Amyloid Angiopathy in Alzheimer's Disease

C. Bergeron, P.J. Ranalli and P.N. Miceli

ABSTRACT: Thirty cases of Alzheimer's disease and 30 age-matched controls were studied to determine the incidence of cerebral amyloid angiopathy and its relationship to age, neuritic plaque formation, and amyloid plaque content. Cerebral amyloid angiopathy (CAA) was present in 86% of AD cases and 40% of age-matched controls. Its frequent occurrence in AD is not merely a reflection of the advancing age of this group: it was seen only in the presence of neuritic plaques, regardless of age, and represents an integral component of AD. Neuritic plaques however, did occur in the absence of CAA in 17% of all cases. The amount of vascular and plaque amyloid tended to be of comparable severity in many cases, but significant discrepancies were observed, with preferential deposition of amyloid in either plaque or vessel. Our results suggest that neuritic plaque formation and amyloid deposition are linked genetically or etiologically, but independently expressed, without a cause-and-effect relationship.

RÉSUMÉ: Une étude histologique semi-quantitative de 30 cas de maladie d'Alzheimer et de 30 cas-témoins fut poursuivie pour déterminer la fréquence de l'angiopathie congophile, ainsi que ses relations avec l'âge des sujets atteints, le nombre de plaques séniles et leur contenu en amyloide. L'angiopathie se retrouve chez 86% des sujets atteints de la maladie d'Alzheimer, mais seulement 40% des cas-témoins. Elle ne se rencontre jamais en l'absence de plaques séniles, quelque soit l'âge, et constitue donc un élément intégral de la maladie d'Alzheimer. Les plaques séniles sont toutefois observées en l'absence d'angiopathie dans 17% des cas. La quantité d'amyloide déposée dans les plaques séniles et les vaisseaux sanguins est souvent comparable pour un cas donné, mais il existe des exceptions très significatives, où une déposition préférentielle se voit soit dans les plaques ou les vaisseaux. Ces résultats suggèrent la conclusion que la formation des plaques neuritiques et la déposition d'amyloide sont reliées soit de façon génétique ou étiologique, mais que leur expression est indépendante et sans relation de cause à effet.

Can. J. Neurol. Sci. 1987; 14:564-569

Cerebral amyloid angiopathy (CAA) is a common neuropathological finding in the brains of patients with Alzheimer's disease (AD).[1-4] A similar angiopathy is also frequently observed in unselected post-mortem series, where its incidence increases with age.[5,6] To determine if CAA is an essential component of AD, or merely reflects the advancing age of this population, we studied its incidence and severity in 30 cases of AD and 30 age-matched controls. The extent of neuritic plaque formation was also evaluated in both groups, and the relationship between vascular and plaque amyloid was examined. While other studies have looked at some aspects of amyloid angiopathy, ours is the first to compare two well characterized age-matched groups and correlate the extent of vascular amyloid, plaque amyloid and neuritic plaque formation simultaneously, using a large tissue sample.

Patients and Methods

Patient Population

Alzheimer Group

Thirty consecutive cases of AD collected at the Canadian Brain Tissue Bank were used for this study. On histological examination of all cases, abundant neurofibrillary tangles and neuritic plaques were present in at least three neocortical sites. The ages ranged from 43 to 83 years old (mean 73.04±8.11). A clinical diagnosis of AD had been made on average 6.1 years prior to death, with a range of 0.5 to 14 years. Clinical details were available on 27 cases; in each of these, a presumptive clinical diagnosis had been made by a neurologist (24 cases), or a psychiatrist (3 cases). All were profoundly demented at the time of death. No information other than the clinical diagnosis of AD was available in the other 3 cases.

From the Departments of Pathology (Neuropathology) (Dr. Bergeron) and Medicine (Neurology) (Dr. Ranalli), Faculty of Medicine, University of Toronto and the Department of Biostatistics, Ontario Cancer Institute, Toronto (Dr. Miceli)

Received March 31, 1987. Accepted July 20, 1987

Reprint requests to: Dr. C. Bergeron, Department of Pathology, Toronto General Hospital, EC-4-316, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4

Control Group

Thirty cases were selected, on the basis of age only, to match the AD group, from a pool of control specimens obtained at the Bank. The ages ranged from 44 to 92 years old (mean 70.87±9.82), not significantly different from the AD group ($T = 0.91$, $p = 0.37$). None of these subjects had clinical evidence of overt dementia, but detailed neuropsychological examinations were not available. They were not known to suffer from any neurological or psychiatric disorder, primary amyloidosis, or any disease predisposing to secondary amyloidosis. All control specimens obtained by the Bank are routinely evaluated for the extent of neurofibrillary degeneration and neuritic plaque formation; subjects with neocortical tangles are excluded from the control group. In the present study the possibility of an early dementia cannot be excluded retrospectively.

Neuropathological Examination

The following regions were evaluated in all but two cases of AD and three controls, where one site was missing: middle frontal gyrus at the level of the anterior commissure, middle temporal gyrus at the level of the hippocampus, parieto-occipital (triple watershed area), and cerebellum. Five micron CB thick sections were cut from paraffin-embedded blocks and stained with alkaline Congo Red, Bielschowsky silver method, and hematoxylin-eosin.

All histological slides were coded to avoid patient identification. The histological determinations for amyloid angiopathy, neuritic plaque formation and amyloid-rich plaques were therefore conducted "blindly", without knowledge of the status of a given case, the scores obtained in other regions, or the results obtained for either of the other two parameters. A certain amount of bias could not be avoided however, in cases of AD with abundant amyloid-rich plaques, where the histological diagnosis was readily apparent when evaluating the extent of vascular amyloid deposition.

Amyloid Angiopathy (CAA)

Vascular amyloid was identified with the Congo Red stain as homogeneous eosinophilic material within the vascular wall, which exhibited apple-green birefringence and dichroism under polarized light. No distinction was made between congophilic angiopathy[7] and dyshoric angiopathy.[8] The entire extent of each section was first examined, using a mechanical stage, at a magnification of 250x. Each section measured on average 2.0 cm x 1.5 cm, and included at least 5.0 cm of cortical ribbon. Those in which no amyloid was detected were discarded and given a score of 0. All others were reassessed, and their amyloid content graded according to the following semiquantitative scale: 1. Rare leptomeningeal and/or cortical vessel involved. 2. Few scattered or clustered leptomeningeal and/or cortical vessels involved. 3. Many leptomeningeal and/or cortical vessels display moderate to severe amyloid deposition, with more than 50% of leptomeningeal vessels involved. 4. All or most leptomeningeal and many cortical vessels display severe amyloid deposition. Neocortical CB vascular amyloid scores were then calculated for each case by adding the regional values and converting them to a scale of 0-10. The sections were graded independently by two observers (PR and CB). The results were concordant in 80% of the observations. Where discrepancies existed, they were never greater than one grade. These sections were re-examined, and a final grade agreed upon by both observers.

Neuritic Plaques (NP)

Bielschowsky stained sections of neocortex were examined in their entire extent as described above, using a mechanical stage, at a magnification of 100x. Primitive plaques were easily recognized as collections of abnormal silver positive neurites in the neuropil. Classical plaques contained, in addition, a central homogeneous brown core, often surrounded by a halo. They were graded semi-quantitatively as follows: 0. no plaques 1. rare 2. present in small numbers in many fields 3. moderate to abundant in many fields 4. very abundant in most fields. A neocortical plaque score was then derived, as described above. The counts were performed by one observer (CB), and when repeated blindly on 15 AD cases and 15 controls randomly selected, 25/30 observations were identical, giving a reproducibility rate of 83%.

Amyloid-rich Plaques (ARP)

Congo Red stained sections of all regions were re-examined as described in the previous section, at a magnification of 100x. Neuritic plaques with a rich content of amyloid were readily identified, including compact or burnt-out plaques as well as the central core of classical plaques, and graded semi-quantitatively: 0. no cores 1. rare cores, less than five per section 2. few 3. frequent cores in many fields 4. many cores in most fields. A neocortical amyloid-rich plaque score was derived as described above. The sections were examined by one observer (CB) with a reproducibility rate of 90%, using the method outlined in the previous section.

Statistical Methods

The data were analysed using the chi-square test and the chi-square test with continuity correction,[9] the chi-square test for linear trend,[10] correlation coefficients with t tests,[11] and linear regression analysis with scatter plots.[12] When the analyses were conducted using neocortical scores, the two AD cases where a cortical site was missing were excluded (cases 2A and 9A), for a total of 28 cases.

RESULTS

Incidence and Distribution of Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) was seen in 86% of the AD group, as compared to 40% of controls (Tables 1A and 1B). The discrepancy between the two groups became even more evident as the severity of CAA increased (Table 2).

The incidence of CAA increased with age in the total patient population (Table 3A). This association was also seen in the control group, but not at a statistically significant level; in AD, no relationship between age and CAA was observed (Tables 3B and 3C). Using linear regression analysis, no significant correlation could be demonstrated between increasing age and the severity of CAA (Figure 1).

CAA was distributed evenly across frontal, temporal and parieto-occipital neocortex in AD, with a less frequent involvement of the cerebellum. In the control group, CAA was less

Table 1A: Alzheimer's Disease. Incidence and severity of cerebral amyloid angiopathy (CAA), amyloid-rich plaques (ARP), and neuritic plaques (NP)

Case #	Age at death	Duration of illness (years)	Neocortical Scores* CAA	ARP	NP
mean ± s.d.	73.0 ± 8.1	6.3±3.5	5.0 ± 3.1	5.8 ± 2.0	7.5 ± 1.0
1A	43	3	7.5	6.6	10
2A**	53	3	3.8	10	7.5
3A	63	7	10	8.3	7.5
4A	66	6	10	10	7.5
5A	66	10	6.6	5	7.5
6A	67	5	0	5.8	7.5
7A	67	7	8.3	10	8.3
8A	69	6	4.2	5.8	6.6
9A**	70	3	2.5	5	7.5
10A	70	14	6.6	5.8	7.5
11A	70	13	7.5	5.8	9.2
12A	71	2	3.3	5	8.3
13A	72	5	0	2.5	8.3
14A	72	6	0	5	7.5
15A	72	9	1.6	5	7.5
16A	73	7	0	3.3	7.5
17A	73	3	4.2	5.8	8.3
18A	74	8	9.2	5	7.5
19A	75	11	7.5	3.3	5
20A	76	4	5	4.2	7.5
21A	76	5	5.8	10	7.5
22A	77	3	3.3	5	8.3
23A	77	10	5	5	7.5
24A	79	n/a	3.3	5	7.5
25A	80	3	8.3	5	7.5
26A	81	5	5.8	5	6.6
27A	82	0.5	5.8	5	6.6
28A	82	n/a	3.3	4.2	5.8
29A	82	n/a	2.5	7.5	7.5
30A	83	5	7.5	6.6	7.5

* Cumulative scores for all neocortical sites, converted to a scale of 0-10.

** One of three neocortical sites unavailable; excluded from statistical analysis.

Table 1B: Control Group. Incidence and severity of cerebral amyloid angiopathy (CAA), amyloid-rich plaques (ARP) and neuritic plaques (NP)

Case #	Age at death	Neocortical Scores* CAA	ARP	NP
Mean	70.8	1.4	1.2	2.4
±s.d.	±9.8	±2.4	±1.7	±2.7
1C	44	0	0	0
2C	51	0	0	0
3C	63	1.6	0.8	2.5
4C	64	3.3	1.6	5
5C	65	0.8	0.8	5.8
6C	65	0	0	0
7C	66	0	0	0
8C	66	0	0	1.6
9C	66	0	0	0
10C	66	0	0	0
11C	67	0	0	0
12C	67	0	2.5	6.6
13C	67	4.2	4.2	7.5
14C	69	0	0	0
15C	70	0	0	2.5
16C	71	8.3	0	0.8
17C	73	0	5	7.5
18C	73	8.3	2.5	5.8
19C	74	0.8	0	2.5
20C	74	0	0	0
21C	74	1.6	1.6	1.6
22C	74	4.2	2.5	4.2
23C	75	0	0	0
24C	76	0	0.8	4.2
25C	77	0	0	0
26C	78	0	0	0.8
27C	84	0	1.6	2.5
28C	86	2.5	5	5.8
29C	89	5.8	1.6	0.8
30C	92	1.6	5.8	5.8

* Cumulative scores for all neocortical sites, converted to a scale of 0-10.

Table 2: Incidence of Cerebral Amyloid Angiopathy in Alzheimer's Disease and Controls

	Alzheimer's disease N = 28	Controls N = 30	p*
Amyloid angiopathy	24 (86%)	12 (40%)	0.0009
Neocortical score >2.5	22 (79%)	6 (20%)	<0.0001
Neocortical score >3.75	18 (64%)	5 (17%)	<0.0006
Neocortical score >5	13 (50%)	3 (10%)	<0.0022

* Continuity corrected chi-square test

often seen in the temporal lobe, and observed only once in the cerebellum (Table 4A). For any given case, the angiopathy tended to be slightly more severe in the parieto-occipital area (Table 4B). In the AD group, the duration of the illness did not influence the severity of the angiopathy ($r = -0.153$, $p > 0.05$).

Incidence and Distribution of Neuritic Plaques

All the AD cases were found to have neuritic plaques, with a mean global score of 7.54±1.0 for neuritic plaques, and 5.8±2.0 for amyloid-rich plaques. In any given case, the plaques were evenly distributed in the neocortical sites examined (Table 4). Small amyloid cores were seen in the cerebellum in a third of the AD cases, largely confined to the molecular layer. Neuritic plaques were found in at least one site in 60% of the control cases, with a mean global score of 2.4±2.7 for neuritic plaques, and 1.2±1.7 for amyloid-rich plaques (Table 1B). The distribution of the plaques in this group was less uniform, within a given case, than that seen in the AD group (Table 4B). In the AD group, the duration of the illness did not influence the degree of neuritic plaque formation ($r = -0.182$, $p > 0.05$), or the amount of amyloid present in the plaque ($r = -0.226$, $p > 0.05$).

Relationships Between Cerebral Amyloid Angiopathy and Neuritic Plaques

A significant ($p < 0.0001$) relationship was observed between CAA and the incidence of neuritic plaques, as well as CAA and amyloid-rich plaques, for the total patient population (Table 5). CAA was never seen in the absence of neuritic plaques, and only rarely seen without amyloid-rich plaques. The converse was not true however, with 14%-20% of cases displaying neuritic plaques or amyloid-rich plaques without CAA.

When vascular and plaque amyloid were encountered together in a given case, their respective neocortical scores often correlated (Figure 2). There were however significant exceptions in

https://doi.org/10.1017/S0317167100037379 Published online by Cambridge University Press

Table 3: Relationship Between Age and the Incidence of Amyloid Angiopathy in Neocortex

A. Total patient population n = 58

Age Range	# of cases with amyloid angiopathy	
Less than 70	10/21	(48%)
70-79	17/27	(63%)
80 and above	9/10	(90%)

Chi-square test for overall association p = 0.075
Chi-square test for linear trend in age p = 0.026

B. Control group n = 28

Age Range	# of cases with amyloid angiopathy	
Less than 70	4/14	(29%)
70 and above	8/16	(50%)

Chi-square test p = 0.4112

C. Alzheimer's Disease n = 28

Age Range	# of cases with amyloid angiopathy	
Less than 70	6/7	(86%)
70 and above	18/21	(86%)

Table 4: Regional Incidence and Severity of CAA, NP and ARP in Alzheimer's Disease and Controls

A. Incidence

	MFG	MTG	TWS	CEREBELLUM
Control Group				
CAA	9/30 (30%)	6/30 (20%)	9/30 (30%)	1/27 (3.7%)
NP	16/30 (53%)	15/30 (50%)	15/30 (50%)	—
ARP	12/30 (40%)	7/30 (23%)	10/30 (30%)	1/27 (3.7%)
Alzheimer's Disease				
CAA	23/30 (76%)	24/29 (83%)	23/29 (76%)	16/30 (53%)
NP	30/30 (100%)	29/29 (100%)	29/29 (100%)	—
ARP	30/30 (100%)	29/29 (100%)	29/29 (100%)	10/30 (33%)

B. Severity*

	MFG	MTG	TWS	CEREBELLUM
Control Group				
CAA	1.8	2.0	2.5	2.0
NP	1.7	1.9	2.2	—
ARP	1.4	1.5	1.7	1.0
Alzheimer's Disease				
CAA	2.2	2.4	2.9	2.4
NP	3.0	3.0	2.9	—
ARP	2.2	2.4	2.3	1.4

* Mean regional score for all positive cases in a given region.
MFG = Middle Frontal Gyrus; MTG = Middle Temporal Gyrus; TWS = Triple watershed area.

Table 5: Relationships between CAA, NP and ARP

	Alzheimer's Disease N = 28	Controls N = 30	All cases N = 58
CAA without NP	0% (0/28)	0% (0/30)	0% (0/58)
CAA without ARP	0% (0/28)	7% (2/30)	3% (2/58)
NP without ARP	14% (4/28)	20% (6/30)	17% (10/58)
ARP without CAA	14% (4/28)	17% (5/30)	15% (9/58)

both groups, with a low CAA score in the presence of abundant plaques and, in the control group, severe CAA with very few plaques (Tables 1A and 1B). Although every effort was made to evaluate the neuropathological parameters independently, Congo Red stained slides displayed both amyloid-rich plaques and vascular amyloid simultaneously. While possibly introducing a bias, the method allowed us to observe the spatial relationships of these changes, which were remarkably inconsistent from one section to the other and one field to the next. On occasion

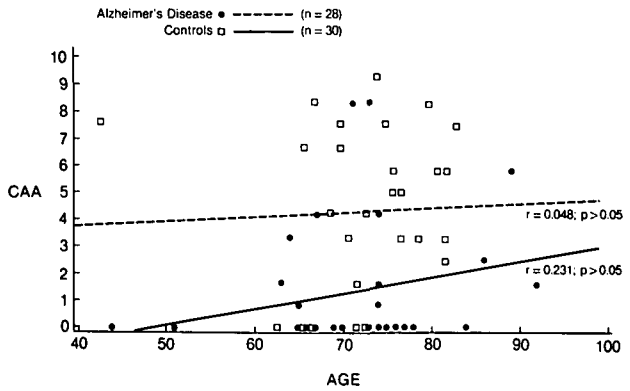

Figure 1 — Linear regression analysis showing no correlation between increasing age and severity of the angiopathy (CAA) in either AD or controls.

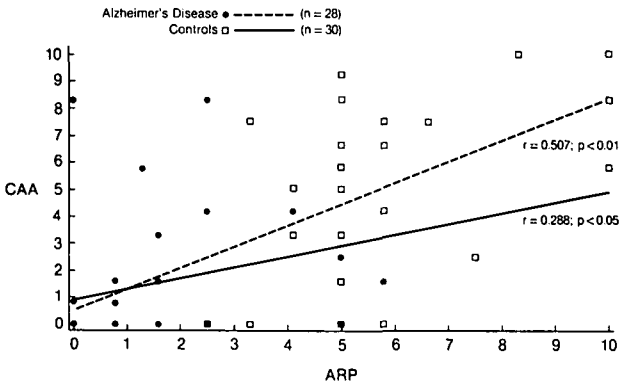

Figure 2 — Linear regression analysis showing a significant correlation between the amount of amyloid present in plaques (ARP) and vessels (CAA), in both AD and controls.

one could observe a remarkable spatial co-localization between severe CAA and large abundant amyloid cores, but fields or sections with striking discrepancies were common; revealing a marked deposition of amyloid in one site, with little or none at the other. There was no correlation between the severity of neuritic plaque formation and that of CAA in either group (Figure 3), and the severity of neuritic plaque formation was significantly correlated with the amount of plaque amyloid only in the control group (Figure 4).

Discussion

The high incidence of CAA seen in our AD group is similar to that reported by others,[1-4] with the exception of Mountjoy et al[13] who found it in only 60% of their cases. The distribution of the lesions is also similar to that described in the literature,[3-6,7,13] except for the cerebellum. CAA was present in that site in 53% of our AD cases, most often accompanied by small amyloid cores. Pro et al[14] found cerebellar amyloid plaques in 41% of their cases, but report only one instance of vascular amyloid in that region, probably reflecting their use of the PAS stain. The combined incidence of cerebellar amyloid plaques and angiopathy in our material is 56%, slightly lower than the 66% found by Rudelli and Wisniewski.[15] Unlike these authors, we found a definite correlation between cerebellar amyloid and the presence and severity of CAA in the supratentorial compartment,

https://doi.org/10.1017/S0317167100037379 Published online by Cambridge University Press

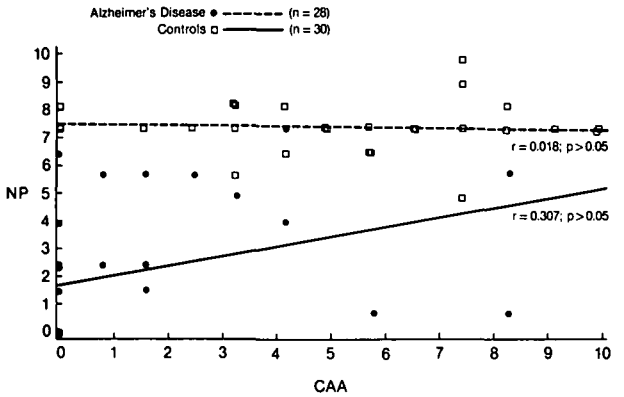

Figure 3 — Linear regression analysis showing no correlation between the severity of neuritic plaque formation (NP) and the amount of amyloid deposited in vessels (CAA) in either AD or controls.

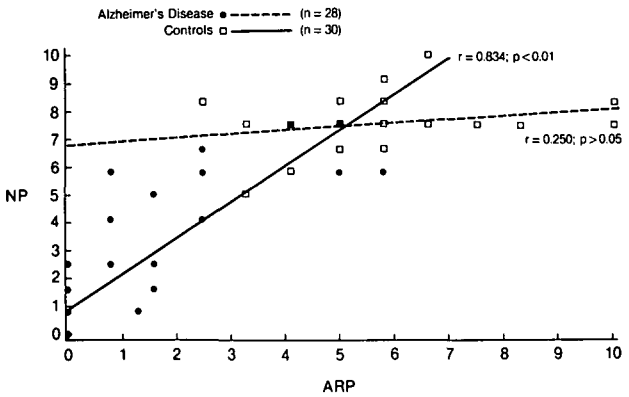

Figure 4 — Linear regression analysis showing a significant correlation between the severity of neuritic plaque formation (NP) and the amyloid plaque content in controls, but not AD.

with cerebellar lesions occurring most often in the presence of extensive angiopathy in cerebral sites. The 40% incidence of CAA in our control group is identical to that found by Mountjoy et al[13] in a similar population. If however, the control group is restricted to subjects with no neuritic plaques, the incidence of CAA is 0, regardless of age. Like Esiri and Wilcock,[4] we were unable to demonstrate the increased incidence of CAA with advancing age found by others.[5,6]

As in many other studies of CAA in aged individuals, we never found CAA in the absence of neuritic plaques.[1,16] Tomonaga[5] and Mountjoy et al[13] reported CAA without plaques in a small number of cases, but they used exclusively Congo Red stains for their study, therefore including only classical and compact plaques, and excluding primitive plaques. Neuritic plaque formation however is not necessarily accompanied by CAA; this is best exemplified by the small number of florid cases of AD encountered in all series, in which there is no CAA despite extensive neuritic plaque formation. One may argue with Glenner et al[1] that a more extensive search, or ultrastructural examination, may disclose vascular amyloid in all cases. Nevertheless, a substantial discrepancy would remain between the amount of vascular and plaque amyloid. Glenner himself has agreed that there does not seem to be any regional linkage between the severity of these two lesions.[2]

The neocortical scores show that the amount of vascular and plaque amyloid often correlate. This association was observed, though not systematically evaluated, by other authors.[3,5,6] In a significant number of cases however, discrepant scores were obtained, with preferential deposition of amyloid in plaques or vessels, or a disproportion between the extent of NP formation and the severity of CAA. A similar disproportion between these two parameters is readily evident in Table 1 of Mandybur's publication.[16] Mountjoy et al[13] found only a weak relationship between plaque and vascular amyloid in their thorough quantitative study; this probably reflects the small sample size inherent to such studies, and emphasizes the lack of a close spatial co-localization between CAA and ARP observed in most studies including ours.[1,3,17]

The amyloid accumulating in cerebral vessels and neuritic plaques is quite possibly identical, and consists of a unique protein unlike any other known amyloid.[18,19] Its gene is located on chromosome 21, and is expressed, probably in precursor form, in many neural and non-neural tissues.[20,21] The only site where this protein accumulates as amyloid however, is the brain of subjects with neuritic plaques. Two pathogenetic models have been invoked to explain this accumulation of amyloid.

The vascular hypothesis postulates the deposition of a systemic amyloid percursor in cerebral blood vessels, leading to an alteration in the blood-brain barrier, with deposition of amyloid in the neuropil and subsequent neuritic plaque formation as a toxic effect of this accumulation.[1] This hypothesis is supported by the fact that the amyloid precursor is indeed expressed in several non-neural tissues, and by the ultrastructural observation of Miyakawa et al,[22] that neuritic plaques are always closely associated with an amyloid-laden vessel. Other EM studies however, did not find such a relationship.[23,24,25] This hypothesis also fails to account for the absence of CAA in up to 20% of cases displaying neuritic plaques, the poor spatial correlation between plaque and vascular amyloid, the distribution of neuritic plaques in a laminar pattern in neocortex,[26,27] and their presence in noncortical sites characteristically uninvolved by CAA.

The second hypothesis postulates a local production of amyloid in the brain, perhaps from extruded paired helical filaments.[19,28,29] Again the poor spatial correlation between vascular and plaque amyloid, particularly in leptomeninges and cerebellum, weaken this hypothesis, as well as the fact that several groups have been unable to demonstrate immunological cross-reactivity between PHF's and brain amyloid.[30,31]

A third hypothesis should be raised, which explains our findings more satisfactorily: the phenomena of neuritic plaque formation and vascular or plaque amyloid deposition are linked perhaps etiologically or genetically, but expressed independently in the brain, with no cause and effect relationship. In other words, individuals who develop neuritic plaques also become subject to amyloid deposition in plaque and/or vessel, but the deposition in either site is independent of the other with no cause and effect relationship. The amyloid is synthesized locally, but its amount and localization vary according to individual, as yet unidentified, factors. Further delineation of the relationship between neuritic plaques and amyloid angiopathy will require the definite identification of the amyloid producing cell(s) in the brain, as well as the local factors that promote its accumulation.

ACKNOWLEDGEMENTS

The authors wish to thank Miss Lori-Ann Austin for her technical assistance, and Mrs. Marilynne Henry for her secretarial help. This work was supported in part by the Medical Research Council of Canada, and the Ontario Mental Health Foundation.

REFERENCES

1. Glenner GG, Henry JH, Shigeyoshi F. Congophilic angiopathy in the pathogenesis of Alzheimer's degeneration. Ann Pathol 1981; 1: 120-129.
2. Glenner GG. Alzheimer's Disease. Multiple cerebral amyloidosis. *In*: Katzman R, ed. Banbury Report 15, Biological Aspects of Alzheimer's Disease. Cold Spring Harbor Laboratory, 1983; 137-143.
3. Mandybur TI. The incidence of cerebral amyloid angiopathy in Alzheimer's disease. Neurology 1975; 25: 120-126.
4. Esiri MM, Wilcock GK. Cerebral amyloid angiopathy in dementia and old age. J Neurol Neurosurg Psychiatry 1986; 49: 1221-1226.
5. Tomonaga M. Cerebral amyloid angiopathy in the elderly. J Am Geriatr Soc 1981; 29: 151-157.
6. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: Incidence and complications in the ageing brain. II. The distribution of amyloid vascular changes. Stroke 1983; 14: 924-928.
7. Pantelakis S. Un type particulier d'angiopathie senile du système nerveux central: l'angiopathie congophile: topographie et fréquence. Monatsschr Psychiat Neurol 1954; 128: 219-256.
8. Surbek B. L'angiopathie dyshorique (Morel) de l'ecorce cerebrale. Etude anatomo-clinique et statistique, aspect genetique. Acta Neuropathol (Berl) 1961; 1: 168-197.
9. Brown MB. BMDP Statistical Software, 1983 Printing with additions, Chapter 11. University of California Press.
10. Cohen J. Some statistical issues in psychological research. *In*: Wolman B, ed. Handbook of Clinical Psychology. New York, McGraw Hill, 1965.
11. Cochran WG. Some methods for strengthening the common chi-square test. Biometrics 1954; 10: 4170-441.
12. SAS Institute Inc. SAS/GRAPH User's guide. Version 5 edition. Gary, N.C. U.S.A., 1985.
13. Mountjoy CQ, Tomlinson BE, Gibson PH. Amyloid and senile plaques and cerebral blood vessels. A semi-quantitative investigation of the possible relationship. J Neurol Sci 1982; 57: 89-103.
14. Pro JD, Smith CH, Sumi SM. Presenile Alzheimer's Disease: Amyloid plaques in the cerebellum. Neurology 1980; 30: 820-825.
15. Rudelli RD, Wisniewski HM. Cerebellar amyloid plaques in Alzheimer's dementia (AD) and senile dementia of Alzheimer type (SDAT). J Neuropathol Exp Neurol 1985; 44: 364.
16. Mandybur TI. Cerebral amyloid angiopathy: The vascular pathology and complications. J Neuropathol Exp Neurol 1986; 45: 79-90.
17. Schwartz P. Amyloidosis of the nervous system in the aged. *In*: Minkler J, ed. Pathology of the Nervous System, New York. McGraw-Hill, 1972, volume 3: 2812-2848.
18. Wong CW, Quaranta V, Glenner GG. Neuritic plaques and cerebrovascular amyloid in Alzheimer's Disease are antigenetically related. Proc Natl Acad Sci USA 1985; 82: 8729-8732.
19. Masters CL, Multhaup G, Simms G, et al. Neuronal origin of a cerebral amyloid. Neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaques and blood vessels. Embo J 1985; 4: 2757-2763.
20. Tanzi RE, Gusella JF, Watkins PC, et al. Amyloid B protein gene: cDNA, mRNA distribution, and genetic linkage near the Alzheimer locus. Science 1987; 235: 880-884.
21. Goldgaber D, Lerman MI, McBride OW. Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. Science 1987; 235: 877-880.
22. Miyakawa T, Shimoji A, Kuramoto R, et al. The relationship between senile plaques and cerebral blood vessels in Alzheimer's disease and senile dementia. Virchows Arch (Cell Pathol) 1981; 40: 121-129.
23. Kidd M. Alzheimer's disease. An electron microscopical study. Brain 1964; 87: 307-320.
24. Wisniewski HM, Terry RD. Re-examination of the pathogenesis of the senile plaque. *In*: Zimmerman HM, ed. Progress in Neuropathology, New York, Grune and Stratton, 1972, vol. 2: 1-26.
25. Friede RL, Magee KR. Alzheimer's disease. Presentation of a case with pathologic and enzymatic-histochemical observations. Neurology 1962; 12: 213-222.
26. Pearson RCA, Esiri MM, Hiorns RW, et al. Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. Proc Natl Acad Sci USA 1985; 82: 4531-34.
27. Duyckaerts C, Hauw JJ, Bastenaire F, et al. Laminar distribution of neocortical senile plaques in senile dementia of the Alzheimer type. Acta Neuropathol 1986; 70: 249-256.
28. Kidd M, Allsop D, Landon M. Senile plaque amyloid, paired helical filaments, and cerebrovascular amyloid in Alzheimer's disease are all deposits of the same protein. Lancet 1985; 1: 278.
29. Allsop D, Landon M, Kidd M, et al. Monoclonal antibodies raised against a subsequence of senile plaque core protein react with plaque cores, plaque periphery and cerebrovascular amyloid in Alzheimer's disease. Neurosci Lett 1986; 68: 252-256.
30. Selkoe DJ, Abraham CR, Podlisny MB, et al. Isolation of low-molecular weight proteins from amyloid plaque fibers in Alzheimer's disease. J Neurochem 1986; 46: 1820-1834.
31. MacDonald SM, Esiri MM. Monoclonal antibody binding to congophilic elements in human Alzheimer brain. J Clin Pathol 1986; 39: 1199-1203.