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Myelinated axon number in the optic nerve is unaffected by Alzheimer's disease

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Abstract

***Aims/Background*—Visual symptoms are a common but not invariable feature of Alzheimer's disease (AD) and such symptoms appear to become more pronounced as the severity of the dementia increases. Pathology in both the pregeniculate and cortical parts of the visual system has been suggested to underlie the visual deficits in AD. In order to investigate the former possibility, the effect of AD on the optic nerve was investigated.**

***Methods*—Intraorbital segments of optic nerve were taken at autopsy from nine patients with AD and seven patients with no history of psychiatric or neurological disease and no abnormal neuropathology. All patients had functional vision before death and appeared free of retinal, optic nerve, or microvascular disease. The optic nerves were processed into resin, semi-thin sections cut perpendicular to the long axis of each optic nerve, and stained with paraphenylenediamine. The sections were then investigated using an image analysis system and standard morphometric techniques.**

***Results*—There was no significant difference in the mean cross sectional neural area of AD compared with control optic nerves. Neither were there any significant differences between myelinated axon surface density, total axon number, or mean cross sectional axon area in AD compared with control optic nerves.**

***Conclusion*—These results indicate that optic nerve degeneration is not a feature of AD and suggest that the visual deficits in the disease result from cortical dysfunction. This view is supported by the fact that visuospatial dysfunction appears to be the most common visual problem in AD.**

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Almost half of patients with senile dementia of the Alzheimer type (SDAT – that is, patients with a clinical diagnosis of Alzheimer-type dementia but without subsequent histopathological confirmation) have been reported to be visually impaired[1] and some present with a specific set of visual symptoms.[2 3] In contrast, other patients with SDAT do not suffer visual impairment.[4 5] Visual disturbances are most pronounced in patients with severe dementia[6 7] and visual symptoms diagnosed early in SDAT appear to increase with the severity of the dementia.[8] However, it must be borne in mind that testing of visual function becomes increasingly difficult as the dementia progresses.[1 6 9]

There appear to be specific patterns of visual dysfunction in SDAT, with disturbances of oculomotor, basic visual, and complex visual function. Abnormal oculomotor activity including saccadic pursuit[10] hypometric saccades, increased saccadic latencies, fixational instability, and acquired oculomotor apraxia[1 5 11] have all been reported in SDAT. Visual acuity is rarely impaired, but abnormal electroretinograms,[12 13] delayed visual evoked potentials,[8 14] depressed contrast sensitivities, visual field deficits, and dyschromatopsia[6] all occur. Complex visual disturbances are also a major feature of SDAT, since patients are impaired in the visual evaluation of common objects, famous faces, spatial locations, and complex figures.[15]

The precise nature of the pathological changes that underlie visual dysfunction in Alzheimer's disease (AD), is a matter of some debate. However, there is general agreement that AD severely affects visual association cortices, with relative sparing of the primary visual cortex.[16–21] Moreover, brains from patients with AD and Balint's syndrome (a specific deficit in visuospatial skills), have significantly more AD pathology in occipital visual areas than those from patients with AD alone.[3 22] Furthermore, patients with SDAT that exhibit visual symptoms show reduced glucose metabolism in their secondary and visual association cortices compared with those without visual symptoms.[5]

Little is known about the involvement of the visual thalamus in AD. The data of Scholtz *et al*[23] suggest that total neuronal number and mean neuronal diameter in the lateral geniculate nucleus (LGN) are similar, whereas mean nucleolar volume, cytoplasmic RNA, lipofuscin content, and tetraploid glia are all significantly reduced in AD compared with control brains. These results, together with the fact that senile plaques occur in all layers of the LGN in AD,[24] suggest that although neuronal death in the LGN is not a feature of AD, degenerative change may occur.

There is far from unanimous agreement about the involvement of the pregeniculate visual pathway in AD. Some authors have reported abnormal electroretinograms[12 13] in SDAT and degeneration of retinal ganglion cells[26–29] in AD, while others have reported normal electroretinograms[9 25] and retinal ganglion cell number to be unaffected.[30–32] Sadun and colleagues[26 29] have reported degenerating axons in, and axonal loss from, the optic nerves of some patients with AD. However, in neither of these reports was

Table 1 Subject details

Subject	*Condition*	*Age (years)*	*Sex*	*Postmortem delay (hours)*	*Cause of death*
1	AD	84	M	36·0	Pulmonary embolism
2	AD	76	M	29·5	Bronchopneumonia
3	AD	89	F	3·0	Pneumonia
4	AD	76	F	15·5	Acute bronchitis
5	AD	73	F	28·0	Carcinomatosis
6	AD	90	F	47·0	Bronchopneumonia
7	AD	75	M	22·5	Bronchopneumonia
8	AD	72	F	19·0	Bronchopneumonia
9	AD	92	F	61·0	Bronchopneumonia
10	Control	74	F	12·5	Metastatic lung cancer
11	Control	66	F	34·0	Multiple lung abscesses
12	Control	62	F	104·0	Myocardial infarction
13	Control	78	M	36·0	Bronchopneumonia
14	Control	93	F	45·5	Bronchopneumonia
15	Control	80	M	13·0	Acute cardiac failure
16	Control	68	F	41·0	Bronchopneumonia

AD=Alzheimer's disease.

adequate information given about the subject groups or methodology and insufficient data were presented to allow critical evaluation of the results. In view of these shortcomings and the fact that there is controversy over the involvement of retinal ganglion cells in AD, the effect of AD on the optic nerve was investigated using morphometric techniques.

Materials and methods

The right optic nerve was taken at autopsy from nine patients (mean age 80·7 (SEM 2·7) years, range 72–92 years) with a clinical diagnosis of SDAT according to both the DSM-III-R[34] and NINCDS-ADRDA[35] criteria and was fixed by immersion in neutral buffered formalin solution. The clinical diagnosis was confirmed subsequently by histopathological examination of the brains.[36] The right optic nerve was also taken from seven patients with no history of neurological or psychiatric disease (mean age 74·7 (4·0) years, range 62–93 years). Histopathological assessment of the brains from these patients revealed them to be free of any neuropathological abnormality. All subjects used in this study had functional vision (although subject 6 had a dense cataract) and appeared free of retinal, optic nerve and microvascular disease. Subject details are given in Table 1.

A segment (approximately 5 mm long) was dissected from the intraorbital part of each optic nerve, immersed in a solution of 1% osmium tetroxide in 0·1 M phosphate buffer (pH 7·2) for 4 h and processed into Araldite resin. The tissue blocks were then coded so that subsequent investigation could be conducted 'blind'. Semi-thin sections (1–2 μm thick) were cut from each tissue block, perpendicular to the long axis of the optic nerve, so that the entire cross section of the optic nerve was present in each section. The sections were then mounted on to glass slides and stained with a 1% solution of paraphenylenediamine (Sigma) in absolute methanol[37] for 10 minutes and placed under a cover slip.

Low power images of three sections from each optic nerve were transmitted from a light microscope via a video camera to an image analysis system (Sight Systems Ltd) and the total surface area of each optic nerve section occupied by nerve fascicles determined. This 'neural area' excluded connective tissue and blood vessels. A photomicrograph was taken of one entire cross section of each optic nerve and printed at a final magnification of ×62. The photomicrograph of each optic nerve was then divided radially into eight segments, which were subdivided into inner and outer regions of approximately equal area. The resulting 16 divisions of each optic nerve were then used as a sampling guide, for counting myelinated axons systematically throughout the nerve directly from the semi-thin section, using a light microscope, video camera, and an image analysis system. One image of a sample area within a nerve fascicle was captured from the centre of each of the 16 regions and displayed on the system monitor at a final magnification of ×4600, representing an actual area of 900 μm^2. The total number of myelinated axons and the surface area of axoplasm within the myelin sheath of each axon were then recorded from each image.

The mean neural area, myelinated axon surface density, mean myelinated axon cross sectional area, and total axon number were then calculated for each optic nerve. The tissue codes were broken and the mean neural area, myelinated axon density, myelinated axon cross sectional area, and total axon number of AD and control optic nerves were compared by means of the Mann-Whitney U test.

Results

Myelinated axons in the semi-thin sections of optic nerve stained with paraphenylenediamine, appeared as dark brown rings of myelin surrounding unstained axoplasm (Fig 1). There was no significant difference ($p=0·71$) in the mean cross sectional neural area of control (5·73 (SEM 0·44) mm^2) compared with AD (5·74 (0·46) mm^2) optic nerves. There was no significant difference ($p=0·87$) in the mean myelinated axon surface density within fascicles of control (0·1488 (0·0117)/μm^2) compared in AD (0·1525 (0·0131)/μm^2) optic nerves. Neither was there any significant difference ($p=0·63$) in the mean total number of myelinated axons in control (859 000 (96 000) compared with AD (881 000 (89 000)) optic nerves. The mean (SEM) myelinated axon cross sectional area in control optic nerves (4·03 (0·42) μm^2) was not significantly different from that in optic nerves from AD patients (3·64 (0·21) μm^2). The data for individual optic nerves are given in Table 2.

Discussion

The results of the current study demonstrate that in subjects with functional vision, AD has no significant effect on the cross sectional neural area of the optic nerve, myelinated axon surface density within optic nerve fascicles, or the total number of myelinated axons in the optic nerve. Degenerating axons, characterised by large homogeneous dark brown circular profiles in paraphenylenediamine stained material, have been previously reported[37] to remain in the optic nerve

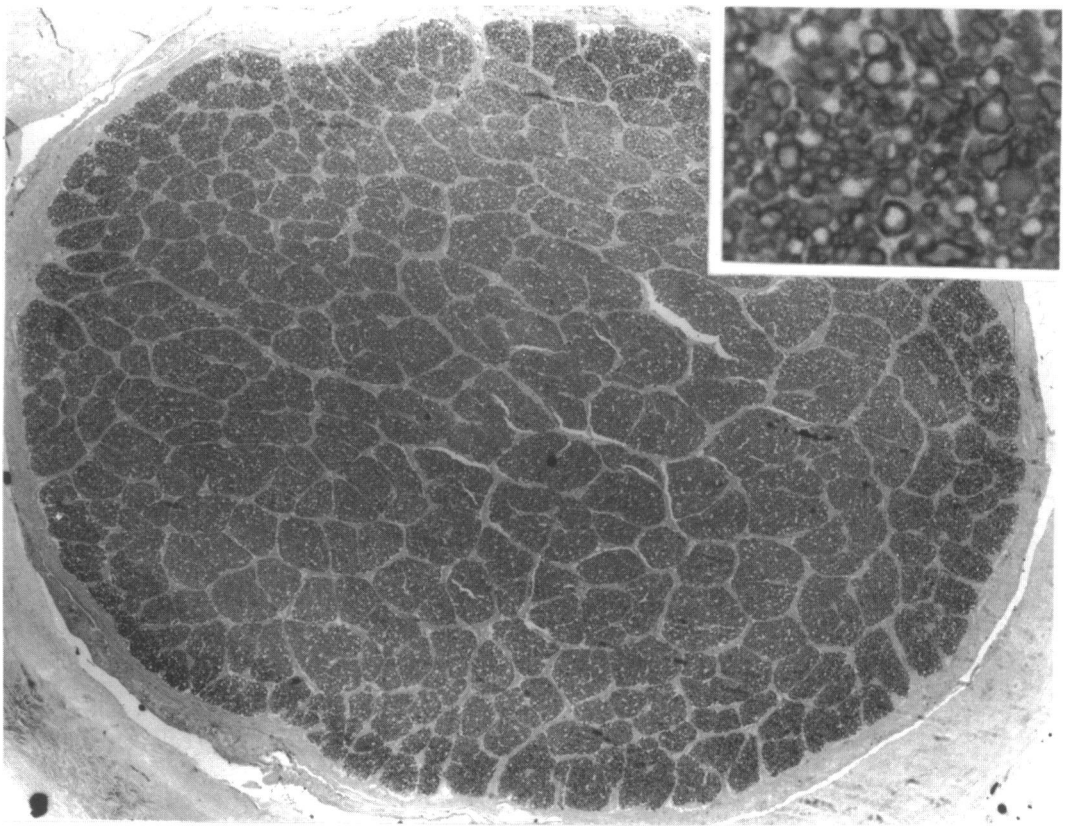

Figure 1 A photomicrograph of a cross section of an entire optic nerve (subject 9, AD) stained with paraphenylenediamine (×35). Inset, a high power (×950) photomicrograph showing stained myelin rings of retinal ganglion cell axons within a fascicle of the same optic nerve.

for months or even years after death of the axon. In agreement with the quantitative results of the present study, no such degenerating profiles were observed in either AD or control optic nerves and the mean cross sectional area of myelinated axons in AD optic nerves was not significantly different from that in controls. These results conflict with those of Hinton *et al*[26] and Sadun and Bassi[29] who reported substantial retinal ganglion cell axon degeneration and loss from the optic nerve in AD. This degeneration was suggested[29] to involve predominantly the large M cell fibres that project to the magnocellular layers of the LGN.[38] The reason for this discrepancy is unclear, but would appear to lie with the selection of the AD patients, since the mean axon density of control optic nerves in the present study (14·88/100 μm^2) was similar to that (13·6/100 μm^2) reported by Sadun and Bassi.[29] Unfortunately, the lack of data about the AD optic nerves and their history, in the reports of Hinton *et al*[26] and Sadun and Bassi[29] prevent meaningful comparison with those of the current study.

Table 2 Histomorphometric data for individual Alzheimer's disease (AD) and control optic nerves

Subject	Condition	Neural area (mm^2)	Axon surface density/100 μm^2	Mean axon cross sectional area (μm^2)	Total axon number
1	AD	6·49	16·39	3·77	1 064 745
2	AD	7·54	11·44	3·33	863 026
3	AD	6·21	12·53	4·95	777 780
4	AD	4·10	20·95	3·33	854 395
5	AD	6·17	17·86	3·01	1 102 388
6	AD	6·75	16·26	3·49	1 097 409
7	AD	3·14	7·89	3·32	255 032
8	AD	6·21	17·18	4·35	1 066 053
9	AD	5·06	16·78	3·21	848 788
10	Control	7·20	16·65	4·56	1 198 666
11	Control	5·69	13·58	6·04	771 953
12	Control	4·46	18·87	2·62	841 515
13	Control	5·81	14·81	3·39	859 685
14	Control	4·03	9·59	3·38	386 680
15	Control	6·87	13·30	4·55	913 601
16	Control	6·00	17·39	3·65	1 043 281

In accord with the results of the current study, Curcio and Drucker[33] found no evidence of a disease specific loss of retinal ganglion cells in AD. However, they did report a 25% reduction in ganglion cell density from the foveal and nasal retina (but not from other regions) of both demented and non-demented patients aged 66–86 years, compared with normal individuals in their mid thirties. The data of Curcio and Drucker[33] suggest that entire optic nerve axon counts may not detect such an age-related loss, since foveal retinal ganglion cells constitute less than 7% of those present in the normal retina. This suggestion is supported by the fact that although a number of reports have indicated a decrease in optic nerve axon number with age,[39–45] only about half[30 41 44 45] revealed a significant decrease. Furthermore, the studies revealed high inter-individual variability compared with the reported age-related decrease in optic nerve axon number. Thus, in view of the fact that the ages of the controls were not given in the studies of Hinton *et al*[26] and Sadun and Bassi,[29] it is possible that age differences could have contributed to the disparity between their results and those of the current study.

In agreement with the results of the current study, several aspects of vision that would be expected to be impaired by optic neuropathy appear to be unaffected in AD. Patients with SDAT do not necessarily present with visual

field deficits[5 6 46] and visual acuity is unimpaired.[5 6 14 15 46 47] Indeed, Sadun *et al*[6] concluded that although virtually all of their patients with SDAT 'had subjective visual complaints, the most common being an inability to read. This was not because of poor vision, since most had adequate visual acuities'. Moreover, if retinal M cells are specifically affected in AD,[29] broad band visual capacities would be expected to be selectively impaired in the disease, but this is not the case.[48] Although dyschromatopsia has been reported in some patients with SDAT,[6 46 49] it is likely to be a cortical dyschromatopsia since patients unable to order colours can name them,[5 46] and Cronin-Golomb *et al*[49] did not detect evidence of retinal or optic nerve disease in their patients with SDAT.

In contrast with the poor clinical evidence for pregeniculate visual dysfunction in AD, there is considerable evidence to suggest that the visual impairment in AD is a disorder of cortical processing. Constructional abnormalities,[50] prosopagnosia,[46] object agnosia,[15] spatial agnosia/Balint's syndrome,[6 15 22] and topographagnosia[51 52] have all been reported to occur in patients with SDAT. In fact, problems with visuospatial function appear to be the most common visual complaints in such patients.[2 6 46 53]

Within the visual cortex, there is a differential distribution of AD neuropathology. Lewis *et al*[18] described a 20-fold increase in neurofibrillary tangle (NFT) density from primary visual cortex (Brodmann area 17) to the immediately adjacent visual association cortex of Brodmann area 18 and a further doubling in the higher order visual association cortex of the inferior temporal gyrus (Brodmann area 20). Similarly, Braak *et al*[20] reported that the density of NFT increased from Brodmann area 17, through area 18, to area 19 (the peristriate region). The direction of this increase in pathology parallels the hierarchical organisation of the primate cortical visual system.[54] Furthermore, Braak *et al*[20] have described that in area 17 the majority of NFT are present in layer II and in area 18 the majority are found in layer III. In Brodmann area 19, a large proportion of the NFT is found in layer V. This shift of NFT to deeper laminae from area 17 to 19, corresponds to the pattern of pyramidal neurons that establish long corticocortical connections.[55] It has been hypothesised that the dementia of AD results from the disruption of the long corticocortical projection systems, functionally isolating individual cortical regions[56] and that the initial insult occurs in the entorhinal cortex and/or subiculum and progresses in a stepwise fashion along corticocortical connections.[57] The observation that AD neuropathology decreases from the temporal stem to area 17[18 20] supports this suggestion, as does the fact that the major visual symptoms of AD appear to be due to dysfunction of higher order processing.[2] The results of the present study showing that the optic nerve is unaffected in AD and the lack of visual symptoms consistent with optic neuropathy in SDAT (see above), also support the contention that visual symptoms in AD are primarily due to cortical visual association area dysfunction.

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