Diagnostic Assessment & Prognosis

Tauopathy in basal ganglia involvement is exacerbated in a subset of patients with Alzheimer’s disease: The Hisayama study

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α-synucleinopathy and only AD pathology existed in the brain. The case presented severe MAPT and Aβ deposits in the brain, including the putamen. Parkinsonism can sometimes be seen in AD cases [5,6]. The density of neurofibrillary tangles (NFTs) correlated with parkinsonism only in the substantia nigra (SN) but not in putamen [7]. The previous study focused on NFTs alone, but we observed that some cases showed severe neurupil MAPT depositions in putamen. Therefore, we decided to focus on putaminal MAPT and Aβ pathology to study the significance of the putaminal involvement. To clarify the pathological basis, we examined a series of autopsied cases obtained between 2009 and 2016 (291 cases) to semiquantitatively evaluate MAPT and Aβ deposits in the putamen of an aging Japanese population.

2. Methods

2.1. Subjects

This study included specimens from a series of autopsies (2009–2016; 291 cases [mean age at death, 82.9 ± 10.9 years, range, 42–105 years]) performed on residents of the town of Hisayama in Fukuoka Prefecture, Japan. In principle, all residents of the town of Hisayama are proposed to be autopsied when they die, and the total autopsy rate is about 75%. The characteristics of the examined cases are shown in Table 1. The clinical diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition–Revised [8]. In addition, we also performed the revised version of Hasegawa’s dementia scale (HDS-R) [9] for assessment of cognitive function. Details of the clinical survey have been described in a previous report [10].

The study was approved by the Ethics Committee of the Faculty of Medicine, Kyushu University and was performed in accordance with the ethical standards described in the fifth revision of the Declaration of Helsinki, 2000.

2.2. Neuropathological assessment

The brains were weighed and fixed in 10% buffered formalin for at least 2 weeks. The specimens included the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, hippocampus with entorhinal cortex and transentorhinal cortex (at the level of the lateral geniculate body), calcaneal cortex, basal ganglia including the nucleus basalis of Meynert, thalamus, SN, locus coeruleus, and the dorsal vagal nucleus. Sections were embedded in paraffin and routinely stained using hematoxylin-eosin (HE), the Klüver-Barrera, and a modified Bielschowsky method [11]. The specimens were immunostained using antibodies against phosphorylated-MAPT (clone AT8, mouse monoclonal, 1:500; Innogenetics, Ghent, Belgium), Aβ (clone 6F/3D, mouse monoclonal, 1:200; Dako, Glostrup, Denmark), Anti-4-repeat tau (RD4, clone 1E1/A6, mouse monoclonal, 1:200; Milli-
2.3. Image analyses using custom software in MATLAB

We developed custom software in MATLAB (MathWorks Inc., Natick, MA, USA) for semiquantitatively analyzing abnormal MAPT and Aβ deposits. From the results of the immunohistochemical analyses using AT8 and 6 F/3D, we chose the regions of interest and captured images with a 20 × objective lens with a total field size of 704 × 528 μm² consisting of 1600 × 1200 pixels (0.44 μm × 0.44 μm/pixel). The minimum size we calculated was 1 pixel: 0.44 × 0.44 μm². The color space of each image captured was converted from RGB to the CIE 1976 L*a*b* color space, which is more suitable for quantifying human vision than the RGB using MATLAB, and then, the Euclidean distance in CIE 1976 L*a*b* color space was calculated. In CIE 1976 L*a*b*, the differences between any two colors can be approximated by taking the Euclidean distance between them [18]. Abnormal MAPT and Aβ deposits were then divided into two groups including the tau deposits and the backgrounds by K-means clustering [19], and small objects of four or fewer pixels were removed as noise. In the extracted image of putaminal MAPT deposits, both NFT and neuropil threads could be extracted (Supplementary Fig. 1A, C). Extraction of putaminal amyloid structures, both diffuse plaques and granular objects, was also possible (Supplementary Fig. 1B, D). We calculated a variety of indices characterizing the extracted abnormal MAPT and Aβ deposits. The total area (μm²) and the percentage of MAPT and Aβ deposits were calculated directly to give the polygon area.

2.4. Semiquantitative analyses of MAPT and Aβ deposits in the putamen

In most cases, homogeneous putaminal MAPT deposits were demonstrated, but some cases showed focal dense MAPT accumulation in the medial part of the putamen (Supplementary Fig. 2). We thought this local accumulation was not reflecting the overall accumulation of putaminal MAPT because the cases with localized MAPT accumulation in the medial putamen did not have severe MAPT accumulation in other broad areas of the putamen. Then, we chose a MAPT-dense region around central areas of the putamen as the regions of interest to represent the overall MAPT deposits. For comparison, putaminal Aβ was homogeneously deposited in all cases.

2.5. Statistical analyses

Statistical analyses were conducted using JMP Pro 13 (SAS Institute, Cary, NC, USA). The P values of the median area of total MAPT deposits were calculated using Mann–Whitney U tests. Significance was defined as P < .05.

3. Results

3.1. Analysis of the areas of p-MAPT and Aβ accumulations according to age at death and neuropathological diagnoses

Putaminal MAPT and Aβ deposits became marked around 70 years of age (Fig. 1). The number of MAPT and Aβ positive cases was 191 of 291 cases and 105 of 291 cases, respectively. Aβ deposition was increased with aging. Putaminal MAPT deposits were quite different even among cases over 70 years of age. The area of MAPT was only weakly correlated with the area of Aβ (Supplementary Fig. 3, correlation coefficient, r = 0.260, P < .01).

Next, we evaluated separately the putaminal accumulations according to the neurological disorders (Fig. 2). Among the nondementia cases, 80 of 155 cases were immunopositive for p-MAPT, 33 of 155 cases were immunopositive for Aβ, and 22 of 155 cases showed immunopositive for both antigens. Demented cases had significantly higher putaminal MAPT and Aβ deposition in comparison with no dementia cases. Median area of MAPT and Aβ of no dementia versus dementia were 0.03 versus 0.35, 0 versus 0.69, respectively, P < .01. AD cases
most frequently showed severe putaminal MAPT accumulation. AD comorbid with other degenerative diseases cases also showed higher MAPT deposition. Vascular dementia (VD), progressive supranuclear palsy (PSP), argyrophilic grain disease (AGD), and senile dementia of neurofibrillary tangle type (SD-NFT) tended to be higher than other diseases, although not as high as AD. Severe putaminal Aβ accumulation was also observed frequently in AD cases. Even in nondemented cases, there were some cases that showed strong Aβ accumulation in the putamen.

### 3.2. Severe p-MAPT and Aβ depositions in the putamen

To investigate the effects of MAPT in detail, we selected cases with an MAPT area of over 1.1% as severe MAPT deposition cases. This threshold indicated that the diffuse deposition of p-MAPT in the putamen was discernible by a macroscopic view (Fig. 3). Severe MAPT accumulation was observed in 7.6% of cases (22 of 291 cases), and in most of the cases with severe MAPT accumulation, deposition of Aβ was also severe (Fig. 3). Additionally, we observed that 5.5% of cases (16 of 291 cases) had focal accumulation on the putamen side, along the lateral medullary lamina (Supplementary Fig. 2). Among severe MAPT cases, 4 cases were documented as having developed parkinsonism in their clinical courses (Table 2). These 4 cases tended to have lower HDS-R score. In regard to SN, all 4 cases had MAPT deposits, but the extent of MAPT and neuronal loss varied among them.

### 3.3. Representative case of AD with parkinsonism

A 75-year-old female (case 1 in Table 2) showed cognitive impairment (HDS-R: 17 of 30 maximum). Magnetic resonance imaging revealed bilateral hippocampal atrophy, and she was diagnosed with AD. In the following year, the score was markedly decreased to 6 of 30. At the age of 78, parkinsonism such as resting tremor, rigidity, bradykinesia, gait disturbance, and mask-like face were observed, and she was diagnosed with Parkinson’s disease. Levodopa medication was started, but the effect was limited. She died of aspiration pneumonia at age 79 years and had a postmortem examination. Pathologically, this case was advanced AD (Braak 6, CERAD frequent, and Aβ phase score A3). A small amount of free melanin was present on the outer side of the SN, and mild degeneration was observed. In the putamen, NFTs and neuropil MAPT accumulation were observed (Fig. 3). MAPT-positive threads were also observed in pencil fibers (Fig. 3). NFTs and threads were stained with 3-repeat and 4-repeat MAPT-specific antibodies (Fig. 3). The shape of Aβ deposition was predominantly coarse granular and some diffuse plaques (Fig. 3). Both MAPT and Aβ accumulations in the globus pallidus were usually less severe. There were no globose NFTs or tufted astrocytes, and it did not match the pathological findings of PSP or corticobasal degeneration. There was no phosphorylated α-synuclein in the brain. In the SN, severe MAPT pathology and amyloid pathology was also found. However, as there were no MAPT accumulations in the pontine nuclei and medullary reticular formation, this case was not diagnosed as PSP. These pathological features of the putaminal MAPT deposition were common findings in most cases with severe MAPT accumulation. In most cases with mild putaminal MAPT, NFTs in large neurons and neuropil threads were homogeneously distributed within the putamen. Phosphorylated α-synuclein-positive Lewy bodies in the SN were detected in 12 of 83 AD without DLB and PD cases (14.5%). The percentage is close to the previous report [20]. There was no correlation between the density of putaminal tau and synucleinopathy in the SN.
3.4. Relationship between putaminal p-MAPT depositions and the different stages of pathological criteria for AD

We found that very high accumulation of putaminal MAPT and Aβ was observed in AD cases. We examined the relationship between putaminal MAPT accumulation and Braak stage, CERAD, Aβ phase score, and NIA-AA (Fig. 4). We subdivided all cases into 3 groups (Fig. 4). Group 1 included the cases of the spread of MAPT confined to the hippocampal formation (Braak 0–2), group 2 showed NFTs accumulated in the limbic system (Braak 3 and 4), and group 3 showed NFTs accumulated in isocortical areas (Braak 5 and 6). The dependence on aging in all groups was mild. When subdivided according to Braak stage, the MAPT-positive area of Braak 0–4 cases did not increase with age. In Braak 5 and 6 cases, static examination showed little correlation between MAPT accumulation and aging (data not shown). Compared to Braak stages 0–4, MAPT pathology of the putamen was significantly increased in Braak stages 5 (vs. 0–3; \( P < .01 \), vs. 4; \( P = .021 \)) and 6 (\( P < .01 \)). In addition, the CERAD frequent, Aβ phase score A3, and NIA-AA score of high AD pathological change also showed a significant increase (\( P < .01 \)).

The accumulation of Aβ in the putamen was reported in the Thal phase. Putaminal Aβ was significantly increased in Braak stage 5–6, CERAD frequent, Aβ phase score A2–A3, and NIA-AA intermediate and high AD pathological change (\( P < .01 \), Supplementary Fig. 4).

4. Discussion

In this consecutive autopsy study, we revealed that there was a group of cases showing marked MAPT deposits in the putamen. Putaminal MAPT was markedly increased, especially at Braak NFT stages 5 and 6, at a later stage than the accumulation in the limbic system. In addition, most of the cases showing marked putaminal MAPT deposits corresponded to the CERAD frequent stage. These pathological associations reinforce that AD most frequently showed severe putaminal MAPT accumulation. However, the influence of aging was relatively small. The increase of putaminal
MAPT accumulation was not simply due to aging, but in most settings was due to pathological events associated with the development of AD pathology. Conversely, 19 of 138 cases showing Braak NFT stages 5 and 6 had no putaminal MAPT accumulation. Previous studies have shown that AD can be classified into three subtypes according to neuropathological features. One is typical AD, another is hippocampal-sparing AD, which shows a relative abundance of NFTs in the hippocampus and cortex, and the last is limbic-predominant AD [21,22]. Although the clinical background of putaminal MAPT accumulation in AD has not been clarified, our neuropathological findings suggest a subcategory of AD with basal ganglia involvement.

In most of the cases showing marked putaminal MAPT, putaminal atrophy and neuronal loss were not remarkable. Immunohistochemistry for p-MAPT revealed a characteristic pattern of MAPT deposition in the putamen. There were numerous neuropil threads and occasional NFTs. NFTs were mainly observed in large neurons. In this study, neuropil threads were also noted in the pencil fibers, indicating medium spiny projection neurons could also be involved in tauopathy. Oyanagi et al. [23] reported that NFTs were mainly in remaining large interneurons and in some medium neurons of PSP and in quite a few medium neurons of AD cases.

Neuropil threads and NFTs were equally immunopositive for 3-repeat MAPT and 4-repeat MAPT. There was no glial tauopathy, such as tuft-shaped astrocytes and coiled bodies indicating PSP [24]. In addition, marked neuropil threads were observed to be pencil fibers; however, there were no astrocytic plaques indicating corticobasal degeneration [25]. The patterns of Aβ deposition in the putamen were diffuse or amorphous plaques, and there were few dystrophic neurites around areas of Aβ accumulation, even if severe MAPT accumulation occurred. It was previously reported that striatal amyloid deposits were predominantly small fibrillary deposits; large fibrillary deposits were also present, but core deposits were seldom seen [26]. Our results are consistent with these reports, and we observed MAPT deposition did not affect the morphology of Aβ in the putamen.

We observed another unique pattern of MAPT accumulation in the putamen alongside the lateral medullary lamina. While accumulations of Aβ were homogeneously distributed in the putamen, previous studies showed NFTs displayed significantly higher densities in the ventral striatal components, such as nucleus accumbens, olfactory tubercle, and the tail of the caudate nucleus [27,28], and the putamen could be involved in tauopathy. This suggests that there are at least two patterns of MAPT propagation. One is diffuse putaminal tauopathy, which appears homogeneously together with Aβ deposition. The other is spread from connected regions such as the SN.

Among the cases with severe putaminal MAPT accumulation, there were some cases in which parkinsonism was clinically observed. As previously reported, α-synucleinopathy is not seen among half of the cases of AD with parkinsonism cases [29]. Degeneration of the brainstem and involvement of amyloid oligomers are also considered as a cause of the impairment of the dopaminergic system of AD [30]. Other neuropathological evaluations of parkinsonism in AD patients showed significant neuronal loss in both the SN and putamen. In the present study, we observed a case of AD with parkinsonism that had severe tauopathy in both the putamen and SN but mild neuronal loss in the SN. It is suggested that severe MAPT deposits in the putamen and SN may cause parkinsonism. It was reported that AD patients with extrapyramidal signs showed lower score of neuropsychological examination than AD without parkinsonism [31]. Our study also showed that AD with parkinsonism tended to have a lower score of HDS-R. More detailed analysis will be required for elucidation of the cause of parkinsonism in AD.

The pathological hallmark of DLB is the presence of Lewy bodies, and co-occurrence of α-synucleinopathies with other neurodegenerative diseases, in particular tauopathies, has been reported [32]. In DLB cases, MAPT and Aβ were shown throughout the brain, including the

| Case no. | Diagnosis | Parkinsonism | HDS-R | Neuronal loss | MAPT Lewy |
|----------|-----------|--------------|-------|---------------|------------|
| 1        | AD        | +            | 6     | 1             | 3          | 0          |
| 2        | AD        | -            | 14    | 1             | 0          |
| 3        | AD        | -            | 4     | 1             | 3          |
| 4        | AD        | -            | 5     | 2             | 3          |
| 5        | AD        | -            | 10    | 1             | 2          |
| 6        | AD        | -            | 4     | 3             | 3          |
| 7        | AD        | -            | 5     | 1             | n.d.       |
| 8        | AD        | -            | 5     | 2             | 0          |
| 9        | AD        | -            | 4     | 1             | 2          |
| 10       | AD        | -            | 14    | 1             | 0          |
| 11       | AD        | -            | 15    | 3             | 3          |
| 12       | AD        | -            | 0     | 1             | 1          |
| 13       | AD        | -            | 9     | 3             | 1          |
| 14       | AD + AGD  | -            | 8     | 1             | 3          |
| 15       | AD + PSP  | -            | 7     | 3             | 3          |
| 16       | AD + VD   | +            | 0     | 2             | 1          |
| 17       | AD + VD   | +            | 0     | n.d.          | n.d.       |
| 18       | AD + VD   | -            | 4     | 3             | 2          |
| 19       | VD        | +            | 0     | 3             | 2          |
| 20       | VD + SD-NFT| -           | 9     | 1             | 2          |
| 21       | SD-NFT + AGD | -       | 20   | 1             | 2          |
| 22       | SD-NFT + AGD | -       | 10   | 1             | 1          |

NOTE. The severity of the substantia nigra lesion was categorized into 4 groups (0: none, 1: sparse, 2: moderate, 3: severe).
Abbreviations: AD, Alzheimer’s disease; AGD, argyrophilic grain disease; HDS-R, revised version of Hasegawa’s dementia scale; MAPT, microtubule-associated protein tau; n.d., not determined; PSP, progressive supranuclear palsy; SD-NFT, senile dementia of neurofibrillary tangle type; VD, vascular dementia.
putamen [33]. In the present study, most of the cases with severe putaminal MAPT deposition had no or little α-synucleinopathy, and DLB was not the main cause of the severe putaminal MAPT accumulation.

PSP, SD-NFT, VD, and AGD cases tended to have higher putaminal MAPT deposits. PSP is a neurodegenerative disease involving the basal ganglia and leads to parkinsonism and dementia [34]. PSP may be mistaken for other neurodegenerative diseases such as Parkinson’s disease and AD. With the advent of Tau-PET, it should be noted that severe MAPT accumulation in the basal ganglia may occur most frequently in AD cases and that certain cases with AD pathology alone developed parkinsonism as well as dementia.

SD-NFT, also known as NFT-predominant dementia, showed NFTs either with no amyloid deposits or only diffuse plaques [35]. In SD-NFT, NFTs are relatively localized to the anteromedial region of the temporal lobe, such as entorhinal cortex, Ammon’s horn, and amygdala. In this study, putaminal MAPT accumulation in SD-NFT cases was somewhat higher but not as high as AD, which is consistent with the distribution of MAPT in SD-NFT.

Regarding VD, it is known that the putamen is one of the preferred areas of vascular lesions and that cerebral ischemia [36] and infarcts [37] may induce hyperphosphorylation of MAPT. These could be related to accumulation of putaminal MAPT in VD.

In AGD, it is known that grains appear mainly in the anteromedial temporal lobe, including the entorhinal cortex, Ammon’s horn, and amygdala [38,39]. In AGD, other MAPT immunoreactive structures are ramified astrocytes and oligodendroglial coiled bodies. They are seen most commonly in the amygdala and temporal stem white matter, respectively. These structures were seldom seen in the putamen. Putaminal MAPT in AGD cases could be influenced by comorbid disease, such as AD, SD-NFT, and VD.

Two limitations of this study also need to be noted. One is that all participants were residents of Hisayama town, Japan. Hisayama town has demographic characteristics representative of the national average of Japan, including the distribution of age, occupational status, and nutrient intake [40] and therefore may not reflect other populations and races. The other is there are not many cases of some neurodegenerative diseases since the subject of this study is the general population. For revealing the exact prevalence of putaminal tauopathy in rare neurodegenerative diseases, additional investigation is needed.

5. Conclusion

In this study, we discovered that there were AD cases with severe putaminal tauopathy, and the increase in putaminal MAPT mainly correlated with severe Braak NFT stages.
MAPT deposition in the putamen may partly account for parkinsonism of AD. With the advent of Tau-PET, it should be noted that severe MAPT accumulation in the basal ganglia may occur most frequently in AD cases, without comorbidity of other neurodegenerative diseases in a general aging population.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2019.04.008.

RESEARCH IN CONTEXT

1. Systematic review: Recent tau positron emission tomography enables a new way to study the basal ganglia involvement in cases such as progressive supranuclear palsy. However, the accurate prevalence and the cause of the putaminal microtubule-associated protein tau (MAPT) pathology in an aged general population have not been investigated.

2. Interpretation: We determined the prevalence of putaminal MAPT pathology in Japanese general population. MAPT accumulation in basal ganglia occurred most frequently in Alzheimer’s disease cases without comorbidity of other tauopathies.

3. Future directions: Our results suggest that the putaminal accumulation of MAPT may account for the parkinsonism of the minor subset of Alzheimer’s disease. Additional investigation of dopamine transporter in the putamen may be necessary to evaluate the degeneration of the nigrostriatal pathway.

References

[1] Consensus recommendations for the postmortem diagnosis of Alzheimer’s disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease. Neurobiol Aging 1997;18:81–2.
[2] Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer’s Association guidelines for the neuropathological assessment of Alzheimer’s disease. Alzheimers Dement 2012;8:1–13.
[3] Honda H, Sasaki K, Hamasaki H, Shijo M, Koyama S, Ohara T, et al. Trends in autopsy-verified dementia prevalence over 29 years of the Hisayama study. Neuropathology 2016;36:383–7.
[4] Hamasaki H, Honda H, Okamoto T, Koyama S, Suzuki SO, Ohara T, et al. Recent increases in hippocampal tau pathology in the aging Japanese population: The Hisayama Study. J Alzheimers Dis 2017;55:613–24.
[5] Portet F, Scarmeas N, Cosentino S, Helzner EP, Stern Y. Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. Arch Neurol 2009;66:1120–6.
[6] Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, Dubois B, Sarazin M, Brandt J, et al. Motor signs during the course of Alzheimer disease. Neurology 2004;63:975–82.
[7] Horvath J, Burkehd PR, Herrmann FR, Bouras C, Kovari E. Neuropathology of parkinsonism in patients with pure Alzheimer’s disease. J Alzheimers Dis 2014;39:115–20.
[8] American_Psychiatric_Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. American Psychiatric Association; 1987.
[9] Katoh S. Development of the revised version of Hasegawa’s dementia scale (HDS-R). Jpn J Geriat Psychiatriy 1991;2:1339–47.
[10] Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, et al. Trends in prevalence of Alzheimer’s disease and vascular dementia in a Japanese community: the Hisayama Study. Acta Psychiatr Scand 2010;122:319–25.
[11] Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol 1991;1:213–6.
[12] Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer’s disease. Neurology 1991;41:479–86.
[13] Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer’s disease. Neurobiol Aging 1997;18:585–8.
[14] Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59.
[15] Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurobiology 2002;58:1791–800.
[16] Fujimi K, Sasaki K, Noda K, Wakisaka Y, Tanizaki Y, Matsui Y, et al. Clinicopathological outline of dementia with Lewy bodies applying the revised criteria: the Hisayama study. Brain Pathol 2008;18:317–25.
[17] McKeith IG, Dickson DW, Lowe J, Emre M, O’Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005:65:1863–72.
[18] AK J. Fundamentals of digital image processing. New Jersey: Prentice Hall; 1989. 68, 71, 3.
[19] J M. Some methods for classification and analysis of multivariate observations. In: . proceedings of the fifth Berkeley symposium on mathematical statistics and probability, 1. Berkeley: University of California Press; 1967, p. 281–97.
[20] Jellinger KA. Lewy body-related alpha-synucleinopathy in the aged human brain. J Neural Transm (Vienna, Austria: 1996) 2004;55:613–24.
[21] Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer’s disease with distinct clinical characteristics: a retrospective study. Lancet Neurol 2011;10:785–96.
[22] Juncko NJ, Brodersen KA, Soto-Ortolaza AI, Ross OA, Liesinger AM, Duara R, et al. Neuropathologically defined subtypes of Alzheimer’s disease differ significantly from neurofibrillary tangle-predominant dementia. Acta Neuropathol 2012;124:681–92.
Oyanagi K, Takahashi H, Wakabayashi K, Ikuta F. Large neurons in the neostriatum in Alzheimer’s disease and progressive supranuclear palsy: a topographic, histologic and ultrastructural investigation. Brain Res 1991;544:221–6.

Komori T. Tau-positive glial inclusions in progressive supranuclear palsy, corticobasal degeneration and Pick’s disease. Brain Pathol 1999;9:663–79.

Komori T, Arai N, Oda M, Nakayama H, Mori H, Yagishita S, et al. Astrocytic plaques and tufts of abnormal fibers do not coexist in corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathol 1998;96:401–8.

Ogomori K, Kitamoto T, Tateishi J, Sato Y, Suetsugu M, Abe M. Beta-protein amyloid is widely distributed in the central nervous system of patients with Alzheimer’s disease. Am J Pathol 1989;134:243–51.

Selden N, Mesulam MM, Geula C. Human striatum: the distribution of neurofibrillary tangles in Alzheimer’s disease. Brain Res 1994;648:327–31.

Kawakami I, Hasegawa M, Arai T, Ikeda K, Oshima K, Niizato K, et al. Tau accumulation in the nucleus accumbens in tangle-predominant dementia. Acta Neuropathol Commun 2014;2:40.

Haan MN, Jagust WJ, Galasko D, Kaye J. Effect of extrapyramidal signs and Lewy bodies on survival in patients with Alzheimer disease. Arch Neurol 2002;59:588–93.

Martorana A, Koch G. “Is dopamine involved in Alzheimer’s disease?”. Front Aging Neurosci 2014;6:252.

Clark CM, Ewbank D, Lerner A, Doody R, Henderson VW, Panisset M, et al. The relationship between extrapyramidal signs and cognitive performance in patients with Alzheimer’s disease enrolled in the CERAD Study. Consortium to establish a registry for Alzheimer’s disease. Neurology 1997;49:70–5.

Irwin DJ, Lee VM, Trojanowski JQ. Parkinson’s disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. Nat Rev Neurosci 2013;14:626–36.

Colom-Cadena M, Gelpi E, Charif S, Belbin O, Blesa R, Marti MJ, et al. Confluence of alpha-synuclein, tau, and beta-amyloid pathologies in dementia with Lewy bodies. J Neuropathol Exp Neurol 2013;72:1203–12.

Golbe LI. Progressive supranuclear palsy. Semin Neurol 2014;34:151–9.

Yamada M, Itoh Y, Otomo E, Sueyama N, Matsushita M. Dementia of the Alzheimer type and related dementias in the aged: DAT subgroups and senile dementia of the neurofibrillary tangle type. Neuropathology 1996;16:89–98.

Fujii H, Takahashi T, Mukai T, Tanaka S, Hosomi N, Maruyama H, et al. Modifications of tau protein after cerebral ischemia and reperfusion in rats are similar to those occurring in Alzheimer’s disease - Hyperphosphorylation and cleavage of 4- and 3-repeat tau. J Cereb Blood Flow Metab 2017;37:2441–57.

Ichihara K, Uchiyama T, Nakamura A, Suzuki Y, Mizutani T. Selective deposition of 4-repeat tau in cerebral infarcts. J Neuropathol Exp Neurol 2009;68:1029–36.

Tolnay M, Schwietert M, Monsch AU, Staehelin HB, Langui D, Probst A. Argyrophilic grain disease: distribution of grains in patients with and without dementia. Acta Neuropathol 1997;94:353–4.

Braak H, Braak E. Argyrophilic grain disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria. J Neural Transm (Vienna, Austria: 1996) 1998;105:801–19.

Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Miyahara Y. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 2008;118:2672–8.