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HISTOPATHOLOGICAL STUDIES ON SENILE PLAQUES IN BRAINS OF PATIENTS WITH DOWN'S SYNDROME

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INDEXING WORDS

Down's syndrome; senile plaque; dyshoric angiopathy; silver stain

SYNOPSIS

Senile plaques(SPs) as a hallmark of Alzheimer's pathology were studied in the brains of 5 cases of Down's syndrome(DS), using silver stains including modified Bielschowsky and new methenamine silver method which had been reported to show almost the same staining pattern as that of beta-protein immunostaining. SPs were observed in the CA1, the subiculum, the molecular layer of the gyrus dentatus, and the cerebral neocortices of all cases examined. In the striatum and the cerebellum, SPs were found in 2 out of 4 cases, both over the age of 30. In the cerebral cortex and the hippocampal formation, SPs were almost exclusively composed of the diffuse type below the age of 30, while primitive and classical plaques first appeared over the age of 30. In case

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1 (aged 16), the cerebral cortex contained a few perivascular plaques associated with amyloid angiopathy known as dyshoric angiopathy. Our results suggest that diffuse plaques and dyshoric angiopathy are possibly earliest stages of SP formation in DS brains.

INTRODUCTION

Individuals with Down's syndrome (DS) show a high predisposition to Alzheimer's disease (AD).[10, 11] Pathological hallmarks of senile plaques (SPs) and neurofibrillary tangles (NFTs) appear in the brains of nearly all patients with DS above the age of 30 years.[11, 31] SPs are heterogeneous structures composed of amyloid deposits, degenerating neurites and reactive cells (microglia and astrocytes).[27] It is customary to distinguish primitive, classical and compact plaques, depending on the distribution and relative amount of amyloid and abnormal neurites.[27] Primitive plaques are composed of distorted or swollen neurites accompanied by small bundles of intercellular amyloid without a central core. Classical plaques are constituted by central homogeneous amyloid core, surrounded by a clear zone or halo corresponding to scattered amyloid or to artifactual space, which in turn is surrounded by a darkly staining corona made up primarily of distended neurites. Compact plaques consist almost exclusively of the central core amyloid occasionally surrounded by a few abnormal neurites. Another type of SPs associated with amyloid angiopathy has also been described as dyshoric angiopathy, in which amyloid deposits infiltrate around microvessels.[8, 20] The principal component of amyloid fibrils in AD and DS is beta protein (also known as A4 protein),[6, 16] which appears to be derived from a much larger precursor "amyloid precursor protein" (APP) by proteolytic cleavage.[7] Although early studies emphasized the neuritic element in SPs, more recent immunohistochemical studies using antibodies to beta protein have demonstrated amyloid deposits referred to as "preamyloid deposits" or "diffuse plaques" which lack apparently abnormal neurites and central core amyloid deposits.[5, 13, 21, 23, 33] Some of these authors have contended that these types of plaques represent the earliest stage of SP

formation.[5, 13, 23] However the evolution of SPs and the relationships among neuritic elements, extracellular deposits of the beta protein and vascular amyloid are poorly understood.[3] The gene for beta protein and APP is on the long arm of chromosome 21, which is present in triplicate in DS.[19] Therefore overexpression of this gene may lead to increased levels of APP and amyloid deposition in DS brains,[21] in which the acquisition of AD pathology at later life is predictable.[11] The comparison of pathological findings similar to those found in AD pathology in DS brains before and after the age of 30 offers a possibility of studying the development of pathological changes in DS and AD.

Among several silver stains for the demonstration of amyloid, modified Bielschowsky and new methenamine silver stains are reported to be sufficiently reliable methods showing almost the same staining pattern as that of beta-protein immunostaining with formic acid pre-treatment.[28, 31, 34] We investigated the cerebral cortex (hippocampal formation and neocortex), the striatum and the cerebellum using modified Bielschowsky and new methenamine silver stains for the demonstration of amyloid in 5 individuals with DS autopsied at the age of 16 to 51.

MATERIALS AND METHODS

Pathological and histometrical studies were carried out on tissue blocks of 5 brains with DS obtained at autopsy and fixed by immersion into 10 % formalin. Four brain areas were selected: (1) hippocampal formation including hippocampus proper, gyrus dentatus, subiculum, (2) neocortex, (3) corpus striatum (putamen and caudate nucleus), and (4) cerebellar hemisphere. No specimens of the hippocampal formation were obtained in case 2 and none of the cerebellum in case 4.

Six-micrometer-thick sections of each tissue block were stained with hematoxylin and eosin, Congo red, Bodian, modified Bielschowsky stains and in several sections with new methenamine silver stains. Four types of plaques were classified by silver stains by the methods of Yamaguchi[32], as follows. (1) Diffuse plaque: poorly defined amorphous or polymorphous areas resembling cotton-wools, stained by the modified Bielschowsky method, in

which distorted or swollen neuritic processes could hardly be distinguished. No compact amyloid cores could be recognized. (2) Primitive plaques: plaques more distinctly circumscribed than diffuse plaques, in which distended neuritic processes were obvious without an amyloid core. (3) Classical plaques: plaques consisting of swollen neuritic processes and a compact center of amyloid. (4) other plaques: Including perivascular plaques and compact plaques. The number of plaques was counted in 8 adjacent fields of 0.25 mm^2 at a magnification of 200 on the following areas: CA1, subiculum, gyrus dentatus, neocortices and striatum. The numbers of plaques were converted into densities of plaques per mm^2.

Amyloid angiopathy and NFT were identified on sections stained by Congo red, and modified Bielschowsky stains, respectively. Modified Bielschowsky stain used in this study is a silver impregnation for parrafin-embedded sections described by Hirano et al.[34]

Table 1. Histometrical studies on senile plaques densities per mm^2 and the distribution densities of cerebellar plaques(Ce-pls), neurofibrillary tangles (NFT) and amyloid angiopathy(AA).

Nr	Age	sex	Histometrical densities of SP per mm^2					Ce-pls	NFT	AA
			Cor	CA1	Sub	DG	Str			
1	16	f	2.0	2.5	3.5	0.5	0	-	-	-
2	27	m	2.5	*	*	*	0	-	-	-
3	35	m	71.0	14.0	16.0	*	2.0	+	++	-
4	39	f	39.5	2.0	12.0	11.5	*	*	++	-
5	51	m	41.0	14.0	18.0	16.5	10.0	+	+++	++

SP = senile plaques; Ce-pls = cerebellar plaques;
NFT = neurofibrillary tangles; AA = amyloid angiopathy
Sub = subiculum; DG = gyrus dentatus; Cor = neocortex; Str = striatum
- :no discernible change
+ :slight change
++ :moderate change
+++ :severe change
* :area not examined

RESULTS

The morphometric data of 5 brains of DS patients are summarized in Table 1. The neocortex and the hippocampal formation of all cases revealed the presence of SPs. The striatum and the cerebellum showed fewer plaques than cerebral cortical areas in 2 out of 4 cases over the age of 30. NFTs were detected in 3 out of 5 cases over the age of 30 in the hippocampal formation and the neocortex. The widespread amyloid angiopathy was observed with Congo red stains in only one case (case 5, aged 51). The highest density of SPs was observed in the neocortical areas of 4 out of 5 cases examined. In cases before the age of 30 the densities of SPs ranged between 2.0 and 2.5 per mm^2. In case 3 (aged 35) the highest density 71.0 per mm^2 was observed, while in older cases the density was decreased to 39.5 and 41.0 per mm^2. Less dense accumulations of SPs occurred in the CA1, the subiculum and the gyrus dentatus, where the densities of SPs made little difference after the age of 30 ranged 12.0 to 18.0 per mm^2 except for 2.0 per mm^2 in the CA1 of case 3. In case 1, the density was 0.5 to 3.5 per mm^2. The striatum showed the lowest concentration of SPs. No plaques were detected under the age of 30. The density was 2.0 (age 35) and 10.0 (age 51) per mm^2. In the hippocampal formation of case 1, the occurrence of SPs was almost restricted to the CA1, the subiculum, and the molecular layer of the gyrus dentatus. The plaques of cases 3 and 5 were distributed laterally across the medial edge of the parahippocampal gyri.

The hippocampal formation and the neocortex

In the hippocampal formation of case 1, plaques were scattered in the CA1, the subiculum and the molecular layer of the gyrus dentatus along the parahippocampal sulcus(Fig 1a). In the CA2, CA3 and CA4 of the hippocampus proper and the lateral two thirds of the parahippocampal gyrus across the medial edge, no plaques were observed. All SPs examined were of the diffuse type, showing poorly defined spherical areas of amorphous materials resembling cotton wools lacking distended neurites(Fig 1b). They were stained somewhat stronger in the center but their

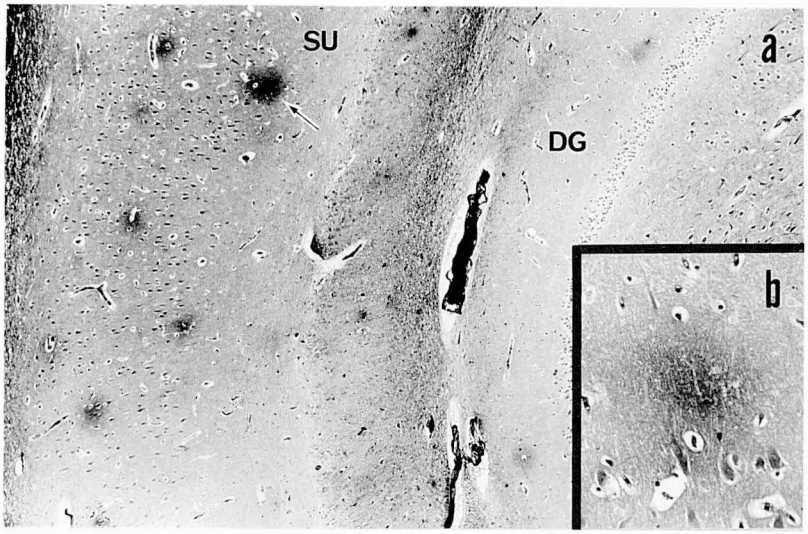

Figure 1: Hippocampal formation of case 1.
a: Diffuse plaques in the CA1(left lower angle), the subiculum(SU) and the molecular layer of the dentate gyrus(DG). Bielschowsky stain, x 43
b: Higher magnification of a diffuse plaque in the subiculum, from Figure 1a(arrow), showing neither amyloid cores nor abnormal neurites. Bielschowsky stain, x 345

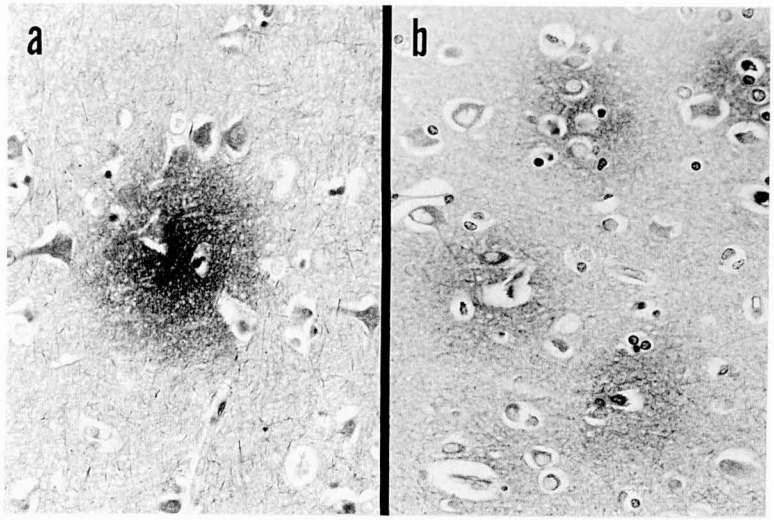

Figure 2: Diffuse plaques in the cerebral cortex.
a: A diffuse plaque in case 1, showing poorly defined spheroid areas without apparently abnormal neurites. Bielschowsky stain, x 345
b: Diffuse plaques in case 2, showing almost the same appearances as those seen in case 1. New methenamine silver stain, x 345

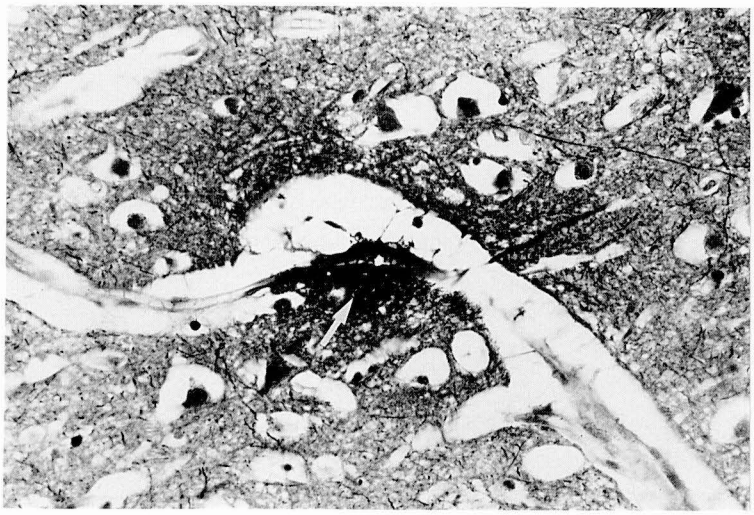

Figure 3: Dyshoric angiopathy in the cerebral cortex of case 1. A senile plaque around a degenerative vessel showing the heavily thickened wall with several branching radiations(arrow). The boundary of a plaque was poorly defined. Bielschowsky stain, x 345

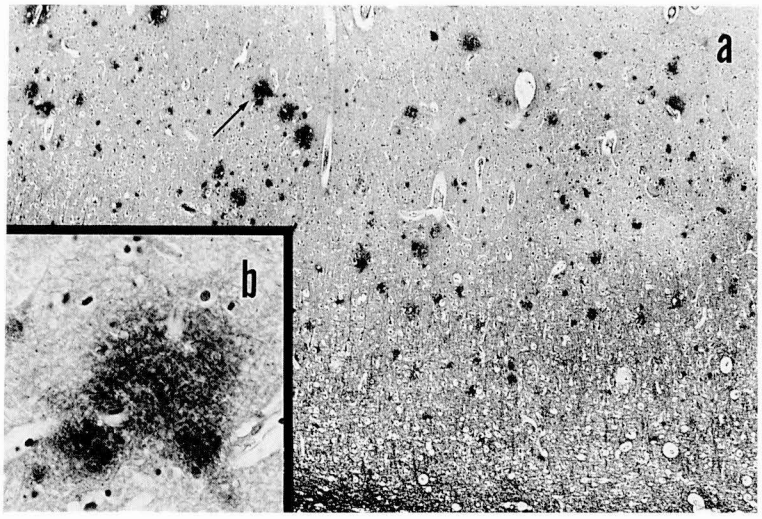

Figure 4: Senile plaques in the cerebral cortex.
a: Numerous plaques of various sizes scattered in the cortex of case 4. Bielschowsky stain, x 43
b: Higher magnification of a diffuse plaque from Figure 4a(arrow), showing more irregular shape than those seen in case 1 and 2. Bielschowsky stain, x 345

intensity decreased toward the margin lacking sharp boundaries. Neither primitive nor classical plaques were detected. At the CA1 area neuronal cells slightly decreased in number without microglial infiltration. There were edematous changes especially around capillary vessels. In the neocortex of cases 1 and 2, SPs were detected mostly in the valley of the gyri. Most SPs were of the diffuse type. Their shapes and sizes were almost the same as those seen in the hippocampal areas(Fig 2a,b). Neither primitive nor classical plaques were detected. Neuronal cells were slightly degenerative but preserved their essential layer structure. Few microglial infiltration could be found there. Perivascular plaques corresponding to dyshoric angiopathy(Fig 3) were encountered without widespread amyloid angiopathy. Vascular walls were markedly thickened, projecting several branching radiations. Fine fibrillary or granular materials accumulated irregularly without a clear boundary around the vessels. In the neocortex of cases 3 and 4, most plaques were of the diffuse type. They were composed of amorphous or fine fibrillary materials more darkly stained with irregular and unclear boundaries lacking swollen neurites(Fig 4a,b). Among them a few primitive plaques with swollen neurites could be recognized, but classical plaques were rare. In the hippocampal formation of cases 3 and 4, primitive and classical plaques accounted for more than one-half of SPs. They were visualized as fibrillary spheroid areas relatively well defined. They had more or less swollen neurites and some of them contained central core amyloids corresponding to classical plaques(Fig5). In case 5, the hippocampus exhibited marked neuronal cell loss with spongy changes and diffuse edema especially in the CA1 and the subiculum(Fig 6a). Classical plaques with central core deposits surrounded by halo and corona were most frequently detected type of SP in the hippocampal formation(Fig 6b). The majority of SPs in the neocortex were of the primitive type, while classical plaques were less frequently detected(Fig 7). There were several dyshoric angiopathy and microglial infiltration. The interstitial glial components were slightly swollen or degenerative.

The striatum

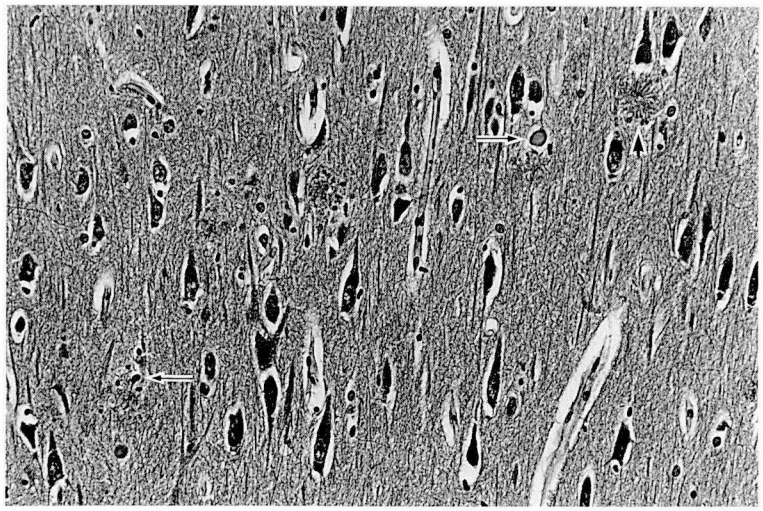

Figure 5: Plaques in the CA1 of case 3, containing central cores(arrowhead) and swollen neurites(arrows). Bodian stain, x218

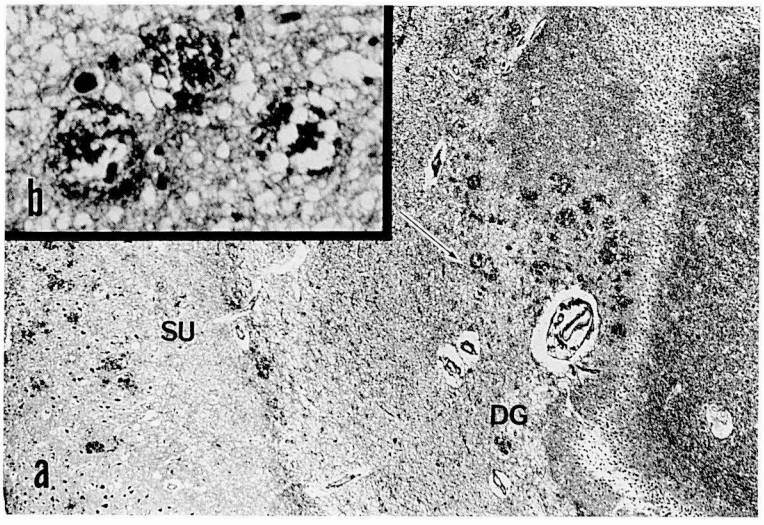

Figure 6: Hippocampal formation of case 5
a: Senile plaques in the neuropil of the dentate gyrus(DG) and the subiculum (SU) associated with spongy degeneration. The subiculum contained numerous neurofibrillary tangles seen as dense tiny dots. Bielschowsky stain, x 43
b: Higher magnification of classic plaques from Figure 6a(arrow). Bielschowsky stain, x 270

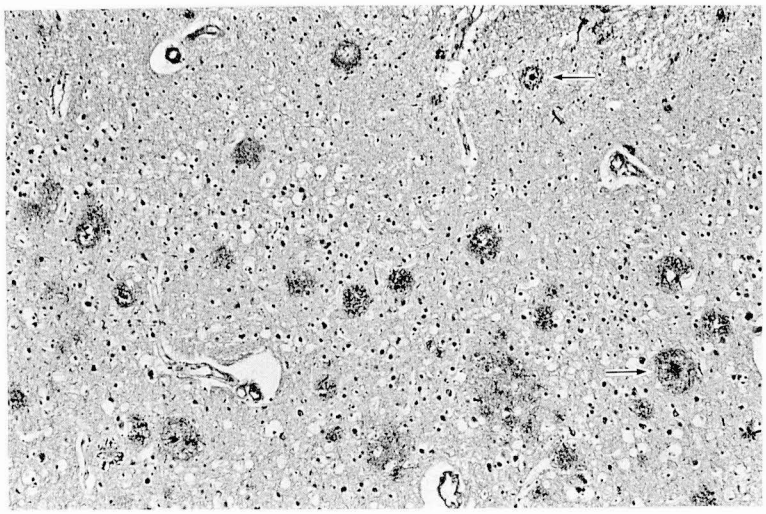

Figure 7: Plaques in the cerebral cortex of case 5 with swollen and distorted neurites compatible to typical primitive plaques, some of which contained central cores(arrows). Bielschowsky stain, x 109

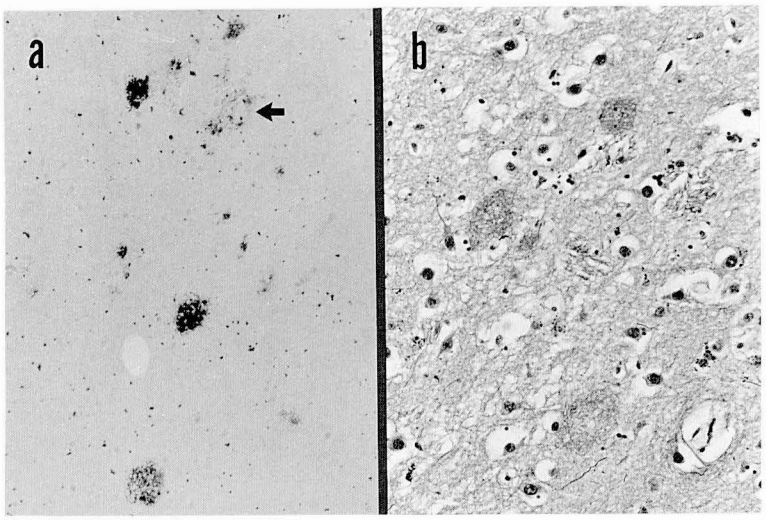

Figure 8: Senile plaques in the caudate nuclei.
a: Plaques with diffuse fibrillary deposits showing unclear boundaries(arrow) and well-defined dense deposits of the compact type in case 3. New methenamine silver stain, x 109
b: Plaques having well-defined oval deposits of the compact type case 5. Bielschowsky stain, x 173

SPs were distributed as clusters in the striatum of case 3. They were seen as spherical dense deposits(compact plaques) and diffuse plaques of various shapes and sizes(Fig 8a). Typical primitive plaques and classical ones were only rarely encountered. The plaques in case 5 revealed a more widespread distribution. They were seen as well defined oval deposits (compact plaques) stained in a similar intensity in each plaque(Fig 8b).

The cerebellum

Most plaques were of the diffuse type in case 3 and of the compact type in case 5 in the molecular layer. Diffuse plaques were seen as fine fibrillar material running horizontally in the molecular layer(Fig 9a). Compact plaques in the Purkinje cell layer were less frequently detected. Perivascular and subpial plaques were rare in both cases. In case 5, plaques were seen as well defined compact areas similar to those found in the striatum(Fig 9b). Dyshoric angiopathy were detected in the molecular layer(Fig 10a,b).

DISCUSSION

In this study we indicated that SPs found in the neocortex and the hippocampal formation were almost exclusively of the diffuse type in patients with DS under the age of 30. In general, plaques are classified as primitive, classical and compact, depending on the distribution and the relative amounts of amyloid and abnormal neurites.[27] These categories correspond to the presumed process of SP development explaining the progression of neuritic degeneration and the accumulation of amyloid of SPs, as follows:[27] Aggregates of degenerating neurites induce the local deposition of amyloid (primitive plaques). As the process of neurites degeneration progresses, amyloid materials are concentrated with cellular reaction to form central core of amyloid (classical plaques). As the neurites degenerate and disappear, the mass of amyloid is surrounded only by astroglial processes and residual neuritic elements(compact plaques). Ulrich described "very primitive plaques" as cotton-wool-like spherical areas lacking abnormal neurites,

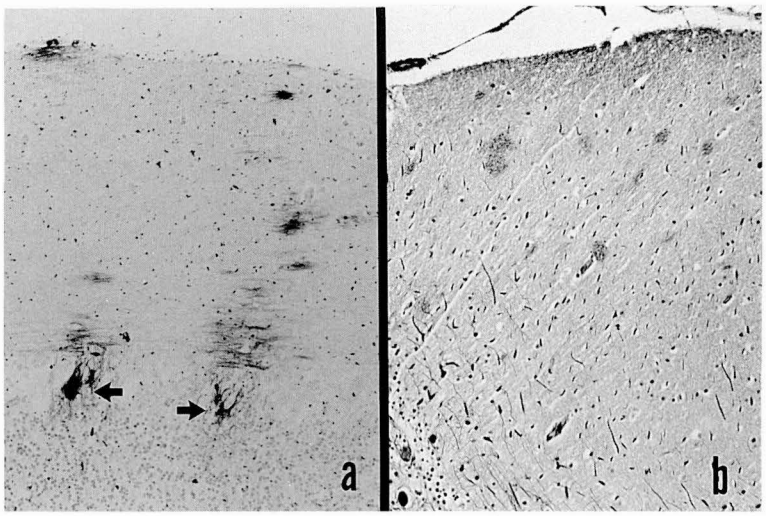

Figure 9: Senile plaques in the cerebellar cortex.
a: Plaques having fine fibrillar materials running horizontally in the molecular layer of case 3. The arrow indicates compact plaques in the Purkinje's cell layer. New methenamine silver stain, x 144
b: Plaques showing well-defined compact appearances in case 5. Bielschowsky stain, x 144

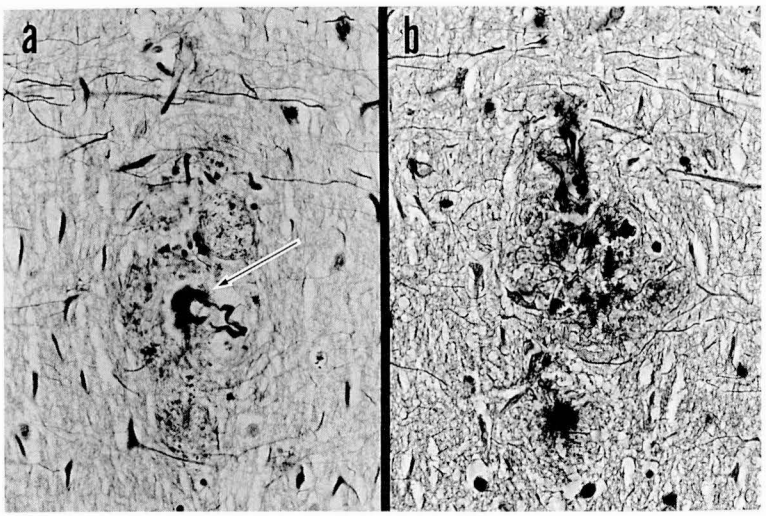

Figure 10 Dyshoric angiopathy in the cerebellum of case 5, showing amyloid deposits around the degenerative vascular wall (arrow). a: Bodian stain, b: Bielschowsky stain, x 435

reporting a "very primitive" pattern in the vast majority of SPs in brains from presenile non-demented people.[25] Recent immunocytochemical studies using antibodies to synthetic amyloid beta peptides have confirmed the presence of this type of plaques in AD and DS brains, described as "preamyloid deposits", "amorphous plaques" and "diffuse plaques".[5, 14, 23, 24, 30, 33] In DS brains, Motte and Williams described stage 1 plaques as relatively small, spherical to ovoid, deposits of granular and fibrillar materials without abnormal neurites, which probably correspond to diffuse plaques in our study.[18] They also reported that plaques of stages 1 and 2, compatible to primitive plaques, were seen predominantly between ages of 25 to 38 years, while they briefly stated that plaques of stage 1 were found in cases of 25, 31, 37, 38, 48 and 51 year of age. The distribution and the proportion of this type of plaques were not mentioned precisely. Rosemuller et al. suggested the hypothesis that beta-protein having infiltrated into neuropils (diffuse plaque) are concentrated with cellular reaction and neuritic changes(primitive plaque) and crystalized to develop classical and compact plaques from the morphological point of view.[20] The fact that the appearance of diffuse plaques preceded primitive and classical plaques in DS brains in this and other studies corresponded with this hypothesis, suggesting extracellular amyloid deposits precede neuritic degeneration.[5, 12, 13, 23] Yankner et al. supported this hypothesis, reporting that conditioned medium from cells transfected with portions of the gene for APP was toxic to neurons in primary hippocampal cultures, and the toxic agent could be removed by immunoabsorption with an antibody directed against the amyloid polypeptide.[35] However, the evolution of SP and the relationship between neuritic degeneration and extracellular deposits of beta protein are still poorly understood.[3] Masliah et al. reported that synaptic density was reduced both within and outside the diffuse plaques, suggesting that amyloid deposition itself is not the inciting lesion, but could rather be a response to pre-existing synaptic or neuronal pathology.[14] Cork et al. also supported this hypothesis, reporting that many abnormal neurites were not associated with A4-immunoreactive deposits.[3] It is difficult, based strictly on morphology, to demonstrate the

temporal development of senile plaques as Wisniewski et al. pointed out a participation of many factors including the site, the amount, the rate of formation of the amyloid deposits in the appearance of plaques.[26] The fact that plaques in the striatum and the cerebellum showed different morphological appearance in our and other studies supported this site-dependent aspect of SP morphology.[2, 22, 32] Another aspect of amount- and rate-dependent morphology of SP inevitably involves the origin of cerebral amyloids.

The origin of beta protein and APP is still unknown; two prevailing hypotheses argue for neuronal and vascular origin. Bahmanyar et al. reported that neurons in the cerebral cortex contained a high concentration of messenger RNA of APP.[1] Koo et al. reported that APP undergoes fast anterograde axonal transport in neurons of the rat peripheral nervous system, suggesting that APP is synthesized in neurons and delivered to nerve terminals, where subsequent alteration of local processing of APP result in deposit of brain amyloid.[9] Vascular hypothesis rests mainly on amyloid angiopathy and dyshoric angiopathy in AD and DS.[8] Miyakawa supported this vascular theory reporting that all of the amyloid cores of classical plaques were formed at basement membranes of capillary endothelial cells.[17] Glenner and Wong purified amyloid protein (beta protein) from the arachnoid vessels of AD and DS brains.[6] Masters et al. demonstrated that beta protein is identical to A4 protein purified from SPs from AD and DS brains.[16] Therefore, the amyloid of SP may have the same origin as that of amyloid angiopathy. Amyloid angiopathy is characterized by amyloid deposition in the media of meningeal and cortical arterioli and in capillary walls. The latter type of amyloid deposit is often accompanied with SP, corresponding to dyshoric angiopathy.[8, 20] In DS brains, several authors reported that amyloid angiopathy was observed over the age of 40, stressing the association of amyloid angiopathy with aging.[18, 29] Lai and Williams briefly reported that amyloid angiopathy occurred in 7 of 12 autopsied cases.[10] Two of 7 cases were before the age of 30, but they did not describe dyshoric angiopathy or perivascular plaques. Dyshoric angiopathy concomitant with diffuse plaques unrelated to vascular amyloid in young DS patients as we indicated in this study suggests that SP

may have two distinct modes of initial amyloid deposition from two different sources; neuronal and vascular origin.[8, 15] Tate-Ostroff et al. reported that the antibody to the extracellular domain of prebeta-protein selectively reacted with the neurons, astrocytes and cerebral blood vessels.[24] Masters et al. offered a unifying hypothesis that beta protein synthesized in neurons forms intracellular NFT and leaks extracellularlly to form SP and to precipitate around vascular walls with high affinities[15], which may explain the concomitance of diffuse plaques and dyshoric angiopathy in very young DS brains as in case 1. The fact that the densities of SPs did not increase with age in hippocampal formation may also be related to this neuronal hypothesis in view of the excessive neuronal loss making the synthesis of beta protein difficult as in case 5. The CA1 in case 4 showed abnormally low density of SPs. We interpreted it as spongy changes due to agonal degeneration as seen in the cerebellar granular cells. The fact that DS brains before the age of 30 did not disclose NFTs in our study and others may provide advantages for the hypothesis that amyloid deposition precedes NFT formation.[12, 20]

The molecular layer of the gyrus dentatus represents one of the most severely involved areas in AD brain. In DS brains, the CA1, the subiculum and the amygdala were reported to be the areas most severely and primarily involved regions.[27, 30] In three cases of DS brains we found that the molecular layer of the gyrus dentatus showed SPs, coinciding with results seen in the recent reports.[18] This layer receives fibers of the perforant path by which hippocampus are connected with wide cortical zones.[4] Pathologic lesions like SPs may cause an isolation of the hippocampal formation from the neocortical input which might be related to intellectual decline in DS patients.

The senile plaques in Down's syndrome before age 30 were apparently composed of two morphologically distinct forms: diffuse plaques and dyshoric angiopathy which might represent one of the earliest forms of senile plaques.

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REFERENCES

1. Bahmanyar, S., Higgins, G.H., Goldgaber, D., Lewis, D.A., Morrison, J.H., Wilson, M.C., Shanker, S.K. and Gajdusek, D.C.: Science. 1987. 237. 77/80. Localization of amyloid beta protein messenger RNA in brains from patients with Alzheimer's disease.
2. Braak, H. and Braak, E.: J. Neuropathol. Exp. Neurol. 1990. 49. 215/224. Alzheimer's disease: Striatal amyloid deposits and neurofibrillary changes.
3. Cork, L.C., Masters, C., Beyreuther, K. and Price, L.: Am. J. Pathol. 1990. 137. 1383/1392. Development of senile plaques.
4. Emson, P.C. and Lindvall, O.: Br. Med. Bull. 1986. 42. 57/62. Neuroanatomical aspects of neurotransmitters affected in Alzheimer's disease.
5. Giaccone, G., Tagliavini, F., Linoli, G., Bouras, C., Frigerio, B. and Bugiani, O.: Neurosci. Lett. 1989. 97. 232/238. Down patients: extracellular preamyloid deposits precede neuritic degeneration and senile plaques.
6. Glenner, G.G. and Wong, C.W.: Biochem. Biophys. Res. Commun. 1984. 122. 1131/1135. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein.
7. Kang, J., Lemaire, H.G., Unterbeck, A., Salbaum, J.M., Masters, C.L., Grzeschik, K.H., Multhaup, G., Beyreuther, K. and Muller-Hill, B.: Nature. 1987. 325. 733/736. The

precursor of Alzheimer's disease amyloid A4 protein resembles a cell surface receptor.

8. Kawai, M., Kalaria, R.N., Harik, S.I. and Perry, G.: Am. J. Pathol. 1990. 137. 1435/1446. The relationship of amyloid plaques to cerebral capillaries in Alzheimer's disease.
9. Koo, E.H., Sisodia, S.S., Archer, D.R., Martin, L.J., Weidemann, A., Beyreuther, K., Fischer, P., Masters, C.L. and Price, D.L.: Proc. Natl. Acad. Sci. USA. 1990. 87. 1561/1565. Precursor of amyloid protein in Alzheimer disease undergoes fast anterograde axonal transport.
10. Lai, F. and Williams, R.S.: Arch. Neurol. 1989. 46. 849/853. A prospective study of Alzheimer disease in Down syndrome.
11. Mann, D.M.A.: Mech. Aging Dev. 1988. 43. 99/136. The pathological association between Down syndrome and Alzheimer disease.
12. Mann, D.M.A. and Esiri, M.M.: N. Eng. J. Med. 1988. 318. 789/790. The site of the earliest lesions of Alzheimer's disease.
13. Mann, D.M.A. and Esiri, M.M.: J. Neurol. Sci. 1989. 89. 169/179. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with down's syndrome.
14. Masliah, E., Terry, R.D., Mallory, M., Alford, M. and Hansen, L.A.: Am. J. Pathol. 1990. 137. 1293/1297. Diffuse plaques do not accentuate synapse loss in Alzheimer's disease.
15. Masters, C.L., Multhaup, G., Simms, G., Pottgiesser, J., Martins, R.N. and Beyreuther, K.: EMBO. J. 1985. 4. 2757/2763. Neuronal origin of a cerebral amyloid: Neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels.
16. Masters, C.L., Simms, G., Weinman, N.A., Multhaup, G., Mcdonald, b.L. and Beyreuther, K.: Proc. Natl. Acad. Sci. USA. 1985. 82. 4245/4249. Amyloid plaque core pretein in Alzheimer's disease and Down's syndrome.
17. Miyakawa, T., Katsuragi, S., Watanabe, K. ,Shimoji, A. and Ikeuchi, Y.: Acta Neuropathol.(Berl.) 1986. 70. 202/208. Urtrastructural studies of amyloid fibrils and senile plaques in human brain.

18. Motte, J. and Williams, R.S.: Acta Neuropathol. 1989. 77. 535/546. Age-related changes in the density and morphology of plaques and neurofibrillary tangles in Down syndrome brain.
19. Robakis, N.K., Wisniewski, H.M., Jenkins, E.C., Devine-Gage, E.A., Houck, G.E., Yao, X., Ramakrishna, N., Wolfe, G., Silverman, W.P. and Brown, W.T.: Lancet. 1987. 1. 384/385. Chromosome 21q21 sublocalisation of gene encoding beta-amyloid peptide in cerebral vessels and neuritic (senile) plaques of people with Alzheimer disease and Down syndrome.
20. Rozemuller, J.M., Eikelenboom, P., Stam, F.C., Beyreuther, K. and Masters, C.L.: J. Neuropath. Exp. Neurol. 1989. 48. 674/691. A4 protein in Alzheimer's disease: Primary and secondary cellular events in extracellular amyloid depositon.
21. Rumble, B., Retallack, R., Hilbich, C., Simms, G., Multhaup, G., Martins, R., Hockey, A., Montgomery, P., Beyreuther, K. and Masters, C.L.: N. Engl. J. Med. 1989. 320. 1446/1452. Amyloid A4 protein and its precursor in Down's syndrome and alzheimer's disease.
22. Suenaga, T., Hirano, A., Llena, J.F., Ksiezak-Reding, H., Yen, S. and Dickson, D.W.: J. Neuropathol. Exp. Neurol. 1990. 49. 31/40. Modified Bielschowsky and immunocytochemical studies on cerebellar plaques in Alzheimer's disease.
23. Tagliavini, F., Giaccone, G., Grangione, B. and Bugiani, O.: Neurosci. Lett. 1988. 93. 191/196. Preamyloid deposits in the cerebral cortex of patients with Alzheimer's disease and nondemented individuals.
24. Tate-Ostroff, B., Majocha, R.E. and Marotta, C.A.: Proc. Natl. Acad. Sci. USA. 1989. 86. 745/749. Identification of cellular and extracellular sites of amyloid beta protein messenger RNA.
25. Ulrich, J.: Ann. Neurol. 1985. 17. 273/277. Alzheimer changes in non-demented patients younger than sixty-five: possible early stages of Alzheimer's disease and senile dementia of Alzheimer type.
26. Wisniewski, H.M., Bancher, C., Barcikowska, M., Wen, G.Y. and Currie J.: Acta Neuropathol. 1989. 78. 337/347. Spectrum of morphological appearance of amyloid deposits in Alzheimer's disease.

27. Wisniewski, H.M. and Terry, R.D.: In: Zimmerman, H.M.,ed., Progress in Neuropathology vol. 2 (Grune and Stratton, New York and London). 1973. 1/26. Re-examination of the pathogenesis of the senile plaques.
28. Wisniewski, H.M., Wen, G.Y. and Kim, K.S.: Acta Neuropathol. 1989. 78. 22/27. Comparison of four staining methods on the detection of neuritic palques.
29. Wisniewski, K.E., Dalton, A.J., McLachlan, C., Wen, G.Y. and Wisniewski, H.M.: Neurology 1985. 35. 957/961. Alzheimer's disease in Down's syndrome: Clinicopathologic studies.
30. Wisniewski, K.E., Wisniewski, H.M. and Wen G.Y.: Ann. Neurol. 1985. 17. 278/282. Occurrence of Neuropathological Changes and Dementia of Alzheimer's Disease in Down's Syndrome.
31. Yamaguchi, H., Haga, C., Hirai, S., Nakazato, Y. and Kosaka, K.: Acta Neuropathol. 1990. 79. 569/572. Distinctive, rapid, and easy labeling diffuse plaques in the Alzheimer brains by a new methenamine silver stain.
32. Yamaguchi, H., Hirai, S., Morimatsu, M., Shoji, M. and Ihara, Y.: Acta Neuropathol. 1988. 76. 541/549. A variety of cerebral amyloid deposits in the brains of the Alzheimer-type dementia demonstrated by beta protein immunostaining.
33. Yamaguchi, H., Nakazato, Y., Hirai, S. and Shoji, M.: Brain Res. 1990. 508. 320/324. Immunoelectron microscopic localization of amyloid beta protein in the diffuse plaques of Alzheimer-type dementia.
34. Yamamoto, T. and Hirano, A.: Neuropathol. Apl. Neurobiol. 1986. 12. 3/9. A comparative study by modified Bielschowsky, Bodian and thioflavin S stains on Alzheimer's neurofibrillary tangles.
35. Yankner, B.A., Dawes, L.R., fisher, S., Villa-Komaroff, L, Oster-Granite, M.L. and Neve, R.L.: Science. 1989. 245. 417/420. Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease.