Pursuit Eye Movement Dysfunction in HIV-1 Seropositive Individuals

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Studies of smooth pursuit eye movements were conducted in 30 ambulatory drug-free HIV-1 seropositive patients who did not yet manifest marked clinical signs of the AIDS Dementia Complex. Seropositive patients demonstrated disturbances in pursuit eye movements that were correlated with extent of immunosuppression, with impairments on neuropsychological tests of fine motor control/ speed, and with independent clinical staging of the AIDS Dementia Complex. The results provide quantitative evidence that oculomotor disturbances are present in HIV-1 seropositive individuals before the manifestation of marked AIDS Dementia Complex. For this reason, and because more severe eye movement impairments have been observed in patients with AIDS, quantitative eye movement studies may provide a useful neurobehavioral procedure for characterizing and monitoring progression of CNS involvement associated with HIV-1 infection from early in its course.

Key Words: HIV-1, AIDS, pursuit eye movements

Abnormalities of the central nervous system frequently accompany the acquired immune deficiency syndrome (AIDS) through opportunistic infections, neoplasms and by way of a subcortical dementia (Brew 1988; Michaels et al 1988; Price et al 1988). Postmortem studies of AIDS patients have revealed histopathologic abnormalities in central white matter, deep grey structures including the basal ganglia and thalamus, and the brain stem and spinal cord (Petito et al 1985; Navia et al 1986). HIV-1 has been identified in the central nervous system at post-mortem (Koenig et al 1986; Resnick et al 1988).

HIV-1 infection of the CNS can lead to a dementing syndrome referred to as the AIDS Dementia Complex (ADC) (Navia et al 1987; Price et al 1988). Neuropsychological studies of this dementia have indicated that impairments of attention and motor control are its most common early manifestations (Tross et al 1988). In later stages of the disorder, cognitive and motor abnormalities become more global and severe.

Quantitative characterization of oculomotor functioning offers a particularly promising approach for studying the disturbances of attention and motor control that are early manifestations of HIV-1 infection of the brain. Such studies may help elucidate the prevalence, severity and course of such dysfunctions. Assessing neurobehavioral functions early in the course of HIV-1 infection is especially important because the question of whether HIV-1 infection causes cognitive impairments early in its course is an important medical-legal and public health issue.

Clinical case descriptions of oculomotor abnormalities in HIV-1-infected patients have been reported (Tervo et al 1986), as have some quantitative studies of eye movements. However, in previous studies samples were typically small, some patients were already manifesting severe ADC, and the possible confounding influence of opportunistic infections, neoplasms, drug abuse history and CNS-active medications was not clarified.

In a study by Currie et al (1988) which focused primarily on the saccadic eye movement system, hypometric saccades and fixation instability were highly correlated with the severity of ADC. Other studies replicated the observation of abnormal saccades in HIV-1 infected individuals (Pfister 1989; Nguyen and Rimmer 1989). Currie et al (1988) reported that pursuit performance was "impaired", but did not quantify *gain* of the pursuit eye movement system which is the direct index of the functional integrity of the pursuit system. Also, they did not report on the relationship between

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pursuit dysfunction and neuropsychological or neurologic abnormalities. Pfister et al (1989) observed impaired pursuit during neurologic exam in 6 of 22 seropositive cases, but 9 of these patients had already been diagnosed with AIDS, and quantitative studies of eye movements were not performed.

The present study was undertaken to evaluate the smooth pursuit eye movement system in HIV-1 seropositive patients in order to determine whether a disturbance in this motor system is present before individuals manifest marked or severe signs of ADC. The relationships between pursuit performance and neuropsychological impairments thought to characterize ADC, and with degree of immune suppression, were assessed to evaluate possible relationships between pursuit impairment and the extent of disease-related behavioral and physiological abnormalities.

METHODS

Thirty ambulatory patients (mean age = 39, SD = 9) with known HIV-1 infection confirmed by Western blot assay were recruited. Twenty-five healthy control subjects were recruited from the hospital staff and from community advertisements. Control cases (mean age = 37, SD = 9) were selected on the basis of having no known risk factors for HIV-1 infection, and no known history of psychiatric or neurologic illness. The large majority of HIV-1 infected patients were homosexual (only 2 had a history of iv drug abuse), and all but one were male. Patients were followed clinically for 6 months after testing; cases were excluded in whom neoplasms or neurologic disease other than ADC were identified. All subjects were fully alert and were taking no medication known or suspected to interfere with eye movements.

Subjects were instructed to visually track a small target (an 'X' subtending 0.7 degrees of visual angle) oscillating in the horizontal plane for 30 seconds at 0.4 Hz across +/-10 degrees of visual angle. Patients were in a chin and head restraint during testing, and tasks were presented in a darkened quiet room. Patients were actively encouraged to focus their attention on the moving target, and performance was monitored on-line so that subjects could be immediately re-alerted if they stopped tracking the target. Eye movements were monitored with infrared reflection (IR) spectacles (Applied Sciences Laboratories). Sensor signals were low pass filtered, digitized at 250 Hz. by a Techmar Labmaster A/D converter, and stored on disk for later off-line analysis with custom software. Calibration targets presented at 9 points across the display screen at increments of 3 degrees of visual angle from center were used as parameters in a linearization function to convert subjects' IR sensor recordings to eye movement in degrees of visual angle.

In one trial, the target oscillated at a constant velocity (a triangular waveform stimulus). Pursuit gain (average pursuit velocity/target velocity) was calculated from performance during this trial because the constant velocity of the target provides a direct comparison base against which the velocity of each sample of pursuit can be compared. The velocity of pursuit was calculated on a sample-to-sample basis after editing out blinks, saccades (samples where acceleration exceeded 700 deg/sec^2), pauses after anticipatory saccades, and infrequent periods of gross inattention.

Pursuit of the first and last target oscillation were excluded, yielding a maximum of 6250 samples (25 seconds of pursuit sampled at 250 Hz.) of tracking for quantitative analysis. The sample-to-sample velocities were averaged and divided by the target velocity to evaluate pursuit gain. In addition, the standard deviation of eye velocity samples was computed for each subject to assess variability in pursuit velocity. Two other measures of pursuit variability were also obtained to characterize gross disturbances in maintaining a steady-state pursuit velocity: the number of samples of pursuit with unusually high velocity (pursuit velocity greater than 1.5 times target velocity) and atypically slow pursuit velocity (pursuit velocity less than 20% of target velocity).

In two other trials, subjects tracked a target moving at a sinusoidal (pendular) velocity, in which the target slowed to zero velocity at the endpoints of target excursion. The total frequency of anticipatory saccades, corrective saccades and square wave jerks (SWJ's) were tabulated during these two 30-second trials. These parameters of saccadic eye

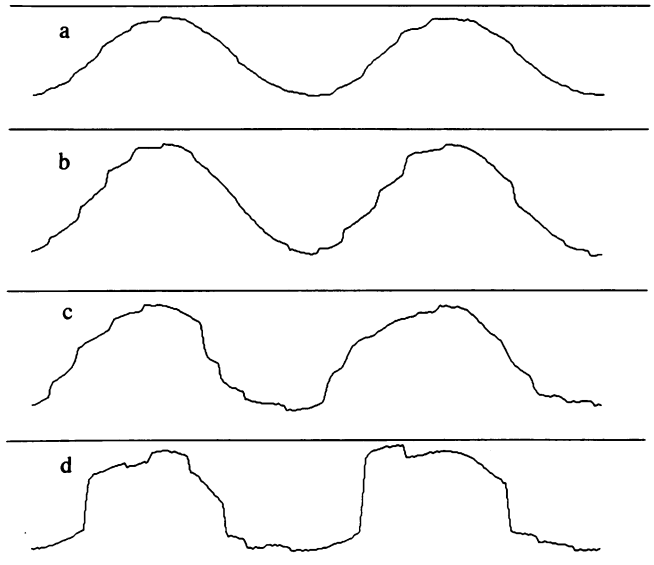

Fig. 1. Pursuit tracking records from 4 HIV-1 seropositive patients demonstrating records with (a) small corrective saccades, and moderate (b & c) and more marked (d) impairments of pursuit. Saccadic eye movements are evident as sudden deviations from the sinusoidal form of the tracking record. Differences in signal amplitude from different patients reflect differences in waveform amplifications rather than differences in degree of lateral pursuit excursion.

movement activity were examined under this condition because the demand for abrupt reversal in pursuit direction at the endpoints of target excursion during pursuit of constant velocity oscillating targets can elicit multiple corrective saccades that are not "catch up" saccades in the sense of compensating for slow pursuit, and which can be difficult to distinguish from intrusive "square wave jerks" and smaller anticipatory saccades.

Neuropsychological evaluation was conducted with the HIV-1 infected sample with widely used and well-standardized tests (see Table 3), including: the Rey Auditory Verbal Learning Test (total recall over 5 trials), the Verbal Fluency Test (FAS word production), the Digit Span, Digit Symbol, Block Design and Vocabulary tests from the WAIS-R, the Trail Making Test Form A and Form B, and the Benton Visual Retention Test. For the Finger Tapping Test and the Grooved Pegboard Test, no lateral asymmetries in performance were identified, so scores for the dominant and non-dominant hand were averaged to provide a single index of performance. A neurological examination of the HIV-1 seropositive patients was conducted, and a ADC rating was assigned (c.f. Price and Brew 1988). The ADC ratings of the patients were as follows: 13 no ADC; 8 equivocal findings; 6 mild ADC; and 3 moderate ADC. No patient had severe or vegetative ADC. Neuropsychological testing, and the neurologist's clinical ratings of ADC stage and gait and limb dys-coordination (on a 4 point severity scale), were conducted without knowledge of results of eye movement studies.

RESULTS

There was no mean decrease in average pursuit gain in the HIV-1 infected individuals compared with that of the normal control group. However, there was significantly increased variability in pursuit velocity during visual tracking. The standard deviation of sample-to-sample velocity measurements was calculated for each subject as an index of pursuit variability. Variability was higher in the patients than controls (t (53) = 2.90, $p < .01$; see Figure 2). The number of samples with unusually fast (t (53) = 2.25, $p < .05$) and slow (t (53) = 2.86, $p < .01$) pursuit velocity were significantly increased in the HIV-1 infected patients. In addition, the frequency of corrective saccades was greater in the HIV-1 infected patients (t (53) = 3.47, $p < .001$).

No pattern of intrusive saccadic eye movements other than occasional SWJ's or anticipatory saccades was observed. There was no increase in anticipatory saccades in the HIV-1 infected patients, and the frequency of SWJ's was actually significantly *lower* in the HIV-1 group than the controls ($t(53) = 2.67, p < .01$). There were no significant lateral asymmetries in any eye movement measure.

ADC ratings were correlated significantly with indices of pursuit variability, suggesting that eye movement abnormalities may increase with progression of disease. Clinical ratings of limb dys-coordination and the presence of abnormal jaw jerk reflex were also associated with the amount of fast and slow pursuit eye movement activity. Greater immune suppression, as indexed by CD4+ ratios, was positively associated with catch-up saccade rate (r (24) = -.43, $p < .05$). Excluding one apparent outlier (see Figure 3) substantially increased this correlation (r (23) = -.68, $p <$

Table 1
Comparisons of HIV-1 infected individuals and normal controls on eye movement measures obtained during visual pursuit tracking

	Normal Controls		HIV-1 Infected Patients	
	$\bar{X}$	SD	$\bar{X}$	SD
Average Pursuit Gain	.86	(.06)	.84	(.08)
S.D. of Each Subject's Pursuit Velocity	.32	(.08)	.38	(.09)[b]
# Pursuit Samples With Velocity > 150% of Target Velocity	232	(102)	302	(131)[a]
# Pursuit Samples With Velocity < 20% of Target Velocity	226	(83)	317	(147)[b]
# Corrective Saccades	29.8	(7.6)	39.4	(12.8)[b]
# Anticipatory Saccades	2.0	(3.7)	2.0	(4.1)
# Square Wave Jerks	5.0	(4.8)	2.1	(2.4)[a]

[a] = $p < .05$
[b] = $p < .01$

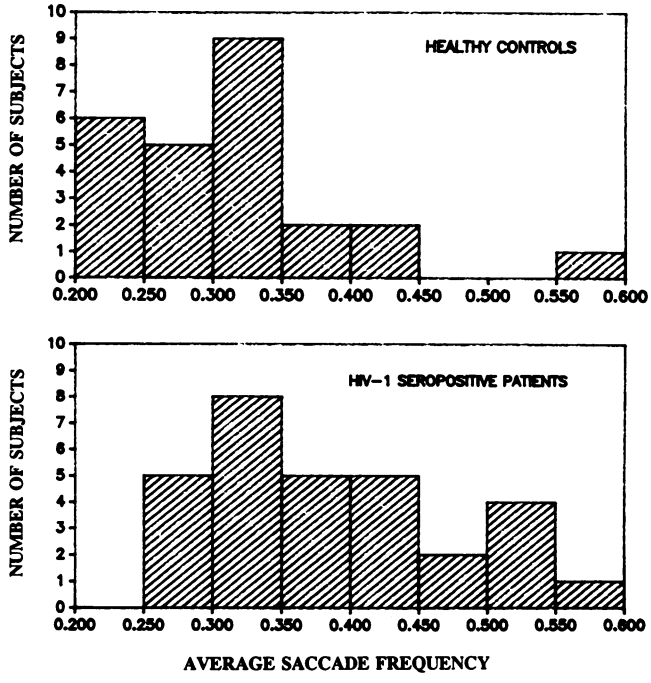

Fig. 2. Standard deviation of all samples of pursuit eye movement activity calculated for each HIV-1 seropositive patient and healthy control subjects.

Table 2
Correlations of pursuit eye tracking performance with ADC staging, CD4+ ratio and clinical and neuropsychological ratings of motor system disturbances

	Pursuit Gain	S.D. of Pursuit Velocity	Fast Pursuit	Slow Pursuit	Catch-up Saccades
Clinical ADC Staging	-.30	.66[c]	.58[c]	.63[c]	.53[b]
Gait Coordination	-.07	.37	.34	.17	.12
Limb Coordination	-.32	.28	.52[b]	.38[a]	.36
Jaw Jerk Reflex	-.11	.32	.59[c]	.38[a]	.38[a]
Finger Tapping Rate	.63[c]	-.07	-.20	-.52[b]	-.21
Grooved Pegboard Time	-.53[b]	.06	.22	.41[a]	.46[a]
CD-4 Lympho-cyte Ratio	.32	-.33	-.35	-.33	-.43[a]

[a] = $p < .05$
[b] = $p < .01$
[c] = $p < .001$

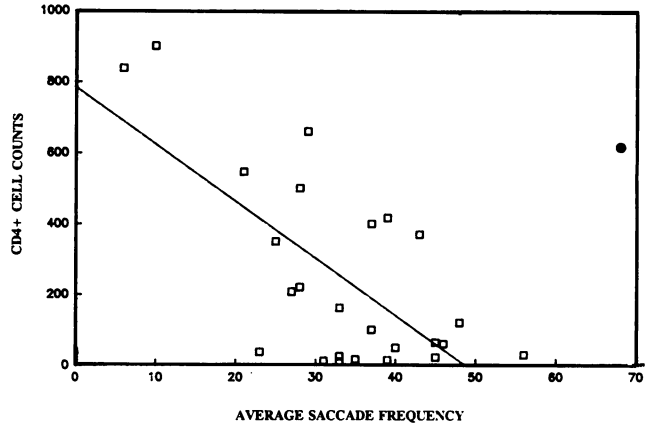

Fig. 3. Frequency of catch-up saccades during 60 seconds of pursuit tracking as a function of the CD4+ cell count. The regression line was drawn with a single outlier (circle) excluded. The correlation between catch up saccades and CD4+ count was -.68 with the outlier excluded and -.43 with that patient included.

Table 3
Performance of HIV-1 infected individuals on neuropsychological tests

	Mean Score	Standard Deviation
Rey AVLT	50.9	10.2
Verbal Fluency (FAS)	40.0	12.9
WAIS-R Digit Span	10.7	2.2
WAIS-R Digit Symbol	10.7	2.5
WAIS-R Block Design	11.9	2.4
WAIS-R Vocabulary	11.6	2.6
Trail Making Test		
Form A	29.1 sec.	14.7
Form B	68.5 sec.	36.0
Benton Visual Retention Test	3.8 errors	2.7
Finger Tapping	44.9	6.4
Grooved Pegboard	75.1 sec.	17.5

AVLT = Auditory Verbal Learning Test (total words recalled from 15 word list over 5 trials); WAIS-R = Wechsler Adult Intelligence Scale — Revised (scaled scores).

.001). There were trends ($p < .10$) toward relationships between CD4+ ratios and all three indices of pursuit variability.

In the HIV-1 infected group, correlations between the eye movement measures and performance on neuropsychological tests were examined in exploratory analyses (see Table 2). Pursuit disturbances were associated with neuropsychological tests of motor functioning (Finger Tapping and Grooved Pegboard Tests). For these relationships, reduction in the velocity of pursuit (amount of slow pursuit and average pursuit gain), rather than variability of pursuit, was associated with slow performance on tests of fine motor control/speed. There were no significant correlations between indices of smooth pursuit and scores on tests of a wide range of cognitive skills including Benton's Verbal Fluency and Visual Retention tests, the Rey Auditory Verbal Learning Test, WAIS-R Digit Span, Digit Symbol and Block Design, and Trail Making Test Forms A and B.

The number of correlations examined raises the risk of Type 1 error, and these associations must be considered tentative until they are replicated. Caution is therefore required in the interpretation of these analyses. However, the pattern of correlations between clinical ratings and neuropsychological test performance with eye movement measures *suggests* that early pursuit disturbance in HIV-1 infected individuals may be associated with reduced performance on motor tasks, but not with higher intellectual functioning.

DISCUSSION

The principal results of this study were as follows: 1) increased variability in pursuit eye movement velocity and increased frequency of corrective saccades were present in HIV-1 infected individuals even in the absence of marked clinical manifestations of AIDS Dementia Complex; and 2) some indices of pursuit eye tracking dysfunction were associated with clinical ratings of the AIDS Dementia Complex, extent of immunosuppression, and with both clinical ratings and neuropsychological tests signs of motor

system impairments. There were no significant correlations between pursuit performance and scores on tests of higher intellectual functions such as verbal fluency, verbal and visual memory, or visual-spatial reasoning.

The finding that detectable oculomotor abnormalities are present in HIV-1-infected individuals before marked dementia develops suggests that pursuit eye movement abnormalities may be an early sign of CNS infection in HIV-1-seropositive patients. The associations between neuropsychological impairments on motor tasks with eye movement measures, and between reduced CD4+ ratios and catch-up saccade rate, are consistent with the inferred linkage between the eye movement deficits and HIV-1 infection of the CNS. Further, these associations suggest that eye movement dysfunctions may increase as HIV-1-induced immunosuppression advances.

There is an urgent clinical need to identify the characteristics and severity of behavioral impairments that occur early in the course of HIV-1 infection of the CNS. Such identified abnormalities might prove useful in identifying individuals at greater risk for ADC, and perhaps for monitoring the neurological benefit of different HIV-1 treatment regimens. Subtle abnormalities in the smooth pursuit eye movement system may be one such sensitive index of CNS infection. If so, these oculomotor abnormalities may provide clues as to the early pathophysiology of HIV-1 infection of the CNS, and oculomotor studies may serve as a noninvasive technique for quantifying progressive changes in the CNS associated with HIV-1 infection.

It is perhaps significant that there was an increased frequency of catch-up saccades during pursuit tracking without a corresponding reduction of pursuit gain (relative eye velocity) in the patient group. Typically, an increase in corrective saccades results from low gain pursuit, because slow pursuit necessitates more frequent "catch-up" saccades to maintain foveation of moving targets (Leigh and Zee 1983). In the absence of reduced average pursuit gain, other possible causes for increased corrective saccade frequency during tracking need to be considered.

In these HIV-1 infected patients, variability in pursuit velocity rather than reduction in average pursuit velocity was the pursuit disturbance observed. It is possible that instability of pursuit velocity may precede an actual decline in average pursuit velocity in HIV-1-infected individuals. In our sample of HIV-1 infected patients, pursuit error caused by periods of slow pursuit was typically followed by corrective saccades, while periods of faster pursuit were followed by brief pauses or periods of low velocity pursuit. The aggregate result was that average pursuit velocity remained within the normal range, but the increased variability in pursuit velocity led to an increased number of corrective saccades initiated to correct for periods of slow pursuit. The overall pursuit disturbance appeared to be one suggesting a disturbance in the ability to integrate sensory feedback and motor control to maintain a stable steady-state pursuit gain.

The physiological disturbance underlying pursuit abnormalities in HIV-1 infected individuals is not clear, as comprehensive understanding of both neural control of pursuit eye movements and the CNS effects of HIV-1 infection are still being developed. However, there are indications that subcortical structures, including the basal ganglia, are affected early in the course of CNS infection by the HIV-1 virus (Rottenberg et al 1987). The clinical presentation of ADC is similar to what has been referred to as "subcortical dementias" (Albert et al 1974), which are characterized by prominent slowing and loss of precision of both motor control and attention without difficulties in language, perception or praxis.

Neurologic diseases with major impact on basal ganglia structures early in their course, such as Wilson's, Parkinson's and Huntington's diseases, cause well-characterized pursuit eye movement abnormalities (Renzi 1988). Oculomotor dysfunctions might be a manifestation of CNS involvement in early stages of HIV-1 infection, perhaps resulting from an early preferential effect on subcortical structures that has been hypothesized in HIV-1 infection. However, cortical dysfunctions can also cause pursuit abnormality, so the localizing significance of pursuit impairments in HIV-1 infection is not yet clear. More comprehensive analyses of eye movement activity are needed to differentiate cortical and subcortical contributions.

In evaluating the significance of our findings of oculomotor abnormalities in HIV-1 infected patients, it is important to consider their severity. The magnitude of the oculomotor abnormalities observed in this study was modest, for example, in comparison with that observed in more severely demented patients with Alzheimer's disease (Hutton 1985) or even severe ADC. The moderate severity of the observed eye movement impairments, however, needs to be considered in light of the phase of illness of the patients studied. To determine whether any impairment in eye movements could be demonstrated early in the course of HIV-1 infection, we deliberately selected a sample manifesting milder manifestations of the AIDS Dementia Complex. As a result, the findings do not reflect the marked disturbance in pursuit eye movements in HIV-1 infected individuals associated with severe ADC (Currie et al 1988). Therefore, the full potential effects of the HIV-1 virus on eye movements probably are not reflected in the results of this study.

As is clear from examining Table 1, while there were significant abnormalities on several measures of eye movement activity in the seropositive patients, there was still considerable overlap between control subjects and HIV-1 infected patients in the early stages of the ADC. Therefore, while pursuit dysfunctions may be a useful index of ADC, they do not appear to be sufficiently robust, on their own, to identify its presence or absence.

Our results do not allow direct inferences to be made about the causal role of the HIV-1 virus in the etiology of the observed pursuit system abnormalities. However, in light of the association between the oculomotor abnormality and both the degree of immunosuppression and indices of motor system dysfunction thought to be caused by the disease, the data seem most consistent with the inference

that the dysfunction in the smooth pursuit eye movement system is an early sign of HIV-1 infection of the CNS. Longitudinal data are needed to study the course of these disturbances, and to verify any prognostic significance to the observed eye movement abnormalities. If these eye movement disturbances do progress with the extent of HIV-1 infection of the CNS, they may provide a quantitative approach for evaluating disease progression and relative benefit from different treatment regimens.

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