Principles and Practice of Clinical Electrophysiology of Vision

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Evoked Potentials in Alzheimer's Disease

Gary L. Trick

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by significant cognitive impairment including confusion and disorientation to time and place.[14] Visual-perceptual disturbances (such as alexia, visuospatial dysgnosia, prosopagnosia, and optic ataxia) can contribute to this disorientation and are often observed in patients with AD.[6, 7, 20] In some AD patients these visual-perceptual deficits appear to be the earliest signs of disease.[6]

Neuropathological studies have uncovered a broad spectrum of anatomical and physiological alterations in the central nervous system of patients with AD, including changes in cerebral morphology, neurotransmitter depletion, and a reduction in cerebral blood flow and electroencephalographic (EEG) activity.[4] These changes are often qualitatively similar to but quantitatively more profound than the alterations associated with normal senescence.[8] The reduction in neuron density in the central nervous system that is associated with AD exceeds the decrease observed in normal senescence and appears to be greater for larger than for smaller neurons.[21] The magnitude of AD-induced neuron loss also appears to vary with cortical region. AD-induced neuron degeneration is greatest in the temporal and parietal lobes and less severe although still significant (approximately 20% beyond age-corrected controls[8]) in the occipital lobe.[9]

While it is clear that AD patients may have pronounced visual-perceptual impairments, the specific pathophysiological basis for these functional deficits has not been determined. Since the cerebral atrophy characteristic of AD is more prevalent in the temporal lobe and the postcentral parietal region than in the primary visual cortex, it has been suggested that the visual symptoms of AD patients reflect dysfunction in the visual association areas with sparing of the primary visual cortex.[7] Indirect support for this conclusion has come from studies of the visual evoked potential (VEP) in patients suspected of having AD. Visser et al.[24] reported an increase in latency of several components of the flash VEP in patients with either senile or presenile dementia. This finding was confirmed by Harding and coworkers[11] (Table 111–1) in a series of studies that demonstrated that the latency of the P2 component of the flash VEP is significantly increased in AD suspects. Furthermore, in this series of studies it was demonstrated that the latency of the P100 component of the pattern-reversal VEP remained normal in the presence of an increase in the latency of the P2 component of the flash VEP. The unusual finding of an increase in the latency of the flash VEP in association with a normal-latency pattern-reversal VEP may be specific for AD. Therefore, this group has suggested using the difference in these two latencies as a diagnostic indicator of AD. It should be pointed out, however, that others have observed an increase in the latency of some components of the pattern-reversal VEP, but the latency increase appears to be confined to the later components (latency, >170 ms) of the response.[5]

Both of these findings (i.e., the increase in latency of the flash VEP in the presence of a normal-latency pattern-reversal VEP and an increase in latency of the later components of the pattern-reversal VEP) have been taken as evidence that (1) the VEP components associated with visual information processing within the primary visual pathway are normal in AD patients and (2) the components related to processing in the visual association areas (e.g., visual

TABLE 111–1.
Summary of the Results of Studies of Flash and Pattern Visual Evoked Potentials in Patients With Alzheimer's Disease

Reference	Patients Tested	Stimulus Conditions	Results
Visser et al.[24]	19 patients with presenile or senile dementia	Flash (0.5 Hz)	Increased amplitude and latency
Harding et al.[10]	12 patients with presenile dementia (Alzheimer's or the arteriosclerotic type)	Flash Checkerboard (56-min checks)	P2: increased latency P100: normal
Coben et al.[5]	40 patients with mild SDAT*	Flash (0.5 Hz) Checkerboard (57-min checks, 1.2 Hz)	Normal Increased amplitude and latency (late components only)
Wright et al.[25]	17 patients with presenile dementia	Flash (2.0 Hz) Checkerboard (56-min checks, 1.0 Hz)	P2: increased latency P100: normal
Harding et al.[11]	20 patients with primary presenile dementia	Flash (2.0 Hz) Checkerboard (56-min checks, 1.0 Hz)	P2: increased latency P100: normal
Orwin et al.[19]	Serial testing of 1 patient	Flash (2.0 Hz) Checkerboard (56-min checks, 1.0 Hz)	P2: increased latency (progressive) P100: normal

*SDAT = senile dementia of the Alzheimer type.

cognition) are abnormal.[5, 11, 19, 25] This result would imply that the visual pathway up to and including the primary visual cortex is functionally normal and, therefore, probably relatively spared by the degenerative processes involved in AD, while in subsequent cortical regions visual processing is perturbed.

Until recently there was no indication that either the retinas or optic nerves of AD patients had been carefully examined for neuron degeneration. Now, however, it is apparent that there is significant damage in the retinocortical pathway of AD patients.[1–3, 12] A two- to threefold decrease in the number of ganglion cells[12] and ganglion cell axons[2] is evident when the retinas and optic nerves of patients with AD are examined histologically. Optic disc measurements indicate that disc and neural retinal rim areas are significantly reduced in patients with AD while the cup-to-disc ratio is increased.[23] In addition, morphometric analysis indicates that the distribution of the cross-sectional areas of the retinal ganglion cell axons in AD patients is narrower and more homogeneous (1.0 to 2.0 μm) than in age-matched controls (0.5 to 6.0 μm), while the retinal ganglion cell soma sizes are significantly larger in controls than in AD patients.[12] Widespread neuronal degeneration has been detected in the layers of the lateral geniculate nucleus,[13] which receive input from the type A retinal ganglion cells (i.e., the magnicellular layers). Neuronal degeneration has also been observed in layer 4 of the primary visual cortex,[13] but it is as yet unclear whether this damage is restricted to particular sublayers of layer 4.

There is accumulating evidence that the human visual system is composed of at least two subdivisions that perform distinct functions.[15–18, 22] Different components of visual information are segregated into largely independent parallel streams that project to distinct cortical loci that extract specific information from the visual image. According to this model (Fig 111–1), one functional stream, the p-cell (or parvocellular) pathway, projects to cortical regions primarily involved in color and form discrimination (e.g., visual area 4, the posterior inferotemporal area, and the anterior inferotemporal area). The second functional stream, the m-cell (or magnocellular) pathway, projects to visual areas that are primarily involved in the global interpretation of spatial organization based upon motion and depth discrimination (e.g., the middle temporal area and the medial superior temporal area). Because degenerating neurons are likely to have a reduced functional capacity prior to end-stage degeneration, these histological data imply that some of the visual dysfunction in AD could result from lesions in the primary visual pathway. These histopathological results also raise the issue of why neurophysiological tests, which are known to be sensitive to subclinical changes in optic nerve function (i.e., pattern-reversal VEPs), have failed to detect evidence of optic neuropathy in AD patients. The pattern of degeneration observed histologically suggests a disproportionate loss of the neural elements specific to the m-cell pathway that could be missed by traditional transient VEP techniques.

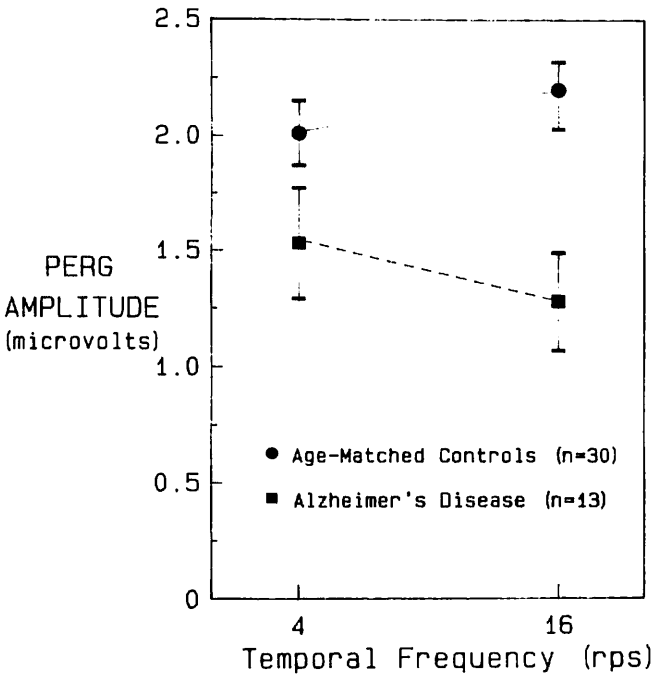

FIG 111–1.
Mean pattern electroretinographic (PERG) amplitude for patients with senile dementia of the Alzheimer type (n = 13) and age-matched controls (n = 30) as plotted for a low (4.0 revolutions per second (rps) and a high (16.0) temporal frequency. *Error bars* indicate 1 SEM.

To test the hypothesis that the large retinal ganglion cells that contribute to the m-cell pathway are preferentially sensitive to AD-induced damage we have used the pattern-reversal ERG (PERG) recorded under conditions that bias the response away from the p-cell contribution.[1] The PERG to both low (4 rps) and high (16 rps) temporal frequency checkerboard patterns (1.0-degree checks) was measured (see Fig 111–1). The intergroup differences were statistically evaluated by using a two-way analysis of variance (ANOVA) with repeated measures. The ANOVA revealed a significant difference in PERG amplitude ($P < .02$). Post hoc evaluation of the results (Scheffe) for each temporal frequency revealed a significant amplitude reduction among the AD patients at 16 rps ($P < .01$) that was not evident at 4 rps ($P > .05$). The PERG amplitude reduction in AD patients observed by us has now been confirmed independently (B. Katz, personal communication). Therefore, the findings are consistent with the notion of a differential loss of the type A retinal ganglion cells that are more sensitive to dynamic stimuli and that contribute to the m-cell pathway. The results of our study indicate that (1) there is a significant reduction in the bioelectrical response of neural elements in the retinocortical pathway of patients with AD and (2) this reduction is largest for conditions that appear to preferentially reflect m-cell function. When taken together, the histopathological and neurophysiological results suggest that a disproportionate degeneration in the type A ganglion cells and the m-cell pathway may be characteristic of AD-induced damage. This interpretation is also consistent with the VEP data on AD since a diffuse flash is a low–spatial frequency stimulus to which the m-cell pathway would be sensitive, while the transient stimulus used in all previous studies of the pattern-reversal VEP in AD would be primarily to elicit the response of the p-cell pathway.

In summary, both the VEP and the PERG are providing important insight into the neuropathological basis of AD. There is now evidence of significant neuron degeneration in the primary visual pathway of patients with AD, but it is not clear whether these changes fully account for the VEP abnormalities observed in these individuals. It appears that the apparent discrepancy between the pattern-reversal VEP studies that revealed no damage to the retinocortical pathway and the histological evidence of neuron degeneration may be explained by the preferential nature of the damage (i.e., primarily affecting the large fibers). Nevertheless, much work still needs to be done in this area, and this includes establishing the diagnostic value of evoked potentials in AD.

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