CLINICAL STUDY

Failure of accommodation in patients with HIV infection

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Abstract

Purpose **The principal objective was to test the hypothesis that HIV-positive patients have significantly reduced amplitudes of accommodation compared with controls. The secondary objective was to investigate accommodative impairment in relation to factors such as age of susceptibility, CD4 count, viral load and current antiretroviral therapies.**

Method **The study was a single-center open prospective study involving a subject population of 43 HIV-positive men aged from 26 to 39 years with no previous history of eye problems and 21 age-matched healthy male controls. The main outcome measure was the amplitude of accommodation, as measured monocularly with a standard push-up technique.**

Results **Amplitudes of accommodation were significantly smaller in the HIV-positive group compared with controls for age groups 25–29 ($p = 0.016$) and 30–34 years ($p = 0.030$) but not in the older group. In total, 30% (8/27) of patients aged between 25 and 34 years had reduced amplitudes of accommodation below age-expected norms. Accommodative failure was not related to current or lowest CD4 count, viral load or specific antiretroviral therapies.**

Conclusion **This study has identified accommodative failure in a significant proportion of HIV-positive patients aged between 26 and 35 years. This problem may be under-recognised, and further studies are warranted to investigate possible causes.**

Key words Accommodation, HIV, Lens, Presbyopia

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We have observed in our clinical practice that a significant proportion of HIV-positive patients complain of accommodative difficulties at ages well below that of presbyopia. A literature review showed that the question of HIV-associated impairment of accommodation has received little attention to date since Newsome first described reduced amplitudes of accommodation in AIDs patients.[1] An ARVO abstract by Wu and associates reported significantly reduced amplitudes of accommodation in a small sample of 10 patients with AIDS compared with controls.[2] However, to date the only published survey to provide a quantitative estimate of the prevalence and severity of accommodative failure across different ages in HIV-positive patients has been by Thierfelder and associates in 1994.[3] They reported reduced amplitudes of accommodation outside normal limits in two-thirds of patients.

The study by Thierfelder and associates was before the advent of highly active antiretroviral therapy (HAART). Since the advent of HAART there has been a decrease in the incidence of AIDS-related opportunistic infections such as cytomegalovirus (CMV), disseminated *Mycobacterium avium* complex and *Pneumocystis carinii* pneumonia infections, and a prolonged survival.[4,5] This effect has occurred even in those patient with severe immunosuppression when HAART was commenced.[6,7] The primary aim of this study was to investigate the extent of accommodative problems in a cohort of HIV-positive patients in the light of current antiretroviral therapies. A secondary aim was to further understand its aetiology by investigating for possible associations between accommodative impairment and factors such as immune status, antiretroviral therapy or intercurrent medical conditions.

The decline in the incidence of opportunistic infections associated with HIV infection and the improved survival rates are likely to make failure of accommodation an increasingly significant clinical problem. Accommodative failure is important for ophthalmologists to recognise as the prescription of presbyopic reading correction makes it one of the most easily treated ocular manifestations of HIV infection.

Method

Subjects

Previously diagnosed HIV-positive patients were invited to attend for a sight test. Patients were recruited via medical staff and

information leaflets, and were invited to take part in the study irrespective of whether they were, or were not, suffering from accommodative difficulties. The study was approved by the hospital ethics committee and followed the tenets of the Declaration of Helsinki. All patients and controls gave informed consent prior to agreeing to participate. Subjects with significant ocular, medical or therapeutic histories known to affect accommodation were excluded. All patients tested were outpatients, and terminally ill or bedridden patients were excluded. Subjects were given an orthoptic assessment and had a full history taken. All subjects underwent autorefraction and subjective refraction to ensure that they had a visual acuity of 20/40 or better in both eyes, obtained under emmetropia or with a refractive error of no greater than ± 1.75 D.

The study group comprised 43 patients meeting the above eligibility criteria, and 21 age-matched normal controls. The mean age and age distribution of the patients was 33.6 ± SD 3.4 years (range 26.1–39.9 years), which was closely matched by the controls' mean age of 32.2 years ± SD 4.1 years (range 26.1–39.9 years) (non-significant difference; $p = 0.151$, unpaired t-test).

Eleven of forty-three (26%) patients were not taking any systemic medications at the time of the study. The remaining 32 patients were on single or combination antiviral agents including stavudine ($n = 28$), lamivudine ($n = 22$), zidovudine ($n = 15$), aciclovir ($n = 12$), didanosine ($n = 12$), indinavir ($n = 11$), ritonavir ($n = 11$), saquinavir ($n = 11$), zalcitabine ($n = 6$), nelfinovir ($n = 3$) and nevirapine ($n = 2$). The median number of medications per patient was 4, range 2–7. None of the patients was taking any other medications.

To analyse the effect of age on accommodative amplitude, the subjects were further divided according to three equal age intervals of 25–29, 30–34 and 35–39 years. Variance analysis showed no difference at the $p < 0.05$ level of significance between the mean ages of the patients versus controls within each age interval (Table 1).

There were no statistically significant differences in the distributions of visual acuity and refractive error, which were well matched between patients and controls. Forty-two of 43 patients had visual acuities in both eyes of 20/30 or better and 1 patient 20/40 corrected. Twenty-seven of 43 were emmetropic whilst the remaining had spherical equivalent refractions within +1.5 to –1.6 D. All 21 controls had visual acuities of 20/20 or better. Twenty of 21 were emmetropic, and 1 subject had a spherical refraction of –1 D.

Testing procedure

Pupil diameter was recorded prior to testing to ensure that there were no pupillary abnormalities evident which could affect accommodation amplitude. No pupil size differences were identified between the patient and control groups.

The amplitude of accommodation was assessed using a traditional push-up method under monocular conditions, using a test card which was moved slowly towards the subject. The subjects were told to report when the test card (N5 print) became blurred and difficult to read. Testing was performed by one experimenter (M.W.) in a standardised manner. The order in which the eyes were tested was randomised.

This was repeated three times and the average of the three test results was taken. Amplitudes of accommodation are presented as a mean of subjects' left and right eyes. All recordings were made in dioptres (D).

Patient chart review was performed to identify any factors in the underlying medical history which could be associated with impaired accommodation. Past and present medical therapy, including antiretroviral therapy, was also recorded. Also recorded was the current and lowest CD4 count, and the current and highest viral load, if available. Patients known to have diabetes were excluded, as this is known to be associated with impaired accommodation,[8] and all patients tested had a documented recent random blood glucose measurement below 11 mmol/l.

Analysis

All variables were tested for normality. To test the hypothesis that the amplitudes of accommodation were significantly different, two-way analysis of variance (ANOVA) was used to compare variables between the groups. Post-hoc Student–Newman–Keuls tests were performed to identify significant differences between patients and controls for each age group.

Possible associated factors such as CD4 count, lowest CD4 count, current viral load and highest viral load (where available) were examined using two-way analysis of variance to examine for significant differences between patients with normal accommodative ranges, and those below 1.96 SD of control mean. We set the level of statistical significance at $p < 0.05$.

Results

Amplitudes of accommodation are shown as a scatterplot (Fig. 1) and grouped by age (Fig. 2). ANOVA identified the subject's age ($p = 0.020$), and whether he

Table 1. *Age distribution of patient and control population, grouped by ages 25–29, 30–34 and 35–39 years*

Age group (years)	Patients (mean + SD, range, number)	Controls (mean + SD, range number)
25–29	27.9 + 1.4 (r. 26.1–29.6, $n = 7$)	27.2 + 1.3 (r. 26.1–29.4, $n = 6$)
30–34	32.9 ± 1.2 (r. 31.2–34.9, $n = 20$)	32.1 ± 0.9 (r. 30.2–33.0, $n = 9$)
35–39	36.9 ± 1.5 (r. 35.1–39.9, $n = 16$)	37.3 ± 2.0 (r. 35.1–39.9, $n = 6$)

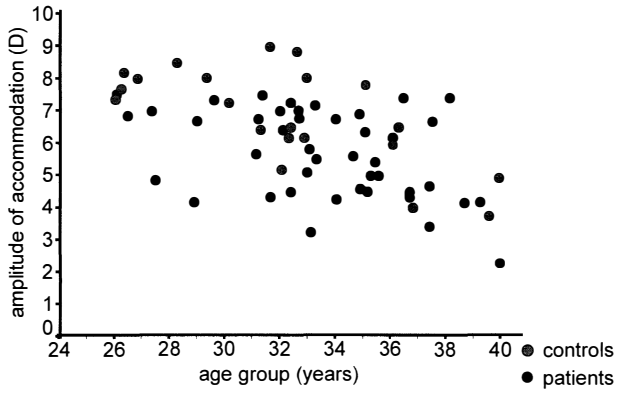

Fig. 1. *Scatterplot of amplitude of accommodation in dioptres versus age for controls and patients.*

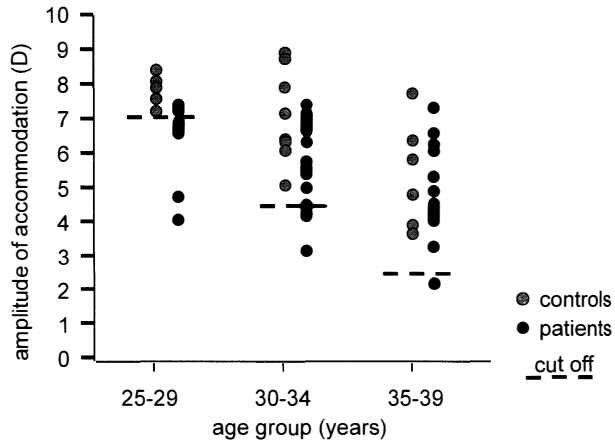

Fig. 2. *Amplitudes of accommodation in dioptres of controls and patients, grouped by age 25–29, 30–34 and 35–39 years. Dashed horizontal lines show subjects outside the normative range (mean –1.96 SD of controls for each age group).*

was a patient or a control ($p = 0.001$), as factors contributing significantly to amplitude of accommodation. The mean amplitude of accommodation was significantly smaller in patients compared with controls in the age group 25–29 years ($p = 0.016$) and age group 30–34 years ($p = 0.030$), but not the age group 35–39 years (Table 2, Fig. 2).

In the age group 25–29 years, amplitudes of accommodation were markedly smaller in the patients: 5 of 7 patients had amplitudes below the control mean –1.96 SD (7.2 D), and outside the control range. The accommodative amplitudes of these patients were substantially depressed to as little as 4 D, to a degree that would have been expected in healthy subjects 10 years older (Fig. 2).

In the age group 30–34 years, 3 of 20 had amplitudes below the control mean –1.96 SD (4.5 D) and 6 of 20 had amplitudes outside the control range (Fig. 2).

For the age group 35–39 years, there was large overlap between controls and patients and only 1 of 16 patients had an accommodative amplitude outside the control mean –1.96 SD (2.5 D).

We did not find any relationship between refractive error and an abnormally reduced amplitude of accommodation. The majority of patients were emmetropic: 21 of 34 (61%) with a normal amplitude of accommodation, and 6 of 9 (67%) with an abnormally reduced amplitude of accommodation. The remainder had low refractive errors (< ± 2 D).

Possible factors associated with impaired accommodation were examined using two-way analysis of variance between those patients with abnormal versus normal amplitudes of accommodation. Mean values were similar and no significant differences were identified for any variables (CD4 count, $p = 0.4$; lowest CD4, $p = 0.1$; viral load, $p = 0.4$; highest viral load, $p = 0.9$). However, the wide individual spread (large SD) of all the variables in our population resulted in a low power to detect significant differences (< 0.6).

Chart review did not identify any particular antiretroviral combinations associated with impaired accommodation.

In none of the patients with impaired accommodative amplitude was a pre-existing neurological or other contributory factor identfied; however, 1 patient did have a history of intravenous drug abuse.

Discussion

This study has confirmed that amplitudes of accommodation are significantly reduced in HIV-positive patients. Overall, 30% (8/27) of patients aged 25–34 years had reduced amplitudes of accommodation below our age-expected limits for normal controls. The age group with the highest proportion of affected patients was 25–29 years, the youngest age group tested. The degree of accommodative impairment was also greatest in this age group, compared with older age groups. In contrast, amplitudes of accommodation in older patients (35–39 years) were largely indistinguishable from controls. One explanation for this is that for ages above 35 years, accommodative

Table 2. *Mean amplitudes of accommodation by age group, with group mean differences and significant test (unpaired t-test)*

Age group (years)	Patient amplitude of accommoation (dioptres) (mean ± SD, range, number)	Control amplitude of accommodation (dioptres) (mean ± SD, range, number)	Mean difference (+ 95% CI) (*p*)
25–29	6.3 + 1.3 (r. 4.2–7.5, *n* = 7)	7.9 + 0.4 (r. 7.3–8.5, *n* = 6)	1.6 (0.4–2.8) $p = 0.016$
30–34	5.9 + 1.2 (r. 3.3–7.5, *n* = 20)	7.1 ± 1.3 (r. 5.2–9.0, *n* = 9)	1.2 (0.2–2.2) $p = 0.030$
35–39	5.1 ± 1.4 (r. 2.3–7.4, *n* = 16)	5.5 ± 1.5 (r. 3.8–7.8, *n* = 6)	0.4 (−1.1–1.8) $p = 0.6$

amplitudes have already declined markedly as presbyopia approaches, so that any pathological process further compromising accommodation will have little effect. One possibility to consider is the role of selection bias in our study. The recruitment methods were tailored to ensure that patients were not recruited on the basis of the presence of symptoms in order to minimize selection bias. Nevertheless we cannot exclude the possibility that those patients with symptoms of accommodative failure were more likely to attend for examination and our findings may represent an overestimate of the true prevalence of impaired accommodation. Larger community-based studies will be needed to address this issue.

Our findings should alert clinicians to the existence of accommodative difficulties in a substantial proportion of HIV-positive patients under 35 years. The decline in severe sight-threatening ocular disease that has accompanied the introduction of HAART means that accommodative impairment may represent a considerable cause of morbidity in the HIV-positive population.

At present, the cause of HIV-associated accommodative failure is not understood. The study by Thierfelder and associates[3] was performed before the advent of highly active antiretroviral therapy (HAART) and failed to find any relationship between accommodative failure and CD4 count. Our results also support this finding. In addition we have not found any relationship between accommodative failure and particular antiretroviral combinations. Putative mechanisms can be proposed by considering the mechanism of accommodation and its age-related decline.

Theories to explain the decline of accommodation with increasing age (presbyopia) can be divided into lenticular and extralenticular theories.[9] Lenticular theories are dominated by the Hess–Gullstrand theory.[10] This suggests that presbyopia arises as a consequence of increasing resistance of the lens to deformation with age, associated with an increasing resistance of the lens to the forces of the capsule. It is thought that the ciliary muscle tone remains relatively constant through life, and that an increasing excess of the ciliary muscle contraction becomes unused with age. The mechanisms to explain how the lens may become increasingly inelastic with age are poorly understood and *in vitro* studies of the relationship between ciliary body force and accommodation with age have not supported the Hess–Gullstrand theory.[11] Nevertheless it remains a possibility that accommodative impairment in HIV-positive patients may arise secondary to changes in the lens resistance to deformation, as a consequence of either age-accelerated changes or pathological change. Experimental studies have shown that transgenic mice containing the HIV-1 protease linked to the lens alpha A-crystallin promoter develop cataract.[12,13] This is typified in the early stages by posterior lens cortex disintegration, while the lens is still clear, progressing to total lens fibre disintegration and cataract in the late stages.[13] It is possible that a similar process occurs in the lens fibres in human HIV infection, and that this may alter the deformation of the lens. This raises the important clinical question of whether those patients with accommodative difficulties should be observed for the future development of cataract. This concern needs to be addressed in future studies.

In addition to lenticular mechanisms, extralenticular mechanisms may be important for the development of presbyopia, and for the accelerated decline of accommodation in HIV-positive patients. A decline in ciliary muscle contraction was first proposed as a cause of presbyopia by Duane.[14,15] However, in normal subjects there is evidence that the decline in ciliary body contractility is only minimal before the age of 45–50 years.[11] In HIV-positive patients it is possible that impairment of the ciliary body muscle occurs, as a consequence of either direct changes to the muscle or parasympathetic neuropathy. The causal role of a parasympathetic neuropathy is a possibility as several studies have shown that autonomic neuropathy is frequently found early in the course of HIV infection. Systemic autonomic impairment has been demonstrated with cardiovascular tests of autonomic function such as heart rate variation to the Valsalva response and systolic blood pressure fall to standing.[16–18] Furthermore a study by Maclean and Dhillon[19] reported impaired pupil cycle times in HIV-positive patients compared with controls, providing direct evidence of ocular involvement of autonomic dysfunction. The published evidence of subclinical ocular autonomic dysfunction in patients with early stages of HIV infection leads us to hypothesise that this is a causative factor for the accommodative failure in our patients, although evidence for this will have to await further studies. Such a mechanism may also be a factor in other diseases known to cause autonomic dysfunction, such as diabetes, which are also associated with reduced accommodative amplitudes.[8]

In summary, this study has identified accommodative failure in a significant proportion of HIV-positive patients aged between 26 and 35 years of age. This problem may be under-recognised, and further studies are warranted to investigated possible causes. As the survival of HIV-positive patients continues to increase, it is important that clinicians are aware of those patients with accommodative failure, which is an easily treatable manifestation of HIV infection.

References

1. Newsome DA. Noninfectious ocular complications of AIDS. Int Ophthalmol Clin 1989;29:95–7.
2. Wu P, Williams JG, Phillips BJ, Khanna A, Friedlander SM, Goldstein DA. Loss of accommodative amplitude in aids patients. Invest Ophthalmol Vis Sci 1997;38 (Suppl):1101.
3. Thierfelder S, Mellinghoff-Kreplin G, Hasenfratz G. Clinical studies of reduced accommodation in patients with HIV-1 infection. Klin Monatsbl Augenheilkd 1994;204:523–6.
4. AIDS-indicator conditions diagnosed in patients reported in 1996, by age group. United States: HIV/AIDS Surveillance Report, Center for Disease Control, Atlanta 1997:8:18.

5. Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K, Schechter MT, *et al*. Decline in deaths from AIDS due to new antiretrovirals [letter]. Lancet 1997;349:1294.
6. Mitchell SM, Membrey WL, Youle MS, Obi A, Worrell S, Gazzard BG. Cytomegalovirus retinitis after the initiation of highly active antiretroviral therapy: a 2 year prospective study. Br J Ophthalmol 1999;83:652–5.
7. Walsh JC, Jones CD, Barnes EA, Gazzard BG, Mitchell SM. Increasing survival in AIDS patients with cytomegalovirus retinitis treated with combination antiretroviral therapy including HIV protease inhibitors. Aids 1998;12:613–8.
8. Pawelski WJ, Gliem H. The accommodation range in diabetics. Ophthalmologica 1971;163:216–26.
9. Atchison DA. Accommodation and presbyopia. Ophthalmic Physiol Opt 1995;15:255–72.
10. Hess C. Arbeiten aus dem Gebiete der Accommodationslehre. Graefes Arch Klin Exp Ophthalmol 1901;52:143–74.
11. Fisher RF. The force of contraction of the human ciliary muscle during accommodation. J Physiol (Lond) 1977;270:51–74.
12. Tumminia SJ, Jonak GJ, Focht RJ, Cheng YS, Russell P. Cataractogenesis in transgenic mice containing the HIV-1 protease linked to the lens alpha A-crystallin promoter. J Biol Chem 1996;271:425–31.
13. Bettelheim FA, Churchill AC, Siew EL, Tumminia SJ, Russell P. Light scattering and morphology of cataract formation in transgenic mice containing the HIV-1 protease linked to the lens alpha A-crystallin promoter. Exp Eye Res 1997;64:667–74.
14. Duane A. Studies in monocular and binocular accommodation with their clinical applications. Am J Ophthalmol 1922;5:865–77.
15. Duane A. Are the current theories of accommodation correct? Am J Ophthalmol 1925;8:196–202.
16. Welby SB, Rogerson SJ, Beeching NJ. Autonomic neuropathy is common in human immunodeficiency virus infection. J Infect 1991;23:123–8.
17. Becker K, Gorlach I, Frieling T, Haussinger D. Characterization and natural course of cardiac autonomic nervous dysfunction in HIV-infected patients. Aids 1997;11:751–7.
18. Freeman R, Roberts MS, Friedman LS, Broadbridge C. Autonomic function and human immunodeficiency virus infection. Neurology 1990;40:575–80.
19. Maclean H, Dhillon B. Pupil cycle time and human immunodeficiency virus (HIV) infection. Eye 1993;7:785–6.