stained (**a–d**) with AT8 (*green*) and thiazin red (*TR*, *red*) and subsequently stained with GAL (**A**, **C**) or CS (**B**, **D**). NFTs are stained with TR (*red*, *asterisk*, **c**, **d**) or with both TR and AT8 (*yellow*, *arrowhead*, **c**, **d**). Each of them are labeled with both GAL (**A**, **C**) or with CS (**B**, **D**). **E**, **e**, **f**, **F** A mirror-section pair of the cortex from a PSP patient. The same blood vessel is indicated at the top (*asterisk*). **G**, **g**, **h**, **H** Higher magnification of *rectangles* indicated in **E**, **e**, **f**, **F**, respectively. Each of AT8-positive neurons (*green*, *asterisk*, **g**, **h**) is stained with GAL (**G**). CS labeled lipofuscin (*arrowhead*, **H**) but failed to label any of these AT8-positive neurons (**H**, *asterisk*) in PSP. Separation of fluorescence signals from **c** (Down's syndrome) into AT8 (cAT8) and TR (cTR), or those from **h** (PSP) into AT8 (hAT8) and TR (hTR). Affinity of AT8-reactive neurons to TR is evident on the section from Down's syndrome (cTR). It is absent or at most weak on the section from PSP (hTR). **I**, **I**, **J** , **J** A mirror-section pair of the cortex from a CBD patient. A plaque-like structure, positive for AT8 (*green*, *asterisk*, **I**, **J**) is stained with GAL (*asterisk*, **I**) but not with CS (*asterisk*, **J**). *Bars* **A**, **a**, **B**, **b**, **E**, **e**, **F**, **f** 100 μm; **C**, **c**, **d**, **D**, **G**, **g**, **h**, **H** 30 μm; **I**, **i**, **j**, **J** 50 μm

Discussion

Various methods of silver staining have been introduced to identify pathological structures, related to neurodegenerative processes, and some of them are currently in diagnostic use [*1*, *2*, *7*, *9*, *13*, *16*, *17*, *23*, *35*]. In spite of their utility, little is known about how the argyrophilic property is engendered [*14*, *18*, *19*, *25*]. Moreover, it is open to question whether argyrophilic properties in different staining methods represent similar processes or features in common, or whether they are different dependent on staining methods [*12*, *30*, *31*]. In the present study, we have shown that argyrophilic profiles of tau-positive structures differ according to diseases. Each NFT of AD/DS was silver-stained with both GAL and CS. In contrast, tau-positive neocortical neurons and glial components of CBD/PSP were similarly stained with GAL but not with CS. The lack of CS labeling in tau-positive structures in CBD/PSP is in agreement with our previous study that demonstrated a similar paucity of argyrophilia using the Bodian method (BOD) in CBD, while NFTs of AD were, in contrast, stained with BOD [*28*]. Because the number of tau-positive deposits visualized with BOD is smaller than that with GAL [*20*], it is possible that a lower sensitivity of BOD in detecting AD-related deposits is exaggerated in detecting PSP/CBD deposits. CS was initially introduced to label AD-related deposits, especially SPs [*7*]. In this study, comparison of mirror-section pairs stained either with GAL or CS showed that each NFT was equally stained with GAL or CS (Fig. 4), indicating that CS is as sensitive as GAL in detecting NFT. The complete lack of CS labeling in PSP/CBD brains is, therefore, not due to difference in sensitivity between GAL and CS. Procedures for CS and GAL are more easily standardized than other silver-staining methods [*3*, *4*]. This excludes the possibility that the complete lack of CS staining in CBD/PSP-related deposits was due to a technical failure. Indeed, all these sections from different diseases were processed simultaneously. Moreover, identification of SPs, probably related to the aging process (Fig. 2), in sections from PSP brains confirmed successful CS staining. CS was therefore found to be useful in distinguishing SPs that may occur on the background of robust tau-related glial pathology in PSP/CBD.

In spite of this sharp contrast either exhibiting (GAL) or not exhibiting (CS) argyrophilia on tau-positive deposits of CBD/PSP, the staining procedure for GAL [*4*] and that for CS [*7*] are quite similar. Alkaline silver iodide is used after pretreatment with lanthanum nitrate for GAL [*4*], while pyridine-silver is the initial step without pretreatment for CS. Because subsequent steps to develop silver particle are essentially identical for GAL and CS, it is likely that the difference in these silver reagents (alkaline silver iodide vs pyridine-silver) is

one of the major factors responsible for this contrast. Its precise mechanism at the molecular level, however, remains to be clarified. One of the current classifications of degenerative tauopathies is based on the biochemical features of tau protein according to three- and four-repeat tau isoforms. It is known that tau-positive deposits of AD/DS are composed of the three- and four-repeat isoforms, while those of CBD/PSP are of predominantly four-repeat isoform [*26*]. Because positive GAL labeling is shared between AD/DS and CBD/PSP, GAL may have an affinity to deposits containing four-repeat tau. Conversely, the lack of CS staining in CBD/PSP is explainable if CS has an affinity to deposits containing three-repeat tau. Indeed, this assumption is compatible because deposits containing both three- and four-repeat isoforms, as in AD/DS, are stained with both CS and GAL. Comparison between AD/DS and CBD/PSP clarified a clear distinction based on silver-staining profile. However, we do not yet know whether this distinction is based directly on difference in tau isoforms or related to more complex composition after tau deposition.

In addition to this complete lack of CS staining, tau-positive deposits in CBD/PSP are characterized by the paucity of TR staining. This possibly represents a relative scarcity of fibrillary composition or different fibrillary composition, as we demonstrated in our previous study [*30*]. The lack of CS staining with abundant GAL staining in cortical neurons of CBD/PSP may be related to this difference. It is then probable that more solid deposition of tau, as seen in AD/DS, is a mixture of three- and four-repeat tau, recognized as NFTs [*29*]. In contrast, deposition of four-repeat tau not accompanied by its three-repeat counterpart is organized into different, probably less fibrillary, structures that escape detection with TR or CS. Our previous study demonstrated that Pick bodies, consisting of predominantly three-repeat isoform of tau, are preferentially stained with BOD but not with GAL [*31*]. This is the reversal of preferential GAL staining seen in CBD/PSP, consisting of predominantly four-repeat isoform of tau. Taken together, each method of silver staining has a preferential affinity to different tau deposits. Although correlation of four-repeat tau deposits to GAL and three-repeat tau deposits to BOD or CS seems consistent, it remains to be determined how each staining method exhibits preferential affinity to corresponding tau deposits in isoform-dependent fashion. Otherwise, this preferential affinity may be dependent on specific deposits, formed in an isoform-dependent manner. Although molecular mechanism to explain how specific argyrophilic properties are engendered still remains to be clarified, these differences will provide with a unique viewpoint to easily recognize specific pathological cascade probably distinct from each other. At present, it is worth being aware of this distinction in search of potential pathological relevance and diagnostic value to be examined in more detail in future studies.

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Regular Paper

Silver staining profiles distinguish Pick bodies from neurofibrillary tangles of Alzheimer type: comparison between Gallyas and Campbell-Switzer methods

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Abstract Silver staining profiles of Pick bodies (PBs) and their relation to tau-like immunoreactivity were examined on hippocampal sections and compared with those of neurofibrillary tangles of Alzheimer type (NFTs). Pairs of mirror sections were double-fluorolabeled with an anti-paired helical filament tau (AT8) antibody and thiazin red (TR), a fluorochrome that identifies fibrillary structures such as NFTs. One of the paired sections was subsequently stained using the Gallyas method (GAL), and the other using the Campbell-Switzer method (CS). By comparison of the same microscopic field on fluorolabeled sections and on both silver-stained paired sections, four different profiles of each structure could be distinguished: AT8 immunoreactivity, affinity to TR, argyrophilia with GAL or CS staining. PBs, containing mainly three-repeat (3R) tau, were positive for CS but not for GAL and its affinity to TR was, at most, weak. This selective affinity of PBs to CS is in sharp contrast with tau-positive structures of corticobasal degeneration/progressive supranuclear palsy, which are positive for GAL but not for CS, as we reported previously. This contrast is explainable if the argyrophilia with CS is related to deposits containing 3R tau, while that with GAL is linked to those containing four-repeat (4R) tau. Indeed, NFTs, containing both 3R and 4R tau, are positive for both CS and GAL, as expected. Taken together, differences in molecular composition of tau protein in these deposits are linked to their argyrophilic properties that are dependent on the staining method. Although explanations for these

empirical differences are not yet available, awareness of this clear distinction is potentially of diagnostic and pathological relevance.

Keywords Argyrophilia - Campbell-Switzer - Diagnosis - Gallyas - Repeat tau

Introduction

Degenerative tauopathies are characterized by tau-positive deposits, and some of them are considered to be diagnostic hallmarks for some clinicopathological entities. Tauopathies are currently classified according to the difference in their molecular species [three-repeat (3R) or four-repeat (4R)] of pathologically phosphorylated tau [*26*]. Disease-specific definition of tau-positive deposits, however, is still a challenge because differentiation based on the their immunohistochemical profiles are so far not very successful in spite of this biochemical difference [*5*, *6*, *10*, *19*, *38*]. Because of the lack of reliable routine histological staining that discriminates these molecular species of tau, combination of biochemical analyses and tau immunostaining is considered the current standard to delineate tau pathology.

Initial observations on these deposits, now known to contain tau protein, were based on silver staining methods. These methods are still widely used for diagnosis of these tauopathies and Alzheimer's disease (AD) [*1*, *2*, *7*, *9*, *12*, *14*, *15*, *22*, *36*]. Further modifications of silver staining methods have been reported [*3*, *4*, *17*, *27*] that claim an improved sensitivity with lower background and easier standardization of the procedure. Because the Gallyas method (GAL) [*12*] and its modification [*4*] are highly successful in visualizing innumerable lesions, it may appear that the differences between silver staining methods are based on their difference in sensitivity. Indeed, various silver staining methods have been demonstrated to have a different sensitivity in detecting AD-related deposits [*8*, *11*, *18*, *23*, *33*, *34*, *35*, *37*].

In our previous study [*32*], we found that tau-positive lesions in corticobasal degeneration (CBD)/progressive supranuclear palsy (PSP) were positive for GAL but negative for the Campbell-Switzer method (CS) [*7*, *25*], another sensitive silver staining method that labels neurofibrillary tangles of AD (NFTs). Because both GAL and CS label equivalent number of NFTs, this discrepancy between CS and GAL observed in CBD/PSP may represent a feature unique to CBD/PSP. This implies that differences in silver staining methods are related not only to their sensitivities but also to the characteristics of each tau deposit. This prompted us to examine argyrophilic features of another type of tau-positive inclusions, Pick bodies (PBs), that contain predominantly 3R tau. Although little is known about how these argyrophilic properties are formed [*13*, *16*], "argyrophilia" is now found to be dependent not only on the sensitivity of each staining procedure but also on the disease process, and, therefore, is of potential importance in histological distinction of tauopathies. Moreover, this difference in argyrophilic property may possibly represent a different architecture or molecular composition of the deposits.

Materials and methods

Four cases of PB disease (PBD) and four cases of AD were enrolled in this study. Pathological diagnosis of AD was based on the published criteria [*21*]. Demographic data on

these cases are shown in Table 1. Brains were fixed in formalin and embedded in paraffin. Serial hippocampal sections were stained either with GAL [*4*, *12*] or CS [*3*, *7*] and the corresponding argyrophilic structures were compared. Mirror section pairs (4 μm thick) from the hippocampus were subjected to subsequent studies to identify possible relation between argyrophilia and tau-like immunoreactivity, as reported previously [*32*]. Pairs of mirror sections were first incubated at 4°C for 2 days with an anti-paired helical filament tau antibody (AT8, 1:10,000, Zwijndrecht, Belgium [*20*]) and the target epitope was visualized with an anti-mouse IgG conjugated with Alexa 488 (1:500, Molecular Probe, Eugene, OR). Sections were then incubated with thiazin red (TR, 1:30,000, Wako, Tokyo, Japan) for 15 min. After being observed under a confocal microscope (Leica TSC/SP, Heidelberg, Germany), one of the section pair was stained with GAL and the other with CS to compare argyrophilic properties of each AT8- or TR-positive structure. Identification of the same microscopic field on the fluorescence images (AT8 and TR) and on the corresponding silver-stained (GAL and CS) pair-wise images allowed us to compare staining profiles of each structure based on four different properties; AT8 immunoreactivity, affinity to TR, argyrophilia with GAL and that with CS.

Table 1 Demographic data of the cases (*PBD* Pick body disease, *AD* Alzheimer's disease)

Pathological diagnosis	Brain weight (g)	Age at death (years)	Duration (years)	Gender
PBD	1,090	56	1.5	M
PBD	1,080	64	5	F
PBD	1,120	67	10	M
PBD	890	83	?	F
AD	755	62	15	F
AD	1,250	65	5	M
AD	1,070	66	10	M
AD	780	72	15	F

Results

On hippocampal sections from AD brains, CS visualized NFTs and neuropil threads (NTs) as well as innumerable senile plaques (SPs) (Fig. 1A). On the neighboring section, GAL also visualized NTFs to an equivalent extent and a larger number of NTs (Fig. 1B), while SPs stained with GAL were limited to those with neuritic reactions. On hippocampal sections from PBD, CS clearly visualized PBs (Fig. 1C, E). In contrast, argyrophilia by GAL (Fig. 1D, F) was nearly absent or, if detectable, very weak (asterisks in Fig. 1D).

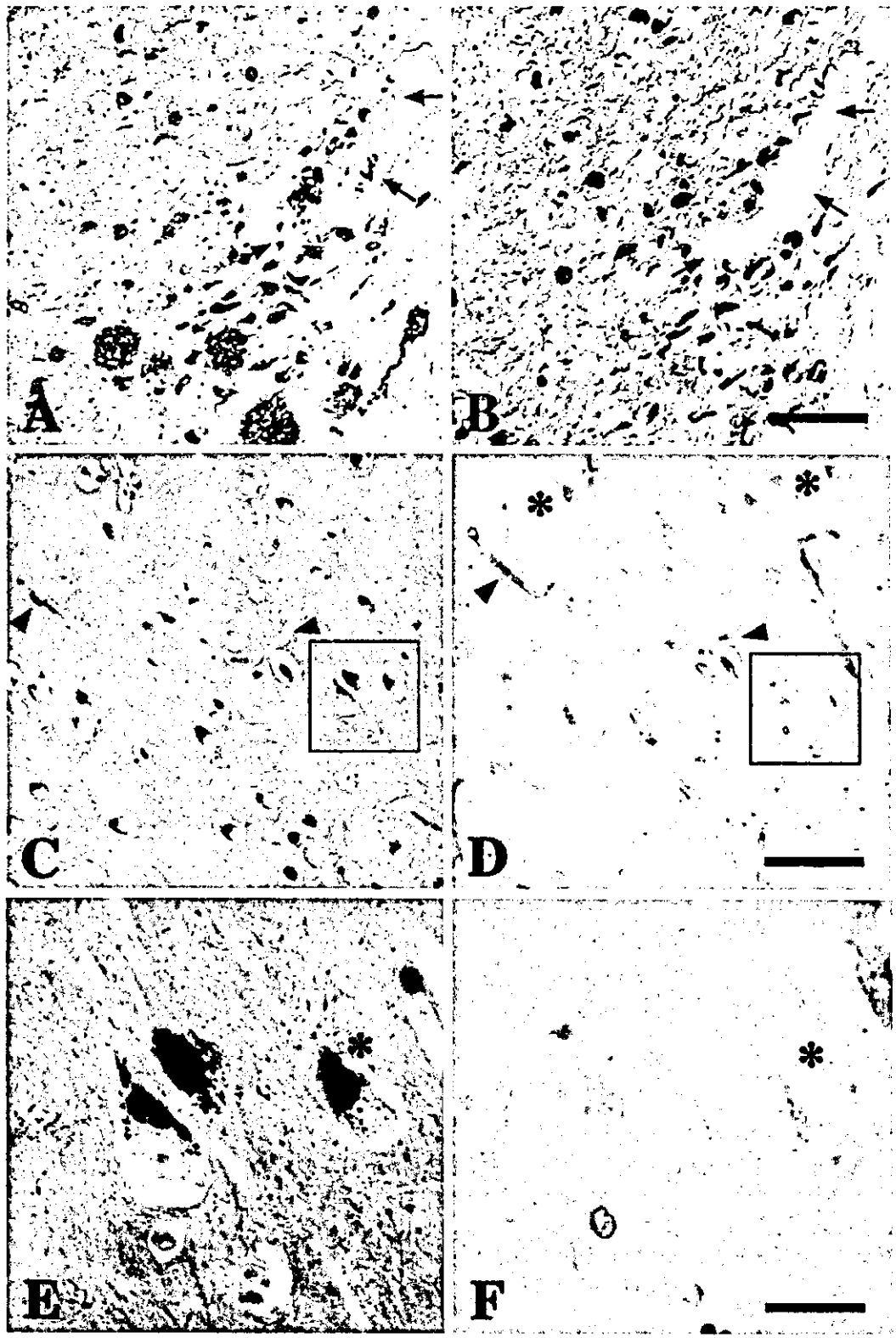

Fig. 1 Discrepant argyrophilia in PBs. **A**, **B** AD; **C–F** PB disease. Serial sections from pyramidal layer of hippocampus. **A**, **C**, **E** CS; **B**, **D**, **F** GAL. NFTs in AD brain exhibit argyrophilia after staining with CS (**A**) and with GAL (**B**) methods. PBs similarly exhibit argyrophilia after staining with CS (**C**, **E**) but their argyrophilia after staining with GAL is, at most, weak (*asterisks* in **D**, **F**). *Arrows* in **A** and **B** and *arrowheads* in **C** and **D** indicate the same blood vessels. **E**, **F** Higher magnification of squared area in **C** and **D**, respectively. *Asterisks* in **E** and **F** indicate the same neuron harboring a PB (*PB* Pick body, *AD* Alzheimer's disease, *CS* Campbell-Switzer stain, *GAL* Gallyas-Braak stain, *NFT* neurofibrillary tangle). *Bars* **A–D** 100 μm, **E**, **F** 25 μm

This contrast was further confirmed on mirror section pairs. Fluorolabeling of a mirror section pair from AD brains with AT8 and TR visualized NFTs and NTs (Fig. 2A, a) that were clearly stained with TR (red) or both TR and AT8 (yellow, Fig. 2A, a, arrowhead), dependent on their evolutionary stage [*29*]. One of the section pair was subsequently stained with CS (Fig. 2B, C), and the other with GAL (Fig. 2b, c). Each of the CS-positive structures was identifiable on the corresponding mirror section stained with GAL, and vice versa. These structures positive for both CS and GAL (asterisks and arrowheads in Fig. 2B, b, C, c) were also positive for TR or for both TR and AT8 (asterisks and arrowheads in Fig. 2A, a). Another section pair from PBD brains, initially fluorolabeled (Fig. 3A, a) and subsequently silver-stained either with CS (Fig. 3B, C) or GAL (Fig. 3b, c), demonstrated that each of AT8-positive PBs (asterisks and arrowheads in Fig. 3A, a) was stained with CS (Fig. 3B, C, asterisk and arrowhead). GAL, however, failed to label these PBs (Fig. 3b, c). Affinity of TR to these PBs was less evident (Fig. 3A, a) compared with that of NFTs (Fig. 2A, a).

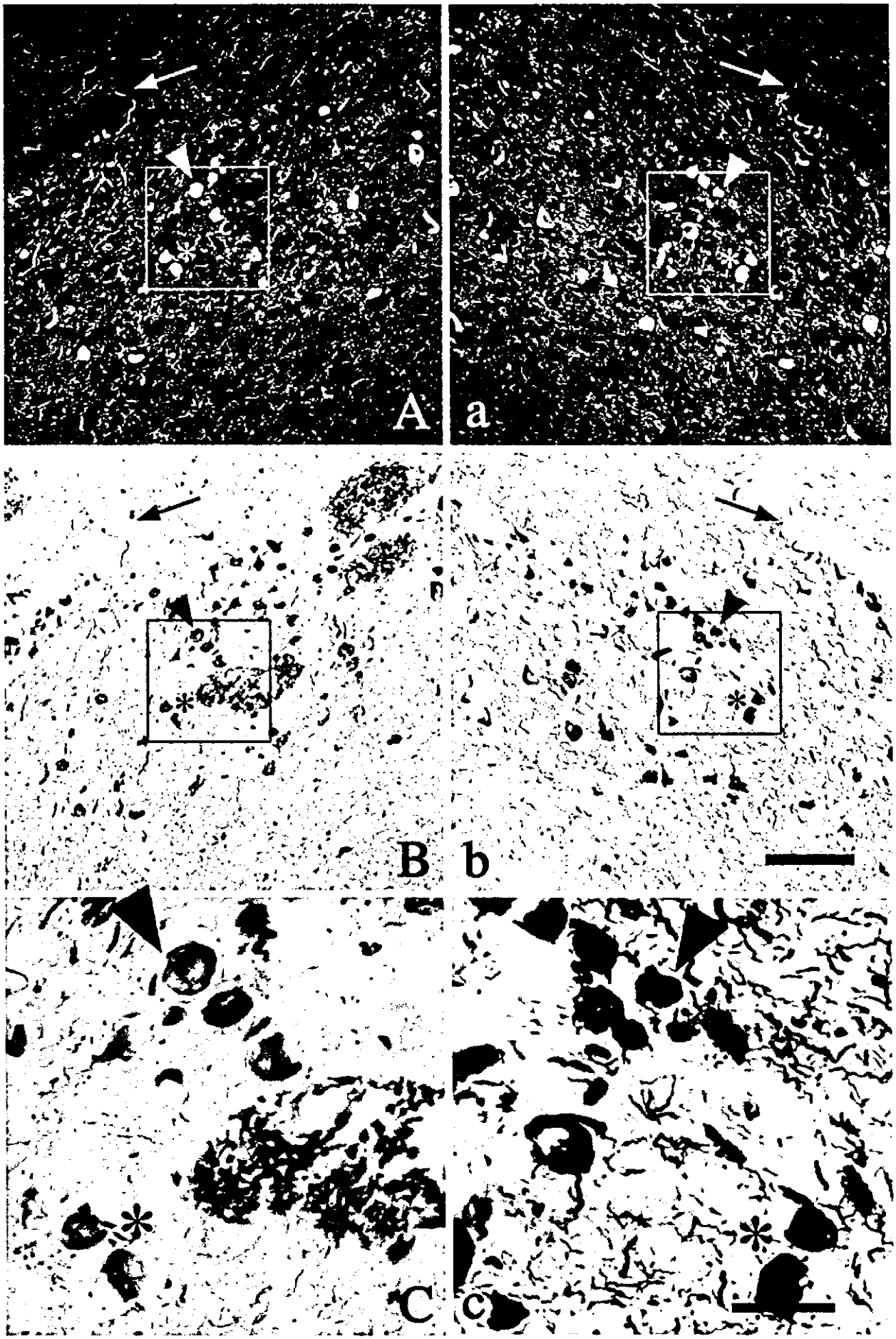
A
a
B
b
C
c

Fig. 2 NFTs exhibit equivalent argyrophilia with either silver staining method. Mirror section pair from pyramidal layer of hippocampus of AD brain initially fluorolabeled (**A**, **a**) with anti-PHF tau (AT8, *green*) and thiazin red (TR, *red*) and subsequently silver-stained with CS (**B**) or GAL (**b**). AT8-positive neurons are also stained with TR to yield *yellow color*, indicating that they are composed of rigid fibrillary structure. Fibrillary structures stained as *red* are extraneuronal NFTs that lost immunoreactivity to AT8. Both AT8-positive NFTs (*yellow*) and AT8-negative NFTs (*red*) exhibit argyrophilia with either CS or GAL method. **C**, **c** Higher magnification of the area indicated in **B**, **b**, respectively. *Arrows* (**A**, **B**, **a**, **b**) indicate the same blood vessel. *Arrowheads* and *asterisks* (**A–C**, **a–c**) indicate corresponding NFTs. *Bar*s **A**, **B**, **a**, **b** 100 μm; **C**, **c** 30 μm

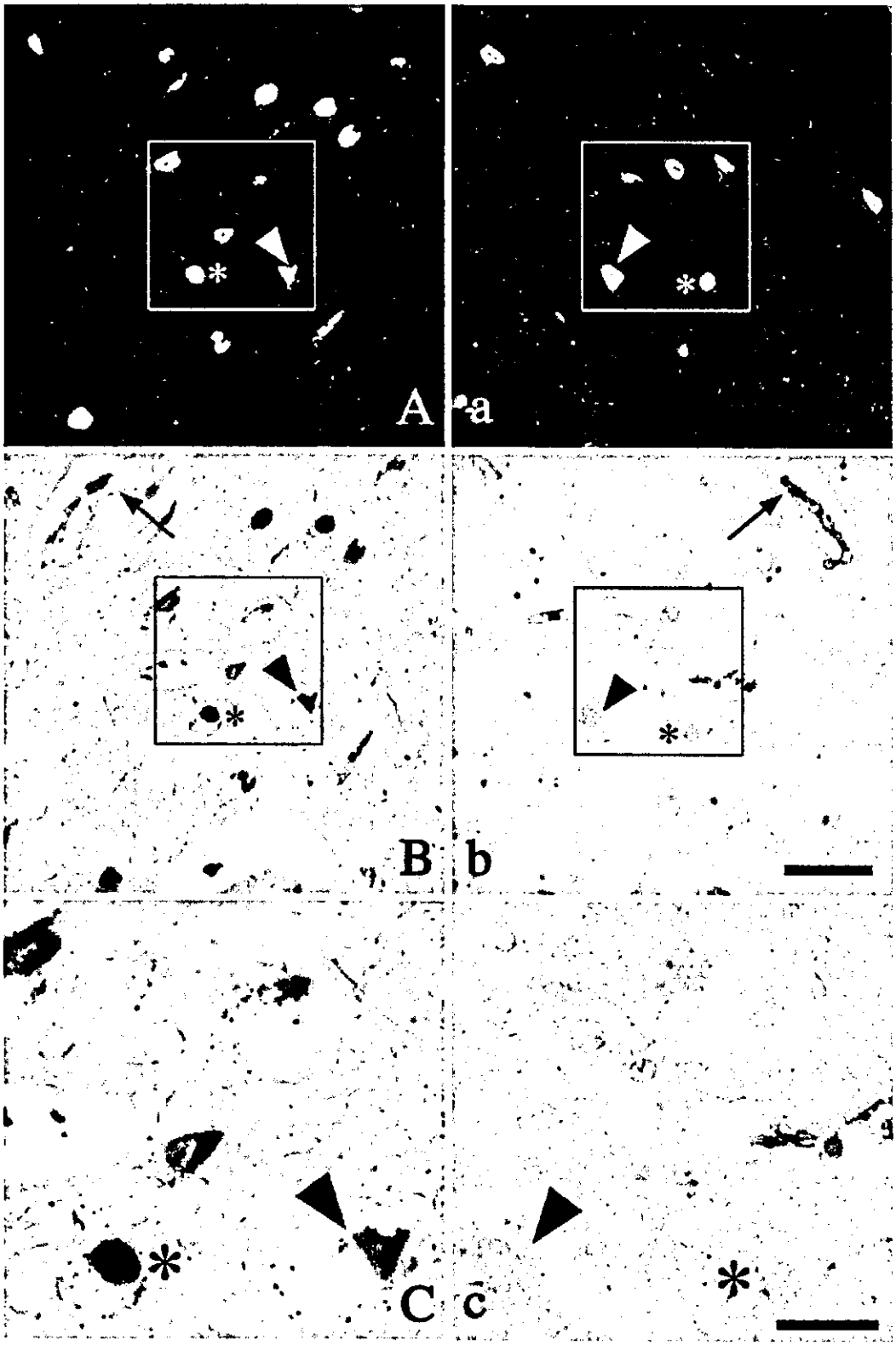

Fig. 3 Argyrophilia of PBs is dependent on the silver staining method. Mirror section pair from pyramidal layer of hippocampus of PBD brain initially fluorolabeled (**A**, **a**) with AT8 (*green*) and TR (*red*) and subsequently silver-stained with CS (**B**) or GAL (**b**). AT8-positive neurons are not stained with TR, indicating that they are composed of less fibrillary structure. **C**, **c** Higher magnification of the area indicated in **B** and **b**, respectively. *Arrows* (**B**, **b**) indicate the same blood vessel. *Arrowheads* and *asterisks* (**A–C**, **a–c**) indicate corresponding PBs (PBD Pick body disease). *Bars* **A**, **B**, **a**, **b** 100 μm; **C**, **c** 30 μm

Discussion

A number of methods of silver staining have been developed to delineate pathological lesions related to neurodegeneration [*1*, *2*, *7*, *9*, *12*, *14*, *15*, *22*, *36*]. Although some of them are highly useful in diagnosis and research, their utility is based merely on empirical relevance because little is known about the mechanism of how argyrophilic properties are engendered [*13*, *16*, *17*, *25*]. For AD-related lesions, the number (quantity) of visualized lesions is dependent on the silver staining method used [*8*, *11*, *18*, *23*, *33*, *34*, *35*, *37*]. This gives an impression that the sensitivity for visualizing AD-related lesions is dependent on the silver staining method. Our previous study [*32*], however, demonstrated that tau-positive lesions in CBD/PSP lacked argyrophilia when they were stained with CS, while they were clearly visualized with GAL. This contrast indicates that each staining method exhibits argyrophilia in disease-dependent manner. In other words, possible difference between silver staining methods is related not only to their sensitivity to detect lesions (quantitative difference) but also to their ability to distinguish lesions in disease-dependent manner (qualitative difference). In the present study, we expanded this approach to PBD, and found that the argyrophilia of PBs was detectable with CS but not with GAL. This staining profile was absolutely complimentary to that observed for tau-positive-lesions in CBD/PSP, which exhibit argyrophilia with GAL but not with CS. Although we have no direct explanation for this empirical distinction, one hypothesis is that argyrophilia with CS is related to tau deposits composed of the 3R species, as we observed in PBD, whereas that with GAL is linked to tau deposits mainly composed of the 4R counterpart, as reported in PSP/CBD [*32*]. NFTs of Alzheimer type, containing both the 3R and 4R species, exhibit argyrophilia with either CS or GAL (Fig. 4).

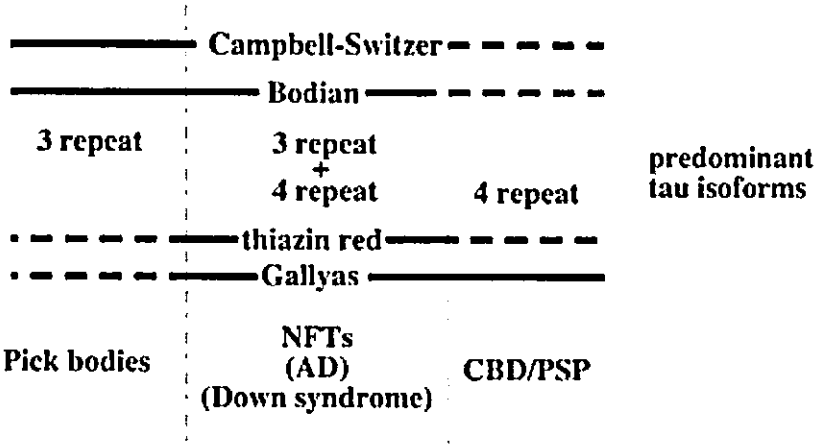

Fig. 4 Argyrophilic properties of tau-positive deposits are dependent on staining methods and on tau isoforms. Diseases are classified according to their predominant tau isoforms. *Solid lines* indicate positive argyrophilia and *interrupted lines* indicate negative argyrophilia (*CBD/PSP* corticobasal degeneration/progressive supranuclear palsy)

Despite this sharp contrast, the staining procedures for GAL and CS are quite similar. Alkaline silver iodide is used after pretreatment with lantanium nitrate for GAL [*4*], while

pyridine-silver is the initial step for CS [*7*]. Because subsequent visualization of silver particles is essentially the same for GAL and CS, this difference of initial silver reagents (alkaline silver iodide versus pyridine-silver) is one of the major factors responsible for this contrast. However, we do not yet know whether this distinction is based directly on the difference in tau isoforms or related to more complex composition after tau deposition. Another difference between PBs and NFTs depends on their affinity to TR, a fluorochrome that labels fibrillary structures such as NFTs [*30*] or Lewy bodies [*24*]. This difference possibly represents a different density of fibrillary structures or qualitative difference in fibrillary composition, as demonstrated previously [*29*, *30*]. The lack of GAL staining, with abundant CS staining, in PBs may be related to this difference. A mixture of 3R and 4R tau, as seen in NFTs, may lead to a more solid organization of fibrils recognized as NFTs [*29*], also identified clearly with TR. In contrast, deposition of 3R tau not accompanied by its 4R counterpart is organized into different, probably less fibrillary, structures that escape detection with TR or GAL. Our previous study demonstrated that PBs, composed predominantly of the 3R isoform of tau, are preferentially stained with Bodian method (BOD) but not with GAL [*31*]. Conversely, tau-positive structures in CBD are scarcely argyrophilic with BOD [*28*]. These data are compatible with the hypothesis that tau deposits, composed of 3R tau, exhibit selective argyrophilia with BOD and CS.

Through these studies, we became aware that each method of silver staining exhibits preferential affinity to tau-positive deposits in an isoform-dependent manner (Fig. 4). Although this correlation is empirical at present, and molecular mechanism to explain how argyrophilic properties specific for disease or tau isoform are engendered still remains to be elucidated, awareness of these differences will help in clearly recognizing and diagnosing specific pathological cascades, which are probably distinct from each other.

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孤発性前頭側頭型痴呆

原発性進行性失語

内原 俊記

▣ はじめに

大脳皮質の機能が部位によって異なることが臨床的に確認されるようになったのは，失語という症状と病変部位の関係が脳血管障害の例を中心に集積されたことによる部分が大きい．大脳皮質の変性がこのような部位に強調されておこれば，対応する失語という症状も変性過程のなかで分離されてとらえられることが想定できる．実際，痴呆性疾患の代表の一つであるPick病の最初の報告では，失語に類する症状から全般的な痴呆へ進展する過程が記載されており，失語に対応する病変として，左側頭葉の限局性萎縮があると推論されている[1]．脳血管障害では孤立した非進行性の病変があり，失語症状と病変の対応は比較的容易だが，変性過程では，1）病変の境界が不明瞭で程度や範囲が進行性に拡大すること，2）反対側や大脳白質，大脳以外の部位(基底核，脳幹等)にも病変が伴う場合が多い点で脳血管障害とは異なり，純粋な失語症状の抽出が困難な場合も多い．特に大脳皮質を中心とする変性過程では，知的機能，認知機能の低下が臨床像の前景にたつ時期が早く訪れる場合が多く，失語があっても解析が十分にできない場合がある．

Primary progressive aphasiaの診断基準要約(Mesulam[4]より)

1．word finding，物品呼称，word-comprehensionの障害がゆっくりと始まり，進行する．
2．言語以外の日常生活は，発症後少なくとも2年間は保たれる．
3．発症前の言語機能が正常である．
4．無為，抑制解除，近時記憶障害，視空間認知障害，感覚-運動障害などが，発症後少なくとも2年間はみられない．
5．この間，失計算，観念運動失行，軽度の構成障害や保続を伴う場合がある．
6．その後これらの症状が出現しても，言語の障害が経過を通じてもっとも目立ち，進行も早い．
7．脳血管障害，脳腫瘍等，画像で確認できる原因疾患がない．

Mesulamらの提唱と用語上の混乱

変性過程に伴う失語に類する症状を変性性失語aphasie dégénérative[2]と総称するという考え方があるが，一定の臨床・病理像に対応するものではない．Mesulamは進行性失語を呈する6例が，1）知的機能の低下が長期にわたりみられず，失語があっても自律した日常生活が保たれ，2）左Sylvius裂周囲の萎縮という特徴をもち，これまでの疾患概念では説明し難い一群として“slowly progressive aphasia without generalized dementia”という臨床概念を提唱した[3]．その後primary progressive aphasia(PPA)という呼び方が提唱され，臨床的な診断基準も示されている(表)[4]．現在提唱されているfrontotemporal lobar degenerationの分類[5]では，言語の障害としてprogressive non-fluent aphasia(PNA)とsemantic dementia(SD)があげられている．PNAはnon-fluent aphasiaを特徴とし，発語量が少なく，語想起に時間がかかり，時に努力性発話，失文法が見られるなど，運動性失語の要素が目立つと考えられ，言語領域の中で前方よりの病変に伴う障害と想定される．一方，SDは言語の意味理解の障害を中心としたfluent typeの失語で，発語や文法の障害がめだたず，復唱も保たれる等の特徴があり，側頭葉を中心としたより後方の障害と類型化されている．上記にあげたPPAの診断基準(Mesulam)は，失語の型に関する定義に乏しく，広い範囲の進行性失語をふくみ得るが，PPAはnon-fluent aphasiaのみをさすとする研究者もあり，注意を要する．しかし運動性失語の要素が少ないSDでも，変性に伴う場合はnon-fluentの場合もあり，fluencyの程度のみで明解な失語の区分ができるとは限らない．実際，変性を基礎におこる進行性失語として報告された例のなかには，あらゆる失語の

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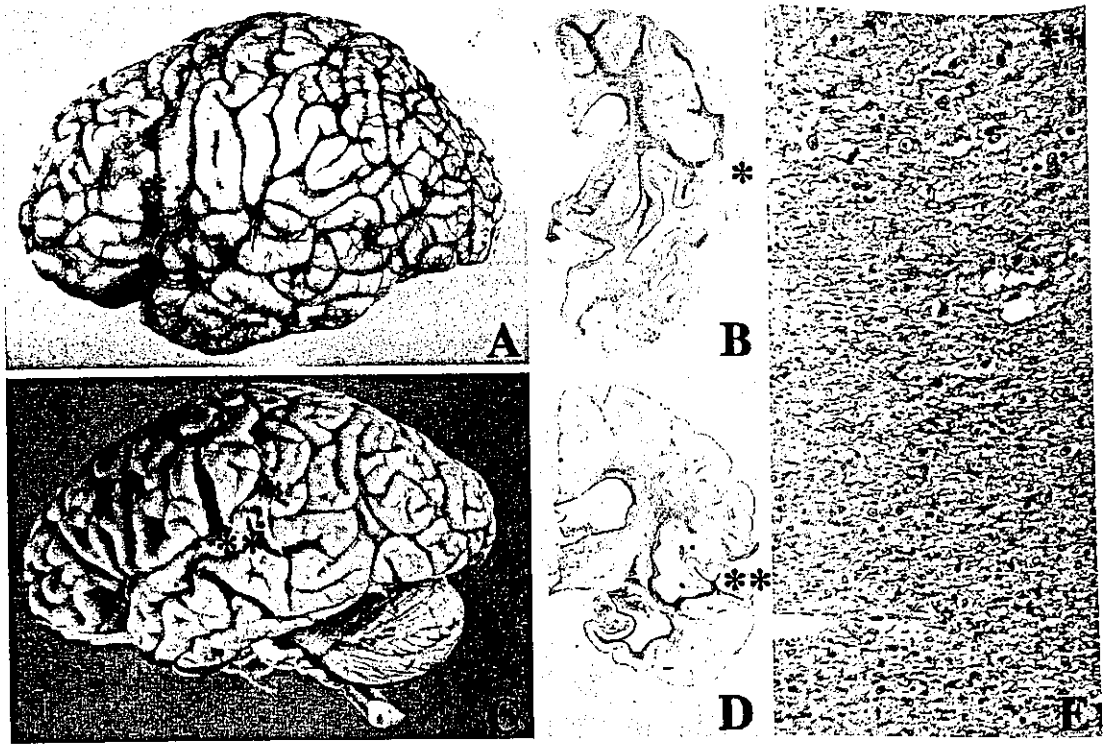

A）62歳発症，transcortical motor aphasia (non-fluent type) に軽度の人格変化を伴い，65歳で死亡した臨床診断 Pick 病例の剖検脳肉眼所見(脳重 1200 g)．前頭葉に萎縮があり，前頭弁蓋部(*)に萎縮が目立つ．

B）同部の前額断 Holzer 染色．弁蓋部(*)を含む前頭葉白質に線維性グリオーシスを認める．　(Mimura ら[10]より改変)

C）58歳，言語の理解困難で発症，感覚性失語と行動異常に筋固縮を伴い 68 歳で死亡した臨床診断 Pick 病例の剖検脳肉眼所見(脳重 1115 g)．上側頭回(**)に萎縮が目立つ．

D）同部の前額断 Holzer 染色．萎縮した上側頭回(**)に強調される線維性グリオーシスを認める．

E）同部の Gallyas 染色．Gallyas 陽性の glial lesions が白質にも広汎に認められる．
(Ikeda ら[11]より改変)

失語を伴い，臨床的に Pick 病と診断された 2 例
病理診断はいずれも corticobasal degeneration だが，大脳の病変分布に違いがある．

型が含まれるという[6]．

大脳皮質病変の病理学的多様性

一方，大脳皮質変性病変の形態や分布に関する病理学的知見は，Mesulam の発表以後大幅に進展したといえる．従来，脳幹の疾患と考えられた進行性核上性麻痺 progressive supranuclear palsy (PSP) にも運動野を中心とする大脳皮質病変があり[7]，大脳皮質基底核変性症 corticobasal degeneration (CBD) では，さらに変化に富んだ大脳皮質病変分布が確認されるようになった[8]．Pick 病では，側頭葉前方下面に強調される左右差のある高度な萎縮が歴史的に特徴的とされてきたが，嗜銀球を有する Pick 小体病 Pick body disease (PBD) に限っても，大脳皮質病変はこの範疇におさまらないことが明らかにされている[9]．また，運動ニューロン疾患に伴う痴呆としてとらえられる疾患は，ユビキチン陽性の封入体が海馬歯状回や側頭葉に見られるが，大脳皮質の変性は当初提唱された範囲を越える場合もあることが知られており，それぞれの疾患で進行性失語を呈した剖検例の報告がある[10~13]．振り返れば，Mesulam が slowly progressive aphasia without generalized dementia を提唱した当時想定した各疾患の臨床・病理像は典型的なものに限定されており，その後これを逸脱する例が既存の病理学的概念の中で見出されてきたということもできる．Hodges ら[14]が prospective に検討した fronto-temporal dementia (FTD) 61 例の剖検例中，non-fluent aphasia と分類された例は 8 例で，内 6 例は PBD だが，SD と分類された例は 9 例で，PBD は 3 例と少なく，運動ニューロン疾患に伴う痴呆が 4 例であったという．この研究はアルツハイマー病 (AD) を除外した群を対象にしたにもかかわらず，amnesia や SD で発症した例が意外に多い．FTD の痴呆や失語の臨床的特徴を，記憶障害が少なくとも初期には目立たない点で AD とは異なるものとしてきたこれまでの考え方[5]に変更を迫る可能性がある．また semantic memory の障害は AD にもみられるが，episode 記憶や視空間認知の障害を伴わない点で AD とは異なる一群を SD として区別する立場があり，さらに詳細な臨床像と病理所見の対比が望まれる．

同一疾患内での失語病型の多様性

病理学的診断が同じでも大脳皮質病変分布は変化に富む