# CLINICAL CHALLENGES, PETER SAVINO, EDITOR

### The Incredible Shrinking Brain

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#### Comments by Alfredo Sadun, MD, PhD

(In keeping with the format of a Clinical Pathological Conference the abstract and key words appear at the end of the article.)

Case Report. A 65-year-old white woman developed slowly progressive loss of visual acuity and field over eight years. Her initial symptom was an inability to follow a golf ball after hitting it, although her golf partner could follow the ball easily. When she took a trip to Europe with her husband, she had trouble reading the moneychangers and trouble ambulating down steps. She began to have severe difficulties while driving in 1985 and quit driving in 1986. She was seen by several ophthalmologists and underwent cataract extraction in both eyes (16 months apart) with a best corrected visual acuity of 20/40 OU. Because of continued symptoms, she was evaluated at two major medical centers by both neurologists and neuro-ophthalmologists. A "negative" CT scan of the brain was obtained in October 1986 (Fig. 1).

In 1989 she continued to lose vision and her visual fields were difficult to evaluate because of fixation losses, yet small central and paracentral scotomas were plotted on kinetic perimetry (Fig. 2). Normal saccades and pursuits were present. She additionally had a normal ERG and VER, and repeat MR of the brain showed a few areas of increased signal in the deep white matter regions (Fig. 3).

By August 1990 the patient's visual acuity was 20/80 in both eyes. Kinetic perimetry was constricted in her left eye more than her right (Fig. 4). Fundus examination was normal. In August of 1991, she developed a relative left homonymous visual field defect (Fig. 5) and repeat MR of the brain revealed bilateral parietal and occipital lobe atrophy (right greater than left) with increased signal in the corresponding periventricular white matter regions (Fig. 6). A complete work-up included a normal CBC, SMAC 22, ESR, B<sub>12</sub> folate RPR, FTA, serum and urine protein electrophoresis, lead and ACE level, as well as a negative Lyme titer. A chest x-ray, carotid ultrasound, awake EEG, and lumbar puncture were normal. In addition a positive ANA 1 to 160 (speckled pattern), a cardiolipin IGG antibody of 7 (3 to 15 low positive) and a normal C3, C4 and anti-DNA were obtained. An evaluation at a Memory Diagnostic Center detected a mentation between 71 and 74 years (mild dementia) with normal recall, judgment and a bright affect.

Cerebral arteriography revealed an abnormality of the right P-1 having the appearance of thrombosis with irregularity of the proximal seg-



Fig. 1. Two views of a brain CT scan with contrast showing only mild ventricular enlargement which was read as "negative" in 1986.



ment with nonfilling of the P-1/P-2 junction and distal right PCA territory. The right PCA filled from the right posterior communicating artery with poor filling of the distal right calcarine branches causing an avascular zone seen in the distal calcarine segment. Mild beading of the proximal calcarine branches were noted.

Despite high-dose systemic corticosteroids, the

patient's visual acuity worsened to count fingers OU and a brain biopsy was performed.

The patient underwent a right occipital craniotomy with biopsy of the right occipital lobe. The dura was grossly normal and the cerebral cortex underneath appeared atrophied with a yellow discoloration. A corticectomy was performed of the right occipital tip and one cubic



Fig. 2. Top: Goldmann kinetic perimetry performed in 1989 showing central and paracentral scotomas, OU. Bottom: Goldmann kinetic perimetry performed one month later, now showing central scotomas, OU, with monocular left inferior quadrantic defect, OD.



Fig. 3. Brain MR performed in July 1989 with enlarged ventricles and increased signal in the deep white matter regions.





Fig. 4. Goldmann kinetic perimetry performed in August 1990 with generalized visual field constriction, OS > OD.



Fig. 5. Goldmann kinetic perimetry performed in August 1991 with new onset of a relative left homonymous visual field defect.

centimeter of meninges with white and gray matter was removed.

The arteries in the subarachnoid space, as well as the arteries which penetrated the cerebral cortex demonstrated concentric eosinophilic thickening of the walls which stained positive for amyloid (Fig. 7). The cerebral cortex showed numerous senile plaques which were well demonstrated on both the Thioflavine S and silver stains (Fig. 8). Marked neurofibrillary tangles Fig. 6. Top: Brain MR performed in August 1991 with progressive enlargement of the ventricular system and mild periventricular white matter disease, right side greater than left. Bottom: Additional views of brain MR performed in August 1991 with isolated atrophy of both parietal lobes with dilation of the posterior horn of the lateral ventricle, right side greater than left.





Fig. 7. Left: Low power Congo red stain of a vessel in the subarachnoid space penetrating the cerebral cortex. Note the positive staining for amyloid in the vessel wall. Right: High power H&E stain of a subarachnoid artery showing vessel wall thickening consistent with amyloid angiopathy.

were also noted within the cortical neurons with some mild astrocytic gliosis (Fig. 9). No inflammatory changes were identified in the meninges, ruling out a cerebral vasculitis. The underlying white matter was unremarkable.

#### Comments

Comments by Alfredo Sadun, M.D., Ph.D., Departments of Ophthalmology and Neurosurgery, University of Southern California, School of Medicine, Los Angeles, CA.



Fig. 8. Modified Bielschowsky silver stain optimized for neuritic (senile) plaques (NP). The NP is the circular-like structure in the center of the slide formed by an absence of the black staining neurites.

A 65-year-old woman presented with complaints of decreased vision. Her other complaints were rather typical for patients with visual problems associated with Alzheimer's disease. She could not follow a golf ball, she had trouble reading figures, and she had trouble ambulating. Within the context of a normal clinical examination, these complaints are classical for patients with Alzheimer's disease.<sup>23,24</sup> However, the most prominent features in the clinical course of the present case were most atypical of Alzheimer's disease. For example, the patient complained of decreases in visual acuity, and this was, in fact, confirmed on repeated examinations. Moreover, the initial visual field changes were characterized primarily by central and paracentral scotomas. Later, asymmetrical peripheral cuts were seen in the visual field which the authors described as a homonymous hemianopsia (Fig. 2B does suggest a quadrantanopsia; however, Figs. 4 and 5 would be better characterized as incongruous left-sided visual field constriction, since there is really no respect for the vertical midline). Moreover, the patient gives a course of visual deterioration, not common in Alzheimer's disease, that is characterized as stuttering.<sup>17</sup>

The most interesting aspect of this case is the histopathology. A fairly large biopsy was taken from the patient's right occipital cortex. Neither inflammation nor spongiform degeneration was noted. However, both neurofibrillary tangles (NFTs) and neuritic plaques (NPs) were found in



Fig. 9. Modified Bielschowsky silver stain optimized for neurofibrillary tangles (NFT). The NFT is the black ovoid-like structure which is adjacent to a clear area representing a neuron nucleus. It is composed of irregular masses of neurofilaments.

large quantities. This, of course, is characteristic for Alzheimer's disease. Even more interesting, concentric eosinophilic thickening of the arterial walls were noted, and this material stained positive for amyloid (Fig. 7). This was consistent with the diagnosis of amyloid angiopathy of the visual cortex.

As the authors point out, amyloid angiopathy is not uncommon in Alzheimer's disease. However, the distribution of these pathological changes in the present case is quite interesting.

NFT's and NPs described in Alzheimer's dis-



Fig. 10. Mean axon density decreases both with age and with disease. (Error bar represents 1 s.e.m.)

ease are usually found in the frontal lobes and "association cortex" areas.<sup>22</sup> They are much less commonly seen in the occipital lobes.<sup>3</sup> Moreover, the diagnosis of Alzheimer's disease cannot be made on these pathological changes alone. Only in combination with premortem clinical findings do NPs and NFTs lead to the definitive diagnosis of Alzheimer's disease.<sup>17</sup>

In our initial study of optic nerve degeneration in Alzheimer's disease, we began with three categories of patients; however, this ultimately evolved into four categories (Fig. 10). We compared optic nerve axonal counts between young healthy patients (Group 1) and normal aging patients (Group 2), and then compared the latter with age-matched patients with a diagnosis of Alzheimer's disease (Group 3). However, we eventually were forced to describe a fourth category, which consisted of those patients presumed on the basis of their clinical assessment to be agematched controls (normals) to our Alzheimer's cohort, but in whom post-mortem changes demonstrated NPs and NFTs indistinguishable from patients with Alzheimer's disease. We deemed this new category "occult Alzheimer's disease." Although these patients could not be clinically described as having Alzheimer's disease, it was interesting to note that degeneration was found in these optic nerves and the axonal population for this last category was halfway between the group of age-masked controls (clinically and histopathologically normal) and the Alzheimer's disease group (clinically and histopathologically consistent with Alzheimer's disease; see Fig. 10). Hence, there is evidence of a subclinical stage in Alzheimer's disease in which the patients are neurologically intact, but on post-mortem examination have histopathological features indistinguishable from other patients with Alzheimer's disease.

Amyloid angiopathy is now being described as existing in several parts of the brain.<sup>2,25</sup> There has been considerable controversy as to whether this amyloid is, in fact, part of the mechanism that leads to neuronal damage. One consideration, for example, is that a generalized ischemia is brought about by the decrease in small arteriolar lumen size due to amyloid angiopathy. In this state of generalized ischemia, certain cell types (for example the largest neurons) might be most vulnerable.

Since Cogan's landmark article in 1985,<sup>5</sup> a great deal has been learned about Alzheimer's disease and the visual system. At the time, Cogan reminded his readers that visual symptoms even

in the absence of ophthalmologic signs might be a harbinger of Alzheimer's disease. We have now come to recognize that Alzheimer's disease comes in many shapes and sizes both from the clinical and pathological points of view. For example, there are certainly cases in whom most of the visual symptoms are referable to impairments in cognition.<sup>5</sup> There are other situations in which the prominent damage might be in the anterior portions of the visual system.<sup>10</sup> This case serves as an example of damage primarily to the posterior visual pathways and the occipital cortex. This case also serves to demonstrate the broad spectrum of histopathological features seen in Alzheimer's disease. However, it should be noted that the diagnosis of Alzheimer's disease remains a combined clinical and histopathological one. Thus, while this case provides an excellent heuristic opportunity, there is legitimate argument as to whether the diagnosis of Alzheimer's disease can be made in the present case, considering the atypicality and paucity of classical clinical features.

#### Concluding comments by Marc H. Levy, MD, Clinical Associate Professor of Ophthalmology, University of South Florida, Tampa, Florida

## Diagnosis: Alzheimer's disease with cerebral amyloid angiopathy

Progressive dementia such as Alzheimer's disease is characterized by both NFTs, which are irregular masses of neuro-filaments and NPs.<sup>1.9.</sup> <sup>13,15</sup> The severity of the dementia has been correlated with both NFTs and NP densities.4,18 At Washington University in St. Louis, the Department of Neuro-Pathology has experience with over 100 patients with Alzheimer's disease. In these patients, the primary visual cortex has fewer total NPs than in the mid-frontal, superior temporal or inferior parietal cortex. The NFTs thread density is minimal in primary visual cortex; many Alzheimer's disease cases have none in a single section from this region and is less than in other cortical areas. The same is true for primary motor cortex. For example, NPs and NFTs are higher in visual association areas than in primary cortex, which are usually less than the frontal, temporal and parietal regions (McKeel DW, Jr: Personal communication, 1992).

Hoff et al<sup>11</sup> summarized pathologic examination of 23 patients; eight had Alzheimer's disease, eight had Alzheimer's disease and a true Balint's syndrome (psychic paralysis of visual fixation, optic ataxia, and visual spatial disorientation [simultagnosia]), three nondemented patients had

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a pure vascular form of Balint's syndrome, and four were normal controls. The summary of that study showed that in the occipital (Brodmann's area 17, 18 & 19) and posterior parietal regions there were more NFTs and NPs (between 12 and 16 times that seen in Alzheimer's disease), and prefrontal cortex (areas 9, 46 & 45) had fewer NFTs than in Alzheimer's disease. The superior colliculus had more NFTs and posterior cingulate (area 23) had more NPs than in Alzheimer's disease.

Amyloid angiopathy was first described as a cause of intracerebral hemorrhage in the late 1970s by Jellinger<sup>12</sup> and Zenkevich.<sup>27</sup> This disease can occur in a sporadic form in patients over the age of 65 or can be inherited as an autosomal dominant in patients between 45 and 65 years of age.<sup>6,7</sup> Although occurring mostly in the occipital and parietal lobes, the lesions occur rarely in the frontal and temporal lobes, as well as the brainstem and cerebellum.<sup>19</sup> Affected vessels are thickened by an acellular hyalin material that stains positive with PAS and polarizes with congo red stains.<sup>8</sup>

In some cases of amyloid angiopathy, the vessel wall seems to be reduplicated or split,<sup>26</sup> and in our case a vessel in the subarachnoid space penetrating into the cerebral cortex stained positive (Fig. 7, left).

In age-matched patients with Alzheimer's disease, amyloid angiopathy is present in 70–90%, depending on the series<sup>16,21</sup> and methods used; it is present in approximately 30% of elderly nondemented controls.<sup>26</sup> Usually one sees cerebral amyloid angiopathy in at least two of the four major lobes in Alzheimer's disease<sup>16</sup> and frequently in three or four lobes. Within a given section there is a great variability of number of vessel profiles involving amyloid angiopathy, ranging from none or one to two to diffuse numbers of blood vessels.

In amyloid angiopathy the acute onset of a partial or complete homonymous visual field defect may be the first sign of the disease secondary to an occipital lobe hemorrhage.<sup>19</sup> In our case, the acute onset of a homonymous visual field defect led us to re-image this patient.<sup>20</sup> Since her right occipital craniotomy with biopsy, this patient's visual acuity and field have remained stable for one year. However, due to the marked amount of occipital lobe involvement we expect visual decline in the future.<sup>14</sup>

Cogan<sup>5</sup> in 1985 said, "Symptoms referable to the visual system may be the earliest and the most prominent signs of idiopathic dementing disease (Alzheimer's type) despite the lack of objective signs in the eyes or visual system." Certainly, this was correct in our case.

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Supported in part by The Sarasota Retina Institute Research Foundation, Sarasota, FL.

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**Abstract.** A 65-year-old white woman developed progressive visuospatial abnormalities over an eight-year course, secondary to Alzheimer's disease with amyloid angiopathy. Imaging studies demonstrated focal atrophy of the parietal and occipital lobes without hemorrhage. This patient manifested simultagnosia without ocular dysmetria or optic ataxia; hence, a true Balint's syndrome was not present. Her visual acuities and fields have remained stable status post-occipital lobe biopsy. (Surv Ophthalmol 39:315–322, 1995)

Key words. Alzheimer's disease • amyloid angiopathy • visuospatial dysfunction