Sweep Visual Evoked Potential Evaluation of Contrast Sensitivity in Alzheimer's Dementia

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Purpose. The purpose of this study was to evaluate primary afferent visual pathway function by objectively testing contrast sensitivity in persons with Alzheimer's dementia (AD), using a sweep visual evoked potential technique.

Methods. Twenty-five patients, 16 with AD and 9 elderly control (EC) subjects, were enrolled from the University of Southern California Rancho Los Amigos Medical Center. The patients with AD had clinical dementia ratings ranging from 0.5 to 3, corresponding to mild to moderate disease. All participants underwent refraction and screening for ophthalmic disease. Subjects were evaluated with the sweep visual evoked potential technique. Each trial consisted of logarithmically increasing contrast over a 10-second period. Subjects were evaluated monocularly at spatial frequencies of 1, 5, and 8 cyc/deg. Patients were not required to integrate and respond to stimuli.

Results. Mean contrast sensitivity thresholds were significantly higher in patients with AD than in EC subjects. The mean contrast sensitivities in the AD group were 4.0%, 9.6%, and 18.6%, at 1, 5, and 8 cyc/deg, respectively. The corresponding sensitivities in the EC group were 2.1%, 5.3%, and 11.4%, at 1, 5, and 8 cyc/deg, respectively. These threshold differences were significant at probabilities of 0.01, 0.05, and 0.07. There was no correlation between clinical dementia ratings and reduction of contrast sensitivity thresholds. Confounding factors such as age, gender, nuclear sclerosis, and visual acuity were evaluated. Visual acuity was the only factor significantly different between AD responders and AD nonresponders at 1 and 5 cyc/deg.

Conclusions. These results suggest patients with AD have deficits in contrast sensitivity attributable to dysfunction of the primary afferent visual pathway. (*Invest Ophthalmol Vis Sci.* 2003;44:875–878) DOI:10.1167/iovs.01-1101

Patients with Alzheimer's dementia (AD) present a particular challenge in the assessment of visual function. They may have difficulty fixating, following instructions, and relating reliable subjective visual information. These patients often report that they bump into things and that they have difficulty reading and recognizing faces.[1,2] Caregivers, rather than the patients themselves, frequently notice these visual symptoms first.

Clinical evaluation of patients with AD reveals a variety of visual deficits, including deficiencies in motion perception, color vision, flicker fusion, copying numbers, stereoacuity, backward visual masking, visual attention, visuospatial construction, and visual memory.[1–7] Contrast sensitivity is the most consistent visual deficit in patients with AD and perhaps the most widely studied visual function. Contrast sensitivity is significantly reduced in patients with AD in comparison with elderly control (EC) subjects.[1,4–10] Visual acuity, however, is usually within normal limits for AD patients compared to age-matched control subjects.[4,5,7]

The histopathologic substrate for the observed clinical visual deficits may be found in both the primary visual pathway and the association cortices.[2,11–14] Retinal ganglion cell loss, optic nerve fiber degeneration, and lateral geniculate nucleus lesions have all been documented in the literature.[11,12,14,15] Senile plaques and neurofibrillary tangles are present in the superior colliculus, optic radiations, primary visual cortex, and visual association cortex.[11,13] Thus, it is not clear whether the perceptual deficits in AD are due to the absence of afferent input or an inability to integrate visual information. Few studies have been attempted to isolate these components and test them independently.

The purpose of this study was to evaluate the function of the primary visual pathway by using the sweep visual evoked potential (VEP) technique. We used a sweep technique to assess primary visual function quickly and objectively in patients with AD and EC subjects.[16] Synchronous recordings of amplitude and phase between the temporal frequencies of 10 and 100 Hz can be made in a few seconds. Thus, minimal behavioral requirements are placed on the patient. This technique presents a square-wave pattern, counterphase modulated in contrast at a high temporal frequency and swept at a low spatial frequency. The monitor displays flickering bars that increase or decrease in width. Response is measured as evoked potentials over the visual cortex in response to visual stimuli.

Methods

Sixteen patients with mild to moderate AD and nine spousal control subjects were recruited from the Alzheimer Center at the University of Southern California Rancho Los Amigos Medical Center. The research followed the tenets of the Declaration of Helsinki and was approved by the University of Southern California Institutional Review Board. Informed consent was obtained from all study participants after the nature and possible consequences of the study were explained. Patients were evaluated for degree of AD at the medical center and referred to the Doheny Eye Institute as part of a vision assessment project for patients with memory loss. All subjects underwent full ophthalmic assessment, including refraction. Other than nuclear sclerosis, no ophthalmic disease was found.

AD was diagnosed through a battery of neuropsychological testing, imagining studies, and blood work. The CERAD neuropsychological battery; the Mattis Dementia Scale for attention, construction, memory,

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TABLE 1. Contrast Thresholds at Three Spatial Frequencies for Elderly Control Subjects and Patients with Alzheimer's Disease

						Spatial Frequency					Spatial Frequency		
Subject	CDR	Age	Sex	VA OD (ft)	NS OD (None to 4+)	1 c/deg OD	5 c/deg OD	8 c/deg OD	VA OS (ft)	NS OS (None to 4+)	1 c/deg OS	5 c/deg OS	8 c/deg OS
1	EC	48	F	20/30	Trace	3.42	5.3	6.31	20/25	Trace	NR	6.24	13.61
2	EC	79	F	20/25	1+	1.41	5.28	19.51	20/25	1+	NR	5.82	8.02
3	EC	73	F	20/30	None	2.13	2.75	NR	20/20	None	1.95	7.07	11.51
4	EC	74	M	20/40	2+psc	NR	4.26	NR	20/25	1+	NR	5.91	16.65
5	EC	74	F	20/20	Trace	1.47	NR	NR	20/20	Trace	NR	NR	11.21
6	EC	79	F	20/40	Not rec.	NR	NR	NR	20/25	Not rec.	NR	5.19	3.98
7	EC	89	F	20/30	None	NR	NR	NR	20/25	None	NR	19.02	NR
8	EC	73	F	20/50	1+psc	NR	NR	NR	20/25	1+psc	NR	5.39	NR
9	EC	57	M	20/20	None	NR	NR	NR	20/25	None	NR	NR	NR
10	1.5	76	F	20/25	2+	1.91	4.11	9.16	20/30	2+	NR	18.65	29.54
11	1	80	M	20/25	1+	5.39	6.66	17.24	20/25	1+	NR	7.91	NR
12	1	62	M	20/40	1+	NR	5.2	15.73	20/40	1+	NR	3.16	12.35
13	2	91	F	20/40	2+	NR	NR	32.38	20/40	2+	4.25	6.21	32.75
14	2	53	M	20/25	1+	3.16	19.45	NR	20/25	1+	NR	20.71	NR
15	2	70	M	20/30	2+	NR	6.5	12.75	20/40	2+	NR	NR	5.64
16	0.5	76	M	20/40	2+	3.82	NR	NR	20/25	1+	7.29	NR	NR
17	1	81	M	20/30	IOL	NR	8.73	NR	20/30	1+	2.82	NR	NR
18	1	76	F	20/60	2+	NR	NR	NR	20/25	IOL	3.39	NR	NR
19	0.5	80	F	20/50	2+	NR	NR	NR	20/40	2+	NR	8.44	NR
20	1	60	M	20/30	1+	NR	NR	NR	20/30	1+	NR	NR	NR
21	1	74	F	20/40	None	NR	NR	NR	20/30	None	NR	NR	NR
22	3	84	F	Not rec.	3+	NR	NR	NR	Not rec.	3+	NR	NR	NR
23	1.5	78	M	20/40	IOL	NR	NR	NR	20/60	2+	NR	NR	NR
24	2.5	75	M	20/40	1+	NR	NR	NR	20/40	1+	NR	NR	NR
25	3	72	F	20/40	None	NR	NR	NR	20/40	None	NR	NR	NR

NR, no Response; IOL, intraocular lens; Not rec., not recorded; VA OD, right eye visual acuity; VA OS, left eye visual acuity; NS OD, right eye nuclear sclerosis; NS OS, left eye nuclear sclerosis; psc, posterior subcapsular cataract.

initiation and preservation, conceptualization, and various other neuropsychological tests, such as the Wechsler Memory Scale, Attention Quotient Tests, Token Tests, Controlled Oral Word Association, Visual Discrimination Test, Finger Tapping, and Boston Diagnostic Aphasia Examination were used. Every patient underwent either a computed tomographic or magnetic resonance scan. Blood tests consisted of a complete blood count with differential, erythrocyte sedimentation rate (ESR), complete metabolic panel, and determination of the levels of cholesterol, triglycerides, B12, folic acid, T4, T3, thyroid-stimulating hormone (TSH), and microhemagglutination–*Treponema pallidum* (MHA-TP) to screen for systemic disease processes that might contribute to cognitive deficits. In addition an electrocardiogram (EKG), chest radiograph, and urinalysis were performed on every patient. The final diagnosis of AD was determined by consensus of a team consisting of a neurologist, psychiatrist, neuropsychologist, physician's assistant, and social worker.

The patients with AD and the EC subjects were matched for age, sex, visual acuity, and degree of nuclear sclerosis and tested for statistical differences in these factors. Visual acuity ranged from 20/20 to 20/60, with a median of approximately 20/30 in all 50 eyes tested. The Clinical Dementia Rating (CDR) scale, the measure chosen for an institutional protocol at the Alzheimer Center at the University of Southern California Rancho Los Amigos Medical Center, was used to assess the level of impairment of each patient.[17] The CDR scores of patients included in our study ranged from 0.5 to 3.0, with a median score of 1.0. Patients with CDR scores of greater than 3 are no longer ambulatory and were not deemed capable for referral to the Doheny Eye Institute for sweep VEP testing. Table 1 summarizes the contrast sensitivity latencies and demographic data of all our subjects.

The sweep VEP technique allows rapid assessment of visual function to a range of spatial frequencies in a 10-second period. This assessment requires considerably less time than standard VEP techniques, which may take up to 30 minutes. For the present study, a vertical sinusoidal luminance grating was presented on the face of a 30-cm video monitor. The grating was counterphase modulated at a temporal frequency of 15 contrast reversals per second (7.5 Hz). During each trial the contrast was increased in 19 equal logarithmic steps, changing every 0.5 seconds.[16] Ten contrast-sensitivity thresholds were averaged for every eye at each spatial frequency.

The patients with AD and EC subjects were seated comfortably, 150 cm from the stimulus display. Screen luminance was held constant for each trial. Each subject wore a Velcro headband that held gold-cup electrodes (Grass Instruments, Quincy, MA) to the scalp. Bipolar electrodes were placed 3 cm above the inion and 3 cm above and lateral to the inion. A ground was attached to the forehead at the midline. Vision in all patients was corrected for refractive errors at their initial ophthalmic examination, and they wore their current refraction during the procedure. Recordings were taken under monocular conditions. Figure 1 is an example of a recording in one patient. Although monocular response is not as robust as binocular response, it has the same general form and is easily differentiated from background electrical activity.

Patients were instructed to fixate on a target in the center of the video screen to minimize eye movements and control for accommodation. Gratings were presented in blocks of 10 trials at three fixed spatial frequencies of 1, 5, and 8 cyc/deg. Contrast was swept from 1%

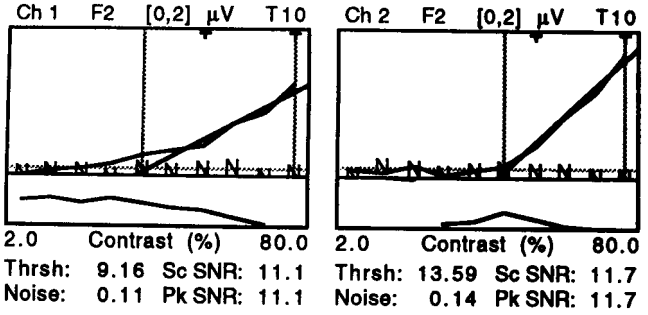

FIGURE 1. Sample sweep VEP of the right eye of a patient with AD with increasing contrast from 2% to 80% at a spatial frequency of 8 cyc/deg.

TABLE 2. Comparison of Responders with Nonresponders

Group	Responders	Non-Responders	*P*-value
All Patients			
n	17	8	
Age (y)*	73.2 ± 10.4	73.6 ± 10.9	0.93
Gender (male)	41%	50%	1.00
NS*	1.1 ± 0.7	0.8 ± 1.0	0.34
Visual acuity*	30 ± 6	35 ± 7	0.15
AD			
n	10	6	
Age (y)*	74.5 ± 10.6	73.8 ± 8.0	0.9
Gender (male)	60%	50%	1.00
NS*	1.3 ± 0.7	1.0 ± 1.1	0.52
CDR*	1.3 ± 0.5	2.0 ± 0.9	0.08
Visual acuity	32 ± 6	39 ± 7	0.08
EC			
n	7	2	
Age (y)*	71.4 ± 10.7	73.0 ± 22.6	0.88
Gender (male)	14%	50%	0.42
NS*	0.8 ± 0.5	0 ± 0	0.02
Visual acuity*	27 ± 4	25 ± 6	0.59

NS, nuclear sclerosis.
* Data are mean ± SD.

to 40% at 1 cyc/deg, 1% to 80% at 5 cyc/deg, and 2% to 80% at 8 cyc/deg. The VEP contrast function curve was computed as a vectorial average of the amplitudes on each of the 10 trials. Each trial lasted 10 seconds.

The amplitude and phase of the evoked response were determined with a discrete Fourier transform algorithm. Contrast thresholds were estimated by the linear extrapolation to zero amplitude in the VEP amplitude versus log contrast function.[18,19]

The computer, using a set signal-to-noise ratio and phase-consistency criteria derived from an extensive empiric data set, automatically fit the regression lines. Statistical analysis used the Rossner[20] method for paired data sets.

RESULTS

Contrast sensitivity thresholds along with the patients' age, sex, and CDR are summarized in Table 1. Seven (78%) of the 9 EC and 10 (62%) of the 16 patients with AD responded to sweep VEP at one or more spatial frequencies. The number of responders versus nonresponders in each group was not statistically different ($P = 0.66$). Responding patients with AD were shown to have significantly higher contrast sensitivity thresholds compared with EC subjects. No differences were detected in the characteristics of the two groups that might impact on the validity of this finding (Table 2). Mean contrast sensitivities in patients with AD were 4.0%, 9.6%, and 18.6%, at 1, 5, and 8 cyc/deg, respectively. Mean contrast sensitivities in EC subjects were lower: 2.1%, 5.3%, and 11.4%, at 1, 5, and 8 cyc/deg, respectively (Fig. 2). The probabilities for the differences between the AD and EC groups were 0.01, 0.05, and 0.07 at 1, 5, and 8 cyc/deg, respectively. Contrast sensitivity thresholds did not correlate with CDR scores.

DISCUSSION

Many studies of contrast sensitivity in patients with AD depend on the patient's subjective response to Pelli-Robson wall charts,[5,9] Vistech wall charts,[6,8] or computer-generated gratings.[6–8] These methods require patients to pay attention to a target, change targets on command, and remember to signal when they perceive the target. In addition to general attentional issues, these tests may be subject to specific disorders of visual cognitive functioning. Techniques that require a response from the patient may be affected both by deficits in attention and visual cognitive functioning, and, as such, they cannot definitively detect deficits in the primary afferent visual pathway.

Psychophysical methods have produced significant results[5–10]; nevertheless, they require a great deal of coaxing and instruction of the patient by the examiner. Pattern and flash VEP investigations yield more objective data but are still subject to the attention deficits inherent in AD. These tests may take many minutes and require methods such as infrared cameras to ensure fixation.[9,21] The sweep VEP technique we used is particularly applicable to patients with AD who have difficulty concentrating, following instructions, or fixating on a target for a prolonged period. Sweep VEP avoids many of these problems by requiring only 10 seconds of fixation per trial. The patient has no other instructions to follow, and no behavioral response is necessary.

Few studies have investigated whether deficits in visual performance are attributable to primary visual pathway dysfunction or to a more generalized visual cognitive deficit. Both Martinelli et al.[22] and Coben et al.[23] raise the question of visual dysfunction localization in their respective VEP studies, but neither answers it. Other studies have correlated visual deficits, or the absence of deficits, with known pathologic changes and

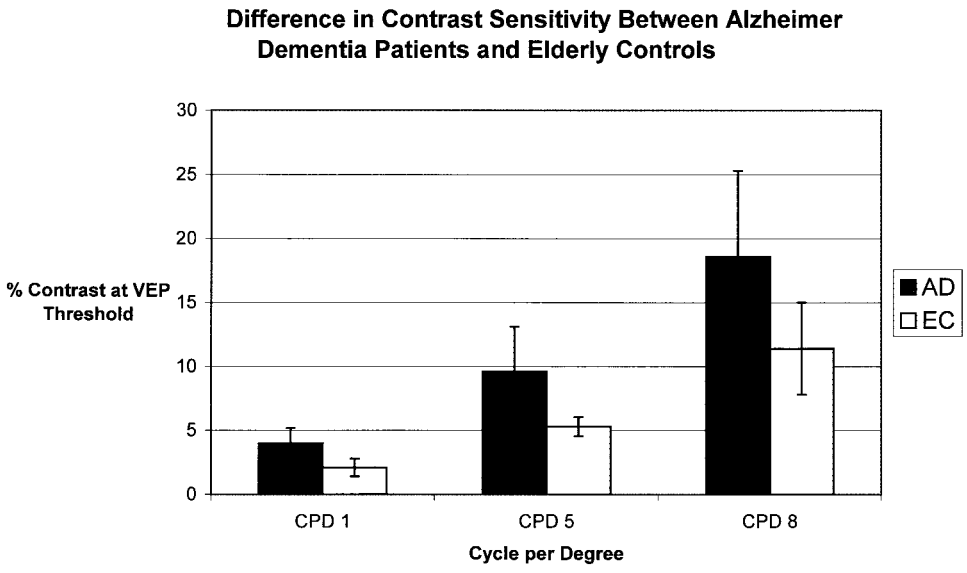

FIGURE 2. Mean contrast sensitivities and standard error in the groups of patients with AD and EC subjects at 1, 5, and 8 cyc/deg. Mean contrast sensitivities of the AD group were 4.0%, 9.6%, and 18.6%, respectively, and of the EC group were 2.1%, 5.3%, and 11.4%, respectively. These differences in thresholds were significant at probabilities of 0.01, 0.05, and 0.07.

vice versa.[5,11] Case studies have also presented visual deficits and suggested localizations to explain visual dysfunction.[1,24] In a study of the dissociation of motion detection and motion perception, Silverman et al.[3] successfully isolated primary visual pathways from visual cognition. They found that motion-detection thresholds by optokinetic nystagmus preceded motion perception in patients with AD. Furthermore, motion-perception thresholds in patients with AD were significantly greater than in EC subjects, whereas optokinetic nystagmus thresholds were not. These findings localize motion perception dysfunction to visual association and integration areas rather than to primary afferent pathway.

Our data show that contrast sensitivity was diminished in patients with AD, especially at lower spatial frequencies. Our results concur with previous studies of contrast-sensitivity perception in AD.[5–10] In our relatively small sample, we found no relationship between the degree of dementia and contrast-sensitivity thresholds. This may suggest that primary visual pathway dysfunction is independent of cortical disease.

Responses were not consistently elicited from patients with AD or EC subjects, when we used the sweep VEP technique. A number of factors combined to reduce the likelihood of recording evoked potentials. The poor responses may relate to age, because prior studies using flash and pattern VEPs have shown decreasing amplitudes and increasing latencies associated with the normal aging process.[25–29] With sweep VEP, this reduction in amplitude becomes more important, given that no averaging is used to increase signal-to-noise ratio. The monocular viewing required for this study, compared with infant studies that used binocular viewing, further affects amplitude. The thicker calvaria in adults may increase impedance, preventing the measurement of evoked potentials in some individuals. Optimal electrode placement may differ between adults and infants. Visual acuity may play a minor role in distinguishing responders from nonresponders, because analysis of our patients with AD showed that responders trended toward better visual acuity than nonresponders.

In summary, using the sweep VEP technique, we found that patients with AD had significant deficits in contrast sensitivity, which are most likely attributable to disease within the primary afferent visual pathway rather than to overall cognitive deficit. We believe that further studies should be conducted with larger sample sizes to confirm these results and that the investigation should be expanded to include other forms of vision testing. Furthermore, a comparison of sweep VEP results from patients with AD with those from patients with other forms of dementia may be helpful as a clinical test to differentiate these disorders objectively.

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