The aspects of various neurodegenerative diseases can be observed overlapping with each other during autopsy. Corticobasal degeneration (CBD) is a rare neurodegenerative disease, whereas Alzheimer disease (AD) is the most common cause of dementia. In this article, we present the combination of CBD and AD in an autopsy case. The patient, an 82-year-old right-handed woman developed asymmetrical parkinsonism, visuospatial dysfunction and memory loss, as well as subsequent non-influent aphasia over the past 10 years. The autopsy revealed characteristic CBD-related pathology, ballooned neurons, globose tangles and astrocytic plaques, mainly in the frontal cortex and basal ganglia. The Alzheimer-related pathology was also present concomitantly. Senile plaques deposited diffusively throughout the hippocampus and neocortices. Neurofibrillary tangles (NFTs) were more confined to the hippocampus. The autopsy demonstrated pathological overlap of CBD and AD, which therefore explained the clinical early development of dementia and parkinsonism.

Key words: Alzheimer disease, cortical basal degeneration, dementia, parkinsonism, tauopathy.

INTRODUCTION

Corticobasal degeneration (CBD) and Alzheimer disease (AD) have distinct clinical and pathological features, although they are both categorized as tauopathies. CBD presents with parkinsonian symptoms and frontal lobe dementia. AD shows prominent memory loss and speech disturbance. The pathological distribution patterns and affecting cell types are also clearly different. Astrocytic plaques and ballooned neurons, mainly in frontal lobes and basal ganglia, are characteristic of CBD. In AD, the typical neurofibrillary tangles (NFTs) and senile plaques distribute diffusively in temporal and parietal lobes. CBD tends to be considered as a pathologically and clinically heterogeneous disorder. The overlap of CBD with other neurodegenerative disorders has been described in the literature. Schneider et al. report 11 autopsy-proved CBD cases, six of which manifest overlap of neuropathologic features of one or more disorders, including AD, progressive supranuclear palsy, Parkinson’s disease and hippocampal sclerosis. The overlap of pathology has also been documented in other types of clinically defined neurodegenerative diseases. However, it has been difficult to differentiate such overlap clinically and correlate postmortem histopathological changes with disease-expression during life.

In this study, we report an 82-year-old woman manifesting overlap of CBD and AD. The clinical symptoms were reviewed and correlated with the pathological findings. Such a combination might not be rare and was indicative of the common pathogenesis of various neurodegenerative disorders.

CASE SUMMARY

An 82-year-old, right-handed woman was admitted to First Hospital of Peking University, Beijing, China, with a history of progressive mental decline and movement disorders for almost 11 years.

At first, she was found to frequently fall backward with no known cause. A visible tremor developed first in the left hand and then in the right. She also showed clumsy movement which prominently affected the left side. At the age of 72, she lost her way home after seeing a dentist. From then
on, she was not allowed to be outside alone. Memory loss developed gradually. She often forgot where she placed items and repeatedly performed the same task due to memory lapse. She was also found to be slow in communicating. She was not as conversant and fluent as previously and had trouble speaking in public. She encountered word-finding difficulties during conversation. Sometimes she could not recall otherwise familiar names. Comprehension ability was still intact. The symptoms deteriorated progressively. At the age of 74, she could not speak long sentences without grammatical mistakes. Her speech was limited to single words or phrases and usually repeated the same words, inhibiting proper communication. Her numerical skills declined so that she had to give up handling her own finances. The movement disorders were also exacerbated. The tremor became more and more obvious in her arms. Festination and movement initiating difficulties were also present. She became unable to cook or dress herself. She was still able to recognize the faces of her family members. At the age of 77, personality changes occurred as well. She was agitated and not so generous in nature as before. She also had temporary suicidal tendencies. She showed apathy and cared for nothing around her. Her walking became slow and stiff. She walked with increasing difficulty in a narrow gait with no swing to her arms. At the age of 78, she was wheelchair-bound, unable to recognize the faces of her family members. During the whole disease progression, she was given medications to relieve parkinsonism and dementia. Madopar, amantadine and donepezil were all tried and failed. No definite improvement was achieved, even in the early stages. At the age of 79, she had a generalized tonic seizure lasting for 1 min. She was hospitalized. Swallowing difficulty and dysarthria developed some time after the seizure. She was functionally mute, only producing single nonsense words. She was confined to the bed with stiff limbs and intermittent tremor. She was incontinent, unable to eat, speak or even cough. Supportive medical treatment was administered until she contracted severe and lethal pneumonia at the age of 82.

The patient’s medical history was unremarkable except for coronary artery heart disease and essential hypertension. Neither the patient nor any of her blood relatives had a history of neurological or psychiatric disease.

A neurological exam taken at the age of 79 revealed total loss in orientation, attention, memory, calculation and visuospatial skills. In addition, she was totally mute and unable to comprehend even the simplest of commands. She was not responsive to verbal stimulus but was responsive to pain. Her eyes could be track and focus on moving objects most of the time. No nystagmus was revealed. The pupils were equal, round, and reactive to light although the corneal reflexes had almost disappeared. Voluntary flexing movements were occasionally seen in her upper limbs. Lead pipe muscle tone appeared in all extremities. Voluntary movements were not present. The tendon reflexes were active in both upper limbs and decreased in the lower limbs. Grasping reflex was seen in her left hand. Bilateral palomental reflexes and sucking reflex were positive. Babinski’s signs were negative. Bilateral Chaddock’s signs were positive.

A full laboratory test was unrevealing. Brain MRI (done at the age of 79) showed multiple lacunar infarctions, demyelination of white matter around the lateral ventricles, and moderate brain atrophy (Fig. 1).

**PATHOLOGICAL FINDINGS**

A consent form was obtained from the legal next-of-kin in accordance with the law. An autopsy restricted to the brain was performed. The brain weighted 1040 g after formalin fixation. The cerebral hemispheres were symmetrical. There was mild atrophy in the frontal lobe showing narrow gyrus and broadened sulci. Other areas, the temporal, parietal and occipital lobes, appeared almost normal in volume.

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The cerebellum was externally unremarkable. Serial coronal sections revealed atrophy in the right hippocampus. Lateral ventricular dilation was prominent on the right side. The underlying white matter was also grossly unremarkable. The right globus pallidus appeared brownish. Shrinkage of the caudate nucleus on both sides was also present. The remaining basal ganglia and the thalamus appeared normal. Discoloration could be seen in the midbrain. Sections of the cerebellar hemispheres did not reveal abnormalities. No tissue softening or herniation was detected.

Microscopic examination in various sections disclosed neuronal loss and astrogliosis which was prominent in the frontal lobe, moderate in the temporal and parietal lobes. The occipital lobe was relatively spared. Visible vacuolation could be seen in layer II and III due to severe neuron loss. Ballooned neurons (Fig. 2a) could be observed in layers IV and V of the frontal lobe cortex. Mild neuron loss and gliosis was apparent in the hippocampus. Granulovascular degeneration and Hirano bodies were also detected. Neuron loss and gliosis were severe in the midbrain, globus pallidus, and moderate in the subsequent sections of striatum and subthalamus. The pontine and medulla oblongata were also affected in a similar pattern. The midbrain showed a remarkable loss of pigmented neurons within the substantia nigra. Some ballooned neurons were found in the subthalamus and basal ganglia. Globose NFTs were evident in the subthalamus nucleus and the remaining pigmented nigral neurons where no Lewy bodies were found. Hyalineization and calcification in the walls of small arteries and patches of ischemic lesions were also present in the basal ganglia. Gallyas silver staining revealed globose tangles, astrocytic plaques and neuropil threads. Massive globose tangles were revealed in the regions of the frontal lobe (Fig. 2b), midbrain, basal ganglia and subthalamus. There were few globose tangles in other areas of the neocortices and brain stem. Astrocytic plaques (Fig. 2c), presenting as broadened, short-side branched aggregations, distributed diffusively in the frontal lobe and were rarely seen in other regions. The neuropil threads could be detected throughout the neocortices, basal ganglia and brain stem. Flame-like NFTs (Fig. 2d) were prominent in the hippocampus and scattered in the neocortices of the frontal, parietal and temporal lobe. Congo red staining showed amyloid deposits in various neocortices and hippocampus. Luxol Fast Blue staining for myelin sheath showed diffusely demyelination, mainly in the white matter of the frontal lobe. U fibers were relatively preserved.

Immunohistochemical staining was carried out using first antibodies against phosphorylated tau, β-amyloid 1–42 and α-synuclein (Abcam Corporation, Cambridge, UK). Phosphorelated tau-positive globose inclusions are prominent in neurons and some glial cells of the frontal lobe (Fig. 2e), midbrain (Fig. 2f), and basal ganglia (Fig. 2g). They were also occasionally found in regions of the parietal, temporal lobes, subthalamus and pontine. Staining was also positive for astrocytic plaques. Coiled bodies were scattered in white matter glial cells. In the hippocampus, a large amount of NFTs were strongly stained with phospho-related tau. Few NFTs could also be found in the neocortices. For each section, no positive inclusions or deposits were revealed in α-synuclein staining. Under β Amyloid 1–42 staining, senile plaques deposited diffusively throughout the neocortices (Fig. 2h,i), basal ganglia and hippocampus (Fig. 2j) although the deposits were relatively few in the occipital lobe. Amyloid deposits were also found in some vessel walls of the basal ganglia and neocortices.

DISCUSSION

Corticobasal degeneration is a rare neurodegenerative disease characterized by both parkinsonian syndromes and frontotemporal dementia. The disease onset is usually asymmetric. Parkinsonism tends to be an early sign of the disorder, presenting as postural instability, rigidity, movement slowness and non-resting tremor. The main manifestations appearing in our patient were compatible with the clinical spectrum of CBD. Moreover, we arrived at the diagnosis of CBD due to the following pathological evidence. Grossly, the brain weight decreased moderately. Atrophy of the anterior part was observed together with asymmetric ventricular dilation. Microscopically, diffusive neuron loss, superficial layers spongiosis as well as astrogliosis were the prominent features in the frontal lobe. The globus pallidus and midbrain were severely affected. The striatum and subthalamus were subsequently involved. Glial cell and tau pathology showed a similar pattern of involvement. All of these findings suggested a type of neurodegenerative disease mainly involving the frontal cortex, basal ganglia and midbrain. Glial pathology revealed that globose tangles, astrocytic plaques and argyrophilic neuropil threads were the dominant changes in the frontal lobe, basal ganglia and midbrain, which were all in accordance with that of CBD. The basal ganglia lesions were also compatible with that of typical CBD.

Nevertheless, the neuropathological findings could not be explained solely by CBD. The hippocampus, typically spared in CBD, was found to be atrophied. Diffusive senile plaques in neocortices, neuron granulodegeneration in the hippocampus, as well as vascular amyloidosis, were all presented. Massive NFTs were revealed whereas the globose tangles were rarely found in this region. The characteristic presence of the remarkable tau-positive tangle pathology was similar to that in AD. The diagnosis of AD could thus be inferred. Moreover, the pathological changes of AD did not seem typical as in other cases. The brain atrophy was not parallel to the more than 10 years clinical course of...
Fig. 2  Ballooned neurons were found in frontal lobe under HE staining (a). Gallyas silver staining revealed globose tangles (b), astrocytic plagues (c) in the frontal lobe and NFTs (d) in the hippocampus. Immunohistochemical staining for phosphorelated tau showed globose tangles in neurons of the frontal cortex (e), midbrain (f) and basal ganglia (g). Immunohistochemical staining for β-amyloid 1–42 showed senile plaques in the temporal (h), parietal lobe (i) and hippocampus (j).
The overlap of CBD and AD

typical AD in which hippocampal volume reduction would be more severe and prominent.\(^9\) NFTs were mostly confined to the hippocampus and were fewer in the neocortices. Therefore we categorized our case into NFT III/IV based on Braak’s criterion and NP B (moderate deposits of neocortical neuritic plaques) based on National Institute for Aging and Ronald and Nancy Reagan Institute of the Alzheimer’s Association criterion, both suggesting the middle probability of AD.\(^10\) Aging and its related Alzheimer-like pathology should also have been taken into account since our patient was over 80. The pathological features in a senile brain may be found in AD, but they tend to be more focal and less severe. The neuropathological assessment in a senile brain shows few NFTs in the hippocampal area, more confined distribution of amyloid deposits and the absence of other types of neurodegenerative lesions.\(^11\) Although an association between aging and AD has been discussed in many articles, there is still controversy on this point. Aging might be associated with cognitive decline and serve as a risk factor, or it may have attenuated the development of AD, at least in our case.\(^12\)

The pathological results were also helpful to rule out other clinical or pathologically related disorders. No tufted astrocytes or other types of glial inclusions were revealed, excluding the diagnosis of other tau-related diseases, such as progressive supranuclear palsy.\(^7,13\) No ubiquitin-positive inclusions in cortical neurons suggest no indication of fronto-type dementia.\(^14\) The absence of \(\alpha\)-synuclein-positive inclusions excluded synucleinopathies such as Parkinson’s disease, Lewy body dementia and multiple system atrophy.\(^15,16\)

While correlating the clinical manifestations with the pathological findings, we found some atypical aspects for CBD and AD which might be a clue for the overlap of two disorders.

Alien limb phenomenon, which is very common and typical in many CBD cases,\(^17\) could not be confirmed in the early and middle stages in our case. Some pathological features were given based on our pathological findings. Alien hand is a type of limb apraxia due to the neglect of half of the body or special area. The underlying pathology commonly correlates with parietal atrophy or parietofrontal associative fiber impairment.\(^18\) In our patient, few pathological features were identified in the parietal lobes of both sides compared with frontal lobes. The relative sparing of the parietal lobe might lead to the absence of limb apraxia.

Progressive speech disturbance is another feature in CBD cases and in our patient.\(^19,20\) Non-fluent type of progressive aphasia was supposed to develop in the early stage although physical examination in the late stage did not reveal the type of aphasia. Speech disorder was considered to appear in AD frequently as fluent aphasia whereas the aphasia in our case was not so typical of that in AD. Aphasia-naming speech apraxia is discussed in other CBD reports.\(^19,21,22\) Therefore, the aphasia in our patient might be a mixed one of both CBD- and AD-type aphasia. Pathological findings gave further support for such a point of view. The frontal lobe was predominant in neuron and glial cell pathology, which might be responsible for the nonfluent speech disorder. The temporal lobe was not so severely affected, which may explain the absence of fluent aphasia, especially in the early stage.

Mental disorder occurred almost concomitantly with parkinsonism.\(^2\) Visuospatial dysfunction was the early sign, followed by trouble with memory, calculation, speech and facial recognition. In the late stage, the patient showed personality change and mood disturbance. CBD usually spares the memory in its early stages and tends to present with fronto-type dementia. Visuospatial dysfunction and memory deficit are the earliest and typical defects in AD. The mental disorders in our case elicited the clinical suspicion of Alzheimer-type dementia in the early stage and frontal lobe dementia in the late stage, both of which were later confirmed by the pathological findings.

Parkinsonism, shown as postural dysfunction and asymmetrical tremor, occurred early and prominently, suggesting severe extrapyramidal system involvement.\(^2\) Although parkinsonism can appear in the progression of Alzheimer disease, it tends to be late-onset and at least 1 year after the development of mental disorders. Early-developed parkinsonism is an indicative sign of CBD and is verified pathologically. Basal ganglia and midbrain involvement are characteristic of CBD and are only less severe than in frontal lobe. Such involvement would unavoidably lead to different types of extrapyramidal system impairment and spasticity in the late stage.\(^23\)

The combination of CBD and AD made the diagnosis in this case more complicated and difficult, although clear clinical and pathological patterns had been outlined. Both of them have in common the presence of the aberrant tau aggregates. The astrocytic plaques and NFTs, strongly stained by phosphorelated tau, were the major points in our case. The molecular analysis of tau components in tauopathies reveals four repeats in CBD, three and four repeats in AD. The common deposits of four repeats would be an explanation for the combination of CBD and AD. The phosphorelated tau protein, not like amyloid, is considered to be the cause of neurodegeneration. Abnormal tau would increase with the increasing dementia severity.\(^24\) It is suggested that the molecular alterations of tau that occur during the initial process of tangle formation in AD are similar with non-AD tauopathies, but the middle and later changes are not common to all diseases.\(^25\) Two or more major proteins interacting could also occur within the same brain and cause variable phenotypes and mixed pathologies, such as AD with \(\alpha\)-synuclein pathology in the brain.

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stem and amygdala, Parkinson’s disease and diffuse Lewy body disease with AD lesions, or frontotemporal dementia with a mixture of various deposits. The new candidate protein, ubiquitinated TDP-43, expressing in frontotemporal lobar degeneration with ubiquitin-positive inclusions and amyotrophic lateral sclerosis, is also present in AD and CBD. These molecular analysis procedures would help to correlate the patho-phenotypic aspects and put some light on the etiology of neurodegenerative disorders.

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REFERENCES


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