976-977.
29. Murakami Y, Higaki T, Yamamoto E, Matsuda O, Nakano T, Takata H, Nagatani K, Ota M, Murao K, Takahashi Y, Chisaka T, Moritani T. A case of gamma globulin-resistant Kawasaki disease complicated with intractable anterior uveitis and treated with oral prednisolone. Progress in Medicine. 2006; 26: 1600-1604. *Japanese.*
30. Farvardin M, Kashef S, Aleyasin S, Nabavizadeh SH, Sajjadi M, Safari M. Sudden unilateral blindness in a girl with Kawasaki disease. J Pediatr Ophthalmol Strabismus. 2007; 44: 303-304.
31. Alves NR, Magalhães CM, Almeida Rde F, Santos RC, Gandolfi L, Pratesi R. Prospective study of Kawasaki disease complications: review of 115 cases. Rev Assoc Med Bras. 2011; 57: 295-300.
32. Grouteau E, Debuisson C, Brochard K, Paranon S, Lesage Beaudon C, Pajot C, Claudet I. Severe global inflammatory involvement of ocular segments and optic disc swelling in a 12-year-old girl with Kawasaki disease. Eur J Ophthalmol. 2011; 21:112-114.
33. Garweg JG, Suter C, Aebi-Ochsner C, Villiger R. Macular oedema in Kawasaki syndrome. Graefes Arch Clin Exp Ophthalmol. 2012; 250: 1101-1104.
34. Cerman E, Eraslan M, Turhan SA, Usta SA, Akalin F. Orbital cellulitis presenting as a first sign of incomplete Kawasaki disease. Case Rep Ophthalmol. 2013; 4: 294-298.
35. Erdem E, Kocabas E, Taylan Sekeroglu H, Ozgür O, Yagmur M, Ersoz TR. Crystalline-like keratopathy after intravenous immunoglobulin therapy with incomplete Kawasaki disease: case report and literature review. Case Rep Ophthalmol Med. 2013; 2013: 621952.
36. Nakada T. Blindness in the acute phase of Kawasaki disease: a case report and review of the literature. Shonika Rinsho. 2016; 69: 1045-1050. *Japanese.*
37. Viswanathan V, Agashe P, Jain V, Nair AG. Crystalline keratopathy due to intravenous immunoglobulin in a 12-year-old girl with Kawasaki disease. J AAPOS. 2016; 20: 466-468.
38. Tsumura Y, Masuda H, Nishina S, Kobayashi T, Ono H, Kato H, Abe J, Ishiguro A. Prolonged optic disc swelling in Kawasaki disease - A case report and literature review. Nihon Rinsho Meneki Gakkai Kaishi. 2017; 40: 377-381. *Japanese.*
39. Hameed A, Alshara H, Schleussinger T. Ptosis as a complication of Kawasaki disease. BMJ Case Rep. 2017 Jun 9; 2017. pii: bcr-2017-219687.

40. Gao Y, Zhang Y, Lu F, Wang X, Zhang M. Rare ocular manifestations in an 11-year-old girl with incomplete Kawasaki disease: A case report. Medicine (Baltimore). 2018; 97: e10974.