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Relationship between Cluster of Differentiation 4 Levels and Neuroopthalmic Manifestations in HIV Patients in Haji Adam Malik General Hospital Medan

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ABSTRACT

Introduction: The neuroophthalmic manifestations of HIV infection involve afferent and efferent visual pathways. Neuroophthalmic involvement is caused by direct infection and opportunistic infections. Screening for neuroophthalmic manifestations should be done even without vision complaints to identify neuroophthalmic signs and symptoms and refer to a neuroophthalmologist soon. The aim of this study was to determine the relationship between CD4 levels and neuroophthalmic manifestations in HIV positive patients

Method: It was a cross-sectional study with primary data sources taken consecutively from HIV positive patients at Haji Adam Malik General Hospital in Medan. Subjects were examined for CD4 levels and also performed the neuroophthalmic and neurological physical examination such as visual acuity examination, visual field, pupil examination and funduscopy.

Results: There were 45 subjects with demographic characteristics the most of subjects were male (71.1%), age group 31-40 years (55.6%) with an average age of 35.98 + 9.23 years, self-employed (46.7%), married (60%) and Bataknese (62.8%). CD4 levels < 200 cells/µL were found at 55.6% with a median value of 162 cells/µL (30-878). The most of neuroophthalmic clinical manifestations were found in 52% of subjects with CD4 levels <200 cells/µL with symptoms of blurred vision (22.2%) and clinical signs of abnormalities on fundoscopy (20%). There was a significant relationship between CD4 levels and neuroophthalmic manifestations in HIV patients (p<0.005).

Conclusion: There was a significant relationship between CD4 levels and neuroophthalmic manifestations in HIV patients (p<0.005).

Keywords

CD4, HIV, Neuroophthalmic, Fundoscopy, Visual

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INTRODUCTION

Human Deficiency Virus (HIV), the etiology of Acquired Immunodeficiency Syndrome (AIDS) already became endemic since 1981.[1] Every day more than 7000 people with AIDS are infected and every 20 seconds AIDS sufferers died which are the fifth cuase of death in adults.[2] Based on data from the World Health Organization (WHO), around 17 million HIV patients get antiretroviral therapy in 2015.[3]

Clinical manifestations of HIV/AIDS were varies related to the degree of the disease.[4] Neuroophthalmic manifestation is often found both in HIV and AIDS patients.[5] Research data previously indicates blindness as the consequence complications HIV infection is reason number morbidity highest with prevalence 6.9% -23%. This research show that the prevalence prevalence manifestation ocular consequence HIV infection was increasing when there was decline CD4 levels. Bekele et al in 2013 found that CD4 levels

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< 200 cells / μL have significant relation for ocular manifestation risk factor in HIV patients, therefore low CD4 levels were ocular disease predictor in HIV.[6]

Recently, there is no consensus stated that screening routine HIV patients performed evaluation disease of ophthalmology by ophthalmoscope examination. Routine ophthalmology screening is recommended in HIV-1 patients with CD4 < 200 cells /μL because the high prevalence ocular disease in this CD4 category, with or without neuroophthalmic sign and symptomps.[7] Clinician should perform screening for neuroophthalmic disorders even without visual symptoms, thus helping to determine the type of signs and symptoms and refer to a neuroophthamologist.[8]

METHOD

It was analytic observational study with cross-sectional design using primary data source on hospitalized patients or Policlinic patints at H.Adam Malik General Hospital Medan in April 2022-October 2022. This study got agreement from Committee Local Health Ethics and Research. Criteria inclusion subject is positive HIV patients based on history, physical examination and serological test, 18 years old, conscious and willing to participate in study by informed consent. Exclusion criteria were patients who were could not be assessed in while performing examinations such as patients with aphasia, dementia, patients who were unable to sit and patients with systemic disease diabetes mellitus and hypertension which caused neuroophthalmic manifestations. Sampling was carried out by consecutive sampling method on 45 HIV positive subjects.

The blood of the subject were taken and to count CD4 level. After history taking, physical and neurological examination, the subjects were also performed neuroophthalmic examination. The histories were neuroophthalmic symptoms like blurry view, diplopia and visual hallucinations. Neuroophthalmic examination such as visual acuity test using the Rosenbaum visual acuity card, field view examination using confrontation technique, light reflex examination to assess pupil reaction, eyeball movement , presence of nystagmus and ptosis and also fundoscopy examination using Elch Allyn D-eye digital fundoscopy . CD4 levels divided into 2 categories : < 200 cells /L and > 200 cells /L, the symptoms and signs neuroophthalmic were divided into presence or absent symptoms. Data study were analyzed by using SPSS software and will served in form table frequency. To evaluate association between CD4 levels with manifestation neuroophthalmic in HIV positive patients, Chi-square test or Fisher's exact test was used .

RESULT

There were 45 eligible HIV positive subjects meet the criteria inclusion. Most of the subjects were 31-30 years category (55.6%), male (71.1%), Batak ethnicity (46.7%). The majority (46.7%) of study participants were self-employed and had a high school education level (53.3%). The mean duration of subjects being diagnosed with HIV was 32.6 ± 35.4 months. The mean duration of the subjects receiving ARVs was 28.8 ± 32.2 months. (Table 1) Characteristics of CD4 levels in subjects study can be seen in table 2. The mean CD 4 level was 259.5 ± 221.4 cells/ μL , divided into CD4 levels ≤ 200 cells/μL (55.6%) and CD4 levels ≥ 200 cells/μL (44.4%).

Neuroophthalmic Signs and Symptoms Characteristics

The most common neuroophthalmic symptom in this study was blurred vision (24.4%) followed by double vision (8%). Symptoms in the form of visual hallucinations in this study were not found. (Table 3)

The neuroophthalmic clinical sign characteristics were in table 4. The majority of the neuroophthalmic clinical signs in this study were funduscopic abnormalities (17.8%), decreased (11.1%), N III, IV, VI parese (8.9%), pupil abnormality (4.4%), visual field abnormality (2.2%) and ptosis 2.2%) . Decreased vision was found in 5 subjects of this study with visual acuity were no light perception (2.2%), 1/300 (2.2%) and 20/25 – 20/800 (4,4%).

Association of CD4 levels and Manifestation Neuroophthalmic

Manifestations of neuroophthalmic signs and symptoms were in table 5. Symptoms of blurred vision were more common in 9 subjects (36%) with CD4 levels < 200 cells/μL, whereas in subjects with CD4 levels ≥ 200 cells/μL blurred vision was found in 2 subjects (10%), but there was no significant association between CD4 levels and blurred vision based on the Fisher's exact test (p = 0.495). Manifestations of double vision symptoms were found in subjects with CD4 levels < 200 cells/μL in 2 subjects (8%), whereas in subjects with CD4 levels ≥ 200 cells/μL there were no double vision symptoms, and based on the Fisher's exact statistical test it was not significant (p = 0.495). Neuroophthalmic symptoms such as visual hallucinations were not found in this study.

Table 1. Demographics Characteristics of Subjects

Characteristics Demographics	n = 45
Gender n, n (%)	
• Male	32 (71.1)
• Female	13 (28.9)
Age , years	
• Mean (SD)	35.9 (9.2)
• Median (Min – Max)	33 (24 – 66)
Age, n(%)	
• 18 – 30 Years	14 (31.1)
• 31 – 40 Years	25 (55.6)
• 41 – 50 Years	3 (6,7)
• > 50 Years	3 (6,7)
Tribe, n (%)	
• Batak	21 (46.7)
• Java	12 (26.7)
• Malay	6 (13,3)
• Minang	3 (6,7)
• Nias	1(2,2)
• Chinese	2(4,4)
Marital Status, n (%)	
• Marry	27 (60.0)
• Not Married	18 (40.0)
Education, n (%)	
• SD	2(4,4)
• Junior High School	9 (20.0)
• Senior High School	24 (53.3)
• College	10 (22,2)
Occupation, n (%)	
• Civil Cervant	1(2,2)
• Private employees	7 (15,6)
• Self-employed	21 (46.7)
• Unemployed	16 (35.6)
Duration since HIV diagnosis (months)	
• Mean (SD)	32.6 (35.4)
• Median (Min – Max)	24 (0 – 132)
Duration of ARV consumption (months)	
• Mean (SD)	28.8 (32.2)
• Median (Min – Max)	12 (0 - 120)

Table 2. Characteristics of CD4 levels in HIV sufferers

Characteristics of CD4 Levels	n = 45
CD4	
• Mean (SD)	259.5 (221.4)
• Median (Min – Max)	162 (30 – 878)
CD4	
• < 200 cells/µL	25 (55.6)
• ≥ 200 cells/µL	20 (44.4)

Table 3. Characteristics of Neuroophthalmic Clinical Symptoms in HIV Patients

Neuroophthalmic Clinical Symptoms	n = 45
Blurred Vision, n (%)	
• Yes	11 (24.4)
• No	34 (75.6)
Double Vision, n (%)	
• Yes	2(4,4)
• No	43 (95.6)
Visual hallucinations	
• Yes	0 (0)
• No	45 (100.0)

Table 4. Characteristics of Neuroophthalmic Clinical Signs in HIV Patients

Neuroophthalmic Clinical Signs	n = 45
Decreased vision, n (%)	
• Yes	5 (11,1)
• No	40 (88.9)
Characteristics of Visual acuity	
- 20/20	40 (88.9)
- 20/25 – 20/800	3 (6,6)
- 1/300	1(2,2)
- *No light perception*	1(2,2)
Visual field abnormalities, n (%)	
• Yes	1(2,2)
• No	44 (97.8)
Pupil abnormalities, n (%)	
• Yes	2(4,4)
• No	43 (95.6)
Conjugate eyeball movement abnormalities, n(%)	
• Yes	0 (0)
• No	45 (100)
Paresis N III, IV, VI	
• Yes	4 (8,9)
• No	41 (91.1)
Nystagmus	
• Yes	0 (0)
• No	45 (100)
Ptosis	
• Yes	1(2,2)
• No	44 (97.8)
Fundoscopic abnormalities	
• Yes	8 (17,8)
• No	37 (82.2)

The most common neuroophthalmic clinical signs in this study were funduscopic abnormalities which were most common in subjects with CD4 levels < 200 cells/µL in 8 subjects (32%), whereas in subjects with CD4 levels ≥ 200 cells/µL none were found funduscopic abnormalities. Based on the *fisher's exact* statistical test, a significant association with CD4 levels related fundoscopic abnormalities (p = 0.006). The other clinical

signs were found in groups subject with CD4 level < 200 cells/µL with visual acuity abnormalities (20%), N III, IV,VI parese (16%), pupil abnormalities (8%), ptosis (4%) and visual field abnormalities (4%), however there was no found significant association based on fisher's exact statistical test between CD4 levels with sign clinical visual acuity abnormalities (p = 0.056), N III,IV,VI parese (p = 0.117), pupil abnormalities (p=0.495), ptosis (p = 1.000) and visual field abnormalities (p = 1.000).

Overall , neuroophthalmic manifestations are most common in subjects with CD4 levels < 200 cells/µL in 9 subjects (36%), whereas in subjects with CD4 levels ≥ 200 cells/µL there were no neuroophthalmic manifestations which can be seen in table 6. Based on the *fisher's exact* statistical test, a significant association was found between CD4 levels and neuroophthalmic manifestations in HIV positive patients (p = 0.002).

Table 5. Relationship between CD4 Levels and Neuroophthalmic Clinical Signs and Symptoms in HIV Patients

Neuroophthalmic clinical signs and symptoms	CD4 levels		P
	< 200 cells/µL	≥ 200 cel/µL	
Blurred View			0.495
• Yes	9 (36.0)	2 (10)	
• No	16 (64.0)	18 (90)	
Double View			0.495
• Yes	2 (8.0)	0 (0)	
• No	23 (92.0)	20 (100)	
Visual hallucinations			-
• Yes	0 (0)	0 (0)	
• No	25 (100.0)	20 (100.0)	
Neuroophthalmic Clinical Signs			
Decreased vision			
• Yes	5 (20.0)	0 (0)	0.056
• No	20 (80.0)	20 (100)	
Visual field disturbance			
• Yes	1 (4.0)	0 (0)	
• No	24 (96.0)	20 (100)	1,000
Pupil Disorders			
• Yes	2 (8.0)	0 (0)	0.495
• No	23 (92.0)	20 (100)	
Conjugate eyeball movement disorders			
• Yes	0 (0)	0 (0)	
• No	25 (100.0)	20 (100.0)	-
Paresis N III, IV, VI			
• Yes	4 (16.0)	0 (0)	0.117
• No	21 (84.0)	20 (100.0)	
Nystagmus			
• Yes	0 (0)	0 (0)	-
• No	25 (100.0)	20 (100.0)	
Ptosis			
• Yes	1 (4.0)	0 (0)	1,000
• No	24 (96.0)	20 (100.0)	
Fundoscopic abnormalities			
• Yes	8 (32.0)	0 (0)	0.006
• No	17 (68.0)	20 (100.0)	

*Fisher's exact test

Table 6. Connection CD4 Levels with Neuroophthalmic Manifestations in HIV Patients

CD4 levels	Neuroophthalmic manifestations		P
	There is	No	
< 200 cells/µL	9 (36.0)	16 (64.0)	0.002
≥ 200 cells/µL	0 (0)	20 (100.0)	

*Fisher's exact test

DISCUSSION

Based on demographic data in this study, the majority of subjects aged 31-40 years (55.6%). These results are relevant to a study by Sharew and Azage's in 2015 which reported that the most age in HIV positive patients was over 37 years (26.5%).[9] Based on data from the Ministry of Health of Republic of Indonesia in 2019, the highest number of HIV infections in 2010-2019 was the age category of 25-49 years or productive age, which is the age of the most HIV patients each year, where the possibility of transmission occurs at a young age.[10] The majority sex in this study were male (71.1%). These results are relevant to a study by Luo et al in 2013 which reported that the sex male was the most common in HIV positive patients (76.1%).[11] Based on data from the Ministry of Health of the Republic of Indonesia in 2019 that both HIV and AIDS, the proportion in the male group is about two times higher (65%) than in the female group (35%).[10]

The most participants were married (60%). These results approach Sharew and Azage's 2015 study in which the majority of subjects were HIV positive married (50.5%).9 Married indicates that a person is sexually active and if there is a feeling of dissatisfaction with their partner, this will trigger the person to look for another ideal man or woman who can be a risk factor for HIV/AIDS transmission.[12]

In this study, there was 55.6% of subjects had CD4 levels < 200 cells/μL and 44.4% of subjects had CD4 levels ⩾ 200 cells/μL. The results of this study are approach to previous research by Narasimhaiah et al in 2018 in India where HIV-positive subjects with the highest CD4 levels were in the group with CD4 levels of 51-199 cells/μL (39.2%) followed by the group with CD4 levels of 200- 499 cells/μL (26.7%). The main target of HIV virus infection is CD4 T lymphocytes so that HIV infection will result in a progressive decrease in CD4 T cell levels due to CD4 cell damage and decreased production caused by direct infection or through immune activation.[9,13,14] The main cause of morbidity and mortality among patients with advanced stages of HIV infection are opportunistic infections. Opportunistic infections usually do not occur in HIV-infected persons until the CD4 count has decreased from a normal level of about 1000 cells/μL to less than 200 cells/μL.[15]

About 50-80% of people with HIV require treatment for ocular disorders. Ocular manifestations in HIV can involve all structures of the eye, from the adnexa to the anterior and posterior segments of the eye.[8,16] Based on this study, neuroophthalmic manifestations were found in 20% of subjects with the most common symptoms were blurred vision (24.4%) and double vision (4.4%), while neuroophthalmic clinical signs in this study were fundoscopic abnormalities (17.8%), visual acuity impairment (11,1%), ocular eye movement nerve paresis (8.9%), pupil abnormalities (4.4%) and ptosis (2.2%). The results of this study approach Makunyane and Mathebula's 2018 study on HIV positive patients there were 31.6% of subjects with manifestations of the posterior eye segment and 16.9% of subjects with neuroophthalmic manifestations, mostly 27% funduscopic abnormalities (9% papilledema and 6.2% optic atrophy) and 1.6% oculomotor nerve parese.[17] The neuroophthalmic manifestations in this study are relevant to the study of Acharya et al in 2012 found in 9.94% of subjects with the most common manifestations were papilledema followed by pupillary disorders, optic neuritis, papil athropy, oculomotor nerve paresis, ptosis and primary papil athropy.[18] Meanwhile, Sudharsan study et al in 2013 in India reported 61 subjects with neuroophthalmic lesions with 49.45% manifestations being optic atrophy, 21.97% papilledema, 14.28% optic neuritis and 9.89% cranial nerve paresis.[19]

The neuroophthalmic manifestations of HIV infection can involve afferent and efferent visual pathways even in asymptomatic patients or without visual complaints.[20] Neuroophthalmic involvement can caused by direct viral effects on nerves or indirectly through opportunistic infections, vascular abnormalities and malignancies due to immunodeficiency.[8,16] However, only a few studies have specifically assessed the association of neuroophthalmological prevalence in HIV. Optic neuropathy in HIV/AIDS is found due to inflammation, ischemia, infection, compression, infiltration and increased intracranial pressure.[16] Optic neuropathy in HIV is most often secondary to opportunistic infections such as CMV, syphilis, varicella zoster, cryptococcus, toxoplasmosis and tuberculosis.[8,16] In addition to optic neuropathy, HIV infection results in microvascular abnormalities that affect the retina, optic disc and cornea.[16] On funduscopic examination, optic nerve abnormalities will be found disc edema in papillitis, disc edema accompanied by macular exudate

in neuroretinitis and the presence of papilledema due to increased intracranial pressure from CNS infection (cryptococcal meningitis, toxoplasma encephalitis, tuberculous meningitis, CMV, neurosyphilis, and tuberculoma.[8,16] The study by Sharma et al in 2018 in India found opportunistic infections in the posterior segment of the eye found most CMV retinitis (6.7%), and the other 6% were choroiditis, papilledema, optic atrophy.[21]

There was a significant relationship between CD4 levels and neuroophthalmic manifestations in this study ($p = 0.002$). These results are relevant to study by Makunyane and Mathebula in 2018 showed that neuroophthalmic manifestations were found in 17% of subjects and about 80% of them had CD4 levels < 200 cells/μL and 20% of other subjects had CD4 levels ⩾ 200 cells/μL and there were significant association between CD4 levels and neuroophthalmic manifestations ($p < 0.05$).[17] In this study it was also found that the majority of subjects had CD4 levels < 200 cells/μL. HIV infection that attacks CD4 T lymphocytes will result in a decrease in CD4 levels which cause in an increased risk of opportunistic infections. In addition to CD4 levels, HIV viral load is a predictor of immune status in HIV positive patients.[14,22] Low CD4 levels in this study may increase the risk of opportunistic infections.[13] ARVs can improve life expectancy in people with HIV/AIDS. Neuroophthalmic manifestations can affect the quality of life in people with HIV/AIDS.[23]

In contrast to the study by Amsalu et al in 2018 reporting a lower prevalence of ocular manifestations, namely 14.2% compared to Bekele et al 2009 (25.3%) and Sharew et al 2013 (25,7%).[15] The lower prevalence of ocular manifestations in the study by Amsalu et al in 2018 is probably due to the longer duration of ARV consumption (> 5 years) in the majority of subjects, which has a positive impact on clinically affected HIV subjects with immune responses and CD4 levels.[24] In this study, the duration of ARV consumption subjects had a median of 12 months (0-120 months), which was less than 5 years.

Lestari et al study in 2013 reported HIV positive patients found that ocular disease in subjects was in 63.67% of subjects with around 80% of subjects having clinical stage 3 and 4 HIV based on WHO criteria. There was a significant association between WHO clinical stage and ocular disease ($p = 0.009$). Subjects who had co-infection associated with ophthalmic abnormalities and had a 2.67 greater risk of developing ophthalmic abnormalities. CD4 levels < 50 cells/μL are significantly associated with the occurrence of ocular disease ($p = 0.003$) and had a 2 times greater risk of developing ophthalmic disorders than subjects with CD4 levels ⩾ 200 cells/μL. Ocular abnormalities are more common in subjects with clinical stages of HIV 3 and 4 who have poor clinical condition and immunity. Poor immunity will increase the risk of coinfection. Coinfection is a cause of morbidity that reduces the immune status of people with HIV/AIDS. Research on HIV/AIDS subjects with tuberculosis and hepatitis C coinfection and without coinfection showed that coinfection would result in poor clinical status, longer treatment time, low CD4 levels and slow immune response.[23]

In this study, the most common neuroophthalmic manifestations were funduscopic abnormalities in the form of papilledema and papilledema followed by decreased vision and paresis of cranial nerves III, IV, VI. The results of this study are relevant to Makunyane and Mathebula in 2018, Lamichhane et al in 2010 and Acharya et al in 2012 that the most common neuroophthalmic manifestations are funduscopic abnormalities in the form of papilledema and papil athrophy followed by cranial nerve paresis III and VI.[17,18,25] Paresis of the eye movement in HIV is most often cranial nerves III and VI caused by opportunistic infections such as toxoplasma encephalitis, cryptococcus and syphilis.[8,16]

This study also found that the mean duration of subjects diagnosed with HIV was 32.6 months and the mean duration of subjects taking ARVs was 32.6 months. Based on study by Amsalu et al in 2018 and Makunyane and Mathebula in 2018, subjects who consumed ARVs for less than 5 years tended to experience neuroophthalmic manifestations compared to duration of ARV consumption > 5 years. It was possible caused consumption period the length of the ARV will be lower plasma levels of HIV RNA permanent, lowering the viral load and will increase CD4 levels and will improve immune status and decrease the infection opportunistic.[17,18]

This study has limitations such as there are other factors that can affect neuroophthalmic manifestations such as duration of infection, other systemic diseases and duration of ARV therapy that has been given. In this study, it was not assessed whether neuroophthalmic abnormalities occurred before or after ARV administration, so it could not be assessed whether neuroophthalmic manifestations were affected by ARV administration. In addition, this study did not assess co-infection in HIV positive patients. Co-infection with HIV such as tuberculosis, hepatitis C can reduce CD4 levels and reduce the immune response so that it can have an impact on opportunistic infections that can cause neuroophthalmic manifestations.

CONCLUSION

The most common neuroophthalmic manifestations found in subjects with CD4 levels < 200 cells/μ L with most manifestations form symptom view blur and disorder fundoscopy. There was a significant relationship between CD4 levels and neuroophthalmic manifestations in HIV positive patients ($p < 0.05$). Neuroophthalmic examination screening should be performed in people with HIV/AIDS, especially in patients with CD4 levels < 200 cells/μL to reduce visual impairment and blindness.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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