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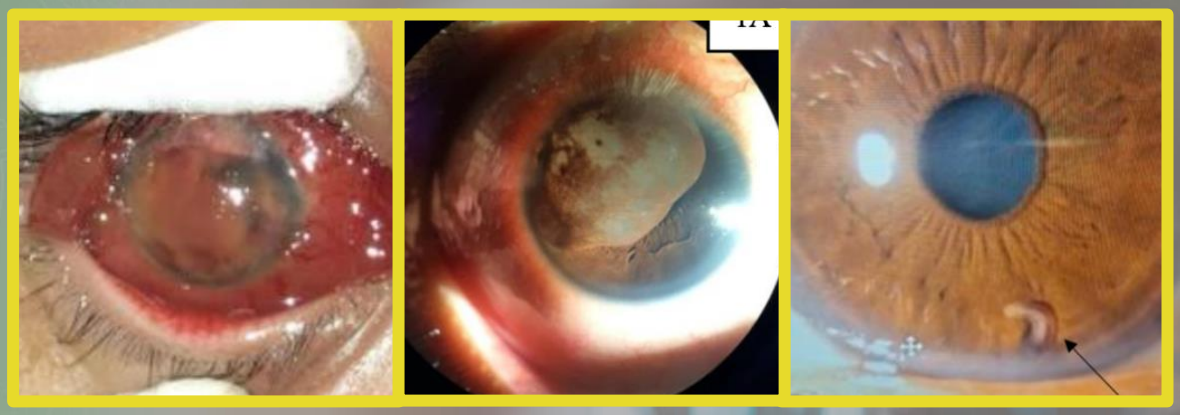

- Analysis of OCT-A Performed Among Optic Atrophy Post NAION Patients Versus Other Causes
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- Ocular Gnathostomiasis in a Farmer from South Sulawesi, Indonesia

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EDITORIAL

Widya Artini Wiyogo

World Leprosy Day, annually celebrated on the last Sunday of January each year, was recently around the corner with the theme for 2025 being "Unite. Act. Eliminate." This theme acts as a compelling call to action, aiming to raise awareness, highlight the challenges faced by those affected by the disease, and encourage collaborative efforts toward its eradication. In accordance with this, one of the published articles in this issue focuses on the critical importance of accurate diagnosis and management of leprosy, reinforcing the need for proper care in combating the disease.

Leprosy, or Hansen's disease, is caused Mycobacterium leprae infection. Indonesia ranks third globally in reported cases, exceeding 10,000 annually, following India and Brazil. In 2021, approximately 10,976 cases were documented in Indonesia with 89% of them classified as multibacillary (MB) type. The disease causes chronic, granulomatous infection which primarily targets the peripheral nerves, mucous membranes of the upper respiratory tract, and skin, causing characteristic skin lesions. Damaged nerves may result in numbness of the affected areas, eventually leading to extremities deformities and disabilities if not managed appropriately. If untreated, leprosy can inflict significant damage on the skin, nerves, limbs, and eyes. Notably, ocular manifestations are seen in 51.6% to 85% of cases.

Clinical ocular manifestations of leprosy can be classified into three main categories: eyelids and adnexa abnormalities, lacrimal system issue, and intraocular abnormalities. Abnormalities of adnexal and lacrimal system may include madarosis (loss of eyelashes and eyebrows), lagophthalmos (inability to fully close the eyelids), entropion, ectropion, dacryocystitis, and obstruction of the lacrimal drainage system. Intraocular abnormalities may involve the cornea, iris, ciliary body, lens, and posterior segment, all of which can significantly affect visual function.[1]

One of the complications of leprosy is lagophthalmos, which can be classified into paralysis, cicatricial, and nocturnal forms. The most common manifestation is corneal damage which affects approximately 60% of cases, primarily due to its physiological dense innervation. Corneal reflex and pain are usually diminished or absent in affected cornea, resulting in corneal hypoesthesia, which puts the cornea’s defence system at risk. The underlying mechanism is believed to involve a complex immune reaction. If not recognized and treated promptly, leprosy

can lead to severe complications, including corneal perforation (13%) and even ocular blindness (16%). The diagnosis of leprosy is supported by two of the three cardinal signs: thickening of peripheral nerves and the presence of acid-fast bacilli. Multidisciplinary collaboration with the Dermatology and Venereology Department is crucial for early detection and comprehensive management.[2]

The KATAMATAKU UI program, led by Prof. Dr. Yunia Irawati, has developed a comprehensive approach to support leprosy care for patients across various regions of Indonesia. The program engages multiple stakeholders to ensure its success and sustainability. It not only relies on health resources but also draws on expertise from diverse fields of Universitas Indonesia, including health sciences, technology, social studies, and humanities, to support education, management, economic empowerment, and technological innovation. Furthermore, the program collaborates with both the government and private sectors, making KATAMATAKU UI an interdisciplinary and multisectoral initiative that comprehensively addresses the needs of leprosy patients and their communities.[3]

Meanwhile, with the technological advancement available today in the world of ophthalmology, it is now possible to obtain a more detailed diagnosis of retinal vascular condition through utilization of optical coherence tomography angiography (OCT-A).[4] This issue also features an article discussing the application of OCT-A to differentiate various causes of optic disc edema, with a particular focus on distinguishing non-arteritic anterior ischemic optic neuropathy (NAION) from other potential causes. While the exact causes of NAION remains unknown, some data suggest it may be linked to a perfusion deficit in the microcirculation of the optic nerve head, which is primarily supplied by the short posterior ciliary arteries. Consequently, vascular factors are believed to play a key role in its pathogenesis. OCT-A provides quantitative assessment of the circulation in both the peripapillary and retinal vasculature. NAION typically presents in funduscopic examination as edema of the optic nerve head, which may be diffuse or segmental and initially hyperemic. After 6-8 weeks from the onset of NAION, the optic nerve head usually becomes atrophic. However, optic atrophy is an end-result of optic nerve insults which can be caused by various etiologies. By utilizing OCT-A, it may be possible to assist in diagnosing NAION and differentiating it from other forms of optic atrophy by studying the vasculature features around the peripapillary and retinal area.

REFERENCES

1. Buku Ajar Oftalmologi. Edisi 1. UI Publishing. Jakarta. 2020
2. Mengenai Kusta. Katamataku Seri 1. UI Publishing. Jakarta
3. Irawati Y. Perspektif Okuloplatik Rekontruksi dalam Pendekatan Terapi dan Rehabilitasi untuk Menangani Masalah Kesehatan Individu Hingga Masyarakat untuk Mendukung Produktifitas Bangsa. Diklat Pengukuhan Guru Besar 2025
4. Jia,Y et al. Optical Coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology 2014 Jul.121(7): 1322032
5. American Academic of Ophthalmology. Neuro-ophthalmology. In:Bhatti MT et al.ed . Basic CLinical Science Course. Section 5. San Fransisco: American Academy of Ophthalmology 2022.p.153-55

ORIGINAL ARTICLE

ANALYSIS OF OCT-A PERFORMED AMONG OPTIC ATROPHY POST NAION PATIENTS VERSUS OTHER CAUSES

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ABSTRACT

Introduction: *Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) is the type of optic neuropathy with crowding structural of microcirculation on optic nerve head. The vascular factor has the role on its pathophysiology. The aim of this study to analyse OCT-A among optic atrophy post NAION patients compared to optic atrophy with other causes.*

Methods: *A retrospective case control study held from medical record of patients. Two group diagnosis of optic atrophy post NAION and optic atrophy due to other causes who performed OCT-A in Dr. Kariadi Hospital Semarang. The analysis of the study including vessel perfusion density (VPD) and flux index (FI) among two groups. The bivariate analysis is using Independent-T test.*

Results: *Totally 40 patients consisted of 20 optic atrophy post NAION (12 bilateral eyes) and 20 optic atrophy with other causes (15 bilateral eyes). Age over 50 years old were 19 post NAION (95%) and 17 other causes (85%). The results found there is statistically significant difference between VPD among post NAION and other causes in average, superior, and nasal (p value <0.05, respectively 0.008, 0.008, 0.030), but there is no significant difference between FI among post NAION and other causes both average, inferior, superior, nasal, and temporal (p value > 0.05). Mean VPD both average, inferior, superior, nasal and temporal in post NAION were lower than other causes (respectively 39,98±3,69, 38,57±6,01, 36,77±5,25, 40,78±4,06, 43,91±3,42).*

Conclusion: *This study found there is statistically significant difference between VPD among optic atrophy post NAION and other causes in average, superior, and nasal. VPD in post NAION were lower compared to other causes.*

Keywords: *Non-arteritic anterior ischemic optic neuropathy, optic atrophy, optical coherence tomography angiography*

INTRODUCTION

Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) is the type of optic neuropathy with crowding structural of microcirculation on optic nerve head (ONH) and found more common approximately 90-95% of anterior ischemic optic neuropathy (AION) cases.[1] NAION is found more common in adults over 50 years of age.[1] NAION is estimated occured in 2.3-10.3 per 100.000 individual in the middle-age and elderly population.[2]

Diabetes mellitus, systemic hypertension, and hyperlipidemia are among the risk factors linked to NAION.[1] The fundamental cause of NAION is still unknown, however some data suggests that it can be related to a perfusion deficit in the microcirculation of the optic nerve

head, which is primarily supplied by the short posterior ciliary arteries. Consequently, vascular factor plays a part in its pathogenesis.[2]

NAION appears as the edema of optic nerve head, it may be diffuse or segmental but initially hyperemic. After 6-8 weeks onset of NAION, the optic nerve head usually becomes atrophic. When it comes to optic nerve head pallor, it indicates the optic atrophy. The optic atrophy can be caused by many etiologies.[1]

OCT-A provides quantitative assesment of the circulation of peripapillary and retinal vasculature vessels.[3] OCT-A has the role and usefulness in identifying the microvascular defects and vessel density reduction in cases of NAION. OCT-A gives much information in ischemic conditions of the optic nerve head.[4] OCT-A contributes to the detection, diagnosis, and treatment of diseases associated to the optic nerve. OCT-A also holds a significant role as a practical, noninvasive instrument for the evaluation of neuro-ophthalmologic conditions.[5] Study from Ling et al. demonstrated that optical non-perfusion area percentages were substantially correlated with both visual acuity and visual field in chronic NAION patients, and they recommended that OCT-A can be used for both diagnosis and follow-up in NAION patients.[6] Some previous studies from Hata et al, Song et al and Liu et al. reported peripapillary vessel density loss in post acute NAION.[7-9] The aim of this study is to find out whether OCT-A could be used to differentiate optic atrophy due to post NAION or other causes.

METHODS

A retrospective case control study from two groups consisted of 20 optic atrophy post NAION patients and 20 patients with optic atrophy of other causes. Inclusion criteria were patients with optic atrophy post NAION and optic atrophy with other causes who performed OCT Angiography in Dr. Kariadi Hospital that had been diagnosed by Neuro Ophthalmologist consultant. Exclusion criteria were patients which had incomplete medical record or the OCT-A results were not valid due to poor signal strength.

OCT-A was performed with Zeiss Cirrus HD-OCT 5000 (Carl Zeiss Meditec, US, SW Ver: 11.0.0.29946). The secondary data collected by medical records. Medical records were reviewed to obtain the clinical characteristics of patients including age, sex, laterality characteristics, etiology of other causes, and also OCT-A results to collect the data of vessel perfusion density and flux index. The normality test is normally distributted. The statistic of bivariate analysis is using Independent-T test to analyse the difference between vessel perfusion density and flux index among optic atrophy post NAION and optic atrophy by other causes.

The significant difference is found statistically significant if the p value < 0.05. Data were analyzed using statistical software program SPSS.

RESULTS

Retrospective case control study from medical records showed two groups of patients consisting group with optic atrophy post NAION and group with optic atrophy due to other causes. Each group consisted of 20 patients. The demographic status found that age over 50 years old were 19 post NAION (95%) and 17 other causes (85%). Both groups showed dominantly similar in age group. Gender from both groups were slightly difference, but tend to be equal.

Table 1. Demographic Characteristics

Demographic Characteristics	Total = 40 N (%)
Age	
Post NAION	
<50 years	19 (95%)
≥50 years	1 (5%)
Other causes	
<50 years	17 (85%)
≥50 years	3 (15%)
Gender	
Post NAION	
Male	11 (55%)
Female	9 (45%)
Other causes	
Male	8 (40%)
Female	12 (60%

Table 2. Laterality Characteristics among Two Groups

Group	Bilateral N = 27	Unilateral N = 13	Total N = 40
Post NAION	12 (60%)	8 (40%)	20
Other causes	15 (75%)	5 (25%)	20

Table 3. Etiology and Laterality of Other Causes

Etiology	Bilateral N = 27	Unilateral N = 13	Total N = 40
Other causes	15	5	20
Toxic ON	1	0	1
Traumatic ON	0	2	2
Macular Distrophy	1	0	1
SOL Intracranial (Mass)	7	2	9
Hydrocephalus	1	0	1
Post Optic Neuritis	4	0	4
Sinonasal Mass	0	1	1
CCF	1	0	1

ON = optic neuropathy; SOL = space occupying lesion; CCF = carotid cavernous fistula

Based on the laterality, in post NAION group there were 12 patients (60%) had bilateral, similar to other causes group had predominantly 15 bilateral (75%). The etiology of optic atrophy due to other causes in this study were most commonly intracranial SOL or mass (9 patients), followed by post optic neuritis (4 patients), traumatic optic neuropathy (2 patients), and 1 patient respectively due to toxic optic neuropathy, macular dystrophy, hydrocephalus, sinonasal mass, and CCF. Unilateral cases were found in traumatic optic neuropathy, sinonasal mass, and 2 of 9 patients with intracranial SOL.

Table 4. The OCT-A Results among Post NAION and Other Causes Groups

	Group	Mean ± SD	p*
Vessel Perfusion Density (VPD)			
Average	Post NAION	39,98 ± 3,69	0,008*
	Other causes	42,41 ± 3,63	
Inferior	Post NAION	38,57 ± 6,01	0,072
	Other causes	41,00 ± 4,67	
Superior	Post NAION	36,77 ± 5,25	0,008*
	Other causes	40,26 ± 5,19	
Nasal	Post NAION	40,78 ± 4,06	0,030*
	Other causes	42,96 ± 3,99	
Temporal	Post NAION	43,91 ± 3,42	0,091
	Other causes	45,47 ± 3,95	
Flux Index (FI)			
Average	Post NAION	0,393 ± 0,050	0,725
	Other causes	0,397 ± 0,048	
Inferior	Post NAION	0,389 ± 0,050	0,422
	Other causes	0,399 ± 0,043	
Superior	Post NAION	0,385 ± 0,049	0,647
	Other causes	0,391 ± 0,045	
Nasal	Post NAION	0,401 ± 0,052	0,966
	Other causes	0,401 ± 0,054	
Temporal	Post NAION	0,395 ± 0,057	0,662
	Other causes	0,401 ± 0,056	

**p value <0.05 (statistically siginificant difference)*

The OCT-A result from two groups were performed with normality test, the result was normally distributed. Therefore, these were then conducted bivariate analysis using Independent-T Test. It is found that the mean of vessel perfusion density (VPD) both average, inferior, superior, nasal and temporal in post NAION were lower than other causes (respectively 39,98 ± 3,69, 38,57 ± 6,01, 36,77 ± 5,25, 40,78 ± 4,06, 43,91 ± 3,42 and 42,41 ± 3,63, 41,00 ± 4,67, 40,26 ± 5,19, 42,96 ± 3,99, 45,47 ± 3,95). There is statistically significant difference between VPD among post NAION and other causes in average, superior, and nasal (p value < 0.05, respectively 0.008, 0.008, 0.030), but there is no significant difference between FI among

post NAION and other causes both average, inferior, superior, nasal, and temporal (p value > 0.05).

DISCUSSION

This study showed that the age over 50 years were predominantly both two groups which had 95% patients of post NAION and 85% patients of other causes. It is consistent with the reported study which stated that the age of NAION is mostly older than 50 years old.[10-11] Gender from two groups showed there is slightly difference, but tend to be equal. This study showed post NAION is slightly more dominant in male with 11 patients (55%) more than female with 9 patients (45%). In other causes group, there were 8 male patients (40%) and 12 female patients (60%). Some previous studies found that male and female are nearly similarly affected in NAION.[12-14] NAION is mostly presented unilateral and in 25% of the NAION population, unilateral NAION could develop into bilateral after 32.4 months from the onset.[10,15,16] In contrast with this study, unilateral NAION were 8 patients (40%) and 12 patients (60%) bilateral. It might be due to the onset of NAION which had developed into bilateral.

OCT-A provides quantitative assesment of the circulation of peripapillary and retinal vasculature vessels.[3] OCT-A has the role and usefulness in identifying the microvascular defects and vessel density reduction in cases of NAION. OCT-A gives much information in ischemic conditions of the optic nerve head.[4] OCT-A contributes to the detection, diagnosis, and treatment of diseases associated to the optic nerve. OCT-A also holds a significant role as a practical, noninvasive instrument for the evaluation of neuro-ophthalmologic conditions.[5] Study from Ling et al. demonstrated that optical non-perfusion area percentages were substantially correlated with both visual acuity and visual field in chronic NAION patients, and they recommended that OCT-A can be used for both diagnosis and follow-up in NAION patients.[6] Ghasemi Falavarjani et al. revealed that, in comparison to normal eyes, eyes suffering from optic atrophy brought on by NAION had thinner RNFL and less vascular density.[17] Liu et al. demonstrated that peripapillary retinal perfusion declined in individuals with NAION who had optic atrophy, and this discovery was linked to RNFL thinning.[9] Sharma et al. observed decreases in microvascular flow in the superficial and choroidal peripapillary regions.[15] According to Balducci et al., patients with NAION had lower ONH and peripapillary vascular density than controls. These measures may help distinguish ischemic conditions from other causes.[4] In both acute and chronic NAION, Rebodella et al. demonstrated a substantial decrease in the peripapillary capillary density, vessel density, and perfusion density in affected versus unaffected fellow eyes.[18]

Peripapillary vessel density loss in post acute NAION had been reported in some studies.[7-9] But it does not mean that OCT-A directly shows the ischemia of ONH in NAION. NAION is believed as a result from infarction of the retrolaminar segments of optic nerve head which are supplied primarily by flow through the short posterior ciliary arteries.[19] A reduction in the peripapillary vessel density in post acute NAION is found correlated with the severity of peripapillary retinal nerve fiber layer thinning.[8] Some studies performed by OCT-A had demonstrated that a reduction in vessel density of ONH and radial peripapillary capillary in the eyes with NAION.[2,4,18.] It is consistent with this study that there were reduction of vessel perfusion density and flux index among post NAION. A decrease of perfusion in NAION might be related to these several possible reasons. First, the neurodegenerative changes following an episode of NAION cause a reduction in number of nerve fibers of ONH and then decrease metabolic demand and blood flow through auto-regulatory mechanisms. Second, the decrease of peripapillary retinal perfusion might be a primary result of an ischemic condition in NAION.[9]

This study analyses and compares OCT-A results among optic atrophy post NAION versus optic atrophy due to other causes. The results of this study showed vessel perfusion density and flux index in post NAION were lower than other causes. There is significant difference of vessel perfusion density among post NAION and other causes. The other causes of optic atrophy in this study were variant. These might be caused by SOL intracranial (mass), post optic neuritis, traumatic optic neuropathy, toxic optic neuropathy, sinonasal mass, hydrocephalus, CCF, and macular dystrophy. In NAION, there were vascular and systemic factors that might influence. In contrast with other causes, there were various etiologies and pathophysiology which might lead to atrophy optic. Some could be caused by non vascular factors. Therefore, the OCT-A results measured by vessel perfusion density and flux index found in post NAION tend to be lower.[4,9,18]

Limitation of this study include that for other causes group, it did not analyse further what etiologies that had better or poorer OCT-A results regarding vessel perfusion density and flux index. All etiologies which causes optic atrophy other than NAION were classified into one group. Further research should be performed to discuss what factors associated in both groups and which sector or quadrant of optic nerve head based on OCT-A is mostly affected.

CONCLUSION

This study found there is statistically significant difference between vessel perfusion density among optic atrophy post NAION and other causes in average, superior, and nasal.

Vessel perfusion density in post NAION were lower compared to other causes. In contrast with flux index, the is no significantly difference among two groups.

REFERENCES

1. American Academy of Ophthalmology. Neuro-Ophthalmology. In: Bhatti MT, et al., editors. Basic and Clinical Science Course. Section 5. San Fransisco: American Academy of Ophthalmology. 2022. p. 153-155.
2. Ling L, et al. Optical coherence tomography angiography assesment of the peripapillary vessel density and structure in patients with nonarteritic anterior ischemic optic neuropathy: a meta-analysis. Biomed Research Journal. 2020. 1-11. Available from: https://doi.org/10.1155/2020/1359120.
3. Jia Y, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology. 2014 Jul. 121(7):1322-32.
4. Balducci N, et al. Optical coherence tomography angopgraphy in acute arteritic and non-arteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2017. 255(1):2255-2261.
5. Bilici S, Duman R. The current clinical role of optical coherence tomography angiography in neuro-ophthalmological diseases. Taiwan J Ophthalmol. 2022. 12(3): 264-272.
6. Ling JW, et al. Optical coherence tomography angiography of optic disc perfusion in non-arteritic anterior ischemic optic neuropathy. *Int J Ophthalmol.* 2017. 10:1402–6.
7. Hata M, et al. Structural and functional analyses in nonaretritic anterior ischemic optic neuropathy: optical coherence tomography angiopgraphy study. J Neuroophthalmol. 2017 Jun;37(2):140-8.
8. Song Y, Min JY, Mao L, Gong YY. Microvasculature dropout detected by the optical coherence tomography angiography in nonarteritic anterior ischemic optic neuropathy. Lasers Surg Med. 2018 Maret;50(3):194-201.
9. Liu CH, Kao LY, Sun MH, Wu WC, Chen HSL. Retinal vessel density in optical coherence tomography angiography in optic atrophy after nonarteritic anterior ischemic optic neuropathy. J Ophthalmol. 2017. 2017:9632647. Avalaible from: https://doi.org/10.1155/2017/9632647.
10. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy. natural history of visual outcome. Ophthalmology. 2008 Feb;115(2):298-305.
11. Sharma S, Kwan S, Fallano KA, Wang J, Miller NR, Subramanian PS. Comparison of visual outcomes of nonarteritic anterior ischemic optic neuropathy in patients with and without diabetes mellitus. Ophthalmology. 2017 Apr 1;124(4):450–5.
12. Pinna A, Solinas G, Masia C, Zinellu A, Carru C, Carta A. Glucose-6-phosphate dehydrogenase (G6PD) deficiency in nonarteritic anterior ischemic optic neuropathy in a Sardinian population, Italy. Investigative Ophthalmology and Visual Science. 2008 Apr;49(4):1328–32.
13. Yao F, Wan P, Su Y, Liao R, Zhu W. Impaired systemic vascular endothelial function in patients with non-arteritic anterior ischaemic optic neuropathy. graefe's archive for clinical and experimental ophthalmology. 2016 May 1;254(5):977–81.
14. Giambene B, et al. Evaluation of traditional and emerging cardiovascular risk factors in patients with non-arteritic anterior ischemic optic neuropathy: a case-control study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2009 May;247(5):693–7.
15. Sharma S, et al. Optical coherence tomography angiography in acute non-arteritic anterior ischaemic optic neuropathy. British Journal of Ophthalmology. 2017 Aug 1;101(8):1045–51.
16. Gandhi U, et al. Optical coherence tomography angiography in acute unilateral nonarteritic anterior ischemic optic neuropathy: A comparison with the fellow eye and with eyes with papilledema. Indian Journal of Ophthalmology. 2018 Aug;66(8):1144-48.
17. Ghasemi Falavarjani et al. Swept-source optical coherence tomography angiography of the optic disk in optic neuropathy. *Retina.* 2016. 36(Suppl 1):S168–77.
18. Rebolleda G, Diez-Alvarez L, Garcia Y, et al. Reduction of peripapillary vessel density by optical coherence tomography angiography from the acute to the athropic stage in non-arteritic ischaemic optic neuropathy. Ophthalmologica. 2018;240(4):191-199.
19. Olver JM, Spalton DJ, McCartney AC. Microvasular study of the retolaminar optic nerve in man: the possible significance in anterior ischemic optic neuropathy. Eye (Lond). 1990;4(Pt 1):7-24.

ORIGINAL ARTICLE

OUTCOMES OF GLAUCOMA DRAINAGE DEVICE IMPLANTATION IN NEOVASCULAR GLAUCOMA PATIENTS AT CIPTO MANGUNKUSUMO HOSPITAL: A 3-YEAR STUDY

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ABSTRACT

Introduction: *Neovascular glaucoma is a challenging type of glaucoma to manage, due to its progressive nature. Achieving good intraocular pressure (IOP) in neovascular glaucoma cases often requires the aid of filtering surgery, preferably with a glaucoma implant/drainage device. This study aims to evaluate the outcomes of glaucoma drainage device (GDD) implantation for neovascular glaucoma patients in Cipto Mangunkusumo Hospital.*

Methods: *A total of 77 eyes with neovascular glaucoma were included in this study, which underwent GDD implantation in Cipto Mangunkusumo Hospital between 2020 to 2022. Baseline data include age, gender, laterality, implant type used, underlying ocular condition, systemic comorbid, visual acuity (VA), IOP, and prescribed glaucoma medications. The postoperative VA and IOP were measured at 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, and 18 months or above. Complications and additional surgical interventions were noted. Success criteria based on the IOP and amount of glaucoma medications were evaluated at least 6 months postoperatively.*

Results: *The mean IOP at baseline was 45.91 ± 13.9 mmHg with 3.42 ± 0.77 glaucoma medications. At 6 months postoperative, mean IOP was decreased to 13.84 ± 8.6 mmHg with 1.21 ± 1.18 glaucoma medications. At 6 months follow-up, 32.0% patients achieved complete success and 48.0% patients achieved qualified success. At 1 year postoperative, the Kaplan-Meier analysis for GDD success in neovascular glaucoma cases was estimated to be 79.2%.*

Conclusion: *GDD implantation is an effective surgical option in treating neovascular glaucoma cases.*

Keywords: *glaucoma drainage device, neovascular glaucoma, glaucoma surgery*

INTRODUCTION

Neovascular glaucoma (NVG) is a progressive type of glaucoma caused by fibrovascular proliferation at the anterior chamber angle.[1] Roughly 3.9–5.8% of glaucoma is caused by NVG, with the estimated prevalence in the general populace ranging from 0.01–0.12%.[1,2] Despite the relatively low prevalence, about half of NVG patients require surgery to achieve the desired level of intraocular pressure (IOP).[3]

Various types of surgical interventions can be used as options for controlling IOP in NVG cases.[4] Trabeculectomy is the most commonly performed filtering surgery for glaucoma

cases, however it has a higher rate of failure if performed on eyes with NVG. As such, glaucoma drainage device (GDD) implantation often becomes the surgical method of choice in NVG patients. Cyclodestructive procedure is usually reserved for refractory cases that are unresponsive to other treatment modalities and in cases with poor visual prognosis.

Although GDD has been quite widely used in various other glaucoma cases, few studies exist that evaluate its effectiveness and safety in neovascular glaucoma patients in Indonesia. As such, this study aims to evaluate the outcomes of GDD implantation for neovascular glaucoma patients in Cipto Mangunkusumo Hospital.

METHODS

This retrospective observational study was performed by reviewing the medical records of all neovascular glaucoma patients who underwent GDD implantation between January 2020 to December 2022 in Kirana Eye Center, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. A minimum postoperative follow-up period of 6 months was required for the data to be included in this study.

Baseline data consisting of age, gender, laterality, implant type used, underlying ocular condition, systemic comorbid, VA, IOP, and prescribed glaucoma medications were collected. Postoperative visual acuity and IOP were examined at 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, and 18 months or above. During the follow-up period, complications and additional surgical interventions were also noted.

Visual acuity was measured using Snellen vision chart and converted to logarithm of minimum angle resolution (logMAR) for numeric analysis or categorized based on the degree of visual impairment according to World Health Organization (WHO). IOP was measured using Icare tonometer or applanation tonometry (if applicable), using mmHg as the unit of measurement. The types of GDD implant used were the valved Ahmed Glaucoma Implant (AGI) and the non-valved Virna Glaucoma Implant (VGI).

Effectiveness of the GDD implant was assessed based on the success criteria of glaucoma implant surgery. This criteria is divided into 3 categories: (1) complete success, where postoperative IOP achieved normal range (6–21 mmHg) or decreased by 20% from baseline without needing any additional glaucoma medications; (2) qualified success, where postoperative IOP achieved normal range (6–21 mmHg) or decreased by 20% from baseline with additional glaucoma medication(s); or (3) failure, where postoperative IOP is below 6 mmHg or above 21 mmHg regardless of glaucoma medication(s) used.[5,6]

The safety profile of GDD implant was assessed based on the rate of postoperative complications and the need for additional surgery/surgeries.

Statistical Analysis

Baseline data were presented with descriptive statistics: numeric variables presented as mean and standard deviation (SD); categorical variables as frequency and percentage. The comparison of VA and IOP pre- and postoperatively were analysed with repeated ANOVA for parametric data and Friedman for nonparametric data. A p value of 0.05 or less was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics Version 25.

RESULTS

A total of 77 eyes were included in the analysis. The demographic data and baseline characteristics of patients are presented in Table 1. Most of the patients were implanted with Virna Glaucoma Implant, with only 3 eyes implanted with Ahmed Glaucoma Implant. The most commonly found underlying ocular condition were diabetic retinopathy and central retinal vein occlusion (CRVO).

Table 1. Baseline Characteristics (n=77 eyes)

Variables	n (%)
Age (years)	54.01 ± 10.40
Follow up duration (months)	13 (6–40)
Gender	
Male	42 (54.5%)
Female	35 (45.4%)
Type of GDD	
Virna Glaucoma Implant	74 (96.1%)
Ahmed Glaucoma Implant	3 (3.9%)
Laterality	
Right	42 (54.5%)
Left	35 (45.4%)
Lens status	
Phakic	45 (58.4%)
Pseudophakic	30 (38.9%)
Aphakic	2 (2.6%)
Year of operation	
2020	13 (16.9%)
2021	24 (31.2%)
2022	40 (51.9%)
Underlying ocular condition	
Diabetic retinopathy	45 (58.4%)
Central retinal vein occlusion (CRVO)	16 (20.8%)

Vitrectomized eye	4 (5.2%)
Ocular ischemic syndrome	1 (1.3%)
Occlusive retinal vasculitis	1 (1.3%)
Systemic comorbid	
Diabetes mellitus	57 (74.0%)
Hypertension	42 (54.5%)
Chronic kidney disease	5 (6.5%)
Cardiovascular disease	7 (9.1%)
Dyslipidemia	4 (5.2%)
Hypercoagulable state	1 (1.3%)
Smoking history	2 (2.6%)
HIV	1 (1.3%)
Myelodysplastic syndrome	1 (1.3%)

Table 2. Numerical comparison of pre- and postoperative visual acuity up to 1 year follow up

Visual acuity (logMAR)	**Median (Range)**	**P value**
Preoperative	2.30 (0.17 – 3.00)	**<0.001**
3 months postoperative	2.30 (0.10 – 3.00)	
6 months postoperative	2.30 (0.10 – 3.00)	
1 year postoperative	2.70 (0.10 – 3.00)	

Friedman test. Post hoc Wilcoxon reveals p value: preoperative vs 3 months 0.002; preoperative vs 6 months 0.003; preoperative vs 1 year 0.001; 3 months vs 6 months 0.898; 3 months vs 1 year 0.169; 6 months vs 1 year 0.014

Table 3. Categorical comparison preoperative and 6 months postoperative based on degree of visual impairment according to WHO

6 Months Postoperative **Preoperative**	***No Visual Impairment***	***Mild Visual Impairment***	***Moderate Visual Impairment***	***Severe Visual Impairment***	***Blindness***
No Visual Impairment	3 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mild Visual Impairment	0 (0%)	0 (0%)	2 (2.7%)	1 (1.3%)	1 (1.3%)
Moderate Visual Impairment	0 (0%)	1 (1.3%)	2 (2.7%)	0 (0%)	0 (0%)
Severe Visual Impairment	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	5 (6.7%)
Blindness	0 (0%)	0 (0%)	3 (4.0%)	0 (0%)	56 (74.7%)
Total (n=75)	3 (4.0%)	2 (2.7%)	7 (9.3%)	1 (1.3%)	62 (82.7%)

Table 4. Categorical comparison preoperative and 1 year postoperative based on degree of visual impairment according to WHO

1 Year Postoperative / Preoperative	*No Visual Impairment*	*Mild Visual Impairment*	*Moderate Visual Impairment*	*Severe Visual Impairment*	*Blindness*
No Visual Impairment	1 (2.2%)	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)
Mild Visual Impairment	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	2 (4.4%)
Moderate Visual Impairment	0 (0%)	1 (2.2%)	1 (2.2%)	0 (0%)	0 (0%)
Severe Visual Impairment	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	3 (6.7%)
Blindness	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	33 (73.3%)
Total (n=45)	1 (2.2%)	3 (6.7%)	3 (6.7%)	0 (0%)	38 (84.4%)

Table 5. Comparison of pre- and postoperative IOP up to 1 year follow up

Intraocular pressure (mmHg)	Median (Range)	P value
Preoperative	47 (13 – 79)	**<0.001**
3 months postoperative	14 (3 – 70)	
6 months postoperative	12 (2 – 60)	
1 year postoperative	15 (3 – 70)	

Friedman test. Post hoc Wilcoxon reveals p value: preoperative vs 3 months <0.001; preoperative vs 6 months <0.001; preoperative vs 1 year <0.001; 3 months vs 6 months 0.016; 3 months vs 1 year 0.389; 6 months vs 1 year 0.073

The mean amount of glaucoma medications used preoperatively were 3.42 ± 0.77, at 3 months postoperative 1.55 ± 1.35, at 6 months postoperative 1.21 ± 1.18, at 1 year postoperative 1.20 ± 1.16, and at 18 months postoperative or above 1.33 ± 1.24. The success criteria of GDD implantation were evaluated at 6 months, 1 year, and ≥18 months postoperative, as shown in Table 6. The cumulative probability of success (complete and qualified) up to 1 year follow up was evaluated with the Kaplan-Meier survival analysis as shown in Figure 1, showing the probability of GDD implant success at 1 year postoperative was 79.2%.

Table 6. GDD implant success criteria

Follow up duration	Complete Success	Qualified Success	Failure	Total
6 months postoperative	24 (32.0%)	36 (48.0%)	15 (20.0%)	75 (100%)
1 year postoperative	14 (31.1%)	21 (46.7%)	10 (22.2%)	45 (100%)
≥18 months postoperative	6 (28.6%)	11 (52.4%)	4 (19.0%)	21 (100%)

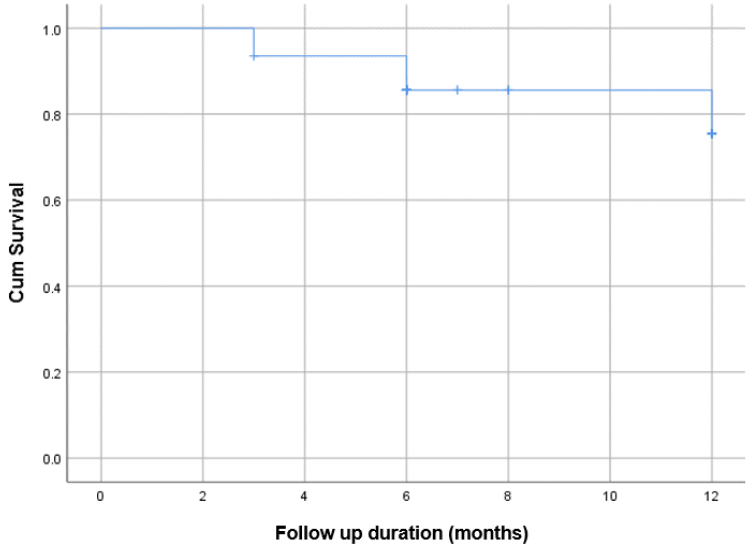

Figure 1. Kaplan-Meier survival analysis of cumulative GDD implantation success

The postoperative complication rate in this study was 40.3% (31 out of 77 eyes), with the details shown in Table 7. There were 28 eyes (36.4%) that required additional surgical intervention related to the post-GDD complications, with details shown in Table 8.

Table 7. Postoperative complications

Complications	n = 77 (100%)
Hyphema/Coagulum	10 (13.0%)
Tube occlusion	6 (7.8%)
Exposed tube	11 (14.3%)
Shallow/Flat COA	12 (15.6%)
Endothelial decompensation	3 (3.9%)
Sympathetic ophthalmia	1 (1.3%)
Based on complication onset	
≤1 year postoperative	26 (33.8%)
>1 year postoperative	5 (6.5%)

Table 8. Additional surgical interventions

Additional glaucoma-related surgeries	n = 77 (100%)
Repair of exposed tube	6 (7.8%)
Tube revision/repositioning	5 (6.5%)
Tube flushing	3 (3.9%)
Tube membranectomy	4 (5.2%)
Laser suture lysis	1 (1.3%)
Bleb aspiration + 5-FU injection	7 (9.1%)
I/A of hyphema/coagulum	2 (2.6%)
COA reformation	11 (14.3%)
Micropulse	2 (2.6%)
GDD explantation	2 (2.6%)
GDD exchange	1 (1.3%)

DISCUSSION

Implantation of glaucoma drainage device is the surgical intervention of choice for cases with refractory glaucoma. This intervention is often reserved for cases where conventional filtering surgery, such as trabeculectomy, had failed to achieve the targeted IOP. However, in cases of neovascular glaucoma, the risk of failure for trabeculectomy is much higher due to how the disease progresses, and as such, GDD became the preferred surgical intervention to achieve IOP control in these patients.[4,7]

Within our study, 74 out of 77 eyes were implanted with the non-valved Virna Glaucoma Implant. The rationale behind this is that the valved Ahmed Glaucoma Implant is much more expensive in comparison, thus is reserved for cases where visual function is still relatively good or in one-eye (only one functioning eye) cases. There was a steady increase in operation amount each year, coinciding with the COVID-19 pandemic which started in 2020, and slowly started to resolve over the following years.

The most often found underlying ocular condition causing NVG in our patients were diabetic retinopathy (58.4%) followed by CRVO (20.8%). This was similar to the finding in the study by Malgi et al,[8] however in that study 40% of NVG were caused by CRVO/BRVO, with roughly a third of NVG cases caused by diabetic retinopathy.

In terms of visual acuity comparison pre- and postoperatively, there were statistically significant change between preoperative VA and all three points of postoperative VA evaluation, as shown in Table 2. However, this change was not clinically significant, as illustrated by the categorical comparisons in Table 3 and Table 4, where most patients were categorized within the same degree of visual impairment at preoperative and postoperative.

A statistically and clinically significant change in preoperative and postoperative IOP was observed, as shown in Table 5. The overall IOP reduction was also accompanied by the reduction of glaucoma medication amount after GDD implantation. This finding was in line with a study by Purtskhvanidze et al,[9] where IOP was reduced from 30.8 ± 6.9 mmHg preoperatively to 14.3 ± 5.4 mmHg postoperatively, and the mean amount of glaucoma medications were reduced from 3.5 ± 1.1 drugs preoperatively to 1.6 ± 1.5 drugs postoperatively.

The effectiveness of GDD as treatment for NVG can be seen from the overall success rate at achieving the targeted IOP. The cumulative success rate (both complete and qualified success) at 6 months, 1 year, and 18 months/above were shown to be around a similar value: 80.0%, 77.8%, and 81.0% respectively. The Kaplan-Meier analysis also revealed a success probability of 79.2% at 1 year postoperative. These findings were similar with studies by

Rojananuangnit et al[5] and Noor et al,[10] where the probability of success at 1 year follow up after GDD implantation were evaluated. Rojananuangnit et al[5] found the probability of success for refractory glaucoma cases implanted with GDD was 76%, while Noor et al[10] found the probability of success for NVG cases implanted with GDD was roughly 70–84%.

Our study found a relatively high rate of complication (40.3%) after GDD implantation, though not all of them required additional surgical intervention. Eight out of 10 eyes with postoperative hyphema/coagulum and 5 out of 11 eyes with exposed tube spontaneously resolved through observation alone. The types of complications found were similar to a meta-analysis by Lin et al,[11] however with different incidence rates. Most of the complications were related to the intraocular manipulation of the GDD surgery, with the exception of 1 patient which developed sympathetic ophthalmia on the contralateral eye 2 years after GDD implantation. Not much of the progression to sympathetic ophthalmia was known, because this patient did not routinely come for follow up examinations after the initial 6 months.

The rate of additional glaucoma-related surgical interventions in this study was also higher than a similar study by Kung et al,[12] which evaluated the rate of reoperation up to 10 years after GDD implantation in NVG patients. In that study, the rate of reoperation was 24.0%, compared to the rate in our study of 36.4%.

Our study had several limitations. Firstly, due to the study duration involving the height of COVID-19 pandemic, there were often incomplete follow up data as patients were severely limited as per the social distancing rule imposed on year 2020 in Indonesia. This study was also done during the transitional period of paper-based medical records to electronic medical records in Cipto Mangunkusumo Hospital, so there were instances where the data were not completely available. Finally, as this was a retrospective study, the quality of data heavily depends on the availability and accuracy of each patients' medical record documentation.

CONCLUSION

GDD implantation offers an effective postoperative IOP control in neovascular glaucoma cases, with significant postoperative IOP reduction. GDD also appears to have a moderate safety profile as a treatment modality for neovascular glaucoma.

REFERENCES

1. Havens SJ, Gulati V. Neovascular Glaucoma. *Dev Ophthalmol*. 2016; 55: 196—204. doi: 10.1159/000431196
2. Liao N, Li C, Jiang H, Fang A, Zhou S, Wang Q. Neovascular glaucoma: a retrospective review from a tertiary center in China. *BMC Ophthalmol*. 2016; 16: 14. https://doi.org/10.1186/s12886-016-0190-8

3. Rani PK, Sen P, Sahoo NK, Senthil S, Chakurkar R, Anup M, et al. Outcomes of neovascular glaucoma in eyes presenting with moderate to good visual potential. *Int Ophthalmol*. 2021; 41: 2359–68.
4. Urbonavičiūtė D, Buteikienė D, Janulevičienė I. A Review of Neovascular Glaucoma: Etiology, Pathogenesis, Diagnosis, and Treatment. *Medicina*. 2022; 58(12): 1870. https://doi.org/10.3390/medicina58121870
5. Rojananuangnit K, Jiaranaisilawong P, Rattanaphaithun O, Sathim W. Surgical Outcomes of Glaucoma Drainage Device Implantation in Refractory Glaucoma Patients in Thailand. *Clin Ophthalmol*. 2022; 16: 4163—78. doi: 10.2147/OPTH.S393730.
6. Dhingra D, Bhartiya S. Evaluating glaucoma surgeries in the MIGS context. *Rom J Ophthalmol*. 2020; 64(2): 85—95.
7. Iwasaki K, Kojima S, Wajima R, Okazaki T, Yokoyama Y, Inoue T, et al. Comparing Surgical Outcomes in Neovascular Glaucoma between Tube and Trabeculectomy: A Multicenter Study. *Ophthalmology Glaucoma*. 2022; 5(6): 672—80. https://doi.org/10.1016/j.ogla.2022.05.003
8. Malgi VS, Gawas L, Iyer AS, Rao A. Clinical profile and outcomes of neovascular glaucoma in the era of anti-vascular endothelial growth factor. *Indian J Ophthalmol*. 2021; 69(10): 2728—33. doi: 10.4103/ijo.IJO_528_21
9. Purtskhvanidze K, Saeger M, Treumer F, Roider J, Nölle B. Long-term results of glaucoma drainage device surgery. *BMC Ophthalmol*. 2019; 19(1): 14. doi: 10.1186/s12886-019-1027-z.
10. Noor NA, Mustafa S, Artini W. Glaucoma drainage device implantation with adjunctive intravitreal bevacizumab in neovascular glaucoma: 3-year experience. *Clin Ophthalmol*. 2017; 11: 1417—22. doi: 10.2147/OPTH.S137470.
11. Lin P, Zhao Q, He J, Fan W, He W, Lai M. Comparisons of the short-term effectiveness and safety of surgical treatment for neovascular glaucoma: a systematic review and network meta-analysis. *BMJ Open*. 2022; 12(5): e051794. doi: 10.1136/bmjopen-2021-051794.
12. Kung FF, Knier CG, Garmany A, Mejia CA, Sargent JM, Dogahe SJ, et al. Need for Additional Glaucoma Surgery and Complications Following Glaucoma Drainage Device Surgery. *J Glaucoma*. 2021; 30(6): 508—14. doi: 10.1097/IJG.0000000000001827.

ORIGINAL ARTICLE

DEVELOPMENT AND APPLICATION OF TARGETED MULTI-PLEX POLYMERASE CHAIN REACTION TO HELP DIAGNOSE INFECTIOUS UVEITIS

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ABSTRACT

Introduction: *Clinical pattern recognition is paramount in uveitis diagnosis. Pathogen detection from ocular fluid samples is often necessary to support infectious uveitis diagnosis, particularly in cases presenting with atypical clinical appearance. This study aims to present the process of developing targeted multiplex PCR and evaluate its application in infectious uveitis diagnosis.*

Methods: *This was a cross-sectional study to evaluate the diagnostic performance of targeted multiplex PCR in infectious uveitis. We obtained ocular fluid samples and reviewed medical records of uveitis patients who underwent ocular fluid analysis at Cipto Mangunkusumo Hospital from February 2022 to March 2023. PCR detection threshold values (DNA copies/mL) were 10.9 for Mycobacterium tuberculosis (Mtb), 672 for Epstein-Barr virus (EBV), 4.77 for Cytomegalovirus (CMV), 6.37 for Toxoplasma gondii (T. gondii), and 5.53 for Herpes simplex virus (HSV). With multiple pathogen selection, this method requires a lower volume of samples than single-plex PCR, as the latter will increase the sample volume linearly with each additional pathogen tested.*

Discussion: *Forty-seven aqueous or vitreous samples were analyzed. The positivity rate was 23.4% (11/47) with Mtb yielding the highest positivity (7/41; 17.1%). With final diagnosis as a reference, targeted multiplex PCR resulted in 32.3% (95% CI: 16.7 – 51.4%) sensitivity, 93.8% (95% CI: 69.8 – 99.8%) specificity, 90.9% (95% CI: 58.4 – 98.6%) positive predictive value, and 41.7% (95% CI: 35.2 – 48.4%) negative predictive value.*

Conclusion: *With its high specificity, targeted multiplex PCR is useful as a confirmatory but not screening tool in uveitis diagnosis. Ocular fluid analysis is an important part of the stepwise diagnostic approach in uveitis.*

Keywords: *Infection, multiplex polymerase chain reaction, uveitis.*

INTRODUCTION

Polymerase Chain Reaction (PCR) has been utilized as a diagnostic tool for detecting microorganisms causing infectious disease. It remains a major challenge for ophthalmologists. In ophthalmology, specifically in uveitis, it is employed to confirm infection by detecting the presence of causative pathogens through the analysis of ocular fluid samples.[1] Uveitis, an intraocular inflammation, can lead to significant vision loss primarily due to its complications, notably complicated cataract and macular edema, particularly when inflammation persists over time.[2] In developing countries, infectious uveitis occurs more frequently compared to developed countries, comprising 30-60% of uveitis cases.[3] In Indonesia specifically, the prevalence of infectious uveitis is estimated to be around 33%.[4,5]

Confirming the diagnosis through detecting genomic fragments of the offending

pathogen is essential in infectious uveitis cases.[1,6] In some fraction of patients presenting with overlapping clinical pictures of other infectious causes or non-infectious causes of uveitis, PCR would help resolve ambiguity and guide the selection appropriate treatment.[7] Each country may have different burdens of infection causes. In Iran, from PCR examination of ocular fluid, 37% tested positive, with the majority being CMV. This PCR test can guide initial therapy to be appropriate in 20% of cases.[8] Just like the study in Iran, this study also found that with PCR examination, inappropriate initial treatment can change in around +- 30% of cases.[9] Meanwhile, a study conducted in Italy, where the most common pathogens are CMV and HSV-1. Similarly, it can also change initial treatment in 20% of cases.[10] Since performing PCR can be laborious, several methods to increase the efficiency of the test have been developed, including the introduction of multiplex PCR.[7,11,12] The key advantage of multiplex over the traditional single-plex PCR is its ability to detect multiple infectious agents in a single test, allowing for faster and more efficient diagnosis.[12] When the attending ophthalmologist suspects infectious uveitis but needs to test multiple pathogens, traditional diagnostic PCR methods typically involve running multiple tests to be performed sequentially.[13] This approach requires larger amounts of ocular fluid, which sometimes be insufficient. Consequently, the process can also be time-consuming and potentially delay the initiation of treatment. This technical difference can be important in clinical settings where early diagnosis and treatment are critical, such as those involving infectious uveitis.[11–13]

We attempted to optimize PCR tests by developing and applying targeted multiplex PCR in the clinics. The pathogen selection of each test relies on the suspicion of the attending uveitis specialist when dealing with patients suspected of infectious uveitis. We aimed to optimize this multiplex PCR test for ready-to-use application to detect pathogens commonly associated with infectious uveitis in Indonesia. While multiplex PCR appears to address some of the limitations associated with singleplex PCR as mentioned above, its suitability, particularly for a new adoption in routine diagnostic procedures in clinical settings, requires evaluation of its diagnostic performance. The optimization process for a newly developed multiplex PCR test is crucial to mitigate the risk of both false positives and false negatives.[14] Therefore, this study aimed to describe our process of developing targeted multiplex PCR and evaluate its diagnostic accuracy in infectious uveitis diagnosis.

METHODS

This was a cross-sectional study to evaluate the diagnostic performance of our newly implemented targeted multiplex PCR in aiding the diagnosis of infectious uveitis in the outpatient clinic of the Ocular Infection and Immunology Division, Cipto Mangunkusumo

Hospital, Jakarta, Indonesia between February 2022 and March 2023. Based on a priori estimation that true infectious uveitis would account for approximately 50% of the tested samples, we calculated the sample size using the formula for a new diagnostic test being investigated in a prospective cohort where disease status and prevalence are known (https://turkjemergmed.com/calculator).[15] With a Type 1 error set at 5% and an estimated specificity of 93% based on our previous study,[7] along with a marginal error of 10%, the estimated sample size ideally would be 50 cases. Therefore, we included all available patients recruited during the aforementioned study period for analysis, totaling 47 patients.

All medical records of newly diagnosed suspected infectious uveitis patients who underwent intraocular fluid analysis for PCR during the study period were reviewed. Patients under 18 years of age were excluded. Cases with a high suspicion of non-infectious uveitis, such as Vogt-Koyanagi-Harada syndrome, Behçet's disease, and other autoimmune-related uveitis, as well as masquerades (conditions mimicking uveitis, such as retinal detachment with signs resembling uveitis or malignancy), were excluded unless they remained in the differential diagnosis. We reviewed patients' demographic and clinical data. Extracted data included age, sex, ocular clinical manifestation, and diagnosis. The final diagnosis data was obtained from the medical records based on the attending uveitis specialist's diagnosis, taking into account follow-up observations and response to the specific antimicrobial treatment, as previously outlined.[7]

As mentioned above, ocular fluid analysis for the PCR test was performed for suspected infectious uveitis patients. The attending uveitis specialist decided whether aqueous or vitreous would be collected for PCR analysis based on the type of uveitis. Aqueous humor was preferred when uveitis presented as anterior uveitis, intermediate uveitis, or panuveitis with significant anterior chamber inflammation (anterior chamber cells grade $\geq$ 2+). Aqueous humor or vitreous samples were taken in a procedural room. Topical anesthesia and disinfectant were used during the procedure. Next, 0.2 mL of sample was collected with a 30-gauge needle. Hexamidine diisethionate 0.05% was also used for disinfection. The samples were then immediately transported to the laboratory for PCR analysis.

The following steps were performed during multiplex PCR analysis begining with the sample collection, where ocular fluid sample was collected, followed by the process of DNA extraction. The commercial extraction kit QIAamp DNA Kit (Qiagen, Germany) was used to extract the DNA from obtained samples according to the protocol instructions "DNA purification from blood or body fluids". The sample volume needed to carry out the DNA

extraction process is 200 µl; if the sample is less than 200 µl, then phosphate buffer saline (PBS) is added to the 200 µl.

The primer and probe used in this study were taken from a study conducted by Nakano et al. (2017)[16] as shown in Table 1.The primer and probe concentrations in this study were standardized to 20 M. Multiplex real-time PCR was carried out by pre-denaturation at 95 °C for 5 minutes, followed by denaturation at 95 °C for 10 seconds and extension at 60 °C for 1 minute for up to 40 cycles using primers and specific probes from the study. The mastermix reaction mixture used was composed of the SensiFAST Probe No-Rox 2X (Bioline) enzyme, nucleic acid-free water, and 2 µl DNA in 20 µl of the final reaction. The mastermix reaction was performed on an ABI 7500 Fast real-time PCR machine (ABI, USA).

The limit of detection (LoD) value of the pathogen in this study was taken from positive samples and then purified by PCR purification (Wizard® SV gel and PCR Clean-Up System, Promega) for (Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), and Mtb target genes. Meanwhile, for Toxoplasma gondii (Toxo), gBlock® gene fragments (Geneaid) were used. The results of PCR purification and gBlock® gene fragments were then used as standards, and a 10-fold serial dilution was performed to quantify unknown samples and obtain LoD values. The LoD values for the pathogens examined (DNA copy/ml) were 10.9 for Mtb, 672 for EBV, 4.77 for CMV, 6.37 for Toxo, and 5.53 for HSV.

Multiplex real-time PCR analysis was performed using 10 times serial dilution of standards (PCR purification and gBlock® Gene Fragments) to obtain the LoD of each target gene. The LoD results are used to determine positive and negative criteria. The positive and negative results of multiplex real-time PCR were further analyzed with a diagnostic test using a two-by-two diagnostic test table calculation. (Table 1)

Table 1. Primer Probes in Multiplex PCR

No	Pathogen (Amplification site)	Primer Forward	Primer Reverse	Primer Probe
1	VZV (ORF29)	5'-ACTTTTACATCCAGCCTGGCG-3'	5'-GAAAACCCAAACCGTTCTCGAG-3'	5'-Cy5-TGTCTTTCACGGAGGCAAACACGT-lowa black FQ-3'

2	CMV (IE-1)	5'-CATGAAGGTCTTTGCCCAGTAC-3'	5'-GGCCAAAGTGTAGGCTACAATAG-3'	5'-Cy5-TGGCCCGTAGGTCATCCACACTAGG-lowa black FQ-3'
3	EBV (BALF5)	5'-CGGAAGCCCTCTGGACTTC-3'	5'-CCCTGTTTATCCGATGGAATG-3'	5'-FAM-TGTACACGCACGAGAAATGCGCC-TAMRA-3'
4	HSV (gB)	5'-CCGTCAGCACCTTCATCGA-3'	5'-CGCTGGACCTCCGTGTAGTC-3'	5'-FAM-CCACGAGATCAAGGACAGCGGCC-TAMRA-3'
5	*Mycobaterium tuberculosis* (IS6110)	5'-CCTGCGAGCGTAGGCGTCGG-3'	5'-CTCGTCCAGCGCCGCTTCGG-3'	5'-FAM-GGCGAACCCTGCCCAGGTCGACA-TAMRA-3'
6	*Toxoplasma gondii* (B1)	5'-TCCCCTCTGCTGGCGAAAAGT-3`	5'-AGCGTTCGTGGTCAACTATCGATTG-3'	5'-FAM-CGAAAAGTGAAATTCATGAGTATCTGTGCAACT-TAMRA-3'

The diagnostic performance of targeted multiplex PCR was evaluated by calculating the sensitivity and specificity of the overall PCR result and based on the pathogen being tested. Sensitivity was calculated by dividing the number of patients with positive test results by the number of patients diagnosed with infectious uveitis. Specificity was calculated by dividing the number of patients with negative test results by the number of patients without a final diagnosis of infectious uveitis. Positive predictive value (PPV) represents the proportion of patients with positive test results who truly have the specified diagnosis of infectious uveitis, obtained by dividing the true-positive PCR results by the total number of patients with positive test results. Negative predictive value (NPV) was calculated by dividing the true-negative results by the total number of patients with negative test results. The final diagnosis was used as the reference to calculate the diagnostic performance of targeted multiplex PCR. The calculation of the

diagnostic performance indices mentioned above was conducted using an online calculator available at https://www.medcalc.org/calc/diagnostic_test.php.

Descriptive statistics were utilized to summarize patient characteristics. Continuous variables such as age were reported as means and standard deviations, while categorical variables such as sex, laterality, anatomical site, and sample type were presented as frequencies and percentages. The differences in age between the positive and negative PCR groups were analyzed using independent samples t-tests. For categorical variables, including sex, laterality, anatomical site, and sample type, Chi-square tests or Fisher's exact tests (when expected cell counts were less than 5) were employed to assess differences between the groups.

Sensitivity and specificity for each pathogen detected by the multiplex PCR method were calculated using standard definitions: sensitivity was determined as the proportion of true positives among those with the condition (true positives / (true positives + false negatives)), and specificity was the proportion of true negatives among those without the condition (true negatives / (true negatives + false positives)). These calculations were performed for each pathogen tested.

To evaluate the cost-effectiveness of multiplex PCR compared to single-plex PCR, the estimated prices for testing two and four pathogens were calculated and compared. Additionally, the positivity rates, sensitivities, and specificities of the multiplex PCR method were compared to those of single-plex PCR methods (routine and non-routine). Statistical significance for differences in positivity rates between multiplex and single-plex PCR methods was assessed using Chi-square tests.All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant for all comparisons.

This study was part of an ongoing larger study entitled 'Ocular Autoimmune Systemic Infectious Study (OASIS)' and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No. 850/UN2.F1/ETIK/PPM.00.02/2022). All patients provided consent using institutional informed consent forms for obtaining aqueous/vitreous samples for the diagnostic procedure.

DISCUSSION

In this study, 47 samples of aqueous or vitreous humor were analyzed. The characteristics of the patients are described in Table 2.

Table 2. Characteristics of patients

Characteristics	Total (N=47)	Positive PCR (N=11)	Negative PCR- (N=36)
Age (years)	39 ±15	30 ± 14	42±14
Sex			
Male	20 (42.6%)	5	15
Female	27 (57.4%)	6	21
Laterality			
Unilateral	28 (59.6%)	5	23
Bilateral	16 (34%)	6	10
Anatomical			
Anterior	6 (12.8%)	0	2
Posterior	13 (27.7%)	3	7
Intermediate	3 (6.4%)	0	2
Panuveitis	22 (46.8%)	5	14
Others*	3 (6.4%)	3	11
Sample			
Aquous	32(68.1%)	6	26
Vitreous	15 (31.9%)	5	10

PCR = polymerase chain reaction using the currently used multiplex-PCR method

* include 2 cases of sclerouveitis and 1 retinal detachment

From 47 samples that were carried out for analysis, 11 (23.4%) were PCR-positive for microorganisms. Mtb was the most commonly included in the multiplex PCR test (N tested = 41) and responsible for the highest positivity rate at 17.1%, as shown in Table 3. The second most common pathogen found in positive samples was CMV (16.7%), followed by VZV, HSV, and Toxoplasma (8.3%, 6.4%, and 4.3% respectively). The most commonly involved anatomical location of uveitis was panuveitis (46.8%) followed by posterior uveitis (27.6%). Interestingly, we observed two cases with sclerouveitis who tested positive: one for Mtb and one for HSV.

The targeted multiplex PCR yielded an overall 32.3% (95% CI: 16.7 – 51.4%) sensitivity, 93.8% (95% CI: 69.8 – 99.8%) specificity, 90.9% (95% CI: 58.4 – 98.6%) positive predictive value, and 41.7% (95% CI: 35.2 – 48.4%) negative predictive value. The sensitivity and specificity for each microorganism are shown in Table 3. Almost all pathogens were highly specific (specificity >90%). The highest sensitivity was found in Mtb and HSV (both were

50%). For Mtb PCR, subanalysis by only calculating the diagnostic values of aqueous samples (vitreous samples not included) resulted in 36% sensitivity and 100% specificity.

Table 3. Positivity rate, sensitivity, and specificity values of targeted multiplex PCR for each pathogen

	N Tested	N positive (%)	Sensitivity (%)	Specificity (%)
Epstein-Barr virus (EBV)	3	0 (0%)	0/0 (% not defined)	(3/3) 100%
Herpes Simplex Virus (HSV)	31	2 (6.4%)	(2/4) 50%	(27/27) 100%
Cytomegalovirus (CMV)	6	1 (16.7%)	(1/4) 25%	(2/2) 100%
Mycobacterium tuberculosis (Mtb)	41	7 (17.1%)	(6/12) 50%	(28/29) 96.5%
Varicella-Zoster Virus (VZV)	12	1(8.3%)	1/1 (100%)	(11/11) 100%
Toxoplasma gondii (T.gondii)	23	1 (4.3%)	1/6 (16.6%)	(17/17) 100%

Identifying the cause of uveitis is crucial for effective treatment, as decision to initiate appropriate antimicrobial treatment can significantly impact visual outcomes. For instance, standalone steroid administration instead of anti-tubercular or anti-toxoplasmosis treatment for cases with ocular tuberculosis or toxoplasmosis, respectively, could lead to rapid disease progression.[17,18] In developing countries where diagnostic testing may be limited, clinical pattern recognition is undoubtfully important.[19] However, the ability of experts to diagnose uveitis based solely on clinical pattern recognition has limitations, as indicated by high level of disagreement among experts in assessing the severity and type of uveitis for given cases.[20] Therefore, objective testing such as microbial tests, as presented herein, remains paramount. Based on our results, the newly adopted multiplex PCR tests in infectious uveitis yielded sensitivity of 32.3% and a specificity of 93.8%. This highlights its importance as a confirmatory test, as its high specificity can help establish the diagnosis when the result is positive.[21]

Previously we have performed diagnostic evaluation in our center regarding the use of routine and non-routine single-plex PCR to diagnose uveitis.[5,7] Based on our previous findings, we consistently observed that approximately 30-33% of uveitis cases encountered in a tertiary

referral hospital would be infectious in origin.[4,7] However, the positivity rate of routine PCR for all uveitis cases as a screening diagnostic tool would be around 20%.[7] Another study we performed to assess the utility of selective PCR yielded low positivity (17.2%).[5] While the sample collection procedure is currently covered by national insurance, the PCR test itself is not covered. Therefore, we believe that our approach in developing a more cost-effective method using multiplex PCR would be beneficial to some extent for our settings, especially considering that complex cases are often expected to present at the referral hospital.

In terms of cost-effectiveness and methods, multiplex PCR was superior to single-plex PCR (Figure 1 and Table 4). Testing each pathogen using single-plex PCR is comparable to a single test for two pathogens using multiplex PCR. Moreover, 20 µl of the final reaction could be used to detect two suspected microorganisms, while using single-plex only one pathogen could be examined. Table 4 shows an illustration of the cost-effectiveness of multiplex PCR as compared to single-plex PCR. As the test is not covered by health insurance, reducing the out-of-pocket expenses would bring benefits to patients.

Table 4. Differences in Price, Positivity Rate, Sensitivity and Specificity of Multi-plex and Singple-plex PCR

PCR Methods	Price (estimate for testing two pathogens)	Price (estimate for testing four pathogens)	Positivity rate	Sensitivity***	Specificity****
Multi-plex					
The current study	Rp 700.000	Rp 1.400.000	23.4%	32.3%	93.8 %
Single-plex					
Routine* (Putera et al)	Rp 1.400.000	Rp 2.800.000	20.0%	33.3%	99.6 %
Non-routine** (Putera et al)	Rp 1.400.000	Rp 2.800.000	17.2%	Not evaluated	

*When performed in all new uveitis patients regardless of suspected causes (including suspected infectious and non-infectious cases, reference: *Heliyon*. 2022;8(10):e10988).

** Performed in selected patients (based on patients' ability to afford the tests and discretion of the attending uveitis specialist, reference: *Infect Drug Resist*. 2022;15:1219-1224).

***Sensitivity and specificity were calculated by matching the PCR results with the final diagnosis. This was not performed in the previous study for non-routine single-plex PCR.

A study by Choi et al. found the sensitivity and specificity of PCR tests for infectious uveitis was 0.431. and 0.985 respectively.[22] Another study conducted in Japan compared the positivity rate of viral uveitis between multiplex PCR and real-time (RT)-PCR. They concluded that multiplex PCR detected more positive results in the same cohort when compared to RT-PCR.[12] We acknowledge that the multiplex PCR testing would also beneficial in cases with high suspicion of co-infection.[11] By amplifying specific regions of DNA from different pathogens, multiplex PCR can identify the presence of several infectious antigen genomes simultaneously.[23]

Our current finding of a high specificity of multiplex PCR is summarized in a review by McKay et al.[24] While the specificity is often higher than the reported sensitivity, the diagnostic utility of laboratory tests is influenced by the disease prevalence in a given setting.[24] In Indonesia, where Mtb is still highly prevalent,[4] however, it remains challenging to diagnose ocular tuberculosis by detecting the presence of Mtb footprints in ocular tissues or fluids using existing diagnostic modalities.[25] Our current findings demonstrated that the diagnostic values of aqueous samples of PCR positive in Mtb only resulted in 36% sensitivity and 100% specificity. We hypothesize that testing vitreous samples may be more beneficial than testing aqueous samples for suspected ocular tuberculosis cases, despite the greater potential challenges associated with the procedure. Nevertheless, our current approach is considered an important step toward the implementation of new diagnostic approach that is more cost-effective in our center, ultimately leading to better treatment decisions for infectious uveitis patients. Considering the high positivity rate for infectious uveitis in our study, it is important to acknowledge that financial barrier for proceeding with PCR test, as explained above, might hinder some patients who cannot afford the test, potentially causing delays in diagnosis and treatment. Given the importance of our findings, we strongly encourage collaboration between healthcare providers and insurance companies to ensure the coverage of this important test in infectious uveitis. This collaboration would not only improve patient access to care but also lead to improved long-term health outcomes.

We acknowledge several limitations of our study. Firstly, while our study population represented suspected infectious uveitis cases that underwent ocular fluid analysis within a year, a larger sample size would better estimate he diagnostic performance for infectious uveitis, especially in less frequent cases such as HSV or EBV uveitis. Additionally, this study

was performed in a single-center tertiary hospital, where the complexity of some cases might pose challenges in diagnosis due to the presence complications and more atypical cases being presented. Lastly, our analysis did not include evenly distributed cases with aqueous and vitreous samples. Examining such cases may offer additional insights into the optimal source of samples for PCR tests in our setting.

CONCLUSION

Our findings showed high specificity of targeted multiplex PCR in detecting infectious uveitis, which could be beneficial for precise diagnosis, particularly in difficult cases. Targeted multiplex PCR serves as a valuable confirmatory tool rather than a screening tool for uveitis diagnosis. Moreover, this method offers a feasible and cost-effective diagnostic approach, effectively addressing common causes of infectious uveitis in Indonesia.

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REFERENCES

1. Thomas J, Nguyen NV, Fashina T, Huang Y, Yeh S, Conrady CD. An update on immunological and molecular tests and their impact in infectious uveitis. Front Ophthalmol. 2023 Mar 21;3:1132131.
2. Durrani OM. Degree, duration, and causes of visual loss in uveitis. British Journal of Ophthalmology. 2004 Sep 1;88(9):1159–62.
3. Tsirouki T, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Kalogeropoulos C, et al. A Focus on the Epidemiology of Uveitis. Ocular Immunology and Inflammation. 2018 Jan 2;26(1):2–16.
4. La Distia Nora R, Sitompul R, Bakker M, Susiyanti M, Edwar L, Sjamsoe S, et al. Tuberculosis and other causes of uveitis in Indonesia. Eye. 2018 Mar;32(3):546–54.
5. Putera I, Riasanti M, Edwar L, Susiyanti M, Sitompul R, Aziza Y, et al. The Utility of Nonroutine Intraocular Fluid Polymerase Chain Reaction for Uveitis in Indonesia. IDR. 2022 Mar;Volume 15:1219–24.
6. Santos HNVD, Ferracioli-Oda E, Barbosa TS, Otani CSV, Tanaka T, Silva LDCSD, et al. Usefulness of aqueous and vitreous humor analysis in infectious uveitis. Clinics. 2020;75:e1498.
7. Putera I, La Distia Nora R, Utami N, Karuniawati A, Yasmon A, Wulandari D, et al. The impact of aqueous humor polymerase chain reaction and serological test results for establishing infectious uveitis diagnosis: An Indonesian experience. Heliyon. 2022 Oct;8(10):e10988.
8. Fekri S, Barzanouni E, Samiee S, Soheilian M. Polymerase chain reaction test for diagnosis of infectious uveitis. Int J Retin Vitr. 2023 Apr 12;9(1):26.
9. Fallon J, Narayan S, Lin J, Sassoon J, Llop S. The impact of polymerase chain reaction (PCR) on diagnosis and management of infectious uveitis at a tertiary care facility. J Ophthal Inflamm Infect. 2022 Dec;12(1):1.
10. Tombolini B, Menean M, Cicinelli MV, Marchese A, Cavalleri M, Brambati M, et al. Diagnostic and therapeutic results of aqueous real-time polymerase chain reaction in infectious uveitis. Canadian Journal of Ophthalmology. 2024 Aug;59(4):e365–70.
11. Bispo PJM, Davoudi S, Sahm ML, Ren A, Miller J, Romano J, et al. Rapid Detection and Identification of Uveitis Pathogens by Qualitative Multiplex Real-Time PCR. Invest Ophthalmol Vis Sci. 2018 Jan 25;59(1):582.
12. Sugita S, Shimizu N, Watanabe K, Mizukami M, Morio T, Sugamoto Y, et al. Use of multiplex PCR and real-time PCR to detect human herpes virus genome in ocular fluids of patients with uveitis. British Journal of Ophthalmology. 2008 Jul 1;92(7):928–32.
13. Sint D, Raso L, Traugott M. Advances in multiplex PCR: balancing primer efficiencies and improving detection success. Methods Ecol Evol. 2012 Oct;3(5):898–905.
14. Elnifro EM, Ashshi AM, Cooper RJ, Klapper PE. Multiplex PCR: Optimization and Application in Diagnostic Virology. Clin Microbiol Rev. 2000 Oct;13(4):559–70.
15. Akoglu H. User's guide to sample size estimation in diagnostic accuracy studies. Turk J Emerg Med. 2022;22(4):177.
16. Nakano S, Tomaru Y, Kubota T, Takase H, Mochizuki M, Shimizu N, et al. Evaluation of a Multiplex Strip PCR Test for Infectious Uveitis: A Prospective Multicenter Study. American Journal of Ophthalmology. 2020 May;213:252–9.
17. Basu S, Das T. Pitfalls in the management of TB-associated uveitis. Eye. 2010 Nov;24(11):1681–4.
18. Dillon AB, Budoff G, McCannel CA, Tsui E, Pullarkat ST, Schwartz SD. Ocular Toxoplasmosis: No Stranger to the Masquerade Ball. Journal of VitreoRetinal Diseases. 2022 Sep;6(5):391–8.
19. Rao N. Uveitis in developing countries. Indian J Ophthalmol. 2013;61(6):253.
20. Kempen JH, Ganesh SK, Sangwan VS, Rathinam SR. Interobserver Agreement in Grading Activity and Site of Inflammation in Eyes of Patients with Uveitis. American Journal of Ophthalmology. 2008 Dec;146(6):813-818.e1.
21. Pewsner D, Battaglia M, Minder C, Marx A, Bucher HC, Egger M. Ruling a diagnosis in or out with "SpPIn" and "SnNOut": a note of caution. BMJ. 2004 Jul 24;329(7459):209–13.
22. Choi W, Kang HG, Choi EY, Kim SS, Kim CY, Koh HJ, et al. Clinical utility of aqueous humor polymerase chain reaction and serologic testing for suspected infectious uveitis: a single-center retrospective study in South Korea. BMC Ophthalmol. 2020 Dec;20(1):242.
23. Nishat H A, Satpathy G, Chawla R, Tandon R. Multiplex PCR for Detection of Herpes Simplex Viruses Type-1 and Type-2, Cytomegalovirus, Varicella-zoster Virus, and Adenovirus in Ocular Viral Infections. JOVR [Internet]. 2021 Jan 20 [cited 2024 Jul 22]; Available from: https://knepublishing.com/index.php/JOVR/article/view/8243
24. McKay KM, Lim LL, Van Gelder RN. Rational laboratory testing in uveitis: A Bayesian analysis. Survey of Ophthalmology. 2021 Sep;66(5):802–25.
25. Ludi Z, Sule AA, Samy RP, Putera I, Schrijver B, Hutchinson PE, et al. Diagnosis and biomarkers for ocular tuberculosis: From the present into the future. Theranostics. 2023;13(7):2088–113.

ORIGINAL ARTICLE

CORRELATION OF CENTRAL CORNEAL THICKNESS TO ACTUAL INTRAOCULAR PRESSURE IN MYOPIA PATIENTS

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ABSTRACT

Introduction: *Central Corneal Thickness (CCT) is promote in the diagnosis and management of glaucoma, especially in myopic patients. Understanding the correlation between CCT and IOP (Intraocular Pressure) aids in glaucoma detection and control. The objective of this study is to determine the correlation between CCT and actual IOP in myopic patients.*

Methods: *This research is an observational study with ethical committee approval, involving medical students from the Faculty of Medicine at Andalas University undergoing clinical clerkships at Dr. M Djamil Padang General Hospital. They were grouped into emmetropia, mild myopia, and moderate myopia. Data included visual acuity measurements, autorefraction, CCT measurements using OCT, and IOP with CCT correction. Samples with eye abnormalities, systemic conditions, myopia > 6D, a history of eye surgery, contact lens wear, and IOP > 21 mmHg were excluded. All data were analyzed statistically.*

Discussion: *The study involved 78 eyes from 78 individuals, consisting of 26 eyes per group. The actual CCT and IOP values in mild myopia, moderate myopia and emmetropia are 506.31 ± 11,263 µm with 15.81 ± 1,234 mmHg, 533.96 ± 21,342 µm with 16.12 ± 1,336 mmHg, and 487.81 ± 28,272 µm with 15.35 ± 1.056 mmHg. There was a strong positive correlation between CCT and IOP (r=0.737, p=0.000), as well as a moderate negative correlation between CCT and actual IOP (r=-0.492, p=0.000).*

Conclusion: *This research reveals a negative correlation between CCT and actual IOP in myopic patients, highlighting the importance of glaucoma screening for myopic patients due to their thinner corneas.*

Keywords: *CCT, central corneal thickness, IOP, intraocular pressure, actual IOP, myopia, glaucoma*

INTRODUCTION

Eye health is a crucial aspect in maintaining the quality of life. Myopia, or "nearsightedness," is a common issue that needs attention, particularly in Asia. Myopia occurs when light rays do not focus on the retina but in front of it. In 2020, approximately 30% of people worldwide suffered from myopia, and it is estimated to reach 50% by 2050. The length of the eye and corneal thickness are key factors causing myopia, which can also increase the risk of glaucoma, the second leading cause of blindness after cataracts. Eye health is closely related to intraocular pressure (IOP). High IOP can lead to glaucoma, damaging the optic nerve. Research indicates that the risk of glaucoma increases 2-4 times in individuals with myopia. Central Corneal Thickness (CCT) is a crucial indicator in evaluating corneal health and

measuring IOP. Thinner corneas tend to yield lower IOP readings (underestimate), while thicker corneas result in higher pressure readings (overestimate). [1,2,3]

In the management of glaucoma, measuring CCT is highly important. Understanding the correlation between CCT and actual eye pressure helps medical practitioners take preventive and appropriate treatment measures. CCT examination is a vital initial step in detecting and controlling glaucoma. Therefore, it is essential for healthcare practitioners to consider CCT factors in actual IOP measurements, especially in myopic patients. The aim of this research is to determine the correlation between CCT and actual IOP in myopic patients.[4,5]

METHODS

This study is an analytical observational comparative numeric (non-paired) study with a cross-sectional design conducted at the Eye Department of Dr. M. Djamil Padang General Hospital from July to September 2023. The research obtained approval from the research ethics committee of the Faculty of Medicine, Andalas University, with the research sample consisting of all medical students at Andalas University undergoing clinical clerkship.

The sample included students aged 20-25 years who were willing to participate in the study. The examinations conducted on the participants included visual acuity testing, autorefractometry, OCT to obtain Central Corneal Thickness (CCT) values, and intraocular pressure (IOP) measurement with Goldman applanation, with IOP results converted to CCT values. Participants with abnormalities in the anterior and posterior eye segments, systemic disorders, myopia > 6D, a history of eye surgery, use of contact lenses within the last 6 weeks, and IOP > 21 mmHg were excluded from the study. The samples were divided into three groups: mild myopia (-0.50D to -3.00D), moderate myopia (-3.25 to -6.00D), and emmetropia, with a minimum sample size for each group based on the formula being 24 samples.

All data were statistically analyzed using SPSS. ANOVA (Analysis of Variance) was employed to compare the mean values of CCT, IOP, and actual IOP across the three groups (a hypothesis test for numeric comparison of more than two non-paired groups). Pearson correlation tests were conducted to assess the correlation between CCT and IOP as well as actual IOP. The significance of the test results was determined if the p-value was <0.05.

Table 1. Characteristics of research subjects based on gender and age.

Characteristics	Emetropia		Mild Myopia		Moderate Myopia	
	n	%	N	%	n	%
Gender						
Man	7	26.9	8	30.8	9	34.6
Woman	19	73.1	18	69.2	17	65.4
Age (Mean ± SD)	22.69 ± 1.158		22.73 ± 0.724		22.69 ± 0.182	

Table 2. Mean values of CCT, IOP, and actual IOP in emmetropia, mild myopia, and moderate myopia groups.

Variabel	Emetropia	Mild Myopia	Moderate Myopia	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
CCT	533,96 ± 21,342 µm	506,31 ± 11,263 µm	487,81 ± 28,272 µm	0,000
IOP	14.85 ± 1.156 mmHg	13.38 ± 1.134 mmHg	12.54 ± 1.392 mmHg	0,000
Actually IOP	15.35 ± 1.056 mmHg	15.81 ± 1.234 mmHg	16.12 ± 1.336 mmHg	0,078

RESULTS

The number of eyes meeting the research criteria is 78 eyes from 78 individuals, divided into 3 groups: 26 emmetropia, 26 mild myopia, and 26 moderate myopia.

According to Table 1, the data show that in the emmetropia group, 19 out of a total of 26 individuals (73.1%) are female with an average age of 22.69 ± 1.158 years. In the mild myopia group, females dominate with a percentage of 69.2%, and an average age of 22.73 ± 0.724 years. Meanwhile, in the moderate myopia group, females also dominate with a percentage of 65.4%, and an average age of 22.69 ± 0.182 years.

Table 2 shows that the mean CCT in the emmetropia group is 533.96 ± 21.342 µm, in mild myopia is 506.31 ± 11.263 µm, and in moderate myopia is 487.81 ± 28.272 µm. There is a statistically significant difference in mean CCT among these three groups with p = 0.000. Table

2 also indicates the mean IOP in the emmetropia group is 14.85 ± 1.156 mmHg, in mild myopia is 13.38 ± 1.134 mmHg, and in moderate myopia is 12.54 ± 1.392 mmHg. There is a statistically significant difference in mean IOP among these three groups with p = 0.000. However, for the mean actual IOP, in the emmetropia group is 15.35 ± 1.056 mmHg, in mild myopia is 15.81 ± 1.234 mmHg, and in moderate myopia is 16.12 ± 1.336 mmHg. The difference in mean actual IOP among these three groups is not statistically significant with p = 0.078.

From Table 3, there is a strong correlation between Central Corneal Thickness (CCT) and intraocular pressure (IOP) in emmetropia with a value of r = 0.681 and p = 0.000. The correlation between CCT and actual IOP in emmetropia is also strong with a value of r = 0.569 and p = 0.000. However, in Table 4, no statistically significant relationship was found between CCT and IOP in mild myopia (p = 0.076). The correlation between CCT and actual IOP in mild myopia is moderate with a value of r = 0.402 and p = 0.042. From Table 5, there is a strong correlation between CCT and IOP in moderate myopia with a value of r = 0.576 and p = 0.002. The correlation between CCT and actual IOP in moderate myopia also shows a moderate relationship with a value of r = 0.436 and p = 0.026.

Table 6 shows that the research results indicate a strong positive correlation between CCT and IOP with a value of r = 0.737 and p = 0.000, indicating a significant positive relationship. Meanwhile, there is a moderate correlation between CCT and actual IOP with a value of r = 0.492 and p = 0.000, indicating a negative relationship.

Table 3. Correlation test results of CCT with IOP and actual IOP in emmetropia.

		IOP	Actually IOP
CCT	r	0.681	-0.569
	P value	0.000	0.002
	N	26	26

Table 4. Correlation test results of CCT with IOP and actual IOP in mild myopia.

		IOP	Actually IOP
CCT	r	0,354	-0.402
	P value	0,076	0.042
	N	26	26

Table 5. Correlation test results of CCT with IOP and actual IOP in moderate myopia.

		IOP	Actually IOP
CCT	r	0,576	-0.436
	P value	0,002	0.026
	N	26	26

Table 6. Correlation test results of CCT with IOP and actual IOP.

		IOP	Actually IOP
CCT	r	0,737	-0.492
	P value	0,000	0.000
	N	78	78

DISCUSSION

This study involved samples aged between 20 to 25 years, with a uniform average age across all three groups. This was done to ensure that age differences did not become a significant confounding factor. Central Corneal Thickness (CCT) tends to decrease with age by about 2-10 μm per decade. The Ocular Hypertension Treatment Study (OHTS), a longitudinal study, showed a CCT decrease of 6 μm per decade, indicating that clinically significant changes in CCT require up to 20 years..[6,7]

In this study, there were more females than males in all research groups, as the samples were consecutively selected and then grouped into emmetropia, mild myopia, or moderate myopia.

CCT is an important parameter in assessing patients potentially at risk of glaucoma. The OHTS study indicated that thinner CCT is a predictor for glaucoma development in ocular hypertension. Over a 5-year period, thin CCT with IOP > 25.75 mmHg is a major risk factor for glaucoma development in patients with ocular hypertension. The risk of developing primary open-angle glaucoma (POAG) in 5 years in patients with CCT ≤ 555 μm is three times higher than in people with CCT > 588 μm. In this study, it was found that the mean CCT in the emmetropia group is 533.96 ± 21.342 μm, in mild myopia is 506.31 ± 11.263 μm, and in moderate myopia is 487.81 ± 28.272 μm. There is a significant difference in mean CCT among these three groups, where CCT in moderate myopia is thinner than in mild myopia and emmetropia. [7,8]

Intraocular pressure (IOP) is the fluid pressure inside the eye, and increased IOP is a major risk factor for glaucoma. Previous studies have reported glaucoma-related risks at all levels of myopia, including low and high myopia. In this study, it was found that the mean IOP in the emmetropia group is 14.85 ± 1.156 mmHg, in mild myopia is 13.38 ± 1.134 mmHg, and in moderate myopia is 12.54 ± 1.392 mmHg. IOP in moderate myopia is lower than in mild myopia and emmetropia. However, after correcting IOP based on CCT examination results, the mean actual IOP in the emmetropia group is 15.35 ± 1.056 mmHg, in mild myopia is 15.81 ± 1.234 mmHg, and in moderate myopia is 16.12 ± 1.336 mmHg. Although the actual IOP in

moderate myopia is higher than in mild myopia and emmetropia, this difference is not statistically significant. Lee AJ's study showed no significant difference in IOP between low myopia, high myopia, and emmetropia in 9-11-year-old children. Meanwhile, Choi JA's study indicated that refractive error in myopia is an independent predictor of higher IOP in non-glaucomatous eyes. The conclusion of these studies emphasizes the importance of assessing age factors in glaucoma screening and diagnosis, where increased IOP is a major risk factor.[9,10,11]

This study found no significant relationship between CCT and IOP in the mild myopia group, but a significant positive correlation was found in the emmetropia and moderate myopia groups, as well as overall. This means that the thinner the CCT, the lower the IOP. There was a significant negative correlation between CCT and actual intraocular pressure in all groups as well as overall. This means that the thinner the CCT, the higher the actual intraocular pressure. Previous studies have shown that IOP measurements are influenced by corneal thickness, with thinner corneas yielding lower readings, and thicker corneas yielding higher readings. Thinner corneas may make the eyes more vulnerable to increased intraocular pressure, contributing to glaucomatous optic neuropathy, a sign of various types of glaucoma. Corneal thickness can also correlate with corneal stiffness, but this only applies to structurally normal corneas. Corneal biomechanics may have a greater influence on intraocular pressure measurements than corneal thickness itself.[12,13,14]

This study has limitations, including not considering other factors that may affect CCT and IOP, such as ethnicity, contact lens use, and other factors affecting IOP such as circadian rhythm, heart rate, respiration, and physical activity. The results of this study also cannot be directly applied to the general population because it was only conducted on medical students at Andalas University undergoing clinical clerkship at Dr. M. Djamil Padang General Hospital.

CONCLUSION

This study reveals a significant inverse correlation between Central Corneal Thickness (CCT) and actual Intraocular Pressure (IOP) in myopic patients, where thinner CCT is associated with higher actual IOP. CCT examination serves as a crucial initial step to aid in the early detection and more effective control of glaucoma progression. This emphasizes the importance of glaucoma screening in myopic patients, particularly considering the thinner corneas in these individuals

RECOMMENDATIONS

Regular examinations are recommended for patients with thin CCT to facilitate early detection of glaucoma. Further research involving emmetropic, hyperopic, and astigmatic subjects, while considering other factors that may influence CCT and IOP, is suggested.

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REFERENCES

1. Tan NYQ, et al. Glaucoma in myopia: diagnostic dilemmas. Br J Ophthalmol 2019; pp :1–9.
2. World Health Organization. World Report of Vision. Geneva, Switzerland: WHO. 2019. pp 1-180
3. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: the Past, Present, and Predictions for the Future. Cureus 12(11). 2020; pp. 1-9.
4. Garcia M, Medina M, et al. Central corneal thickness, intraocular pressure and degree of myopia in adult myopic population aged 20 to 40 years in Southeast Spain: determination and relationships. Clin Ophthalmol. 2011; pp. 249-258.
5. Maiciulaitiene R, Januleviciene I. Correlation Between Structure and Function in Glaucomatous Damage. Biophysical Properties in Glauc`oma. Switzerland: Springer, 2019: pp 145-9
6. Qiu K, Lu X, Zhang R, Wang G. Relationship of corneal hysteresis and optic nerve parameters in healthy myopic subjects. Scientific reports. 2017. 7:17538
7. Carbonaro F, Hysi PG, Fahy SJ, et al. Optic disc planimetry, corneal hysteresis, central corneal thickness, and intraocular pressure as risk factors for glaucoma. Am J Ophthalmol. 2014 Feb;157(2):441-6.
8. Gordon MO, Kass MA.What We Have Learned From the Ocular Hypertension Treatment Study. American Journal of Ophthalmology, 189, xxiv–xxvii. 2018.
9. Rapuano CJ, Stout JT, McCannel CA. Aqueous humor, iris, and ciliary body. In: Fundamental and principles of ophthalmology. San Francisco: American Academy of Ophthalmology. 2022-2023. pp. 269-279.
10. Lee AJ, et al. Intraocular pressure associations with refractive error and axial length in children. Br J Ophthalmol 2004;88:5–7
11. Choi JA, et al. Age-Related Association of Refractive Error with Intraocular Pressure in the Korea National Health and Nutrition Examination Survey. PLOS ONE 2014, 9(11): e111879. doi:10.1371/journal.pone.0111879
12. Medina MG, et al. Central corneal thickness, intraocular pressure, and degree of myopia in an adult myopic population aged 20 to 40 years in southeast Spain: determination and relationships. Dove Press Journal, Clinical Ophthalmology 2011:5 249–258
13. Priyadarshini TA. Correlation Between Central Corneal Thickness (CCT) and Retinal Nerve Fiber Layer (RNFL). Disertation. The Tamilnadu DR MGR Medical University. Chennai. 2013
14. Sng CCA, Ang M, Barton K. Central corneal thickness in glaucoma. Curr Opin Ophthalmol 2017, 28:120–126 DOI:10.1097/ICU.0000000000000335

ORIGINAL ARTICLE

DETERMINING THE ETIOLOGY OF UVEITIS IN INDONESIA: THE ROLE OF CLINICAL MANIFESTATION AND SEROLOGICAL TEST IN INFECTIOUS UVEITIS

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ABSTRACT

Introduction: *Uveitis is a heterogeneous group of intraocular diseases that significantly causes vision disabilities in patients worldwide. Establishing an etiological diagnosis can be challenging because of the extensive and varied clinical patterns and differential diagnoses across regions. Knowledge of these patterns is crucial in aiding physicians with diagnosis, reducing the need for costly ancillary tests, and facilitating timely management.*

Methods: *We conducted a retrospective descriptive study using medical records data from a tertiary referral hospital in Indonesia over two years (2016-2017), involving 299 patients with uveitis.*

Results: *Among the 299 patients, 152 were men (152/299, 50.8%) with a median age of 36. Panuveitis was the most frequent anatomical entity (152/199, 53.2%). Infectious etiology, primarily toxoplasmosis and tuberculosis, remained prevalent. Despite various final diagnoses, serological tests for IgG Toxoplasma and CMV were predominantly reactive in 192/251 (76.5%) and 228/236 (96.6%) of tested patients. At presentation, 106/299 (35%) of patients were categorized as blind, and 64/106 (60%) were without improvement. Complications were observed in 167/299 (55%) of patients, including cataracts (133/299, 44%) and glaucoma (32/299, 10%), contributing to 70/106 (66%) of blindness in our series.*

Conclusion: *Panuveitis and infectious etiology, particularly toxoplasmosis and tuberculosis, were the most common causes of uveitis. Clinical patterns were better able to distinguish them than laboratory results. Understanding these uveitis patterns can guide physicians in diagnosing before performing expensive ancillary tests. Ocular complications were related to severe visual function; thus, timely referral in severe cases is essential.*

Keywords*: Uveitis, Indonesia, epidemiology*

INTRODUCTION

Uveitis is a heterogeneous group of intraocular diseases that are regarded as a major cause of vision disabilities in patients around the world.[1] It includes a range of inflammatory eye conditions mainly affecting the uvea and its surroundings, such as the retina, optic disc, and vitreous. Incidence and prevalence varied globally but were seen higher in developing and tropical countries because of the greater risk of infectious etiologies.[2] It is also a leading cause of blindness in working-age populations and accounts for up to 25% of all blindness in developing countries.[3]

Establishing an etiological diagnosis can be challenging due to the extensive and varied clinical patterns and differential uveitis diagnoses across different regions. Various

factors, including genetics, ethnicity, geography, socioeconomic status, environment, and referral patterns, influence these patterns.[4] Practicing ophthalmologists, especially in Indonesia, may face challenges in establishing etiological diagnoses due to costly ancillary tests. Therefore, understanding these patterns is crucial for aiding physicians in diagnosis, reducing the need for costly ancillary tests, and facilitating timely management. Delayed diagnosis can increase the risk of sight-threatening complications, leading to a substantial socioeconomic impact.

Published uveitis epidemiological data in Southeast Asia, specifically Indonesia, are scarce. We aimed to update the epidemiological, clinical, and laboratory characteristics among uveitis patients referred to our clinic, a national tertiary referral center in Indonesia.

METHODS

We retrospectively investigated the clinical records of 299 new patients with uveitis to the Immunology and Infection Clinic, Department of Ophthalmology, National referral Cipto Mangunkusomo Hospital-Kirana, located in Jakarta, between January 2016 and December 2017. Patients with less than 6 weeks of follow-up and an inactive clinical appearance of uveitis were excluded.

We collected demographic and clinical data, including age, sex, onset, diagnosis, laterality and anatomic location of inflammation, visual acuity, complications, and laboratory test results. Several laboratory tests include chest X-ray, serology test for Cytomegalovirus (CMV) and Toxoplasma, Mantoux tests, Interferon Gamma Release Assay (IGRA), and Polymerase Chain Reaction (PCR) on the aqueous or vitreous. The ethics committee of the Faculty of Medicine, University of Indonesia has approved this study.

Anatomic diagnoses were evaluated according to the classification of the Standardization of Uveitis (SUN) Working Group as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis, while the etiological diagnosis was classified into infectious, noninfectious, masquerade, and idiopathic.[5,6] SUN categorized the onset of uveitis as sudden or insidious.[5] Diagnosis of specific uveitis disorders or systemic disease association was based on detailed clinical history, complete ocular examination, extensive review of systems, supporting laboratory results, response to therapy during the 6-week period, and selected medical consultations to other disciplines. Specific diagnoses for systemic conditions such as Vogt-Koyanagi-Harada (VKH), Behcet disease, and Sarcoidosis were made using diagnostic

criteria established or published by the corresponding specialty societies or specialist panels.[7–9] The term idiopathic was used when the specific diagnosis for uveitis could not be made.

The best corrected visual acuity of the affected eye was collected and analyzed and classified into degrees of visual impairment according to the World Health Organization (WHO).[10] Statistical analyses were performed using SPSS for Mac software, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 summarizes the demographic and general characteristics of the presentation of all patients. A total of 299 patients were included within the 2 years of the study. The patients were 152/299 (50.8%) male, and the overall median age with interquartile range (IQR) at presentation was 36 (25-48) years. Of the 299 patients, 172 (57.5%) had unilateral uveitis. The clinical symptoms onset was most commonly sudden (181/299, 60.5%).

Table 1. Demographic and general characteristics of 299 patients with uveitis

Characteristics	No. of patients (%)
Sex	
Male	155/299 (50.8%)
Female	147/299 (49.2%)
Age in years*	36 (25-48)
Laterality of uveitis	
Unilateral	172/299 (57.5%)
Bilateral	127/299 (42.5%)
Clinical Onset	
Sudden	181/299 (60.5%)
Insidious	118/299 (39.5%)

*median with IQR (Interquartile range)

Table 2 shows the etiological diagnosis of the 299 patients, further subdivided by anatomical classification. Overall, the cases presented in our clinic were predominantly (199/299, 66.6%) caused by infection, and 34/299 (11.4%) cases were classified as idiopathic. The four most common etiological diagnoses were toxoplasmosis (96/299, 32.1%),

Tuberculosis (TB) (60/299, 20.1%), Cytomegalovirus (CMV) (21/299, 7%), and VKH (21/299, 7%). Panuveitis most frequently occurred among 159/299 (53.2%) of patients, followed by posterior uveitis in 115/299 (38.5%). The most common cause of anterior uveitis was idiopathic uveitis (7/19, 36.8%), followed by Herpes simplex virus (HSV) (4/19, 21%). TB caused half of intermediate uveitis cases, while toxoplasmosis was the most frequent cause of posterior uveitis (74/115, 64.3%). TB was the most common cause of panuveitis (43/299, 27%), followed by toxoplasmosis (22/299, 13.8%).

Table 2. Anatomic classification and etiological diagnosis of uveitis

Etiological diagnosis	**No. of patients (%)**	**Anterior** **n (%)**	**Intermediate** **n (%)**	**Posterior** **n (%)**	**Panuveitis** **n (%)**
		19/299 (6.4%)	6/299 (2%)	115/299 (38.5%)	159/299 (53.2%)
Infectious	199/299 (66.6%)	9/19 (47.4%)	3/6 (50%)	110/115 (95.7%)	77/159 (48.4%)
Toxoplasmosis	96/299 (32.1%)	-	-	74/115 (64.3%)	22/159 (13.8%)
TB	60/299 (20.1%)	2/19 (10.5%)	3/6 (50%)	12/115 (10.4%)	43/159 (27%)
CMV	21/299 (7%)	2/19 (10.5%)	-	16/115 (13.9%)	3/159 (1.8%)
HSV	9/299 (3%)	4/19 (21%)	-	4/115 (3.4%)	1/159 (0.6%)
Syphilitic uveitis	6/299 (2%)	-	-	1/115 (0.8%)	5/159 (3.1%)
VZV	3/299 (2%)	1/19 (5.2%)	-	2/115 (1.7%)	-
Suspected Lyme disease	2/299 (0.6%)	-	-	1/115 (0.8%)	1/159 (0.6%)

ARN	1/299 (0.3%)	-	-	-	1/159 (0.6%)
Cat-scratch disease	1/299 (0.3%)	-	-	-	1/159 (0.6%)
Noninfectious	48/299 (16.1%)	3/19 (15.8%)	1/6 (16.7%)	0/115 (0%)	44/159 (27.7%)
Associated systemic disease					
VKH	21/299 (7%)	1/19 (5.2%)	-	-	20/159 (12.6%)
Behcet disease	11/299 (3.6%)	1/19 (5.2%)	-	-	10/159 (6.3%)
Sarcoidosis	4/299 (1.3%)	-	-	-	4/159 (2.5%)
SLE	1/299 (0.3%)	-	-	-	1/159 (0.6%)
Sjogren's syndrome	1/299 (0.3%)	1/19 (5.2%)	-	-	-
Multiple sclerosis	1/299 (0.3%)	-	1/6 (16.7%)	-	-
Specific ocular disease					
SO	6/299 (2%)	-	-		6/159 (3.8%)
Lens-induced uveitis	1/299 (0.3%)	-	-	-	1/159 (0.6%)
MFCPU	1/299 (0.3%)	-	-	-	1/159 (0.6%)
Eales disease	1/299 (0.3%)	-	-	-	1/159 (0.6%)

Masquerade	18/299 (6%)	-	-	2/115 (1.7%)	16/159 (10.1%)
Non-neoplastic	17/299 (5.6%)	-	-	2/115 (1.7%)	15/159 (9.4%)
Neoplastic	1/299 (0.3%)	-	-	-	1/159 (0.6%)
Idiopathic	34/299 (11.4%)	7/19 (36.8%)	2/6 (33.3%)	3/115 (2.6%)	22/159 (13.8%)

TB : Tuberculosis; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus; ARN: Acute retinal necrosis; VKH: Vogt-Koyanagi-Harada; SLE: Systemic Lupus Erythematosus; SO: Sympathetic Ophthalmia; MFCPU: Multifocal choroiditis with panuveitis.

To review the number of visual impairments and the impact of uveitis treatment, we also analyzed baseline visual acuity and its changes on final follow-up (Table 3). On presentation, most patients came with mild or no visual impairment (111/299, 37.1%), and 90/111 (81.1%) of those patients remained stable. However, at baseline, many patients (106/299, 35.5%) were categorized as blind. When considering the anatomical classification of uveitis, it is noted that patients who experienced blindness were predominantly those with panuveitis (66/106, 62.3%) (Table 4).

Uveitis complications were one of the leading causes of blindness. We found that 167/299 (55.9%) patients had complications, and 36/167 (21%) had multiple complications. The common complications were cataracts (133/299, 44.5%), glaucoma (32/299, 10.7%), and retinal detachment (21/299, 7%). Out of the patients with complications, 70/167 (42%) presented with blindness. Among them, the majority (43/70, 61,4%) did not experience any improvement in visual acuity and remained blind due to complications.

Patients with uveitis underwent several laboratory tests. We found that patients with an etiological diagnosis of TB have positive Mantoux and/or IGRA tests in around 47/48 (97.9%) patients, while specific imaging of TB on chest X-ray was only shown in about 13/55 (23.6%) patients. Thirty-one (31/299, 10.4%) patients had positive serology results for human immunodeficiency virus (HIV). The serology results for HIV were found positive, mainly in patients with an etiological diagnosis of CMV (15/31, 48.4%) and syphilitic uveitis (4/31, 12.9%). Serological tests for Toxoplasma and CMV were also done for most patients (Table

5). We found that IgG Toxoplasma and IgG CMV were predominantly reactive in 192/251 (76.5%) and 228/236 (96.6%) of tested patients, respectively. This is shown throughout various final diagnoses, such as TB with 44/54 (81.5%) reactive IgG Toxoplasma and 48/50 (96%) reactive IgG CMV. It is also shown in noninfectious etiology, such as VKH with 9/17 (52.9%) reactive IgG Toxoplasma and 16/16 (100%) reactive IgG CMV.

Table 3. Comparison of baseline and final visual impairment

Visual impairment	Baseline	Final follow up		
	No. of patients (%)	Unchanged n (%)	Improvement n (%)	Deterioration n (%)
Mild or no visual impairment	111/299 (37.1%)	90/111 (81.1%)	-	21/111 (18.9%)
Moderate	65/299 (21.7%)	21/65 (32.3%)	30/65 (46.2%)	14/65 (21.5%)
Severe	17/299 (5.7%)	3/17 (17.6%)	10/17 (56.8%)	4/17 (23.5%)
Blindness	106/299 (35.5%)	64/106 (60.4%)	42/106 (39.6%)	-
Total	299	178/299 (59.5%)	82/299 (27.4%)	39/299 (13%)

Table 4. Presenting visual impairment and anatomical uveitis classification

Visual impairment	No. of patients (%)	Anatomical classification			
		Anterior n (%)	Intermediate n (%)	Posterior n (%)	Panuveitis n (%)
Mild or no visual impairment	111/299 (37.1%)	9/111 (8.1%)	6/111 (5.4%)	49/111 (44.1%)	47/111 (42.3%)
Moderate	65/299 (21.7%)	4/65 (6.2%)	0/65 (0%)	21/65 (32.3%)	40/65 (61.5%)

Severe	17/299 (5.7%)	1/17 (5.9%)	0/17 (0%)	10/17 (58.8%)	6/17 (35.3%)
Blindness	106/299 (35.5%)	5/106 (4.7%)	0/106 (0%)	35/106 (33%)	66/106 (62.3%)
Total	299	19/299 (6.4%)	6/299 (2%)	115/299 (38.5%)	159/299 (53.2%)

Table 5. Additional laboratory results characteristics according to etiological diagnosis

Etiological diagnosis	Toxoplasma Serology		CMV Serology		Positive Mantoux test and/or IGRA n (%)
	Reactive IgM n (%)	Reactive IgG n (%)	Reactive IgM n (%)	Reactive IgG n (%)	
Infectious					
Toxoplasmosis	10/87 (11.5%)	82/85 (96.5%)	1/77 (1.3%)	74/79 (93.7%)	12/48 (25%)
TB	2/56 (3.6%)	44/54 (81.5%)	1/49 (2%)	48/50 (96%)	46/47 (97.9%)
CMV	1/19 (5.3%)	8/19 (42.1%)	5/19 (26.3%)	19/19 (100%)	0/5 (0%)
HSV	0/7 (0%)	4/7 (57.1%)	0/7 (0%)	7/7 (100%)	4/6 (66.7%)
Syphilitic uveitis	0/4 (0%)	2/4 (50%)	0/4 (0%)	4/4 (100%)	0/2 (0%)
VZV	0/2 (0%)	1/2 (50%)	0/2 (0%)	2/2 (100%)	1/2 (50%)
Suspected Lyme disease	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/2 (0%)
ARN	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
Cat scratch disease	-	-	-	-	-
Noninfectious					
Associated systemic disease					
VKH	0/17 (0%)	9/17 (52.9%)	2/17 (11.8%)	16/16 (100%)	6/8 (75%)
Behcet disease	1/9 (11.1%)	7/7 (100%)	1/9 (11.1%)	7/7 (100%)	4/5 (80%)
Sarcoidosis	0/3 (0%)	3/3 (100%)	0/3 (0%)	3/3 (100%)	0/1 (0%)

SLE	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
Sjogren's syndrome	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	2/2 (100%)
Multiple sclerosis	0/1 (0%)	1/1 (100%)	-	-	0/1 (0%)
Specific ocular disease					
SO	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	2/2 (100%)
Lens-induced uveitis	-	-	-	-	-
MFCPU	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)
Eales disease	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	-
Masquerade					
Non-neoplastic	0/14 (0%)	8/14 (57.1%)	0/14 (0%)	13/13 (100%)	0/10 (0%)
Neoplastic	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	-
Idiopathic	0/29 (0%)	20/28 (69%)	2/28 (7.1%)	27/27 (100%)	8/25 (32%)

TB : Tuberculosis; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus; ARN: Acute retinal necrosis; VKH: Vogt-Koyanagi-Harada; SLE: Systemic Lupus Erythematosus; SO: Sympathetic Ophthalmia; MFCPU: Multifocal choroiditis with panuveitis.

DISCUSSION

This retrospective study demonstrated that panuveitis and infectious etiology (Toxoplasmosis and TB) were the most common uveitis. We found that the median age of patients in our tertiary referral center was 36 years old and predominantly male. Furthermore, we found that the majority of patients were blind on presentation, and ultimately, most of them were without improvement. Complications of uveitis were predominantly due to cataracts and

glaucoma. These complications contributed to almost half of blindness in this study. We also found that several laboratory tests might help physicians diagnose. Still, serological test results for Toxoplasma and CMV might be misleading since they are reactive in almost every patient with various etiological diagnoses.

Referred patients were in their productive age at about 36 years old. Similar findings were reported by several studies in Asia, which showed that uveitis was most commonly found in the third decade of age.[2,11–14] Most patients were found to have unilateral involvement of uveitis. Studies in Iran and Thailand also have the same finding, especially in anterior and posterior uveitis.[2,13] We found that most referred patients were with panuveitis. These findings were in contrast to other studies in several developed countries and Asian countries, where anterior uveitis was commonly found.[2,14,15] Our study occurred in a national tertiary referral center; hence, most panuveitis was seen in referred patients.

We found that the main causes of uveitis were infections such as toxoplasmosis and TB. This result was confirmed in the previous study in Indonesia, where infections represented the most frequent cause of uveitis, especially toxoplasmosis and TB.[16] Studies in Iran and Thailand found toxoplasmosis as the main infectious etiology.[2,12,13] Studies in Saudi Arabia and Japan showed that TB was the most commonly found infectious etiology.[11,17] Most commonly found anterior uveitis were idiopathic cases. In several studies, anterior uveitis was associated with HLA-B27, but we could not perform the HLA-B27 test because it was not covered by national health insurance, hence the possibility of underdiagnosis.[2,13] This study demonstrated that intermediate uveitis was most commonly found with causes of TB as much as 50%. Another study found that TB only caused 7% of intermediate uveitis.[11] Indonesia is an endemic region of TB where prevalence was 395 in every 100.000, thus explaining this discrepancy. We found that the presenting visual acuity in most patients was mild or no visual impairment and blindness. This showed the severity of uveitis cases when referred to a tertiary referral center. A study by Yeo et al.[18] stated that panuveitis was the strongest predictor for severe visual loss. This is consistent with our study, which found that panuveitis was largely present in patients with blindness.

Visual loss in uveitis was also associated with treatment and complications. We found 55.9% of patients with complications, and more than half of those patients were blind on presentation. Other studies also found cataracts to be the most common cause of visual loss related to uveitis.[18] Several other studies found macular edema the main reason for visual loss.[19] Conversely, our study only found macular edema as much as 2% which might be explained by

the difficulty of Optical Coherence Tomography (OCT) to be performed on severely affected refractive media in most patients.

Diagnosis of uveitis was made by recognizing clinical patterns and supporting ancillary tests. Definitive diagnosis of TB was difficult because it needed evidence that *Mycobacterium tuberculosis* (Mtb) existed in ocular fluid or tissue and diagnosis of TB was mostly made presumptively. Several ancillary tests were done to support presumptive TB diagnosis, such as specific imaging of active TB lesion on chest X-ray, microbiologically from extraocular fluids such as sputum, and immunological evidence of TB infection with Mantoux or IGRA test. IGRA tests were more specific than Mantoux because of false positive results in vaccinated patients and exposure to other mycobacterium.[20]

Several laboratory tests were done routinely in almost every newly arrived patient to help screen etiological diagnosis. However, we did not find it to be efficient and did not help suggest a specific diagnosis. We found that serological tests of IgG Toxoplasma and CMV were to be reactive in almost every patient with various final diagnoses. Therefore, serological tests for Toxoplasma were only suggested to exclude toxoplasmosis diagnosis if the patient had a non-pathognomic clinical manifestation of ocular toxoplasmosis.[21]

Limitations of our study include potential referral bias as the data were collected from a single institution, namely, a tertiary referral center. It is plausible that our data may be biased towards more severe and chronic cases, thus differing from those in community settings. Given the retrospective nature of this study, it is important to acknowledge that medical records may be incomplete, and the data quality may vary, potentially including errors or inconsistencies. We also acknowledge the underestimation of HLA-B27 prevalence due to limitations in the investigation. Nonetheless, we believe that the findings of our study offer valuable insights into the epidemiology and clinical patterns of uveitis patients in Indonesia. A comprehensive understanding of uveitis patterns in each region, particularly its clinical features, can assist physicians in making diagnoses before performing expensive ancillary tests and prevent unfavorable outcomes.

CONCLUSION

Infectious etiology remains the leading cause of uveitis in Indonesia, with a majority of patients presenting to the ophthalmology clinic with blindness. Therefore, it is important to rule out infection when diagnosing uveitis. This study underscores the importance of selecting ancillary tests, as our study results demonstrate their potential for redundancy. Furthermore, effective communication and collaboration among physicians across different regions are

crucial. Early and timely referrals are indispensable given the close associations between ocular complications and severe visual impairment.

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REFERENCES

1. Luca C, Raffaella A, Sylvia M, Valentina M, Fabiana V, Marco C, et al. Changes in patterns of uveitis at a tertiary referral center in Northern Italy: analysis of 990 consecutive cases. Int Ophthalmol [Internet]. 2017 [cited 2018 Sep 17]; Available from: http://link.springer.com/10.1007/s10792-016-0434-x
2. Soheilian M, Heidari K, Yazdani S, Shahsavari M, Ahmadieh H, Dehghan M. Patterns of uveitis in a tertiary eye care center in Iran. Ocul Immunol Inflamm. 2004;12:297–310.
3. London NJS, Rathinam SR, Cunningham ET. The epidemiology of uveitis in developing countries: Int Ophthalmol Clin. 2010;50:1–17.
4. Shirahama S, Kaburaki T, Nakahara H, Tanaka R, Takamoto M, Fujino Y, et al. Epidemiology of uveitis (2013–2015) and changes in the patterns of uveitis (2004–2015) in the central Tokyo area: a retrospective study. BMC Ophthalmol. 2018;18:189.
5. Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509–16.
6. Deschenes J, Murray PI, Rao NA, Nussenblatt RB. International Uveitis Study Group (IUSG) Clinical Classification of Uveitis. Ocul Immunol Inflamm. 2008;16:1–2.
7. Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, et al. Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease: Report of an International Committee on Nomenclature. Am J Ophthalmol. 2001;131:6.
8. International Study Group for Behcet. Criteria for diagnosis of Behcet's disease. The Lancet [Internet]. 1990 [cited 2021 Jun 22];335. Available from: https://linkinghub.elsevier.com/retrieve/pii/014067369092643V
9. Herbort CP, Rao NA, Mochizuki M, the members of the Scientific Commi. International Criteria for the Diagnosis of Ocular Sarcoidosis: Results of the First International Workshop on Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm. 2009;17:160–9.
10. WHO. International classification of diseases (11th Revision). [Internet]. 2018. Available from: https://icd.who.int/en
11. Al Dhibi HA, Al Shamsi HN, Al-Mahmood AM, Al Taweel HM, Al Shamrani MA, Arevalo JF, et al. Patterns of Uveitis in a Tertiary Care Referral Institute in Saudi Arabia. Ocul Immunol Inflamm. 2017;25:388–95.
12. Pathanapitoon K, Kunavisarut P, Ausayakhun S, Sirirungsi W, Rothova A. Uveitis in a tertiary ophthalmology centre in Thailand. Br J Ophthalmol. 2008;92:474–8.
13. Sittivarakul W, Bhurayanontachai P, Ratanasukon M. Pattern of Uveitis in a University-based Referral Center in Southern Thailand. Ocul Immunol Inflamm. 2013;21:53–60.
14. Yang P, Zhang Z, Zhou H, Li B, Huang X, Gao Y, et al. Clinical Patterns and Characteristics of Uveitis in a Tertiary Center for Uveitis in China. Curr Eye Res. 2005;30:943–8.
15. Cimino L, Aldigeri R, Salvarani C, Zotti CA, Boiardi L, Parmeggiani M, et al. The causes of uveitis in a referral centre of Northern Italy. Int Ophthalmol. 2010;30:521–9.
16. La Distia Nora R, Sitompul R, Bakker M, Susiyanti M, Edwar L, Sjamsoe S, et al. Tuberculosis and other causes of uveitis in Indonesia. Eye. 2018;32:546–54.
17. Keino H, Nakashima C, Watanabe T, Taki W, Hayakawa R, Sugitani A, et al. Frequency and clinical features of intraocular inflammation in Tokyo. Clin Exp Ophthalmol. 2009;37:595–601.
18. Yeo TK, Ho SL, Lim WK, Teoh SC. Causes of Visual Loss Associated with Uveitis in a Singapore Tertiary Eye Center. Ocul Immunol Inflamm. 2013 Aug;21(4):264-9.
19. Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SRJ, Joshi L, et al. Long-Term Clinical Outcome and Causes of Vision Loss in Patients with Uveitis. Ophthalmology. 2014;121:2387–92.
20. Albini TA, Karakousis PC, Rao NA. Interferon-gamma release assays in the diagnosis of tuberculous uveitis. Am J Ophthalmol. 2008;486–8.
21. Kijlstra A. The value of laboratory testing in uveitis. Eye. 1990;4:732–6.

CASE REPORT

SCLERAL BUCKLING FOR RETINOPATHY OF PREMATURITY: A CASE REPORT

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ABSTRACT

Introduction: *The selection of management for advanced retinopathy of prematurity (ROP) requires careful consideration. The purpose of this study is to report the effectiveness of scleral buckling in patient with retinopathy of prematurity stage 4B of both eyes within 3 months.*

Case Report: *A 4-month-old female presented to the Pediatric Ophthalmology Unit at Cipto Mangunkusumo General Hospital with a lack of eye contact. Her eyes had been moving erratically and sometimes squinted since 3.5 months old. She was born prematurely at 30 weeks and received oxygen therapy for 3 weeks. Diagnosed with stage 4B retinopathy of prematurity in both eyes, scleral buckling was performed at 49 and 52 weeks postmenstrual age.*

Discussion: *In this advance case of Retinopathy of Prematurity (ROP), scleral buckling (SB) effectively slowed progression in the right eye but was less successful in the left due to severe disease and delayed intervention. Timely treatment is crucial; this case highlights the importance of early intervention, as the late surgery at 48 weeks postmenstrual age contributed to the ongoing issues in the left eye. Adhering to screening guidelines and improving treatment timing are essential for better outcomes in advanced ROP cases.*

Conclusion*: Management of ROP depends on its type. For advanced ROP with retinal detachment, surgery is needed. Scleral buckling is an option when intraocular surgery is too risky. Short-term results show scleral buckling is effective for the right eye. Long-term follow-up is needed to confirm its effectiveness in advanced ROP.*

Keyword**:** *Retinopathy of prematurity, scleral buckling, retinal detachment*

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the most common causes of preventable childhood blindness worldwide.[1] Retinopathy of prematurity refers to a condition of vasoproliferative retinal disorder that affects premature infants.[2] The incidence among infants of any stage of ROP with weight less than 1251g was 68%. In 2010, approximately 184,700 infants and 14.9 million preterm infants were affected ROP, which 20,000 became blind or severely visually impaired, and 12,300 had mild-to-moderate visual impairment.[3] Some studies show that ROP is higher in very low birth weight infants (BW<1,500 g), newborns with a GA<30 to 32 weeks, or premature infants with an unstable clinical condition.[1,4]

Early exposure to high oxygen levels is believed to be a key risk factor.[5] The pathological growth vessels were developed as the result of high oxygen level treatment, and may lead to retinal permanent damage, retinal detachment and also macular folds.[3]

There are several management options for patients with ROP based on the stage. Advanced stages of ROP require surgical management. Two options of surgery have been described, including vitrectomy and scleral buckling.[2] The surgery of patient with ROP is difficult to perform. The surgical intervention absolutely have to operate well without complication: no lens touch, no retina touch and no retinal tear.[6]

The consideration about the best time and the type of surgery that gave the most beneficial result for stage 4 ROP were still controversial.[7] Compared to SB, vitrectomy could relieve vitreoretinal traction and removes endogenous vasodilator and angiogenic factors that contribute to vascular activity.[6] However, vitrectomy is an intraocular surgery which also have complication that may occur, which are choroidal detachment, retinal tear and also amblyopia.[8]

Data from the Cryotherapy for Retinopathy of Prematurity study described that stage 4 ROP had 88% chance progression to stage 5 if involves eight of 34 ROP sectors of the retina. From this data, we can conclude that scleral buckling would be a reasonable alternative in stage 4 ROP retinal detachment.[9] The advantages of SB procedure are not involving the intraocular, no cataract formation may occur, and also cost effective. However, the SB procedure also have the disadvantages, which are scleral perforation, the need of performing second surgery to divide the buckle in order to promote the eye growth.[6]

The outcome of retinal detachment surgery for newborn, both anatomical and functional are poor. Based on ETROP study, only 10% of stage 4A detachment had a favorable visual acuity outcome, none of stage 4B nor stage 5. However, the study found that 16 of 48 eyes attained successful macular attachment.[1,9]

Scleral buckling was chosen despite of vitrectomy in this stage 4B ROP of both eye due to the higher risk that may occur if we perform the intraocular surgery. The aim of the surgery are also to relieve the vitreoretinal traction and prevent the ischemia in the detached retina.[10]

This case report was evaluated the effectiveness of scleral buckling in patient with retinopathy of prematurity stage 4B of both eyes within 3 months. By describing this case, hopefully it can be understood the consideration of choosing a management option and the right timing in a patient with advanced ROP.

CASE ILUSTRATION

A baby girl, 4 months old, came to the Pediatric Ophthalmology Unit in Cipto Mangunkusumo General Hospital (RSCM) Kirana with the chief complain did not make eye contact of both eyes. Her eyes have been moving on their own since she was 3.5 months old, and she sometimes looks like squint. The parent said that if the mother provided any light stimulation, the patient did not follow the light direction.

The patient was born of a twin gestation at 30 weeks and had birth weight of 1300 grams. There was a history of CPAP oxygenation for 1 week and nasal canule oxygen for 2 weeks. There was no ROP screening in East Belitung, but the pediatrician suggests the parent to check the patient to the ophthalmologist when she was 3 months old.

When the patient is already 3 months old, the parent brings the patient to ophthalmologist in East Belitung, but the facility is inadequate. The patient was diagnosed with suspected ROP with a differential diagnosis of cataract. The patient was then referred to RSCM to get further evaluation and management.

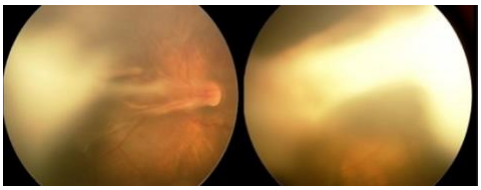

Figure 1. Fundus photograph of the right and left eyes before the surgery (January 11th 2022)

The Pediatric Ophthalmology division performed ultrasonography and RetCam imaging, diagnosing retinopathy of prematurity stage 4B in both eyes. The patient was then referred to the Vitreoretinal division, which planned an examination under anesthesia for both eyes on January 14th, 2022. The examination showed that the right eye had ROP stage IV B and the left eye had ROP stage IV-V. The right eye exhibited fibrovascular tissue extending from the optic nerve to the temporal area with macular dragging, while the left eye showed vitreous haziness and fibrovascular proliferation covering almost all quadrants (Figure 1).

The patient then planned to perform scleral buckling of both eyes by vitreoretinal division. Scleral buckling was performed on January 20th 2022 for the right eye and the left eye on February 9th 2022, which was 49 and 52 weeks based on the premenstrual age (PMA).

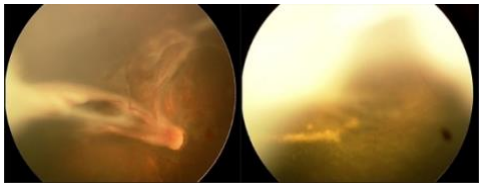

Figure 2. Fundus photograph of the right and left eye one month after the surgery (March 8th 2022). The right and left eye condition was quite the same

After the surgery, the patient was examined with retcam by the pediatric ophthalmology division, and the condition of the fundus remained the same. (Figure 2) There was no progressivity of the ROP found based on the retcam. The patient then went back to Belitung and planned to control in 3 months. The parent said that after 3 months post-surgery, the patient could follow the light stimulation, and the retcam showed the same whitish lesion on the right eye (only in peripheral), but the whitish lesion on the left eye looks more obvious and the eyeball looks smaller. (Figure 3).

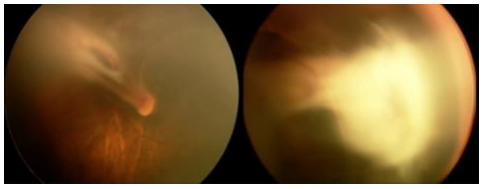

Figure 3. Fundus photograph of the right and left eye three months after the surgery (May 17th 2022). The right eye condition remained the same, the left eye was denser

DISCUSSION

Retinopathy of prematurity is a retinal vasoproliferative disorder initiated in part by incomplete or abnormal retinal vascularization in premature infants. The ischemic condition of the retina, caused by a lack of retinal vessels in the immature retina, leads to the release of growth factors that promote vascular growth. This proliferation of retinal vessels disrupts the normal vascular growth process. Vitreous hemorrhage and tractional retinal detachment may occur as the disease progresses. If left untreated, ROP can result in the development of a dense, white fibrovascular plaque behind the lens and complete tractional retinal detachment.[11]

Incidence of ROP in USA was ranging from 40% in infants with a birth weight of 1101–1200 g to 90% in infants of 501–600 g, while in Indonesia, the incidence of all stages of ROP, those with a gestational age of < 32 weeks ranged from 18-30%.[12] The patient of this case was born of a twin gestation at 30 weeks and had birth weight of 1300 grams.

A study by Bortea et al confirmed several known ROP risk factors, including gestational age, birth weight, ventilation, CPAP, and surfactant administration, which were all significant

risk factors for ROP. Here, the baby has a history of using CPAP for 1 week and nasal cannula oxygenation for 2 weeks.

The clinical manifestation in this case is no eye contact found in both eye and a very subtle leukocoria in the right eye, and more obvious in the left eye. The retcam of the right eye showed fibrovascular tissue extending from the optic nerve to the temporal with macular dragging, and the left eye showed vitreous haziness and almost all quadrants were covered by fibrovascular proliferation.

Based on current guidelines from the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus, ROP screening is recommended for infants with a gestational age of 30 weeks or less, birth weight of 1500 g or less, or a complicated clinical course. The first examination should be conducted after 4 weeks' chronologic (postnatal) age or at a corrected gestational age of 31 weeks, not later than 6 weeks' chronologic age.[2] Screening program ensures early detection and timely intervention, which prevent the development of the retinal detachment (advanced stages of ROP).[14] In this study, the patient came to Pediatric Ophthalmology clinic when 48 post menstrual age (PMA), which is quite late based on the screening guidelines. There are several management options for patient with ROP, which depends on the stage. According to CRYO-ROP study, premature infants were treated with cryotherapy at the threshold point, at which time the neovascularization was equally to progress (to retinal detachment) or to regress. Transpupillary laser treatment to ablate non-vascularized retina has effectively replaced cryotherapy, due to more favorable visual outcomes and fewer systemic complications.[15] Vascular endothelial growth factor (VEGF) is an important mediator in retinopathy of prematurity (ROP). The use of anti-VEGF treatment in phase 2 ROP has given promising results, mainly in severe cases.[16]

Anti-VEGF is superior in patient with ROP zone I compared with laser coagulation. Equal treatment success with anti-VEGF and laser coagulation in patient with ROP zone II. Combined treatments have been described in several studies to overcome the disadvantages of both treatments.[8]

When laser treatment, cryotherapy, or intravitreal anti VEGF has not prevented the progression of ROP to stage 4 or 5 (retinal detachment), surgical treatment may be indicated.[2] There are 2 surgery options for a patient with advanced ROP. Small-gauge lens sparing vitrectomy has largely replaced SB in stage 4 ROP, as there is evidence that the procedure is more effective to release the vitreoretinal traction. Other advantages of vitrectomy include the removal of endogenous vasodilators and angiogenic factors (VEGF) from the vitreous scaffold

and prevention of fibrovascular membrane formation.[6] Here, we did not find any neovascularization nor any active hemorrhage based on the retcam, so vitrectomy was not chosen as the treatment option for this patient.

Vitrectomy for ROP ideally performed at stage 4A ROP, which the focal TRD is not involving the macula. This aim to achieve good anatomical and functional result.[17] In this case, the stage is 4B, which is more severe than 4A, and also there was an involvement in the macula, this also one of the reasons we considerate to perform scleral buckling rather than the vitrectomy. First, performing vitrectomy in this patient seems not effective, and the patient risk more prone to intraocular complication, such as retinal tear, choroidal detachment, and endophthalmitis.[6,18] On the other hand, the scleral buckling was worked as the globe grows rapidly in infants, which allows the RPE to absorb the subretinal fluid and contribute the fix surface of the retina.[19] Despite of the benefit and risk consideration for this patient, the scleral buckling was selected as the surgery option in this case.

The study by Papageorgiou et al investigated the efficacy of SB in stages 4A and 4B ROP in infants who did not undergo vitrectomy, due to lack of pediatric vitrectomy instrumentation. In all seven eyes had history of previous treatment, six eyes had performed diode laser photocoagulation for stage 3 + ROP in zone II, and one eye had previous intravitreal ranibizumab injection for stage 3 + ROP in posterior zone II. But the progression of the retinal detachment was still going, so the surgical intervention was considerate to perform. In this study, in seven eyes (100%) the vascular activity regression was occured, which was evident by the disappearance of the neovascular tufts in the detached ridge and recession of plus disease. The retina reattached gradually and the funduscopic findings were stable for several months after the removal of SB. The anatomical outcome was satisfying in all cases. Complete retinal reattachment was achieved in five eyes and residual small peripheral retinal detachments without evidence of traction in two eyes were found at last follow up.[6]

There was no guideline for the right timing of the scleral buckling procedure for retinopathy of prematurity. A retrospective, non-randomized, observational case series by Yokoi et al evaluate 3 patients 23-25-week PMA with ROP stage 4A was reattached completely.[19] Another study by Papageorgiou, determined the efficacy of SB in 5 patient 23-30-week PMA (3 stage 4A and 2 stage 4B), the retina of 5 patients were also reattached.[6] A retrospective study by Beyrau showed that ROP patient stage 4 23-26-week PMA treated with SB were also giving high anatomical success rate.[20] Here, the scleral buckling procedure was performed at 49 and 52 weeks based on the PMA, which was too late compared to other study.

The scleral buckling procedure in this case was effective in slowing the progression of ROP in the right eye over a short-term period, as evidenced by the lack of progression observed in the right eye on the RetCam after 3 months. Unfortunately, due to a more severe condition in the left eye and the timing of the surgery being too late, the left eye showed progression

Study by Chow et al evaluate the refractive changes associated with the scleral buckling surgery, and performed streak retinoscopy before and after the surgery.[21] Here, the subjective refraction examination was performed by observing the patient respond to object and light stimulation, however, the objective refraction examination before and after the management were not performed to evaluate if there was any development of the refraction. Another study by Yokoi et al also determined the early efficacy of scleral buckling by fundus fluorescein angiography (FFA), but unfortunately, the FFA was not also performed in this case.[19] Another modality to evaluate the result of the surgery is VEP and USG.[9] Since the scleral buckling procedure for retinopathy prematurity is uncommon at our center, there are several issues that must be improved for the future surgery. A systematic review is needed regarding surgical strategies consideration in patients with advanced stage ROP.

CONCLUSION

The scleral buckle is a treatment option for advanced retinopathy of prematurity patients with retinal detachment if it is assumed that intraocular surgery presents a greater risk.[22] Here, the patient did not come earlier and the progressivity of the disease is quite far. The progressivity of the left eye for 3 months is still going on. The treatment consideration of ROP is based on the staging of the patients, so it is important to take a careful history taking and complete examination. The right and timely treatment could slower and even stop its progression.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Quimson SK. Retinopathy of Prematurity: Pathogenesis and current treatment options. Neonatal Netw. 2015;34(5):284-7.
2. American Academy of Ophthalmology. Pediatric ophthalmology and strabismus: basic and clinical science course section 6. San Francisco: American Academy of Ophthalmology; 2020.
3. Brown AC, Nwanyanwu K. Retinopathy of prematurity. [Updated 2021 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from the following: https://www.ncbi.nlm.nih.gov/books/NBK562319/

4. Hong EH, Shin YU, Cho H. Retinopathy of prematurity: a review of epidemiology and current treatment strategies. *Clin Exp Pediatr*. 2022;65(3):115-126.
5. Kanski JJ. The clinical ophthalmology 9th edition. New York: Elsevier; 2019.
6. Papageorgiou E, Riri K, Kardaras D, Grivea I, Mataftsi A, Tsironi EE, Androudi S. Scleral buckling surgery for stages 4A and 4B retinopathy of prematurity in critically ill neonates. Int Ophthalmol. 2022 Apr;42(4):1093-1100.
7. Sen P, Bhende P, Maitra P. Surgical outcomes in aggressive retinopathy of prematurity (arop)-related retinal detachments. Indian Journal of Ophthalmology. 2023 Oct 20;71(11):3454–9.
8. Spandau U, Kim SJ. Pediatric vascular disease. Switzerland: Springer Nature; 2019.
9. Faia LJ, Trese MT. Retinopathy of prematurity. In: Ryan SJ, Sadda SR, Hinton DR, Schachat AP, Wilkinson CP, Wiedemann P, et al, editors. Retina (Fifth Edition). :W.B. Saunders; 2013. London: Elsevier Health Sciences.
10. Rishi P, Rishi E, Gupta A, Mathew CS, Shah BJ. Non-drainage scleral buckling with solid silicone elements. Oman J Ophthalmol. 2014 May;7(2):55-60.
11. American Academy of Ophthalmology. Retina and vitreous: basic and clinical science course section 12. San Francisco: American Academy of Ophthalmology; 2020.
12. Edy Siswanto J, Sauer PJ. Retinopathy of prematurity in Indonesia: incidence and risk factors. J Neonatal Perinatal Med. 2017;10(1):85-90.
13. Borțea CI, Stoica F, Boia M, et al. Risk factors associated with retinopathy of prematurity in very and extremely preterm infants. *Medicina (Kaunas)*. 2021;57(5):420.
14. Chandra P, Chawla D, Deorari AK, et al. Screening and Management of Retinopathy of Prematurity. Journal of Neonatology. 2020;34(1-2):63-82. doi:10.1177/0973217920934397.
15. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. Lancet. 2013 Oct 26;382(9902):1445-57.
16. Wu AL, Wu WC. Anti-VEGF for ROP and pediatric retinal diseases. Asia Pac J Ophthalmol (Phila). 2018 May-Jun;7(3):145-151.
17. Kusaka S. Current concepts and techniques of vitrectomy for retinopathy of prematurity. Taiwan J Ophthalmol. 2018 Oct-Dec;8(4):216-221.
18. Suren E, Cetinkaya E, Kalayci M, Özkan SEÖ, Kucuk MF, Erol MK. Endophthalmitis in retinopathy of prematurity after intravitreal aflibercept injection. Case Rep Ophthalmol Med. 2020 Dec 21;2020:8861435.
19. Zhong Y, Yang Y, Yin H, Zhao M, Li X, Liang J, Cheng Y. Evaluation of segmental scleral buckling surgery for stage 4A retinopathy of prematurity in China. Front Med (Lausanne). 2022 Aug 3;9:969861.
20. Bishnoi K, Prasad R, Upadhyay T, Mathurkar S. A Narrative Review on Managing Retinopathy of Prematurity: Insights Into Pathogenesis, Screening, and Treatment Strategies. Cureus. 2024 Mar 14;16(3):e56168.
21. Iwase S, Kaneko H, Fujioka C, Sugimoto K, Kondo M, Takai Y, Kachi S, Terasaki H. A long-term follow-up of patients with retinopathy of prematurity treated with photocoagulation and cryotherapy. Nagoya J Med Sci. 2014 Feb;76(1-2):121-8.
22. Hansen ED, Hartnett ME. A review of treatment for retinopathy of prematurity. Expert Rev Ophthalmol. 2019;14(2):73-87.

CASE REPORT

DIAGNOSTIC CHALLENGES IN RETINOBLASTOMA WITH PANOPHTHALMITIS-LIKE MANIFESTATION: A CASE REPORT

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ABSTRACT

Purpose: *To highlight the importance and challenges of diagnostic examination and modalities to diagnose retinoblastoma with varieties of manifestation such as panophthalmitis-like.*

Case Report: *A 4-year-old boy presented with red and swollen right eye since two days prior to admission. The position of the right eye was hypotrophy with restricted eye movement towards all directions and there was a presence of proptosis with edema, spasm, hyperemia with yellowish crust. Ultrasonography result came with severe anterior-posterior vitreous haziness with calcified mass suggesting an intraocular tumor of the right eye. Orbital CT-scan was performed and suggestive of panophthalmitis with superior palpebra abscess of the right eye. The inflammation was proposed due to prior intraocular surgery of cataract extraction and trabeculectomy that led to progression and worsening of the retinoblastoma, such invasive surgery led to atypical presentation of panopthalmitis-like. Patient initial visit was due to symptoms of leukocoria and squinting, but even though ocular ultrasonography was performed, the patient had failed to be diagnosed with retinoblastoma. Patient had CT scan and was confirmed of an intraocular mass with calcification inside the right eye with some palpebral abscess. MRI was performed to confirm the extension of the mass, which fortunately did not extend outside the eye. The patient then underwent chemo reduction therapy, before finally got enucleation with dermatofat graft surgery. Histologic examination confirmed the diagnosis of retinoblastoma. This case was an example of how sometimes clinical misdiagnosis among retinoblastoma can happen which can be due to inadequate diagnostic examination or atypical presentation. Preventing clinical misdiagnosis of retinoblastoma can improve the treatment and likelihood of survival of patients with retinoblastoma.*

Conclusion: *Clinical misdiagnosis of retinoblastoma can happen without adequate diagnostic tools and prowess which may result in mismanagement and/or delayed treatment leading to poorer prognosis of patient with retinoblastoma.*

Keywords: *Retinoblastoma, panophthalmitis, diagnostic challenges*

INTRODUCTION

Retinoblastoma is the most common primary malignant intraocular tumor in children. It is a life-threating tumor that affects the vision, ocular structure, and life. Retinoblastoma originates from the retina and can affect one or both eyes. It typically occurs in children less than 5 years old, with the average age for diagnosis is 2.5 years if one eye is involved and 1 year when both eyes are involved. Worldwide, it is reported that about 6000 children develop retinoblastoma each year.[1] Current prevalence of retinoblastoma is approximately 1 in 20.000 live births.

Retinoblastoma contributes to 1% of childhood cancer deaths, and up to 5% blindness in children. Retinoblastoma is initiated by a mutation in the RB1 gene (a tumor suppressor gene) with no gender or race predisposition. Mutation can develop by familial/germline or sporadic mutation, which leads to uncontrolled cell growth.

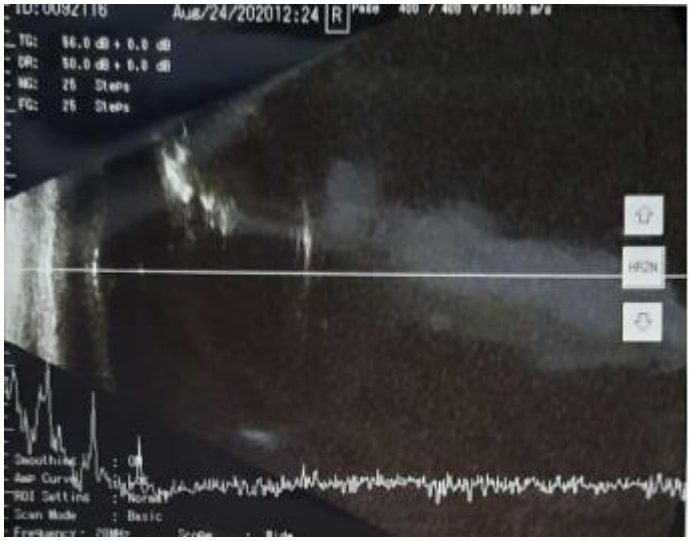
Most common clinical presentation is the presence of leukocoria in children under three years old, which can occur unilaterally (40%) or bilaterally (60%). Second most common sign is squinting/strabismus, which manifests as a constant, unilateral, either esodeviation or exodeviation. In some retinoblastoma cases, diagnosis can be challenging and be mistaken for other condition due to atypical presentation or insufficient diagnostic technique available. Diagnostic challenges therefore may arise from this presentation that may mimic other condition such as infections or benign lesions. Without proper diagnostic tools and prowess, ophthalmologists face the risk of misdiagnosis, delayed, or even mistreatment. Early diagnosis and prompt treatment leads to a better survival rate. In developed countries it is estimated to be around 90%, whilst in developing countries, it can be as low as 40% due to late/misdiagnosed and delayed treatment.[1] The main principles of retinoblastoma management are to save patient's life, preserve the eyeball, and if possible, save vision. The choice of treatment modality will be determined by clinical classification, laterality, age, and visual prognosis. In cases of advanced unilateral intraocular retinoblastoma, enucleation generally is indicated.

This paper reports a case of retinoblastoma with panophthalmitis-like manifestation. The aim of this report is to emphasize the importance of proper diagnosing retinoblastoma by using different examination modalities thus allowing ophthalmologist to diagnose and manage the case properly from the start.

CASE ILUSTRATION

A boy, 4 years old, came to the ER with a chief complaint of his right eye swollen, painful, and red since 2 days before admission. First eye symptoms started about 2 years before admission, when the parent realized that his right eye sometimes squints inward, especially when he is tired. One year later, whitish appearance on his black part of the eye was seen in his right eye but no other complaints such as pain, redness, watery eyes, nor discharges. However, the parents did not go seek any therapy. There was no history of trauma nor spectacles use. Five months afterwards, the patient and his parents went to Aini Hospital and

was diagnosed with congenital cataract and referred to RSAB Harapan Kita Hospital for ocular ultrasound examination. Ultrasound examination revealed a mass inside the vitreous that extends from the anterior to the posterior vitreous, which may indicate persistent hyperplastic



primary vitreous (PHPV) **(Figure 1)**.

Figure 1. **Ultrasonography at the previous hospital.** There appear to be a hyperechoic mass from anteriorposterior vitreous on the B scan, however the vector on the A-scan did not center the mass hence did notcorrelate to any spike. The mass appeared to be a stalk-like mass which made the working diagnosis of PHPV.

The patient was diagnosed with working diagnosis of congenital cataract with PHPV and secondary glaucoma. Patient then underwent cataract extraction and trabeculectomy surgery the following month. During the cataract extraction operation, it was noted that there was a pinkish mass lesion behind the lens capsule, which is thought to be in accordance with PHPV found in the USG. After the operation, the parents notice that the eye contact of his right eye did not improve and there was persistent increasing redness.

Two weeks before admission, patient was then referred to RSCM Kirana for further procedure and was suggested for CT scan that will be done in general anesthesia. Four days before admission the patient complained of headache, especially on the right side and later patient develop mild fever without any cold or cough. Two days before admission, his right eye was getting more swollen, red, and painful. The parents brought the patient to RSAB Harapan Kita Hospital and was diagnosed with acute secondary glaucoma. Patient was given acetazolamide 2 x 250 mg, paracetamol 3 x 5 ml, timolol maleate 0.5% 2x right eye, and then referred to RSCM Hospital Emergency Room due to no improvement.

Remarkable history of toothache, but no other complaints such as ear pain or discharge, urinary pain, seizure, asthma, or allergy. Patient was born with BW of 3000 gr, normal delivery

with spontaneous crying. No history of intensive care/transfusion. Patient had complete immunization, with normal growth and development.

From the ophthalmological status upon arrival, the right eye was proptosis with the position was hypotrophy with restricted eye movement towards all direction. The visual acuity was hard to be evaluated. Intraocular pressure was 33 mmHg. The proptosis of the right eye was toward inferior with edema, spasm, hyperemia with yellowish crust. **(Figure 2)**

Figure 2. Proptosis of the right eye with yellowish crust. On the initial examination, the palpebra was edematous spasm, and hyperaemic resembling panophthalmitis.

There was no palpable mass upon examination. The conjunctiva was chemotic with conjunctival and ciliary injection. **(Figure 3)** Cornea hazy with microcystic edema, at the 12, 9, and 3 o' clock position was 2, 2, 1 nylon sutures respectively with no infiltrates. Staining on the cornea was negative. Anterior chamber was flat, with full coagulum mixed with fibrin. Other part of the right eye was hard to be evaluated. The left eye was within normal limit.

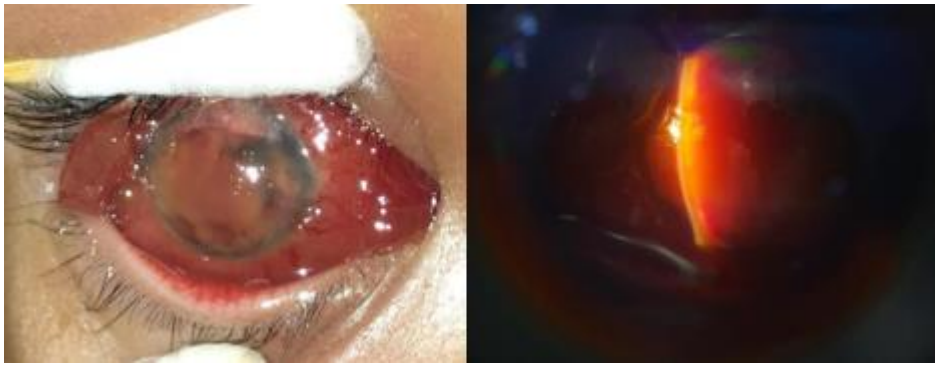


Figure 3. Anterior segment of the right eye. Conjunctiva was chemotic all quadrant with conjunctival and ciliary injection. The cornea was hazy with anterior chamber was flat with full of coagulum and fibrin. Other part of the right eye was hard to be evaluated.

Further examination was done using orbital ultrasonography and CT-scan. Ultrasonography showed severe vitreous haziness with calcified mass suggesting an intraocular tumor of the right eye. **(Figure 4)** From the B-scan, the mass was diffusely located from the anteriorposterior vitreous. Shadowing effect from the mass was also noted. The A-scan revealed the mass to be hyperechoic, in accordance with calcification nature of the mass.

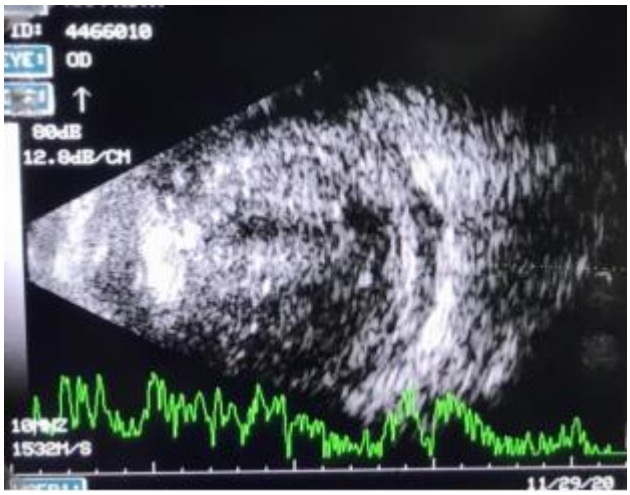


Figure 4. Ultrasonography of the right eye in RSCM Kirana. The B-scan showed diffuse intraocular mass from anterior-posterior vitreous with shadowing effect. A-scan spikes showed hiperechoic profile of the mass. The USG suggestive of hiperechoic intraocular mass suspected of later stage of retinoblastoma.

Orbital CT-scan was performed to evaluate the proptosis and the intraocular condition of the right eye. The result came in as suggestive of panophthalmitis with superior palpebra abscess of the right eye. (Figure 5) MRI with contrast was performed and the result correlate to the CT scan with solid lesion with malignant characteristic with calcific component and intraocular hemorrhage. The lesion extended to the intraconal and extraconal but no intracranial involvement. Lab result showed increased CRP 13.2 mg/L with slight leukocytosis 13.710/ul.

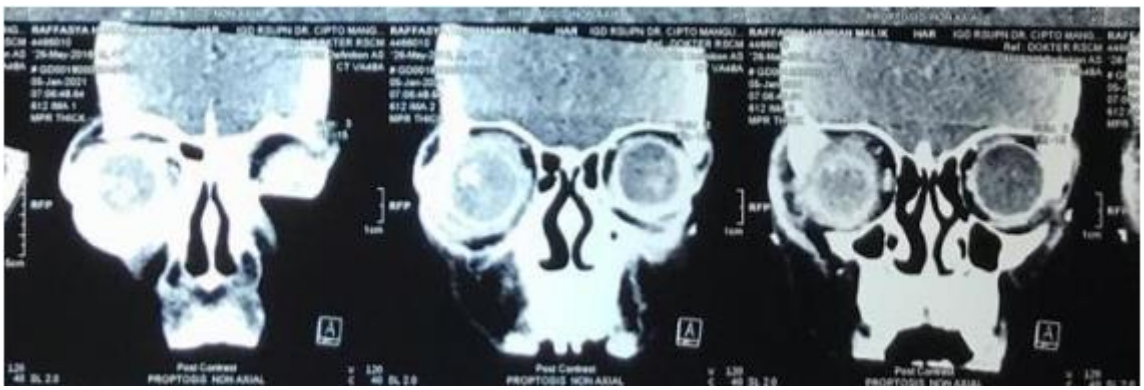


Figure 5. CT scan of the Orbita. Intraocular calcific mass inside the right eye, with abcess in the surrounding palpebra tissue. The mass did not extend outside the globe.

Patient was diagnosed with intraocular tumor of the right eye with suspected retinoblastoma with panophthalmitis-like manifestation and secondary glaucoma due to history of cataract extraction and trabeculectomy of the right eye. Patient was given levofloxacin eye drop hourly, timolol maleate 0.5 2x right eye, acetazolamide 3 x 125 mg p.o, kalium aspartate 1 x 300 mg p.o, paracetamol syrup 3 x 250 mg p.o. From the pediatric department, the patient was given systemic antibiotic of ampicillin-sulbactam 4 x 500 mg IV and planned to perform lumbar puncture and bone marrow puncture.

The result from the bone marrow puncture showed normal cells, no indication of metastasis. The patient was continued with the antibiotic therapy then planned to do chemoreduction for 3 cycles before performing enucleation of the right eye. After the chemoreduction, the right eye swelling has decreased with signs of enophthalmus. **(Figure 6).**

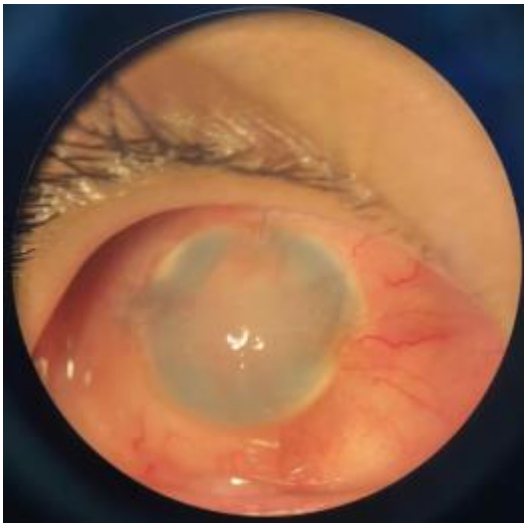


Figure 6 Right eye post chemoreduction. After 3 cycles of chemotherapy, the palpebra and conjunctival edema has decreased. The cornea was edematous with neovascularization. The right globe becomes shrunken.

Enucleation with dermatofat graft was performed. Histologic examination revealed poorly differentiated retinoblastoma tumor mass with no invasion towards anterior segment, choroid, intrasclera, nor ekstrasclera. The patient was then recommended to continue the chemotherapy for 6 cycles. After 3 months, the patient was doing well with no apparent relapse or complication after the surgery.

DISCUSSION

The rate of clinical misdiagnosis has indeed decreased over the decades, owing to the advancement of diagnostic tools. However, in developing countries, patient usually come at an advanced stage with atypical presentation. Atypical cases can simulate Coats' disease, panuveitis, retinal detachment, and persistent hyperplastic primary vitreous (PHPV).[2] In a retrospective analysis by Vahedi and colleagues on children referred for suspicion of retinoblastoma over a period of 7 years, 3 408 out of 486 (74%) cases had unilateral or bilateral retinoblastoma, while 78 (16%) cases had other lesions. These simulating lesions included Coats' disease (25%), congenital malformations (30%; coloboma, PHPV, microphthalmia, isolated or associated with retinal dysplasia), other tumors (13%; astrocytomas and medulloepithelioma), combined hamartomas (8%), inflammatory diseases (8%; Toxocara canis, cat scratch eye or toxoplasma), and other diseases (16%; corneal opacities, congenital cataract or retinal detachment).[3] In a study in India, only 4 out of 280 enucleated eyes (1.4%) over a four-year period were clinically and histopathologically discordant. Granulomatous endophthalmitis, retinal astrocytoma, Coat's disease, and persistent hyperplastic primary vitreous (PHPV) were among the misdiagnosed conditions. Infiltrative retinoblastoma is typically the most difficult to identify, owing to its insidious growth and lack of intraocular calcification.[4]

The most common sign of retinoblastoma is leukocoria. However, several other condition may also present with leukocoria such as Coats disease, persistent fetal vasculature (PFV), ocular toxocariasis, retinopathy of prematurity (ROP), Astrocytic hamartoma, vitreous hemorrhage, coloboma, endogenous endophthalmitis, rhegmatogenous retinal detachment, and many more. This is why leukocoria needs to be diagnosed carefully and thoroughly to differentiate it from these so-called pseudo retinoblastomas. Misdiagnosis can lead to delay and administer of inappropriate treatment.

Retinoblastoma-associated erade syndromes are another issue in some cases of retinoblastoma. Masquerade syndrome is an unusual neoplasm that can imitate an inflammatory illness involving the anterior or posterior segment, or even the extraocular compartment. The patient in this case had signs of panophthalmitis, including proptosis with restricted eye movement and "hot eye" appearances. As a result, the inflammatory process can be known as orbital pseudocellulitis. The inflammation can be generated by intratumoral necrosis, which attracts lymphocytes, or it can be imitated by retinoblastoma cell collections

that mimic iritis, hypopyon, or hyalitis.[5] According to Stafford et al. out of 825, 6.6% of histologically confirmed retinoblastoma cases were misdiagnosed as primary ocular inflammation.[6] Balmer et al.[7] also reported 185 instances with retinoblastoma and found that 14% of them had an unusual presentation, with intraocular or extraocular inflammation.

Most of retinoblastoma cases can be diagnosed when it present intraocularly with typical features such as leukocoria. However, there are a few challenging cases where the clinical manifestation is atypical that can lead to clinical misdiagnosis. Retinoblastoma can mimic any orbital or ocular pathology, especially more advanced stages. Atypical presentations reported includes endophthalmitis/panophthalmitis, secondary glaucoma, uveitis, corneal edema, cataract, iris nodules, hyphema, pseudihypopyon, iris neovascularization, exposure keratopathy.[8] Therefore, ocular tumor should always be considered when an atypical presentation is unresponsive to the usual therapy. It is reported that 7% of cases presented as masquerade syndrome and were initially diagnosed as primary ocular inflammation.[9] Such as orbital cellulitis accounted for 4.8% of retinoblastoma cases in Saudi Arabia and 5.4% of cases in Chennai, India.[10,11]

Diffuse infiltrating retinoblastoma is the most common kind of retinoblastoma that presents with an intraocular inflammatory character. Because there is no identifiable tumor mass and no intralesional calcifications, it can be difficult to spot. As a result, it's critical to distinguish between orbital cellulitis, retinoblastoma-associated orbital pseudocellulitis, and retinoblastoma orbital extension. The majority of children with true orbital cellulitis had a history of sinusitis, fever, and leukocytosis, as well as a normal pupil and fundus. Most individuals with intraocular necrotic retinoblastoma, on the other hand, do not have a fever orsignificant leukocytosis. In our case, the early presentation might not had signs of proptosis and other panophthalmitis-like manifestation, however, it might be due to surgical intervention that causes inflammatory reaction and/or progression of the right eye.

Clinical misdiagnosis is more likely to occur in advanced stages of the disease. In South Asiancountries including India, delayed presentation of retinoblastoma is common, and the majority of patients are diagnosed at a fairly advanced stage when the fundus details are not visible. Owing to improvements in preoperative diagnostic imaging, the rate of misdiagnosis leading to paediatric enucleations has decreased over a period of time. Huang et al reviewed 369 paediatric enucleations over a period of five decades at their centre and reported that the rate of misdiagnosis decreased with each respective decade studied, with the highest rate of

6.5% (18 of 276 eyes) in the 1960s and 0% (no misdiagnosis) from 1990 to 2008.[12] One of the various clinical manifestations of retinoblastoma was secondary glaucoma and cataract.[13] In this case, we can note there was a secondary glaucoma before and after the cataract surgery. Secondary glaucoma in RB was reported to be around 17- to 23% of cases.[14] The clinical presentation of glaucoma in RB can vary as neovascular glaucoma with or without angle closure, pupillary-block glaucoma, or uveitic glaucoma. Shieldet al and Yoshizumi et al noted that the most common mechanisms of secondary glaucoma inRB were iris neovascularization (30–72%), pupillary block (27%), and tumor seeding of the anterior chamber (2%).[15]

Iris neovascularization (NVI) can cause formation of fibrovascular membranes that contract and causes ectropion uvea and form peripheral anterior synechae (PAS), leading to angle-closureglaucoma. The most important factors leading to NVI are ischemia, necrosis, inflammation, and possibly tumor- angiogenesis factor.[15] Vitreous hemorrhage due to NVI may cause the diagnosis of retinoblastoma more difficult. The presence of a large RB with secondary glaucoma and vitreous hemorrhage is predictive of optic-nerve involvement, hence glaucomain RB is arguably an indication for performing an enucleation. Generally, glaucoma in RB is managed medically with aqueous suppressants, but once neovascular glaucoma develops, medical management usually fails, and enucleation is often required. Glaucoma filtration or shunt operations are absolutely contraindicated because of the risk of extraocular spread of viable tumor cells.[14] In this patient, due to the uncertainty of RB diagnosis from the start, the trabeculectomy operation may increase the risk of tumor spreading. Therefore, although glaucoma may be a secondary clinical issue in cases of RB, the presence of high IOP especially with NVI may help clinician to assess the overall poor prognosis and the likely hood of RB neeeding enucleation management.

In order to diagnose retinoblastoma, other than clinical examination, there are few examinationthat help distinguish the disease. Although histology is still the gold standard in evaluation of tumor extension and progression risk factor, a tumor biopsy or surgery carries high risk of dissemination. Therefore, there are main ancillary tests that can be used with retinoblastoma are ocular ultrasonography (USG), computerized tomography (CT), and magnetic resonance imaging (MRI). In cases where the fundus cannot be examined or does not enable diagnosis to be made with certainty, then evaluation can firstly be done through USG. It is an inexpensive and non- invasive examination to assess the mass dimension and also can produce distinctive hyperechoic calcification seen in retinoblastoma. In retinoblastoma cases that present with calcifications, sonography has an 80% accuracy rate.[16] In cases of

retinoblastoma, it is important that USG is correctly aimed at the suspected mass. The tumor can be visualized as a hyperechoic mass with irregular borders. It can be in the form of a widespread lesion or a well-defined confined lesion. Combined B-scan with A-scan can also clearly showed the calcium deposits as highly hyperechoic, which is a pathognomonic characteristic.[17] Any related retinal detachment or choroidal thickening can also be detected with ultrasound imaging. Hyper-reflective particles representing the calcified tumour seeding into the vitreous cavity may be visible in the vitreous surrounding the lesion. In addition, calcification of tissue can absorb and reflect the echo so strong that cause posterior signal to that medium become absent, this is known as shadowing.

Other diagnosis that mimics retinoblastoma with leukocoria and abnormal eye movements should be suspected of retinoblastoma until proven otherwise. Cataracts are localized to the lens, and so should appear uniformly echogenic with the rest of the eye appear normally. In persistent fetal vasculature, The vascularity supplying the fetal eye fails to resorb, becomes hypertrophic, and remains patent. Because the vascularity extends from the lens to the back, the USG should reveal a vascular channel flowing from the optic nerve to the lens, an intact retina, and a posterior chamber free of bulk.[18] In other cases, USG is not recommended as thebest modality to diagnose definitively. Advanced Coats disease and retinoblastoma appear very similar on USG, therefore it requires MRI to show a posterior chamber free from mass but with detached retina and abnormal vasculature.

If the diagnosis was hard to be made based on USG, then the next modality that can be used isto perform CT scan or MRI I. A CT scan is useful in detecting calcification that may have not been identified through ultrasonography, however it can be potentially dangerous with cumulative examinations.[19] CT scans are also avoided because of reports that the radiation induces secondary primary cancers in people carrying RB1 mutations. CT is considered as the best imaging tool for detection of calcification and areas as small as 2 mm can be reliably detected. However, due to the radiation exposure and the superior soft tissue resolution of MRI over CT makes MRI a better modality for differentiating retinoblastoma from other simulating lesions.[20]

The presence of calcification is critical for retinoblastoma diagnosis. In retinoblastoma, calcification properties such as size and configuration can be extremely varied. Calcium deposits can be small or big, single or multiple, punctate, diffuse, or in the form of fine speckled foci. While calcification is seen in over 90% of instances of retinoblastoma, it can also be seen

as a dystrophic process in a range of other ocular disorders, especially if they are chronicand untreated. Calcific foci can appear in retinal astrocytoma and granulomatous endophthalmitis. Unless the eye has experienced persistent degeneration, Coats' disease and PHPV do not normally contain calcium. Conditions like granulomatous endophthalmitis, PHPV, and astrocytic hamartomas can appear as intraocular masses on MRI and show mild tosubstantial elevation following contrast injection, similar to retinoblastoma.[21]

One of the most important poor prognostic factors for the management of RB is the delay in diagnosis.[22] As patients in the developing countries are usually diagnosed in late stages of thedisease, because of the difficulty in getting adequate health care, they present with a more advanced stage and, therefore, have less survival rates. The patients in the developed countries and those who have better socioeconomic status generally present at an earlier stage and get adequate health care leading to a higher survival rate as compared to patients from developing countries.[22]

Management of retinoblastoma is usually individualized and should consider among these factors such as extent of the disease at diagnosis (classification), status of the opposite eye, overall health of the child, and socioeconomic circumstances including access to expert care. Ultimately the most important objective is to help the patient survive, while the second is to preserve the globe. For intraocular retinoblastoma, the primary treatment is chosen on the likelihood of cure (patient survival), eye salvage, final eyesight, the condition of the fellow eye, all of which areevaluated for its short-term and long-term complications of the treatment. primary treatments for intraocular disease include enucleation, intravenous chemotherapy (IVC) with focal therapy(laser therapy, cryotherapy), intra-arterial chemotherapy (IAC) with focal therapy, and focal therapy alone when tumours are small at diagnosis. External beam irradiation (EBRT) is no longer indicated as a first-line treatment for primary intraocular retinoblastoma because it increases the risk of subsequent malignancies, especially in children under the age of one.

Enucleation is a first-line therapy for most eyes with retinoblastoma globally, especially thosewith latter classification. Eyes with clinical symptoms such as neovascular glaucoma, pthisis bulbi (a shrunken, non-functional eye), and anterior disease are not acceptable for conservativetherapy and require enucleation to determine if additional therapy is required for high-risk pathological abnormalities.[23] Older ages, a longer time between diagnosis and enucleation, anterior tumor or blood, scleral invasion, invasion of the post-laminar optic nerve,

and orbital cellulitis were all clinical variables substantially linked to high-risk features.[24] In this patient, there was indeed a marked inflammation post operatively that resemble panophthalmitis, in addition with secondary glaucoma, which render the decision to perform enucleation of his right eye.

Any attempt to save an eye with features indicating a high risk of extraocular extension exposesthe patient to the risk of undetected disease with the potential for metastasis. High-risk traits were seen in 15–33% of Group D eyes and 50–61% of Group E eyes, according to the Murphree et al.[25] Shields et al, found that 24–39% of Group E eyes were at high risk.[36] Enucleation of the high-risk eye signals people in the circle of care that adjuvant chemotherapy to lower the risk of metastatic illness should be considered.[37] Disease-specific survival is significantly worse (p0.001) if enucleation of Group E eyes is delayed longer than 3 months, for example because to preceding systemic chemotherapy, and therefore should not be delayed. However, in some cases where the patient's family require some time to accept the decision or even decline to do enucleation, then chemotherapy may be offered.[28]

In this patient we decided to do 3 cycles of chemoreduction therapy to decrease the pseudo-panophthalmitis inflammation, reduce the proptosis, and prepare for enucleation surgery. It was also critical that in this period that the patient's family are well informed of the management plan. Although, it may be a very sensitive topic, as at first the patient's family expected that the patient just undergone cataract surgery and had secondary inflammation. Fortunately, the patient's family are well cooperative and the chemoreduction therapy went well without major side effect. Chemoreduction is a method of reducing tumor volume to allow for therapeutic measures that are more focused and less damaging.[29] To achieve adequate tumorshrinkage, the chemotherapy regimen is usually given for 6 rounds. After obtaining significanttumor reduction and sub-retinal fluid resolution, focal therapy to the specific tumors is performed at cycle 2. Chemoreduction is used to shrink tumors so that targeted therapies can be delivered to a smaller tumor volume, preserving more vision and potentially avoiding enucleation and external beam radiotherapy. After two cycles of chemoreduction, retinoblastomas had a 35% decrease in tumor base and a nearly 50% decrease in tumor thickness.[30] Subretinal fluid disappeared in 76% of patients, and both vitreous and subretinal seeds disappeared after therapy.[31,32] As a result, it is clear that retinoblastoma is susceptible to existing chemotherapeutic regimens.

CONCLUSION

It is imperative that the diagnosis is made as promptly and accurately to improve the likelihood of survival and reduce morbidity. Misdiagnoses in retinoblastoma can happen due to different differential that ranges from benign to malignant diseases, however, owing to the improved diagnostic techniques the rate has steadily decreased.

This case report hopes to remind ophthalmologist that many ocular conditions in childhood may mimic retinoblastoma with similar initial sign of leukocoria. Leukocoria, or any other unexplained ocular sign in an infant should always, until proved otherwise, invoke the possibility of a malignant tumour and perform all the necessary means for prompt diagnosis including diagnostic tools. In case of diagnostic dilemma, the option of regular follow-up versus prompt enucleation with an informed consent for misdiagnosis has to be considered after exerting proper diagnostic work up.

REFERENCES

1. Dimaras H, Corson TW. Retinoblastoma, the visible CNS tumor: A review. J Neurosci Res. 2019 Jan;97(1):29-44.
2. Sanders TE. Pseudoglioma: a clinico-pathologic study of fifteen cases. Trans Am Ophthalmol Soc 1950;48:575–614.
3. Ilyas S, Yulianti SR. Ilmu penyakit mata. Badan Penerbit Fakultas Kedokteran Universitas Indonesia. 2017.
4. Chawla B, Khurana S, Sen S, et al. Clinical misdiagnosis of retinoblastoma in Indian children. Br J Ophthalmol 2013-304321
5. Shields J. Diagnosis and management of in- traocular tumors. St Louis: Mosby; 1983. pp. 437–533
6. Stafford WR, Yanoff M, Parnell BL. Retinoblastomas initially misdiagnosed as primary ocular inflammations. Arch Ophthalmol. 1969 Dec;82(6):771–3.
7. Balmer A, Gailloud C, Munier F, Lendi B, Uffer S. Manifestations inhabituelles du ré-tinoblastome [Unusual presentation of retinoblastoma]. Klin Monatsbl Augenheilkd. 1994 May;204(5):313–5.
8. Ganesh RN, et al. Panophthalmitis masquerading as retinoblastoma— an eye opener. Comp Clin Pathol (2013) 22:523–527
9. Stafford WR, Yanoff M, Parnell BL. Retino- blastomas initially misdiagnosed as primary ocular inflammations. Arch Ophthalmol. 1969 Dec;82(6):771–3.
10. Mullaney PB, Karcioglu ZA, Huaman AM, al-Mesfer S. Retinoblastoma associated orbital cellulitis. Br J Ophthalmol. 1998 May;82(5): 517–21.
11. Walinjkar J, Krishnakumar S, Gopal L, Ra- mesh A, Khetan V. Retinoblastoma present- ing with orbital cellulitis. J AAPOS. 2013 Jun; 17(3):282–6.
12. Huang S, Rutar T, Bloomer M, Crawford JB. Analysis of clinical misdiagnoses in children treated with enucleation. Arch Ophthalmol. 2010 Aug;128(8):1009-13.
13. Howard GM, Ellsworth RM. Differential diagnosis of retinoblastoma: a statistical survey of 500 children. II. Factors relating to the diagnosis of retinoblastoma. Am J Ophthalmol 1965; 60: 618-621
14. de Leon JM, Walton DS, Latina MA, Mercado GV. Glaucoma in retinoblastoma. Semin Ophthalmol. 2005 Oct-Dec;20(4):217-22.
15. Moazed K, Albert D, Smith TR. Rubeosis iridis in “pseudogliomas.” Surv Ophthalmol 1980; 25: 85-90
16. Silva CT, Brockley CR, Crum A, Mandelstam SA: Pediatric ocular sonography. Semin Ultrasound CT MR.2011;32:14– 27.
17. Aironi VD, Gandage SG. Pictorial essay: B-scan ultrasonography in ocular abnormalities. Indian Journal of Radiology and Imaging. 2009;19(2):109-115
18. de Graaf P, Göricke S, Rodjan F, Galluzzi P, Maeder P, Castelijns JA, et al. Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol. 2012 Jan;42(1):2–14.

19. Smirniotopoulos JG, Bargallo N, Mafee MF. Differential Diagnosis of Leukokoria: Radiologic-Pathologic Correlation. Radiographics 1994; 14:1059–79.
20. McCarthy M, et al. Comfort First: an evaluation of a procedural pain management programme for children with cancer. Psychooncology. 2013; 22:775–782.
21. Smirniotopoulos JG, Bargallo N, Mafee MF. Differential Diagnosis of Leukokoria: Radiologic-Pathologic Correlation. Radiographics 1994; 14:1059–79.
22. S. Canturk, I. Qaddoumi, V. Khetan et al., "Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators," The British Journal of Ophthalmology, vol. 94, no. 11, pp. 1432–1436, 2010
23. Shields CL, et al. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology. 2006; 113:2276–2280
24. Kaliki S, Srinivasan V, Gupta A, Mishra DK, Naik MN. Clinical Features Predictive of High-Risk Retinoblastoma in 403 Asian Indian Patients: A Case-Control Study. Ophthalmology. 2015
25. Murphree AL. Intraocular retinoblastoma: the case for a new group classification. Ophthalmology clinics of North America. 2005; 18:41–53
26. Kim JW. Retinoblastoma: evidence for postenucleation adjuvant chemotherapy. International ophthalmology clinics. 2015; 55:77–96.
27. Zhao J, Dimaras H, Massey C, et al: Pre-enucleation chemotherapy foreyes severely affected by retinoblastoma masks risk of tumor extension andincreases death from metastasis. J Clin Oncol 29:845-851, 2011
28. Mallipatna AC, Sutherland JE, Gallie BL, Chan H, Heon E. Management and outcome of unilateral retinoblastoma. J AAPOS. 2009; 13:546–550
29. Orbital Dermis-Fat Graft Transplantation: Results in Primary and Secondary Implantation Turk J Ophthalmol 2015; 45: 65-70
30. Shields CL, Shields JA. Editorial: chemotherapy for retinoblastoma. Med Pediatr Oncol. 2002;38:377-378.
31. Shields CL, De Potter P, Himelstein BP, et al. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthal- mol. 1996;114:1330-1338.
32. Shields CL, Shields JA, De Potter P, et al. The effect of chemoreduction on retinoblastoma-induced retinal detachment. J Pediatr Oph- thalmol Strabismus. 1997;34:165-169.

CASE REPORT

ISOLATED UNILATERAL PTOSIS DUE TO JUVENILE OCULAR MYASTHENIA GRAVIS, CASE REPORT

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ABSTRACT

Introduction: *Ocular myasthenia gravis in children is an uncommon autoimmune condition impacting the neuromuscular junction. Typical manifestations include weakness in the levator palpebrae, orbicularis oculi, or extraocular muscles, leading to symptoms such as ptosis and binocular diplopia.*

Case Report: *a 5-year-old girl was brought in with the primary concern of her right eyelid drooping for the last 11 days. The weakness of the eyelid is more pronounced during daytime and nighttime but improves upon waking up in the morning. The patient did not experience difficulties in speaking, swallowing, or breathing. There was no extremity weakness. Ophthalmologic examination reveals orthophoric eye position without restriction of eye movement. The patient exhibited drooping of the right eyelid. Repetitive Nerve Stimulation (RNS) confirmed the presence of a lesion at the neuromuscular junction. Consequently, the diagnosis was made of myasthenia gravis causing the right eye ptosis. Seven months after beginning treatment with oral pyridostigmine, there was a noticeable improvement in the patient's condition during a follow-up examination.*

Discussion: *Juvenile ocular myasthenia gravis, can present with isolated unilateral ptosis. Diagnosis of mechanical/congenital ptosis, external ophthalmoplegia, and Horner syndrome has ptosis as a manifestation was ruled out.*

Conclusion: *The diagnosis and initial management of juvenile ocular myasthenia gravis play a crucial role in preventing disease progression. First-line therapy with oral pyridostigmine is safe and effective. The prognosis for ocular myasthenia gravis in prepubertal patients is generally favorable.*

Keywords: *Ptosis, ocular, myasthenia gravis, juvenile, case report*

INTRODUCTION

Myasthenia gravis (MG) is an uncommon, long-lasting autoimmune disorder characterized by the attack of certain antibodies on the acetylcholine receptor (AChR) located at the post-synaptic membrane of the neuromuscular junction.[1,2,3] The occurrence rate stands at 3 to 9.1 incidents per million children annually, with only 10 to 15% exhibiting involvement of the eyes.[4] The typical age at which symptoms begin is 6 years old. [5] When Myasthenia Gravis appears in individuals younger than 18 years, it is referred to as Juvenile Myasthenia Gravis (JMG).[6]

Typical features of ocular myasthenia gravis include weakness in the extraocular muscles, levator palpebrae, and orbicularis oculi muscles. Ptosis is often the first sign observed.[4,7] Myasthenia gravis is characterized by variability and exhaustion. The weakness changes not only with each day but also from one hour to the next, generally becoming more pronounced towards the evening.[8] In any child presenting with ptosis and/or double vision, myasthenia gravis should be suspected. The diagnostic procedures for this condition encompass repetitive nerve stimulation (RNS), measuring serum levels of acetylcholine receptor antibodies, the Prostigmin test, the ice pack test, and the fatigue test.[9, 10] The objectives of reporting this case is to provide an overview of myasthenia gravis and its clinical manifestations in children, where its incidence is considered rare.

CASE DESCRIPTION

A 5-year-old girl presents with chief complaints of right upper eyelid ptosis. Symptoms have progressed over the past 11 days and fluctuated and this may be marked towards the evening and night whereas it disappears the next morning after resting at night. The patient did not exhibit weakness in the upper or lower extremities, nor did they have slurred speech, hoarseness, or a history of head or facial trauma. There were no additional complaints, and no family history relevant to the illness. Physical examination revealed the right eyelid had more ptosis than the left. The margin reflex distance 1 (MRD 1) measurement was 0 mm for the right eye and 5 mm for the left eye, with normal values ranging between 4 to 5 mm.

At first admission, the child came into the pediatric ophthalmology and neuro-ophthalmology department because of her eye complaint. On examination eye position was orthophoria. The patient's Best Corrected Visual Acuity (BCVA) measured 6/7.5 for the right eye and 6/6 for the left. They underwent both a fatigue test and an ice pack test on the eyelid, both of which yielded positive results. Following the fatigue test, the patient's right eye Margin Reflex Distance 1 (MRD 1) deteriorated to -2 mm. Conversely, after the ice pack test, the right eye's MRD 1 showed improvement, reaching 2 mm as depicted in Figure 1. Examination of the conjunctiva, cornea, anterior chamber, iris, pupil, lens, vitreous, intraocular pressure, and funduscopic aspects all presented as normal. No signs of ophthalmoplegia were found in the extraocular muscle test (as shown in Figure 2). Initially, the child was diagnosed with right eye ptosis suspected ocular myasthenia gravis, and thus referred to the pediatric neurology department for further examination and management.

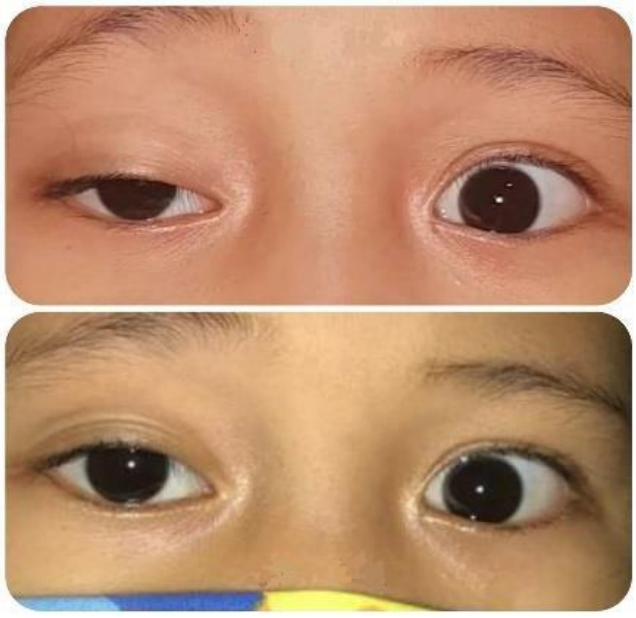

Figure 1. Ptosis in the right upper eyelid reduced after the ice pack test

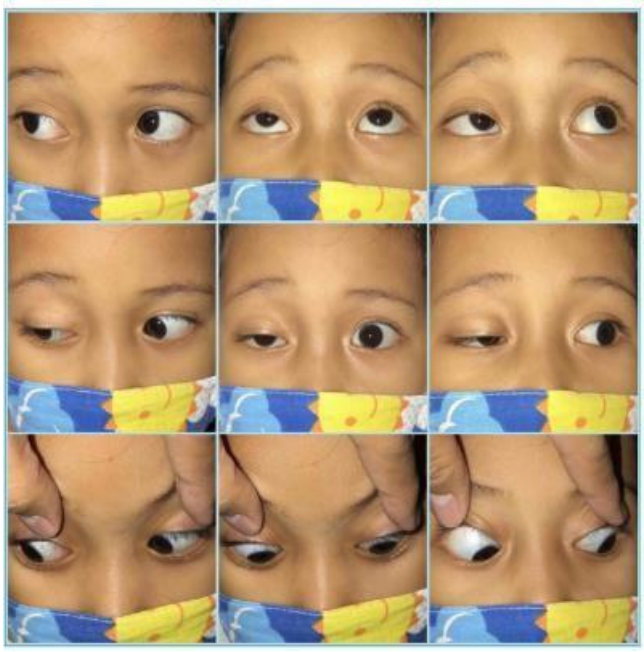

Figure 2. Nine gaze examination. Eye movement good in all directions

Head CT-Scan result was within normal limits. There were no extraocular muscle lesions or intra/extra conal mass bilaterally. Bleeding, infection, infarct, and SOL signs were not found in intracerebral and intracerebellar. An electromyography study that included Repetitive Nerve Stimulation (RNS) testing was conducted on a patient, focusing on the right orbicularis oculi and the right abductor digiti minimi muscles. The decrement test showed no significant change in the right abductor digiti minimi muscle but indicated a significant 48.1% decrement in the right orbicularis oculi muscle. These results led to the confirmation of a

neuromuscular junction disorder, specifically diagnosing the patient with myasthenia gravis. The diagnosis was supported by clinical history, physical examination, and the results from the diagnostic tests, identifying the patient's condition as Unilateral Ptosis caused by Juvenile Ocular Myasthenia Gravis.

The patient was initially treated with oral acetylcholinesterase inhibitors, Pyridostigmine bromide, at a dosage of 23 mg every 6 hours, totaling 90 mg per day (6 mg/kg/day). Throughout regular check-ups, the patient exhibited improvements and a positive response to the treatment, with a notable reduction in ptosis (as depicted in Figure 3). After seven months of ongoing treatment, there was a noticeable improvement in the right upper eyelid's MRD of 1 to 4 mm and an interpalpebral fissure of 9 mm (within the normal range of 9 - 10 mm). It is important for the patient to continue with regular check-ups to manage the medication effectively and monitor for any signs of recurrence of the disease.

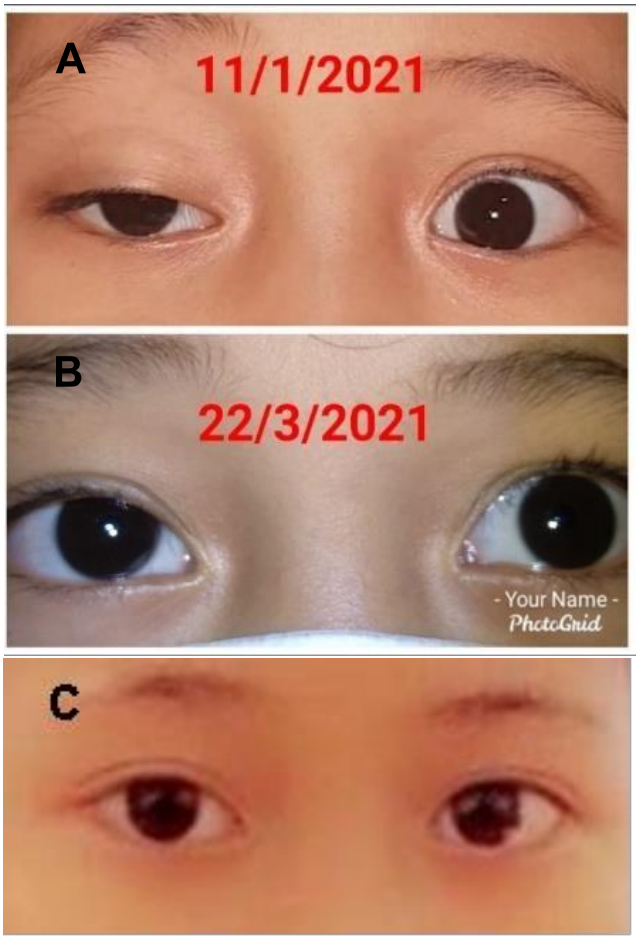

Figure 3. (A) Before treatment, (B) After 2 months of treatment, (C) After 7 months of treatment

DISCUSSION

Myasthenia gravis is a long-lasting autoimmune disorder where antibodies target the acetylcholine receptor at the neuromuscular junction on the post-synaptic side. This causes dysfunction of skeletal muscle. Typical signs and symptoms include skeletal muscle fatigue and fluctuating weakness. Onset generally occurs in adults but can also occur in children.

Pediatric myasthenia gravis is a general term in which myasthenia gravis attacks patients under 18 years of age.[6] Pediatric myasthenia gravis is divided into neonatal, congenital, and juvenile. Neonatal myasthenia is a temporary condition in babies that occurs due to the transfer of antibodies from a mother who is positive for myasthenia. Congenital myasthenic syndrome (CMS) in children generally occurs from birth. CMS results from disruptions in the signal transmission at the neuromuscular junction, whereas juvenile myasthenia occurs when antibodies are produced that target receptors on the post-synaptic side of the neuromuscular junction. The juvenile type is the most common form in pre–pubertal age (< 12 years old). It did not have a familial pattern and had the characteristics of an autoimmune mechanism.[11,12] Based on the location where clinical manifestations existed, there are ocular and generalized myasthenia gravis. In the ocular type, myasthenia muscle weakness is only limited to extraocular muscles and other eye-surrounding muscles with no other systemic manifestations. Children with ocular myasthenia gravis have a low rate of transition into a generalized type of the disease.[13,14,15] Typical signs and symptoms in ocular type myasthenia gravis include ptosis, diplopia, ophthalmoplegia, and orbicularis weakness.[8] In ocular myasthenia gravis (OMG) extraocular muscles are often affected because they have faster tone and higher synaptic frequency. compared to striated muscles in the extremities.[6]

The exact cause of myasthenia gravis isn't fully comprehended at present. It's believed that the disease arises from a mix of environmental elements, like infections, and genetic components, specifically the human leukocyte antigen (HLA). The presence of this antigen increases the incidence of myasthenia gravis especially in children who are seropositive to the acetylcholine receptor.[16]

This case study describes a 5-year-old female patient who exhibits unilateral ptosis, or a drooping eyelid, affecting her right eye. The severity of the ptosis can be assessed by measuring the gap between the upper and lower eyelids, as well as the margin-reflex distance (MRD). MRD 1 refers to the measurement from the upper eyelid margin to the corneal light reflex when the eye is looking straight ahead. Ptosis can result from numerous conditions, making it crucial

to differentiate between ptosis caused by myasthenia and other types.

The patient, in this case, reports has normal globe size and no strabismus or ophthalmoplegia signs observed during the examination. Mechanical ptosis due to tumors in the eyelid can be excluded. In this case, congenital ptosis due to levator muscle abnormalities, such as muscle fibrosis, was ruled out because the issue with ptosis appeared just days before the pediatric ophthalmology consultation and eyelid creases were noticeable. Conditions like myogenic ptosis, which includes diseases like myasthenia gravis and chronic progressive external ophthalmoplegia, neurogenic ptosis, such as Horner syndrome, and botulism are systemic acquired disorders that could cause ptosis. However, the patient retained good limb muscle strength and exhibited no speech impediments or swallowing difficulties, thus eliminating the possibility of chronic progressive external ophthalmoplegia and botulism. Additionally, the patient's pupil reflexes were normal, and the iris colors were identical, which contradicts the symptoms of Horner syndrome. Consequently, after conducting a thorough physical examination and various diagnostic tests, the final diagnosis for the patient's unilateral ptosis was juvenile ocular myasthenia gravis.

Specific ophthalmology examination in ocular myasthenia gravis includes ice pack test, fatigue test, cogan lid twitch, and Prostigmin test. The ice pack test is considered positive if there's at least a 2 mm decrease in drooping of the eyelid (ptosis) after placing an ice pack on the impacted eyelid for two minutes. In this particular case, the ice pack test returned a positive result. The test demonstrates a specificity of 88% and a sensitivity of 96%. Meanwhile, the fatigue test involves instructing the patient to gaze upwards at the examiner's hand for a duration of 1 to 2 minutes without blinking. In this patient, there is fatigue in the right upper eyelid after looking upwards for a determined time.[9, 17].

To diagnose myasthenia gravis, several diagnostic procedures are used, such as repetitive nerve stimulation (RNS)/single-fiber electromyography (SFEMG), and testing for serum acetylcholine receptor antibodies. The Repetitive Nerve Stimulation test boasts a specificity of 100% and a sensitivity rate of 82%. Repetitive Nerve Stimulation (RNS) examination of the orbicularis oculi and abductor digiti minimi muscles yielded positive results for neuromuscular junction lesions. The Acetylcholine receptor (AChR) antibody test shows a sensitivity of 41% in patients with ocular myasthenia gravis, and a negative outcome doesn't automatically rule out a diagnosis of myasthenia gravis.[9, 10] Given the medical history, physical examination, and diagnostic tests conducted, a diagnosis of ocular type Juvenile myasthenia gravis (characterized by unilateral ptosis due to myasthenia gravis) can be established.

Management for myasthenia gravis aims to reduce the symptoms and severity of the disease so that it does not develop into a generalized type. Appropriate therapy in early-onset produces the best clinical response. The administration of pyridostigmine as an acetylcholinesterase inhibitor is the first-line therapy. Acetylcholinesterase inhibitors prevent the breakdown of acetylcholine by acetylcholinesterase at the neuromuscular junction. This prolongs the action of acetylcholine, leading to a variable improvement in muscle strength. The starting dose of pyridostigmine for children ranges from 0.5-1 mg per kilogram of body weight per day, divided into 3–4 doses. The dose can be increased to up to 1.5 mg/kg body weight, taken 5 times a day, with a maximum dose of 450 mg/day. Side effects from acetylcholinesterase inhibitors can include nausea, diarrhea, stomach cramps, slow heart rate, and increased saliva and respiratory tract secretions.

If there is no good response to the therapy, acetylcholinesterase inhibitors can be combined with immunosuppressive agents such as prednisone. Remission occurs in 65 – 75% of pediatric cases.[12, 18]

This patient was treated with pyridostigmine oral bromide 6 mg/kgbw/day (90 mg/day, 23 mg every 6 hours) and vitamin B Complex 1x/day and started to show gradual improvement of ptosis in the right eye.

Other treatment modalities include cyclosporine, azathioprine, rituximab, intravenous immunoglobulin, plasma exchange, and thymectomy. Complications of myasthenia gravis are myasthenic crisis and cholinergic crisis.[12, 18]

The long-term prognosis of juvenile myasthenia gravis with appropriate early diagnosis and effective therapy is good. Pediatric patients with myasthenia gravis have a higher rate of remission (both with treatment and spontaneous remission) than adults. There are 50–60% of cases with ocular symptoms will develop general weakness in 2 years or more so adequate management is needed in addition to paying attention to factors that can aggravate the degree of illness. Routine treatment will reduce diplopia complications and improve quality of life.[19, 20]

CONCLUSION

Juvenile myasthenia gravis constitutes an uncommon autoimmune disorder in young individuals, with cases of eyelid drooping possibly leading to its differentiation from ocular myasthenia gravis. To confirm the diagnosis, clinical assessments including tests for eye movement, exhaustion, application of an ice pack, and pharmacological evaluations are crucial, alongside Repetitive Nerve Stimulation (RNS) or testing for antibodies against acetylcholine

receptors. In this case, after the patient was given pyridostigmine therapy, clinical improvement began to appear after 1 month of treatment and continued to improve thereafter. Long-term monitoring and management are important to reduce the risk of recurrence and progression to generalized myasthenia gravis. The characteristics and management of myasthenia gravis in children are similar to adult patients. although there are some differences in clinical signs and response to therapy. The prognosis for ocular myasthenia gravis in children is generally better than in adult patients.

REFERENCES

1. Castro D, Derisavifard S, Anderson M, et al. Juvenile myasthenia gravis: a twenty-year experience. J ClinNeuromuscul Dis. 2013; 14: 95–102
2. Gilhus NE. Myasthenia Gravis. N Engl J Med. 2016 Dec 29;375(26):2570-2581.
3. Nair AG, Patil-Chhablani P, Venkatramani DV, Gandhi RA. Ocular myasthenia gravis: a review. Indian J Ophthalmol. 2014 Oct;62(10):985-91
4. Solano A, Jimeno V, Montoya L, Espinosa N. Pediatric ocular myasthenia gravis: Case report and literature review. Pan Am J Ophthalmol 2019;1:16.
5. Huang X, Li Y, Feng H, Chen P, and Liu W (2018) Clinical Characteristics of Juvenile Myasthenia Gravis in Southern China. Front. Neurol. 9:77.
6. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. J Clin Med. 2021 May 21;10(11):2235
7. Vázquez-Roque FJ, Hernández-Oliver MO, Medrano Plana Y, Castillo Vitlloch A, Fuentes Herrera L, Rivero-Valerón D. Resultados del tratamiento quirúrgico en la miastenia gravis juvenil. Neurología. 2017;32:137–142.
8. Jeong A, Min JH, Kang YK, Kim J, Choi M, et al. (2018) Factors associated with quality of life of people with Myasthenia Gravis. PLOS ONE 13(11): e0206754. https://doi.org/10.1371/journal.pone.0206754
9. Evoli A and Iorio R (2020) Controversies in Ocular Myasthenia Gravis. Front. Neurol. 11:605902.
10. Bou Ali, Hanna Salort-Campana, Emmanuelle Grapperon, Aude-Marie Gallard, Julien Franques, Jérome Sevy, Amandine Delmont, Emilien Verschueren, Annie Pouget, Jean Attarian, Shahram. (2016). New strategy for improving the diagnostic sensitivity of Repetitive Nerve Stimulation in myasthenia gravis: RNS in MG. Muscle Nerve. 55. 10.1002/mus.25374
11. Bardhan M, Dogra H, Samanta D. Neonatal Myasthenia Gravis. [Updated 2023 Jan 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan
12. O'Connell K, Ramdas S and Palace J (2020) Management of Juvenile Myasthenia Gravis. Front. Neurol. 11:743. doi: 10.3389/fneur.2020.00743.
13. American Academy of Ophthalmology. Pediatric Ophthalmology and Strabismus. Section 6 San Fransisco: AAO; 2022-2023. p. 152-153
14. Vanikieti K, Lowwongngam K, Padungkiatsagul T, Visudtibhan A, Poonyathalang A. Juvenile Ocular Myasthenia Gravis: Presentation and Outcome of a Large Cohort. Pediatr Neurol. 2018 Oct;87:36-41.
15. Li W, He L, Jin X, Li L, Sun C, Wang C. Isolated dysarthria as the sole manifestation of myasthenia gravis: a case report. J Int Med Res. 2022 Jul;50(8):3000605221109395.
16. Xuelin Feng, Wenhui Li, Jie Song, Xiaoni Liu, Yuehua Gu, Chong Yan, Hui Wu, Jianying Xi, Shuizhen Zhou, Chongbo Zhao, HLA typing using next-generation sequencing for Chinese juvenile- and adult-onset myasthenia gravis patients, Journal of Clinical Neuroscience, Volume 59, 2019, Pages 179-184, ISSN 0967-5868
17. Natarajan, Byju Saifudheen, Kondanath Gafoor, V Jose, James. (2016). Accuracy of the ice test in the diagnosis of myasthenic ptosis. Neurology India. 64. 1169. 10.4103/0028–3886.193780.
18. Mehndiratta MM, Pandey S, Kuntzer T. Acetylcholinesterase inhibitor treatment for myasthenia gravis.Cochrane Database of Systematic Reviews. 2014, Issue 10. Art. No.: CD006986. DOI: 10.1002/14651858.CD006986.pub3
19. Suzuki SM, Hiroyuki I, Tomihiro N, Yuriko M, Masayuki T, Emiko K, et al. (2014). Quality of life in purely ocular myasthenia in Japan. BMC neurology. 14. 142. 10.1186/1471–2377–14–142.
20. Mishra S. Juvenile Myasthenia Gravis: A Short Review. Prog Asp in Pediatric & Neonat (1)-2018. PAPN. MS. ID. 000127

CASE REPORT

OCULAR GNATHOSTOMIASIS IN A FARMER FROM SOUTH SULAWESI, INDONESIA

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ABSTRACT

Introduction: *Ocular Gnathostomiasis is a rare parasitic infection caused by the third-stage larvae of the spiruroid nematode. Gnathostome species are mostly seen in tropical and subtropical areas. It is a food-borne zoonosis caused by the consumption of raw or undercooked freshwater of fish, amphibians, reptiles, birds, and mammals, all of which are known to harbor the larval stages of Gnathostome species.*

Case Report: *A 37-year-old farmer complained of seeing moving objects in his left eye accompanied by blurred vision. At the previous visit, the patient had a history of red left eye with increased intraocular pressure, a visual acuity (VA) of 20/30 with the best corrected visual acuity (BCVA) of 20/20 and normal intraocular pressure. Slit lamp examination showed slight hyperemia of the conjunctiva and a live worm moving in the anterior chamber (AC). The worm was immediately removed using corneal clear incision and sent for parasitological examination.*

Discussion: *Ocular Gnathostomiasis was found at the eye of a man from Siwa, South Sulawesi with complaints of recurrent redness of the eyes accompanied by increased intraocular pressure and a history of living in an area with a habit of eating raw freshwater fish should be considered the possibility of harboring helminth in the eye. The worm was immediately removed using corneal clear incision and post operative was treated with Albendazole 400 mg daily for 21 days and Prednisolone 50 mg*

Conclusion: *Patients with complaints of recurrent eye redness increased intraocular pressure, and a history of living in an area with a habit of eating raw freshwater fish should be considered the possibility of harboring helminth in the eye especially Gnathostome.*

Keywords: *Gnathostomiasis, human, ocular, Indonesia*

INTRODUCTION

Human Gnathostomiasis, a food- borne zoonosis, is caused by the third- stage larvae of Gnathostome spp. Human Gnathostomiasis can occur through three modes of transmission: oral, transplacental, and skin wounds.[1,2,3] Gnathostome has thirteen species, but only six species can cause disease in humans. Gnathostome was first described by Richard Owen in 1836 in the stomach of a young tiger that died at the London Zoo.[1,2] Gnathostome nematodes require two intermediate hosts and one definitive host to complete their life cycles.[3,4]

The most mode of transmission in humans is through oral by eating raw or undercooked meat of definitive hosts (cats, dogs), intermediate hosts (freshwater fish, snails, frogs, chickens), paratenic hosts (birds) containing third- stage larvae, or by drinking water contaminated by infected copepods.[3]

Infection in humans can be found in the skin (migratory panniculitis), central nervous system (meningitis, encephalitis), respiratory system (bronchitis, pleuritis), genitourinary tract, digestive tract, and in the eyes. Ocular gnathostomiasis is rare but have been reported and involves the eyelids, conjunctiva, cornea, anterior chamber, vitreous cavity, and retina.[4,5]

Clinically, Gnathostome infection is suspected if there is a history of intermittent skin swelling or subcutaneous movement object (localized or non-localized) with or without peripheral blood eosinophilia (>0.4x 109 L), or 2) there is an increase of eosinophils without a clear cause.[6]

Here, we report the first case of Ocular Gnathostomiasis in a farmer from South Sulawesi, Indonesia.

CASE ILUSTRATION

In June 2022, a 37-year-old man was referred from the regional hospital in Siwa to the local eye clinic in Makassar because due to the feeling of a moving object in his left eye. Five months earlier, in January 2022, the patient came with complaints of a red left eye which was then treated with topical antibiotics and steroids. Three months later, in April 2022, the patient returned with the same complaint. Slit lamp examination at that time showed hyperemic conjunctiva with increased intraocular pressure of 25 mm Hg which was later concluded as anterior uveitis and secondary glaucoma. Topical antibiotics and steroids are still being continued plus glaucoma eye drops.

The patient had no history of skin injuries or eye surgery, and in the last 1 year, there was no history of local or systemic disorders. He lives and works as a farmer in Wajo where the people generally have ponds to raise fish to eat or sell. The people there have a habit of eating raw freshwater fish mixed with lemon.

From the ophthalmological examination, VA in the left eye was 20/30 and with BCVA 20/20, intraocular pressure was 11 mmHg as measured by non-contact tonometry. A slit lamp examination showed eyelid edema, conjunctival hyperemia, and a live worm swimming in the anterior chamber of the left eye (Figure 1). Funduscopic examination showed a normal posterior segment in both eyes, as well as the results of routine blood tests within normal limits. There was no abnormalities in the right eye.

The worm was removed by corneal clear incision and the patient was given topical steroids and antibiotics. The parasite was immersed in a physiological saline solution and arrived 40 minutes later at the Laboratory of Parasitology, Faculty of Medicine, Hasanuddin University. Worms and liquid were poured into a petri dish with a grid with a guard width of 0.5 mm. With

the OptiLab microscope camera using a 4x magnification lens, it can be seen that the parasite consists of two parts, the head and body, with an overall length of 9 mm and 3 mm in width. The parasite moves by pushing the rounded head out of the neck and then the neck forward to reverse the head so that the movement is like a shortening and lengthening movement. The head is round and covered by 4 rows of transverse cuticle spines so it looks like is wearing a turban and the alimentary canal extends from proximal to distal. Due to problems during the fixation and staining processes, the internal structure of the parasite cannot be properly observed. By finding four rows of hooks on the head and fine spines covering the body, the worm was identified as a stage 3 larva of gnathostome sp. (Figure 2).

The patient was treated with Albendazole 400 mg daily for 21 days and Prednisolone 50 mg for 7 days tapering the dose off 10 mg every week for three weeks. The patient was treated with Albendazole 400 mg daily for 21 days and Prednisolone 50 mg for 7 days tapering the dose off 10 mg weekly for three weeks. No abnormalities were found in the eye when the patient came two months later.

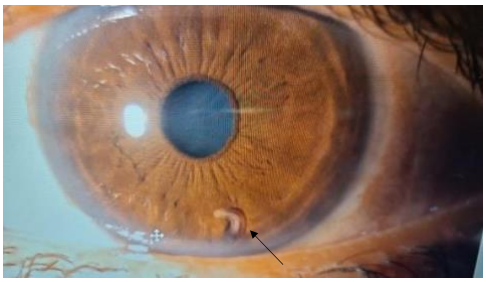

Figure 1. A slit lamp examination showed a live worm (arrow) in the anterior chamber.

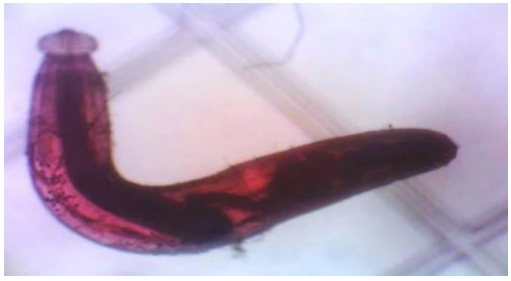

Figure 2. Gnathostome 3 larval stage with 4 rows of cuticle spines that resemble heads likewearing a turban

DISCUSSION

Carnivorous and omnivorous animals are Gnathostome's definitive host where the adult parasites live in tumor- like masses on the wall of the stomach, esophagus, or kidneys. Adult worms produce eggs after copulation and are excreted with feces. If eggs fall into the water, the eggs become embryos and hatch into the first-stage larvae (L1) which will then enter

the body of the freshwater copepods which acts as the first intermediate host. Fish or other animals that ingest the copepods become second intermediate hosts whereas the larvae develops into the second-stage larvae (L2) and the third-stage larvae (L3). When the second intermediate host is ingested by the definitive host, L3 develops into the adult parasite on the gastric wall. Alternatively, the second intermediate host may be ingested by the paratenic host, in which case L3 does not develop further but remains infective.[3]

Humans act as accidental and dead-end hosts for Gnathostome. After ingestion of third-stage larvae in raw or inadequately cooked meat, raw freshwater fish, or other intermediate hosts.[3,4,5,6]

The larvae will enter the gastrointestinal wall and migrate to the skin through subcutaneous tissue, and penetrate other tissues including eyes, ears, breasts, lungs, gastrointestinal tract, thoracic spinal cord, and genitourinary system. Larvae cannot mature into adult forms in humans but wander around and cause various clinical disorders due to inflammatory reactions triggered by larval migration.[3,7,8]

Ocular gnathostomiasis is rare. The most frequent manifestation of intraocular Gnathostomiasis is anterior uveitis because the worms are mostly localized in the anterior segment of the eye. Other symptoms are eyelid edema, conjunctival chemosis, hyphemia, retinochoroidal and vitreous hemorrhage. Central retinal artery occlusion has also been reported.[9,10] In this case, the clinical manifestations we found was recurrent conjunctival hyperemia, increase intraocular pressure, and a live worm in the anterior chamber of the left eye. We did not found eosinophilia which is the hallmark of parasitic infections. The absent of eosinophilia is probably because the avascularity of the anterior chamber.[8]

While there is no effective non- invasive treatment for human gnathostomiasis, surgical removal of the larvae is considered the most effective treatment for this disease. The drug of choice for human gnathostomiasis is Albendazole 400 mg twice daily for 21 days, which has a cure rate of over 90%. Ivermectin has been reported to have similar therapeutic efficacy to albendazole and is effective either at 0.2 mg/kg as a single dose or 0.1 mg/kg given on 2 consecutive days. Corticosteroids can be given alone (Prednisolone, 60 mg/day for 7 days), and cause the larvae to migrate and then die naturally in larvae that may still be in other places that are not visible.[2,3] In this case, the patient was treated with Albendazole 400 mg daily for 21 days and Prednisolone 50 mg for 7 days tapering the dose off 10 mg weekly for three weeks.

CONCLUSION

Patients with complaints of recurrent eye redness increased intraocular pressure, live worm moving in the anterior chamber and a history of living in an area with a habit of eating raw freshwater fish should be considered the possibility of harboring helminth in the eye especially Gnathostome. Surgical removal of the larvae is considered the most effective treatment for this patient. No abnormalities were found in the eye when the patient came two months later.

Based on the history taking, ophthalmologic examination, and parasitological result, the diagnosis was Ocular Gnathostomiasis which is the first case in South Sulawesi, Indonesia.

REFERENCES

1. Prakhunhungsit, Supalert, et al. Subretinal gnathostomiasis: a successful focal laser photocoagulation for a living parasite. American Journal of Ophthalmology Case Reports. 2021.
2. Francisco Bravo, Bernardo Gontijo. Gnathostomiasis: An emerging infectious diseaserelevant to all dermatologists. 2018
3. Guo-Hua Liu et al. Human gnathostomiasis: A neglected food-borne zoonosis. 2020.
4. Agarwal, Mamta et al. Ocular gnathostomiasis presenting as branch retinal artery occlusion.Ocular Immunology and Inflammation. 2020.
5. Biswas J, Gopal L, Sharma T, Badrinath SS. Intraocular gnathostome spinigerum, clinico-pathological study of two cases with review of literature. Retina. 1994.
6. David A.J. Moore, Janice McCroddan, Paron Dekumyoy, and Peter L. Chiodini. Gnathostomiasis: an emerging imported disease. 2003.
7. Preeti Rawat, Manushree Gautam, Nikhila C Jain, Rajdeep Jain. Intraocular gnathostomiasis:a rare case report from Central India. 2006.
8. Padhi, Tapas Ranjan et al. Ocular parasitoses: a comprehensive Review. Survey Of Opthalmology. 2017
9. Gopal S. Pillai, Anil K, Shamsul K. Intraocular gnathostomiasis: report of a case and reviewof literature. The American Society of Tropical Medicine and Hygiene. 2012.
10. Nawa Y, Katchanov J, Yoshikawa M, Rojekittikhun W, Dekumyoy P, Kusolusuk T, Wattanakulpanich D. Ocular gnathostomiasis: a

CASE REPORT

TREATMENT STRATEGIES OF AN IRIS IMPLANTATION CYST: A CASE REPORT

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ABSTRACT

Introduction: *Iris cyst can be divided into primary and secondary, both originating from epithelial cells. Although rare, the entity has a high recurrence rate. This clinical case report highlights the treatment strategies to treat and prevent the recurrency of iris cyst.*

Case Report*: We report a rare presentation of a secondary iris cyst in a 20-year-old male with a history of cataract surgery 17 years prior. The patient underwent fine-needle aspiration and intracystic alcohol injection. However, the iris cyst recurred eight months after the procedure. Afterward, the invasive strategy of iris cyst excision was conducted. Eight months after the secondary iris cyst surgery, the patient showed no signs of recurrence.*

Discussion*: Iris cyst is known to have a high recurrence rate, however, a minimally invasive treatment is still preferred, supported by previous studies showing no recurrence in treatment with fine-needle aspiration and intracystic alcohol injection. In our case, the iris cyst relapsed eight months after this procedure, warranting for surgical excision. Eight months after the excision, the patient showed no signs of recurrence.*

Conclusion*: Although the recurrency of iris cyst is high, the authors suggest starting with non-invasive treatment with follow-up ensuring no recurrence before opting for a more invasive treatment.*

Keywords: *fine-needle aspiration; iris cyst excision; intracystic alcohol injection; implantation cyst; secondary iris cyst*

INTRODUCTION

Iris cyst is a rare entity differentiated into two types, primary and secondary. Primary cysts are of neuroepithelial origin, while secondary iris cysts originate from the implantation of surface epithelial cells.[1,2] The primary cyst is usually stable, whereas the secondary cyst tends to increase in size and could cause complications such as corneal edema, secondary glaucoma, and uveitis.[1] This report presents a case of a secondary iris cyst with a history of cataract surgery 17 years prior, the patient then underwent fine-needle aspiration and intracystic injection alcohol injection. Eight months later, the iris cyst relapsed and caused complaints of blurry vision. Considering the high occurrence of recurrence, excision of the iris cyst and iris reconstruction surgery were then favored. Considering the rarity of iris cyst, this case report

aims to highlight treatment approach starting with non-invasive procedure, and further discussed a more invasive procedure when facing recurrence.

CASE ILUSTRATION

A 20-year-old male was admitted with slowly progressive blurry vision of the right eye since ten days before admission. Pain and redness in the right eye were also reported. He had a history of cataract surgery on both eyes 17 years prior. The patient had no complaints after surgery. Upon examination, visual acuity was hand movement on the right eye and 6/30 on the left eye corrected with spectacle. Intraocular pressure of the right and left eye were 13 mmHg and 10 mmHg, respectively. The right cornea showed superficial neovascularization and a scar on the superior area. The iris cyst lined with pigment filled up to half the anterior chamber, blocked the pupil and touched the cornea's endothelium [Figure 1]. The AS-OCT examination confirmed the cystic appearance [Figure 2].

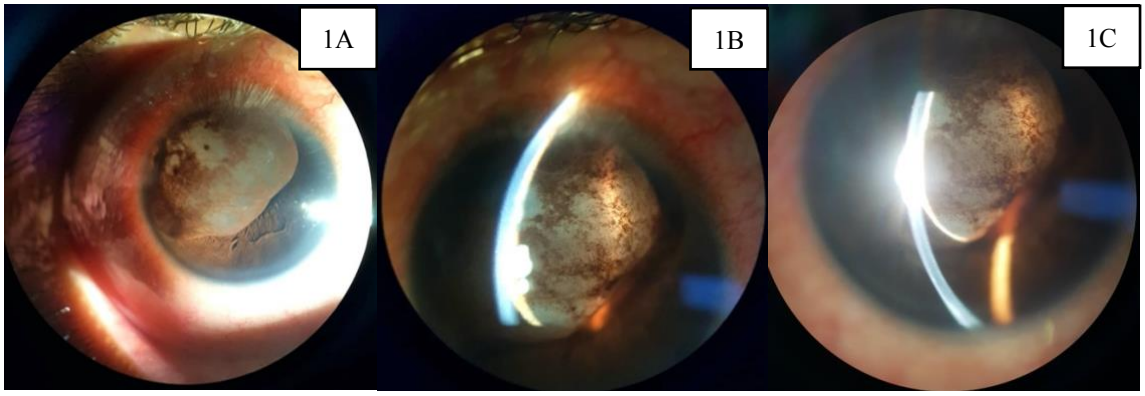

Figure 1. (A). Iris cyst on the first visit blocked the visual axis. (B) and (C) Iris cyst touched the cornea’s endothelium.

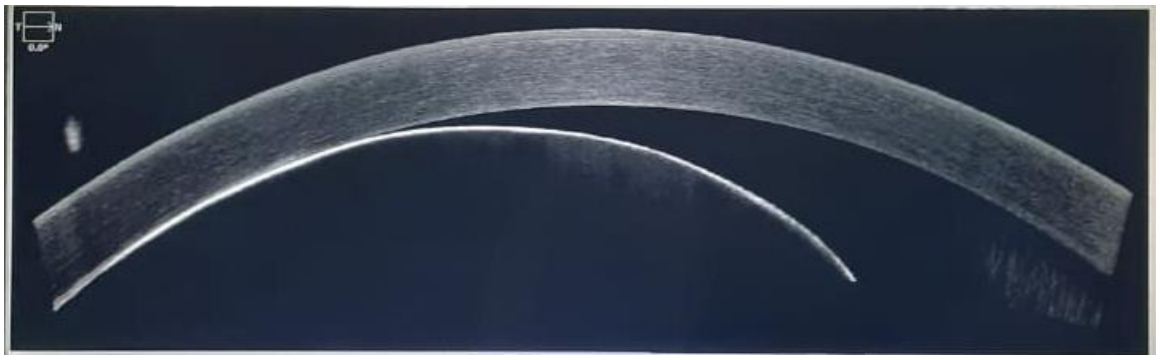

Figure 2. AS-OCT examination confirmed the cystic appearances of the iris cyst

The patient was diagnosed with secondary iris cyst of the right eye (implantation cyst type). Afterward, he underwent fine-needle aspiration with the intracystic injection of 96% alcohol. First, the fluid of the cyst was gently drained using a 30G needle. During this step, depth of anterior chamber must be monitored carefully, because a decrease in depth would mean a high possibility of connection between anterior chamber with epithelial iris cyst prompting for a high risk of alcohol leakage. Without changing needles and in the same position, the procedure was then followed by injection of medical grade ethanol (EtOH) 96% into the cyst, the alcohol was left inside for about one minute. After the cyst wall became greyish-white, EtOH was aspirated. The changing of color indicates desctruction of the lining epithelium. After this procedure, the patient was treated with atropine 1% 3x, levofloxacine eye drops 6x, and prednisolone acetate 6x.

On the first day after the procedure, the visual acuity of the right eye showed improvement, which was 6/60 with an IOP of 9 mmHg. The iris cyst collapsed on the peripheral side, but there were cyst capsule remnants with a corneal endothelial touch from 9 o'clock to 12 o'clock. On two months follow-up, no signs of recurrence was found. Due to the far distance between patient’s house to our hospital, the patient then had difficulties for regular follow-ups [Figure 3].

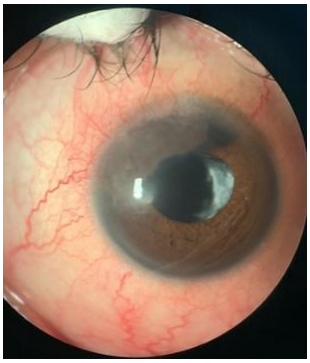

Figure 3. Two weeks after fine-needle aspiration and 96% EtOH intracystic injection, figure shows visible capsule remnant at the peripheral site.

At eight month post-procedure, the patient came to our hospital with a chief complaint of slowly progressive blurry vision of the right eye since one month prior. On ocular examination, the visual acuity was 6/30, and the IOP was 7,6 mmHg. Enlargement of the cystic mass was detected, filling the anterior chamber from 8 o'clock peripherally to 1 o'clock. It reached the edge of the supero-temporal pupil [Figure 4]. A surgical approach was favored. The patient underwent excision of the iris cyst and iris reconstruction surgery. The cyst sample was sent for histopathological examination and the result confirmed the diagnosis of implantation iris cyst. At five-month follow-up visit, the corrected visual acuity was 6/30. There were no complaints reported, and no recurrence of the iris cyst was found [Figure 5].

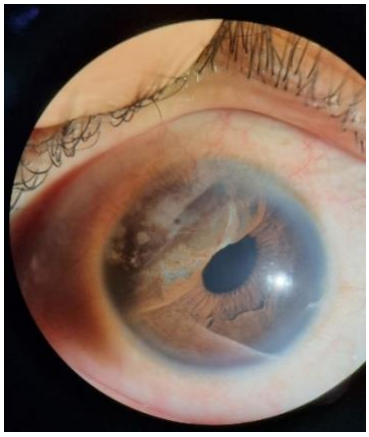

Figure 4. Eight months (right) follow-up. There is a recurrence of the iris cyst

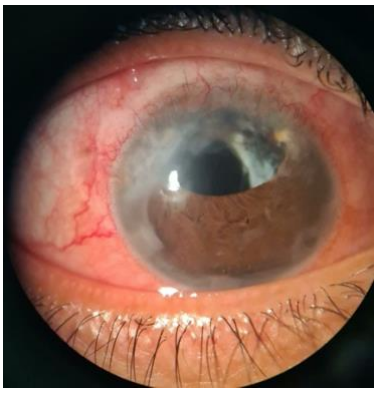

Figure 5. Five months after the iris cyst excision. There is a wide iris defect on the superior part.

DISCUSSION

Iris cyst is a rare condition, but secondary iris cysts are more common than primary cysts.[3] In this report, we found an implantation type of secondary iris cyst. The diagnosis was

made based on the patient's history of cataract extraction, and the base of the iris cyst was at the exact location of the previous surgical scar. The pathogenesis of implantation type iris cyst is related to introduction of the surface epithelial cells to the anterior chamber after previous surgery. After treatment, iris cyst recurrence is quite common due to the presence of these surface epithelial cells.[1,4] To address this problem, the treatment of iris cyst should aim to eradicate the surface epithelial cells.

Some of the indications for surgical management include visual axis disturbance, lens opacity, secondary glaucoma, recurrent inflammation and corneal endothelial decompensation.[3] In this case, the iris cyst obstructed the visual axis, which resulted in patient's hand movement visual acuity on the first visit. The cyst wall, which is adhered to the corneal endothelium, could cause corneal edema and endothelial decompensation. Fine-needle aspiration and intracystic alcohol injection were selected as initial treatments to reserve the ocular integrity. After the cyst fluid was aspirated using a 30G needle, the alcohol was injected through the same hole and left inside for approximately one minute until the cyst wall turned greyish-white as the indicator of inactive surface epithelial cells.[5] Until two months after injection, no recurrence was reported. This intracystic ethanol irrigation method followed the method reported by Behrouzi et al., who reported 93 cases of iris cyst which were resolved after the irrigation, with no recurrences after one-month post irrigation.[6]

In our case, the recurrence occurred eight months after initial treatment. The cyst had reached the edge of the pupil, and the patient started to complain of visual disturbance. He lived far from the hospital, which hindered routine follow-up visits post-procedure. Recurrence could happen because of remaining surface epithelial cells in the cyst wall, therefore, conservative approach such as the first procedure done to the patient had shown recurrence 8 months later.[7] In this situation, the definitive treatment with iris cyst excision was preferred.

A study by Shanbhag et al. showed that out of six cases treated with cyst aspiration and excision, recurrence on the same area was found in three cases. After aspiration of the fluid, followed by collapse of the cyst, the cyst wall attachment to the underlying iris must be of concern. In iris cyst excision, the aim is to cut the surrounding area of the cyst to ensure no surface epithelial cell is left.[7,8] The iris cyst was excised with a one-millimeter margin on each side of the cyst. The cyst wall attached to the portion of the iris should be excised using scissors or a vitrector. Sector iridectomy has shown statistically significant result in lowering the incidence of recurrence. Therefore, complete cyst excision with sector iridectomy should be considered when less invasive surgical approaches show poor results.[7] It was then followed by iris reconstruction procedure. After the procedure, the remaining defect was still quite large.

Fortunately, because it was located on the superior part, the defect was covered by the superior lid on the primary position. The patient reported no complaints. Eight months after the excision, there was no signs of iris cyst recurrence. Despite the promising results, further follow ups for signs of recurrence are recommended.

CONCLUSION

Iris cyst is a rare disease, but recurrences are quite frequent. We report a rare presentation of a secondary iris cyst in a 20-year-old male with a history of cataract surgery 17 years prior. Eight months after fine-needle aspiration and intracystic alcohol injection, the iris cyst relapsed. Invasive strategy of iris cyst excision was then favored to ensure no recurrence. The iris cyst was excised with a one-millimeter margin on each side of the cyst, followed by reconstruction procedure. Until the time of writing this case report, eight months after surgery, the patient exhibits no signs of recurrence. Although high in recurrence, the authors still suggest starting with non-invasive treatment followed by meticulous follow-up ensuring no recurrence.

REFERENCES

1. Georgalas I, Petrou P, Papaconstantinou D, Brouzas D, Koutsandrea C, Kanakis M. Iris cyst: A comprehensive review on diagnosis and treatment. Surv Ophthalmol. 2017; 63(3):347-64.
2. Shield JA. Primary Cysts of The Iris. Tr. Am. Ophth. Soc. 1981;79:771-808.
3. Rao A, Gupta V, Bhadange Y, Sharma R, Shields JA. Iris Cysts: A Review. Semin. Ophtalmol. 2011;26(1):11-22.
4. Venkateswaran N, Ching SST, Fischer W, Lee F, Yeaney G, Hindman HB. The Diagnostic and Therapeutic Challenges of Posttraumatic Iris Implantation Cysts: Illustrative Case Presentations and a Review of the Literature. Case Rep Ophthalmol Med. 2015;2015:1-11. http://dx.doi.org/10.1155/2015/3759behrouzi7
5. Haller JA, Stark WJ, Azab AMR, Thomsen RW, Gottsch JD. Surgical Management of Anterior Chamber Epithelial Cysts. Am J. Ophtahlmol. 2002;135(3): 309-13.
6. Behrouzi Z, Khodadoust A. Epithelial Iris Cyst Treatment with Intracystic Ethanol Irrigation. Ophthalmology. 2003;110(8):1601-5.
7. Philip SS, John DR, Ninan F, John SS. Surgical Management of Post-Traumatic Iris Cyst. Open Ophthalmol J. 2015;9:16behrouzi-6.
8. Shanbhag SS, Ramappa M, Chaurasia S, Murthy SI. Surgical management of acquired implantation iris cysts: indications, surgical challenges and outcomes. Br J Ophthalmol. 2018;0:1-5. doi:10.1136/bjophthalmol-2018-312738

CASE REPORT

THE MULTIPLE OCULAR MANIFESTATION OF A NEGLECTED NEWLY DIAGNOSED MULTIBACILLARY LEPROSY WITH GRADE II DISABILITY

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ABSTRACT

Introduction: *Leprosy is a chronic granulomatous infection cause by Mycobacterium leprae that could involving the eye with prevalence within 51,6% to 85%. Despite the high prevalence of leprosy and ocular manifestation, ophthalmologist consultation is not routinely performed, thus leads to unrecognized ocular complications. This case report aims to portrays the ocular manifestation of multibacillary leprosy with grade II disability.*
Case report: *A 71-year-old woman presented with severe corneal ulcer with perforation leading to the iris-lens prolapse resulted in total blindness of the left eye; peripheral ulcerative keratitis and neurotropic ulcer of the right eye; lagophthalmos, corneal hypoesthesia, and madarosis of both eyes. The Dermatovenereology Department consultation revealed claw hand, ulnar nerve thickening on both upper extremity, and hypoesthesia on both upper and lower limb. The acid fast bacteria were identified from auricula skin scraping specimens with +3 bacterial index (BI) and 75% morphological index (MI). The patient was diagnosed with LE severe corneal ulcer with iris-lens prolapse, RE peripheral ulcerative keratitis (PUK) and neurotropic ulcer, RLE lagophthalmos, and multibacillary leprosy with grade II disability newly diagnosed. Left eye evisceration was performed after initiated the multidrug therapy (MDT) regiment.*
Conclusion: *The ocular manifestation found in this case are corneal hypoesthesia, madarosis, corneal ulcer with perforation, iris-lens prolapse, peripheral ulcerative keratitis, and neurotropic ulcer. The management is directed to pathogen eradication and specific management on ocular manifestation. The collaboration with Dermatovenereology Department is required for comprehensive screening and management.*

Keywords: *leprosy, ocular manifestation, lagophthalmos, corneal perforation*

INTRODUCTION

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*. The organism mainly affect the peripheral nerve, skin, mucous membrane, respiratory tract, reticuloendothelial system, muscle, bone, testicular, and the eye. [1] The prevalence of leprosy was 140.594 cases worlwide in 2021. Indonesia is the third country reported >10.000 cases anually after India and Brazil. The incidence in 2021 was 10.976 caseswith 89% multibacillary type (MB).[2,3]

Mycobacterium leprae growth optimally in colder environment. The anterior chamber, which has 3^{O}C lower temperature than the surrounding environment, is the most frequent

predilection site.[1,4,5] Ocular manifestation of Leprosy account for 51,6% to 85% cases.[6,8,9,10] Corneal involvement was the most frequent manifestation (60%) due to the dense innervation. The late recognition and treatment leading to devastating complication such as corneal perforation (13%) even the ocular blindness (16%).

CASE ILUSTRATION

A 71-year-old woman presented to the emergency department with a progressive visual impairment leading to vision loss of the left eye for 2 weeks. The whitish appearance started to develop three days later. She also reported redness, mild ocular pain, and mucopurulent discharged in both eyes. There was history of recurrent ocular redness, discomfort, and tearing that left untreated before. Incomplete eyelids closure was experienced for 40 years. Systemic review found the history of extremity numbness and hand deformities for five and three years respectively.

Ophthalmology examination revealed the visual acuity was good projection of light perception on the left eye and 6/24 on the right eye. Lagophthalmos, madarosis, and diminished corneal sensation were observed on both eyes along with mucopurulent discharged, conjunctival and pericorneal injection. A limbus to limbus epithelial-stromal defect with positive fluorescein staining, thinning, bulging, and corneal micro perforation were found in the left eye. B-scan ultrasound of both eyes were normal.

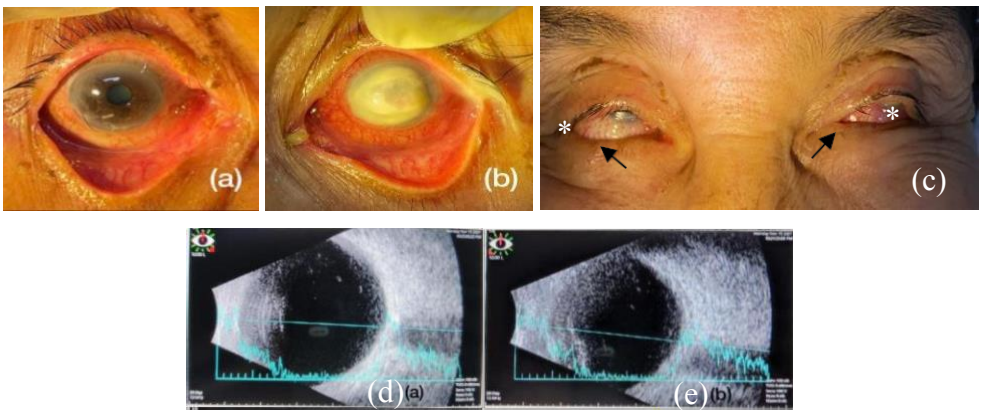

Figure 1. Anterior segment photographs and ultrasonography. (a) Conjunctival hyperemia of the right eye, (b) Severe corneal ulceration with epithelized micro perforation (c) Lagophthalmos (asterisk) and madarosis (black arrow), (d) and (e) normal ultrasonography of both eyes.

Systemic examination revealed the bilateral claw hand. Meanwhile, drop foot and hypoesthetic skin lession were absent. Hematology, imunoserology (Mantoux test, VDRL, TPHA, HIV), chest x-ray, and mantoux test were within normal limit. Conjunctival swab and

corneal scraping specimen were sent for gram staining, KOH staining, culture, and antibiotic sensitivity reported the negative result, excluding the etiology of bacterial and fungal infection.

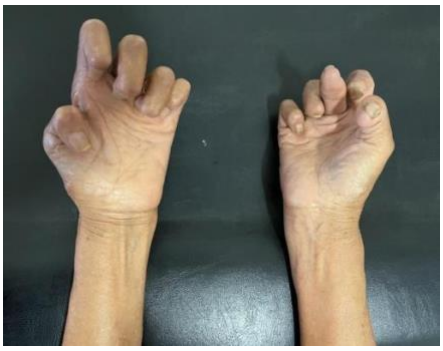

Figure 2. Bilateral claw hand

The patient was diagnosed with left eye severe corneal ulcer with perforation, right eye conjunctivitis, bilateral lagophthalmos and madarosis due to suspected ocular Leprosy. She was hospitalized and treated with ciprofloxacin infusion 400 mg bid, topical cefazoline fortified, levofloxacin eyedrop, chloramphenicole eye ointment, topical atropine for the left eye and autologous serum 20%, fluorometholon eyedrop and *bandage contact lens* (BCL) for the right eye. Periosteal graft was planned for the left eye. The surgical procedure couldn't be performed at that time because the patient hasn't received any leprosy treatment so the Anesthesiologist couldn't agree to perform general anesthesia. So, the patient was managed conservatively while initiated the leprosy regiment.

Dermatovenerology consultation confirmed the presence of bilateral claw hand, ulnar nerve thickening, diminished sensory functions of cranial nerve (CN) V, and motoric function of CN VII (lagophthalmos), ulnar nerve, and posterior tibial nerve. Hypoesthesia was also found in facial, palm, and sole distribution. Ziehl-Neelson staining confirmed the presence of acid fast bacterial with +3 for the bacterial index (BI) and 75% for the morphological index (MI). The patient was assessed with multibacillary leprosy newly diagnosed with grade II disability and received multidrug therapy (MDT) for 12 months in ambulatory setting.

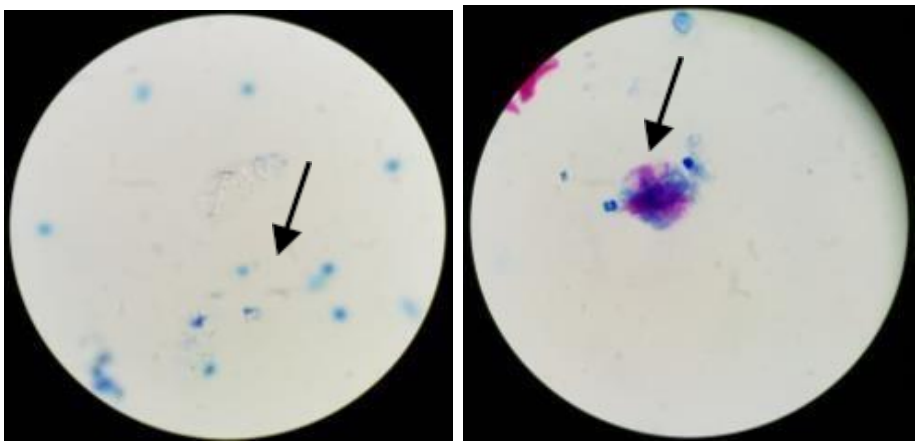

Figure 3. Ziehl Neelsen staining. Acid fast bacterial were obtained from skin scraping examination of the auricular specimen.

The patient was readmitted with left eye corneal perforation and lens prolapse that experienced for 2 weeks after discharged with no light perception for the visual acuity. Additionally, there was a peripheral ovoid epithelial stromal defect in eight o'clock sector with a typical lucid interval suggested a peripheral ulcerative keratitis. The visual acuity of the right eye was 6/24. The patient was takenthe MDT for leprosy so the evisceration under general anesthesia was performed in the left eye.Meanwhile, optimal lubrication and bandage contact lens was continued for the right eye.

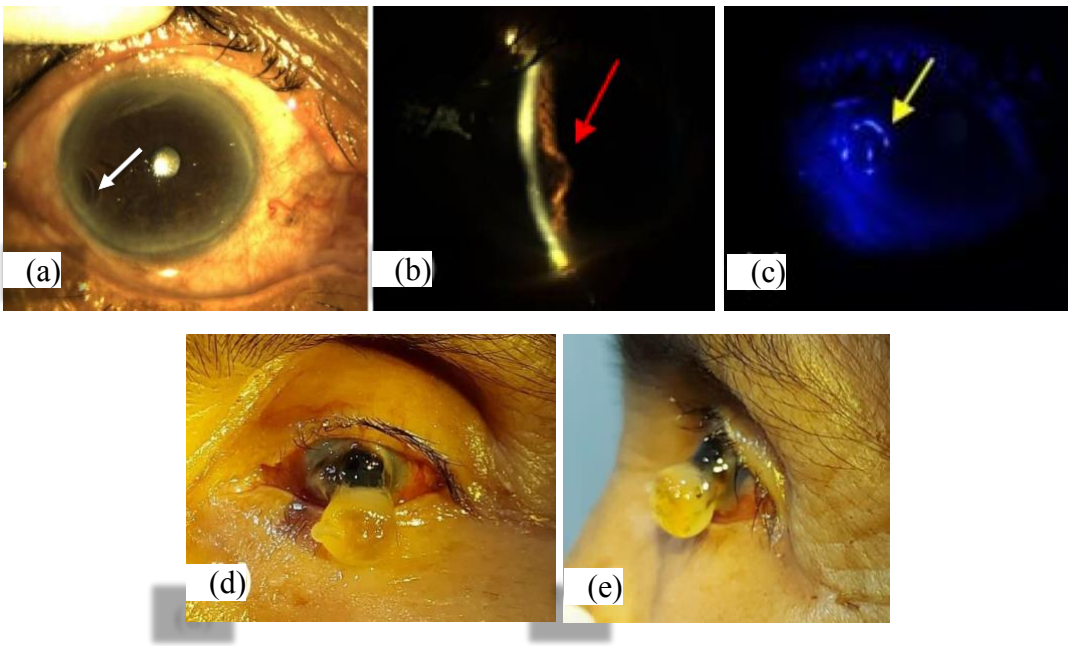

Figure 4. Anterior segment photographs on second admission. (a) Right eye peripheral ulcerative keratitis (PUK), (b) Corneal thinning in slit view that unstained with fluorescence (c), (d) Anterior view of left corneal perforation with lens and vitreous prolapse, (e) Left eye lateralview of the lens and vitreous prolapse through the corneal perforation.

Serial follow up revealed the development of right eye ovoid corneal defect in inferior paracentral region suggested a neurotropic ulcer which managed medically. As the disease progressed, pannus formation started to develop and the visual acuity was slightly worsened.

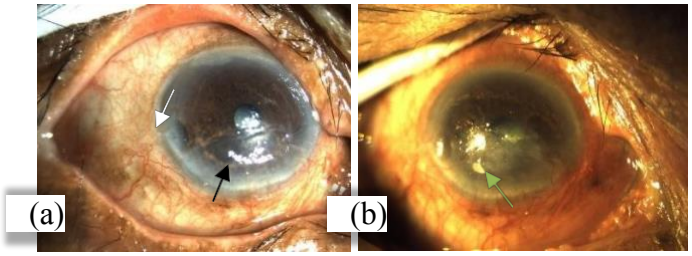

Figure 5. Anterior segment photograph of the right eye on 5 and 8 months follow up. (a) Developing of neurotropic ulcer (black arrow), persistent PUK (white arrow), (b) Pannusformation.

DISCUSSION

We reported a 71-year-old woman with multi bacillary leprosy newly diagnosed with grade II disability demonstrated multiple ocular manifestations. The diagnosis of leprosy was supported by two of three cardinal signs such as thickening of peripheral nerve and the presenceof acid fast bacterial. The older age and probability of genetic predisposition may contribute asthe risk factors that lead to the disease progression identified in this patient.

World health organization (WHO) classified leprosy based on the bacterial density and the number of skin lesions into paucibacillary and multibacillary type.[1,3,6] Bacterial index +3 without skin lesion finding categorized the patient as the multibacillary leprosy that has the higher risk of spreading, deformity development, and two times greater risk of ocular manifestation. [4]

A neglected leprosy infection in this case was estimated to occur for about 30 years preceding the ocular problem. The ocular manifestation of leprosy was positively associated with disease duration. Reddy et al., (2019) reported the probability of ocular manifestation was increased with the longer course of leprosy, 33%, 66,6%, and 86% for <5 years, 5-10 years, and >10 years durations respectively.[9] Besides, the bacterial load and host immunity also contribute to the ocular expansion of leprosy.[10]

Ocular involvement in leprosy caused by direct infection, neuronal, hematogenous, and lymphogenous spreading, and immunology reaction.[5,6,12,13] Lagophthalmos, madarosis, corneal hypoesthesia, neurotrophic ulcer, peripheral ulcerative keratitis, corneal perforation resulted in ocular blindness in this case were presumed to be associated with leprosy.

The destruction of facial nerve directly by *Mycobacterium leprae* could diminished the orbicularis muscle function leading to lagophthalmos. The inability to close the eyelid developed as the disease progressed, as experienced by the patient. Grade II disability was known as one of the risk factors of lagophthalmos in leprosy.[14]

The cilia, along with the eyelid, play the important protective role to the ocular surface. The loss of cilia of the eyelid margin (madarosis) in leprosy, that typically begin in the lateral portion, occurred due to direct invasion of the bacterial to the hair follicles. It was commonly found in multibacillary and lepromatous type.[15]

The abnormality of the eyelid and the adnexal structure increase the risk of ocular surface damage due to infection, inflammation, retained foreign body, and tear film instability. Corneal inflammation and infection worsened by the corneal hypoesthesia leading to devastating condition.[15]

Invasion of M. leprae to the ophthalmic division of trigeminal nerve and corneal nerve atrophy produce the decreased of corneal sensitivity. Furthermore, it may cause a higher pain threshold, decreased of blink reflex and tear production. Significant decreased of corneal sensitivity tend to occur in long standing multibacillary type along with lagophthalmos.[5,12] Unfortunately, less of symptoms awareness due to hypoesthesia predispose the patient in a neglected condition and delayed medical treatment.[5]

Lagophthalmos and corneal hypoesthesia resulted in development of corneal ulcer and perforation due to exposure keratitis (secondary infection) or primary infection. Other risk factor associated with corneal ulcer in leprosy are the multibacillary type, decreased of blinkingrate, tear film production, trichiasis, ectropion, lacrimal duct obstruction, hand ulcer, gardeningactivity, nutrition deficiency, poverty, and low education level.[5,15]

Peripheral ulcerative keratitis (PUK) was persistently found in the right eye as an ovoid thinning area typically appear in a zone within 2 mm of the limbus. Mild adjacent conjunctival hyperemia and tearing were reported. Ocular pain was typically absent due to corneal hypoesthesia. Complex immune reaction was thought to be the underlying mechanism related to leprosy. Whereas the differential diagnosis such as exposure keratopathy due to lagophthalmos condition was excluded due to the location that was not situated in inferior.[12,16,17]

Neurotropic ulcer was developed 5 months after the initial presenting as a grayish ovoid epithelial stromal defect with elevated edge located in inferior paracentral area, leading to decreased of visual acuity of the right eye. It presented in a predilection site that uncovered by protective effect of Bell's phenomenon. The pathomechanism was associated with trigeminal nerve damage resulted in corneal hypoesthesia and delayed wound healing.[17,18]

Pannus formation was formed covered the neurotrophic ulcer months later. As reported by previous study, pannus was found in 50,1% case of leprosy due to healing response that mostly occurred in lepromatous type.[9] Corneal inflammation could trigger the neovascularization and the growth of fibrous tissue. [7]

The obvious ocular manifestation such as lagophthalmos, corneal opacity, and severe visual impairment (<6/60) and blindness along with claw hand deformity classified the patient into grade II disability for WHO criteria. Unfortunately, grade II disability combined with sensory abnormality could threaten the patient's safety issue.

Previous study revealed a tendency of persistent ocular complication as the disease treated completely. Moreover, the new ocular complication would be continued to develop 5,6% each year with 3,9% are sight threatening. It associated with persistent immunologic reaction and steady neuronal damage. The risk of ocular complication was not significantly different between the treated patient and those completely eradicated.[6,10] As a consequence, patient monitoring and evaluation clinically and bacteriologically are very important for early treatment and further disability prevention.

CONCLUSION

The ocular manifestations found in this case are lagophthalmos, madarosis, corneal hypoesthesia, peripheral ulcerative keratitis, neurotrophic ulcer, and corneal perforation that potentially sight threatening in the left eye. The treatment was director for the pathogen eradication and specific management of ocular manifestation. Multidisciplinary collaboration with Dermatovenerology Department needed for early detection and comprehensivemanagement purpose.

REFERENCES

1. Amiruddin, M. Dali. 2012. Penyakit Kusta; Sebuah Pendekatan Klinis. Brilian Internasional,Jakarta.
2. WHO. 2022. Global leprosy (Hansen disease) update, 2021: moving towards interruption of transmission.
3. Kemenkes RI. 2021. Profil Kesehatan Indonesia 2021.
4. Kumar B. 2017. IAL Textbook of Leprosy second edition. The Health Sciences Publisher, NewDelhi.
5. Grzybowski, A., Nita, M., Virmond, M. (2015). *Ocular leprosy. Clinics in Dermatology, 33(1),79–89.*
6. Pavezzi PD, do Prado RB, Boin Filho PAˆ, Gon AdS, Tuma B, Fornazieri MA, et al. (2020) Evaluation of ocular involvement in patients with Hansen's disease. PLoS Negl Trop Dis 14(9).
7. Kemenkes RI. (2019). Permenkes No 11 Tahun 2019 Tentang Penanggulangan Kusta.
8. Samuel, C., Sundararajan, d., (2014). Ocular manifestations in hansen's disease-A clinical study. International Journal of Medical Research and Health Science 3(4):829.

9. Reddy G.N., Reddy G.A. (2019). Ocular manifestation of leprosy. Tropical Journal of Ophthalmology and Otolaryngology 4 (7).
10. Malik, A. N. J., Morris, R. W., & ffytche, T. J. (2011). The prevalence of ocular complications in leprosy patients seen in the United Kingdom over a period of 21 years. Eye, 25(6), 740–745.
11. Roldan-Vasquez, A., Roldan- Vasquez, E., & Vasquez, A. M. (2021). Uveitic Glaucoma and Hansen's disease, A case report. American Journal of Ophthalmology Case Reports, 22, 101096.
12. Fischer, M. (2017). Leprosy - an overview of clinical features, diagnosis, and treatment. JDDG:Journal Der Deutschen Dermatologischen Gesellschaft, 15(8), 801–827.
13. Biswas, Jyotirmay; Pradhan, Arkaprava. (2022). Commentary: Ocular lesions in leprosy -Shouldwe forget? Indian Journal of Ophthalmology: 70 (7).
14. Bairappagari MEJ, Thompson KJ, Daniel E**. (**2017). The eye in leprosy, Chapter 3.1. *In* ScollardDM, Gillis TP (ed), International textbook of leprosy.
15. Höllhumer R. Peripheral ulcerative keratitis: A review of aetiology and management. Afr VisionEye Health. 2022;81(1).
16. American Academy Ophthalmology. External disease and cornea 2020-2021 basic and clinical science course (BCSC). San Francisco: American Academy Ophthalmology.
17. Iraha S., Yamaguchi t., Inoue T. (2022). Bilateral corneal perforation caused by neurotrophic keratopathy associated with leprosy: a case report. BMC Ophthalmology 22:42.
18. Chirania P, Das D, Agarwal B, Kuri GC. Hansen's disease with ocular manifestations: A caseseries. TNOA J Ophthalmic Sci Res 2021;59:3