

## Corticobasal degeneration – clinico-pathological considerations

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### Abstract

*Corticobasal degeneration (CBD) is a rare sporadic 4-repeat tauopathy. We report here the first Polish case of pathologically proven CBD. Our patient developed clumsiness of the right hand at age 63 years. During the course of his illness he suffered from progressive asymmetric parkinsonism unresponsive to dopaminergic therapy. Focal dystonia affecting right upper extremity, non-fluent aphasia, dysphagia, supranuclear vertical gaze palsy, imbalance and myoclonus ensued. The patient died of pneumonia at age 71 years. Head magnetic resonance imaging revealed the presence of asymmetric cortical atrophy contralateral to the clinically more affected right side. Median somatosensory evoked potentials performed bilaterally demonstrated significant reduction of cortical evoked potential amplitudes recorded from the left scalp electrodes. Neuropathological examination showed cortical atrophy of the frontal and parietal lobes with superficial spongiosis and diffuse cortical gliosis. Numerous ballooned neurons were found in frontal and parietal cortices. The most remarkable pathology was extensive tau-immunoreactivity of glial and neuronal cell processes, significantly pronounced in the frontotemporal cortex, basal ganglia, thalamus and brainstem. Recent research studies have resulted in better clinical, pathological and genetic characterization of sporadic tauopathies. It is hoped that similar progress will ensue in the development of symptomatic and eventually curative treatments for these rare conditions.*

**Key words:** corticobasal degeneration, neuropathological examination, immunohistochemistry, tauopathy

### Introduction

Corticobasal degeneration (CBD) is a sporadic neurodegenerative disorder with an insidious onset and gradual progression. The first description of CBD was provided by Rebeiz et al. in 1968 [18]. They reported on clinical features, emphasizing the presence of progressive asymmetric rigidity, apraxia and other cortical and subcortical signs in patients with degeneration of the cerebral cortex, substantia

nigra and dentate nucleus. Furthermore, they pointed out the presence of so-called swollen and achromatic neurons (i.e. devoid of Nissl substance) [18].

Fully validated clinical diagnostic criteria for CBD have not been established. However, the proposed criteria include progressive clinical course with asymmetric onset, speech apraxia, cortical signs (apraxia, cortical sensory loss, alien limb phenomenon and cortical reflex myoclonus) and motor signs such as asymmetrical akinetic-rigid syndrome without

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response to levodopa and limb dystonia [13,15]. More recently, the name of this disorder has been changed to corticobasal degeneration [8], but its neuropathologic equivalent is still called corticobasal ganglionic degeneration (CBGD) [1,21]. Pathologic examination is necessary to make a definite diagnosis of CBD [1,15].

CBD is a rare disorder, accounting for about 4–6% of all parkinsonian cases. There is only one Polish case of CBD described in the literature. In this particular case, the diagnosis was based on the clinical and radiological findings; however, autopsy examination was not available [10].

CBD remains underdiagnosed, at least partly due to the considerable clinical and pathological heterogeneity [5,16]. The majority of CBD cases present with strikingly asymmetric parkinsonism unresponsive to levodopa therapy, dystonia and cortical signs.

It was thought that dementia appears in the late stages of CBD. More recent studies demonstrated that dementia can even be the very first symptom. Cases of CBD presenting with behavioural and personality changes, suggesting fronto-temporal dementia and with supranuclear gaze palsy, suggesting diagnosis of progressive supranuclear palsy (PSP), have also been described [9,13,15].

We present the first pathologically confirmed Polish CBD case.

## Case report

This 69-year-old, right-handed male was admitted to the Department of Neurology, Ageing, Degenerative and Cerebrovascular Disorders in Katowice, Poland in 2003.

He was forced to retire prematurely at age of 63 years due to a clumsiness of his right hand.

He worked as a technician in a chemical laboratory. His family history was negative for neurodegenerative disorders. At age 68 years he had significant difficulties using his right hand. He had cognitive impairment with Mini-Mental State Examination (MMSE) of 18/30 points. His facial expressions were decreased. Primitive reflexes such as palmomental and grasp reflexes were present on the right side only. He had slight limitation of upward and downward gaze. His speech was non-fluent. There was severe asymmetric apraxia, more so on the right side. He could not use his right hand at all. Severe rigidity affecting his right arm, and to a lesser extent right leg and left extremities, were observed. There was an intermittent dystonic posturing in his

right upper extremity. Deep tendon reflexes were symmetric with flexor plantar responses. There was a slight tendency to a lateropulsion but without postural instability.

Psychological tests revealed acalculia, impairment of right-left orientation, finger gnosis and graphesthesia, decreased verbal fluency and impaired memory (inability to learn new information, delayed recall memory), and disturbances of executive functions (planning, sequencing, abstracting, organizing). Head MRI revealed atrophy of the left hippocampus (Fig. 1A), asymmetric atrophy of the left parieto-temporal cortex with enlargement of the lateral ventricle (Fig. 1B), and a mild small vessel ischaemic disease in the periventricular white matter. SPECT study with <sup>99m</sup>Tc-HMPAO showed hypoperfusion in the left fronto-parieto-temporal region. Auditory and visual evoked potentials were normal.

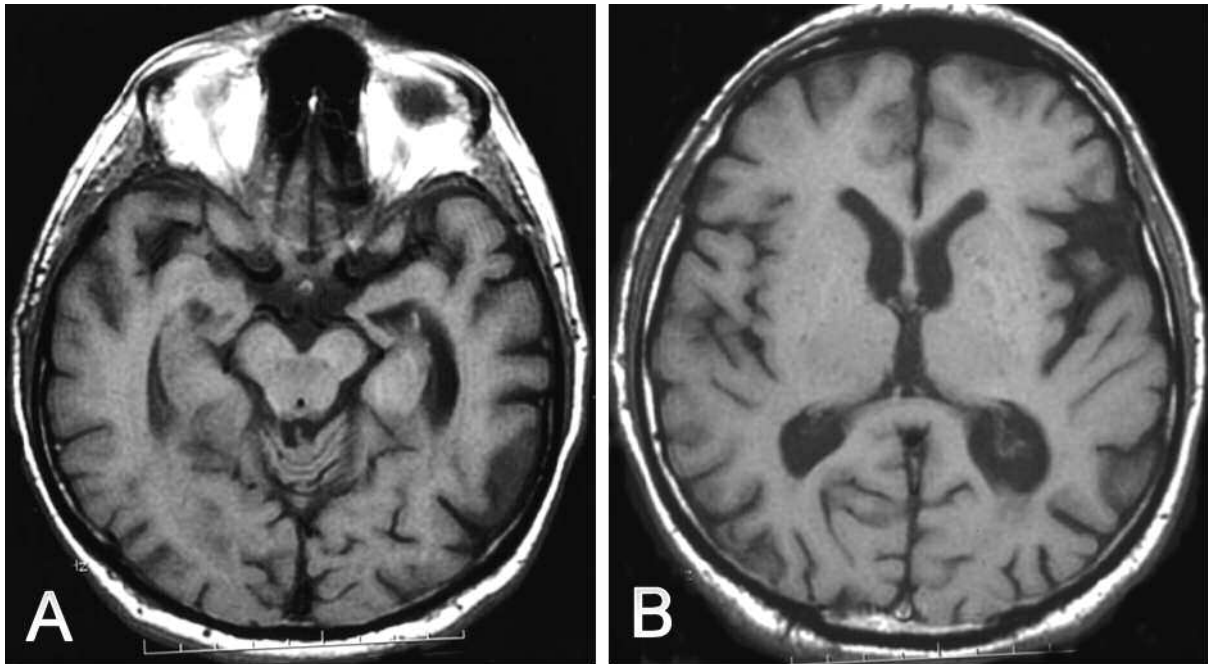
The median somatosensory evoked potentials demonstrated normal absolute and interpeak latencies bilaterally. However, left N20, N35 and N20-P25 cortical evoked potentials' amplitude was reduced more than 50% with stimulation of the right median nerve. Routine blood and urine results were normal. Therapeutic trials including oral levodopa and intravenous amantadine provided no benefit. He was diagnosed as a probable CBD.

The disease gradually progressed. Eight months later apraxia of the left hand increased and he became completely dependent in all daily living activities. Five months later (at age 70) he became unsteady and fell. His speech deteriorated (non-fluent aphasia) and full upward and downward gaze palsy appeared. Shortly after this he experienced an incident of nocturnal grand-mal seizure. EEG performed the next day showed no epileptiform activity. MMSE decreased to 11/30 points. Repeat head MRI performed one year after initial examination displayed more pronounced cortical atrophy, more on the left side. Seven months later he remained awake. He was unable to sit, and he could use only a few words. He developed dysphagia and myoclonic jerks affecting his right arm and leg. He remained urinary continent. He died of aspiration pneumonia at age 71 years.

## Neuropathologic examination

### Gross examination

After fixation in 10% formalin the brain was divided along the midline and the right hemisphere



**Fig. 1 A, B.** Axial T1-weighted magnetic resonance imaging (MRI) of the brain performed two years before death. **A.** Atrophy of the temporal region including hippocampus, more pronounced on the left side with secondary enlargement of the temporal horn. **B.** Asymmetric atrophy of the left parieto-temporal cortex with dilatation of the lateral ventricles

was saved for future anatomical and biochemical studies. The left hemisphere was dissected further and subjected to histological examination. The fixed brain weighed 1300 grams. The cerebral hemispheres were asymmetrical, with the left smaller than the right (Fig. 2A), especially in the temporo-parietal areas. The sulci and gyri revealed subtle cortical atrophy that was most marked in the superior parietal lobule. The corpus callosum was thin in its posterior body and splenium. The ventricular system was mildly dilated, especially the frontal horn of the lateral ventricle. Basal ganglia showed mild atrophy of the head of the caudate and rust-like discoloration of the globus pallidus (Fig. 2B). There was mild depigmentation of the substantia nigra and locus ceruleus (Fig. 2C).

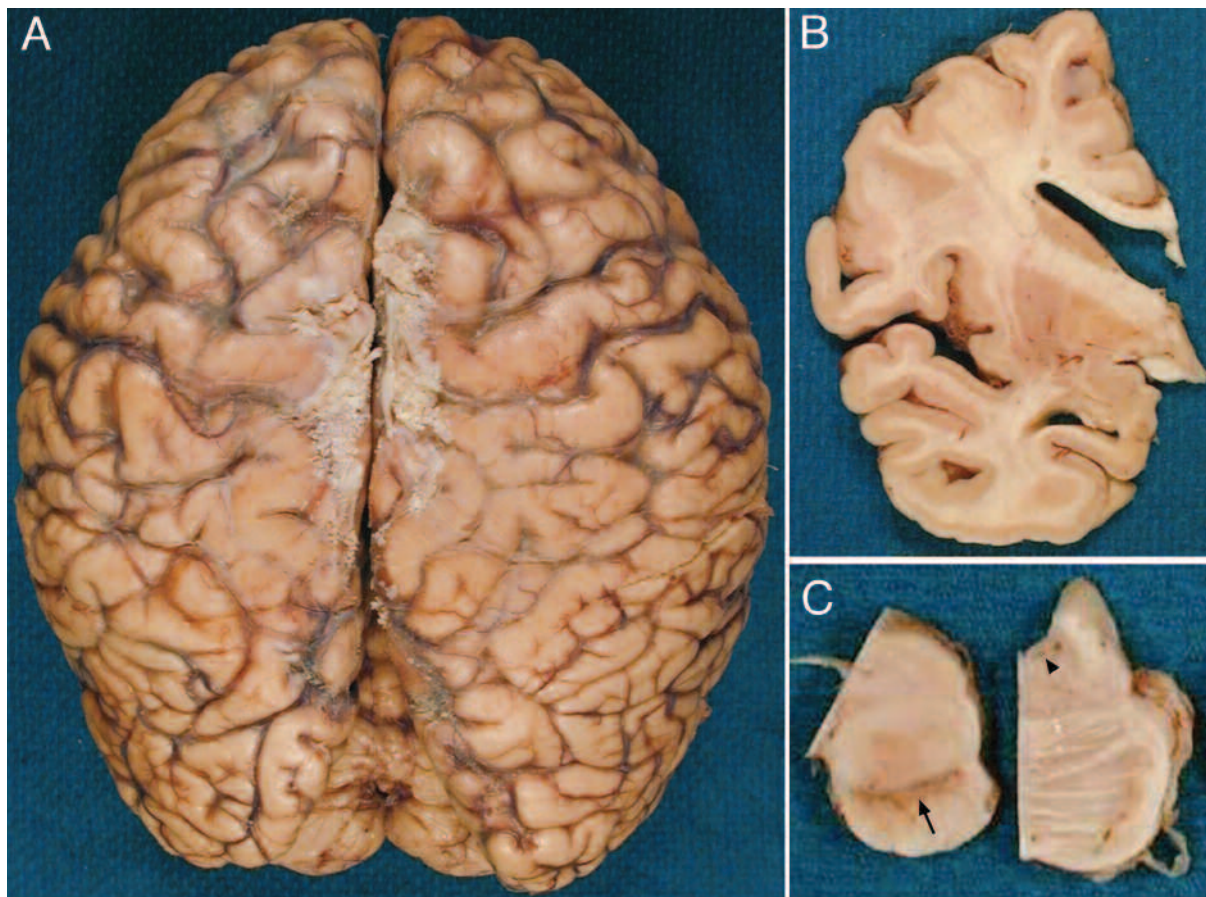
### Microscopic examination

Sections of the neocortex, hippocampus, basal forebrain, basal ganglia, thalamus, midbrain, pons, medulla and cerebellum were examined with HE and with thioflavin-S fluorescent microscopy. Sections of the cortex, hippocampus, basal ganglia, thalamus, midbrain, pons, medulla and cerebellum were also

studied with immunocytochemistry for tau. Sections of cingulate gyrus were additionally studied with immunocytochemistry for  $\alpha\beta$ -crystallin.

### Immunohistochemistry

For immunohistochemistry 5- $\mu$ m-thick sections were deparaffinized and steamed in  $dH_2O$  for 30 min. Sections were studied with antibodies for phospho-tau (CP13, Peter Davies, Albert Einstein College of Medicine, Bronx, NY, United States, dilution 1:500, incubation time 45 min) and  $\alpha\beta$ -crystallin (non-commercial polyclonal, dilution 1:10000, incubation time 45 min). The tau monoclonal antibody CP13 recognizes hyperphosphorylated tau at serine residues 202/205. This antibody has been well-characterized elsewhere [11].  $\alpha\beta$ -crystallin belongs to the class of small heat-shock proteins and is widely used for detection of ballooned neurons [7]. Antibody staining was performed on the autostainer using the DakoCytomation Envision +HRP System (K4007 for monoclonal and K4003 for polyclonal antibody). 3,3'-diaminobenzidine (DAB) was used as chromogen. The sections were counterstained with hematoxylin.



**Fig. 2 A–C.** Gross examination of the brain and brainstem. **A.** Upper view. Asymmetric atrophy of the cerebral hemispheres (left hemisphere is smaller than the right). Atrophy is more prominent on the left side, corresponding with the MRI findings. **B.** Frontal section of the left hemisphere at the level of the basal ganglia. Mild atrophy of the head of the caudate and rust-like discoloration of the globus pallidus are seen. **C.** Transverse sections of the midbrain and the pons. There is mild depigmentation of the substantia nigra (arrow) and locus ceruleus (arrowhead)

### Microscopic findings

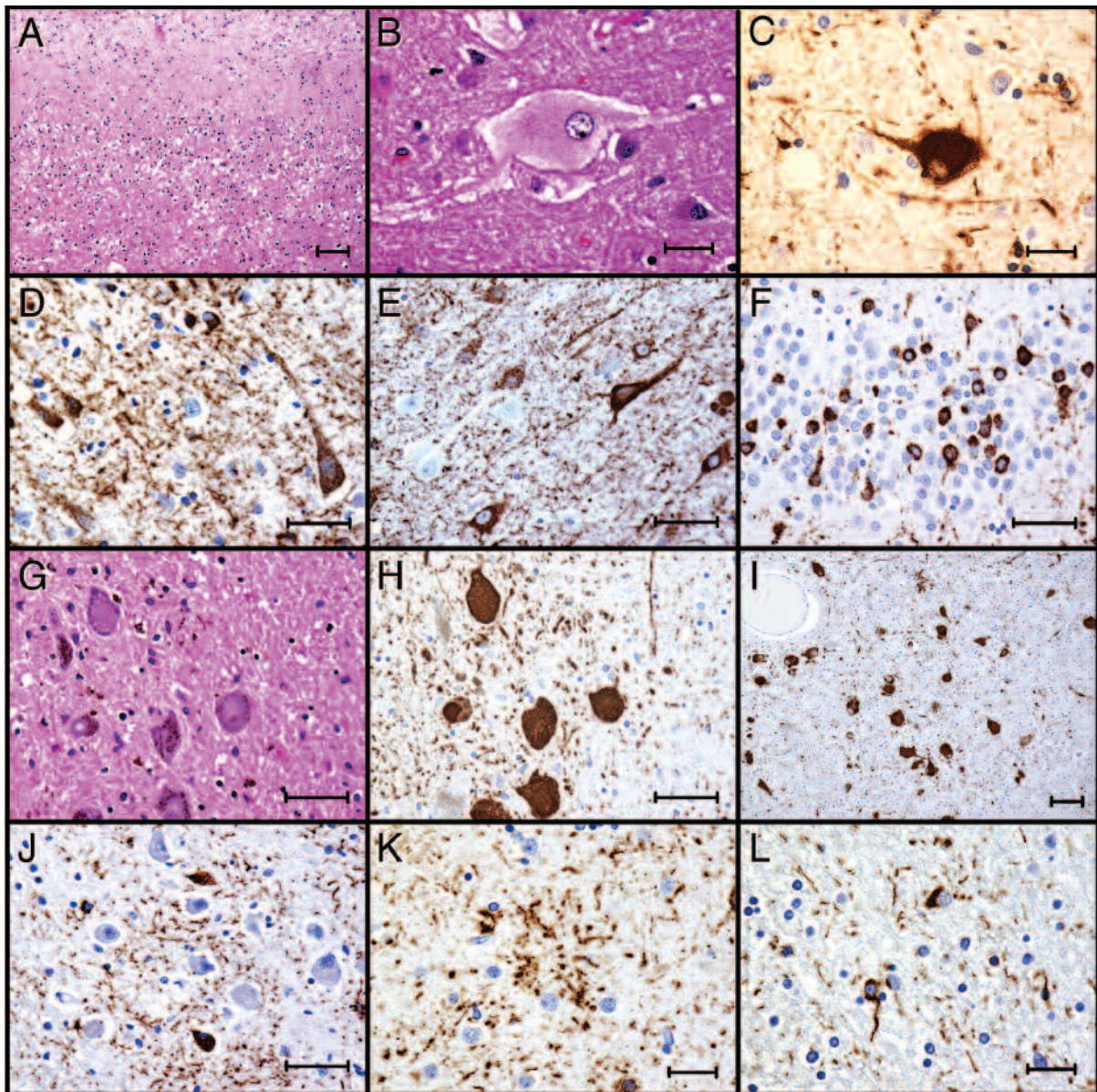
The sections from the frontal and parietal lobes, especially the superior frontal gyrus and superior parietal lobule, showed cortical atrophy with superficial spongiosis and diffuse cortical gliosis (Fig. 3A). There were numerous ballooned neurons (BN); many of these showed enlargements of proximal cell processes (Fig. 3B). BN were numerous in superior frontal, superior parietal and cingulate gyrus, but also present in convexity cortices of midfrontal gyrus and inferior parietal lobule. BN stained strongly with antibody against  $\alpha\beta$ -crystallin (Fig. 3C).

The hippocampus had preservation of neuronal populations throughout all sectors of Ammon's horn. The basal nucleus of Meynert had a nearly

normal neuronal population. The globus pallidus had mild increased iron pigment and mild gliosis. The subthalamic nucleus had no atrophy or gliosis. The substantia nigra had moderate neuronal loss with extraneuronal neuromelanin and gliosis.

With thioflavin-S fluorescent microscopy no senile plaques (SP) were found. The average counts of neurofibrillary tangles (NFT) stained with thioflavin-S per 40x field in selected structures were as follows: endplate (0–1), CA1 (1–4), CA2/CA3 (6–8), endplate (0–1), subiculum (3–7), basal nucleus of Meynert (0–3). The Braak neurofibrillary tangle stage was consistent with stage III.

The most remarkable pathology was extensive tau-immunoreactivity of cell processes in grey and



**Fig. 3.** Microscopic examination. **A.** Atrophy of the parietal cortex with superficial spongiosis and diffuse cortical gliosis. HE staining. Bar=100  $\mu$ m. **B.** Ballooned neuron in the cingulate gyrus. Note enlargement of proximal neuronal processes. HE. Bar=25  $\mu$ m. **C.** Ballooned neuron in the cingulate gyrus stains strongly with anti- $\alpha\beta$  crystallin antibody. Bar=25  $\mu$ m. **D.** Diffuse tau deposits in neuronal bodies (tangles and pretangles) and in cell processes (threads) in the motor cortex, **E** in the CA1 hippocampal sector, and **F** in the dentate fascia. Phospho-tau immunostaining. Bar=50  $\mu$ m. **G.** Intraneuronal cytoplasmic inclusions (so-called corticobasal bodies) in the substantia nigra. HE staining. Bar=50  $\mu$ m. **H.** The same area as in fig. G. Corticobasal bodies stain strongly with anti-phospho tau antibodies. Bar=50  $\mu$ m. **I.** Similar inclusions are seen in neurons of the locus ceruleus. Bar=100  $\mu$ m. **J.** Pretangles and numerous neuropil threads in the inferior olivary nucleus. Phospho-tau. Bar=50  $\mu$ m. **K.** Astrocytic plaque in the caudate nucleus. Phospho-tau. Bar=25  $\mu$ m. **L.** Oligodendroglial coiled bodies in the cingulate gyrus. Phospho-tau. Bar=25  $\mu$ m

**Table I.** Distribution of neuronal and glial tau deposits within the brain

Region	NFT and pretangles	Coiled bodies	Astrocytic plaques	Tau+ threads
Temporal cortex	+++	++	++	+++
Superior frontal cortex	+++	+++	+++	+++
Motor cortex	+++	++	+	+++
Caudate/putamen	+++	++	+++	+++
Globus pallidus	++	+	–	++
Basal nucleus	+++	+	–	+++
Hypothalamus	++	+	–	++
Ventral thalamus	+++	–	–	+++
Anterior thalamus	++	–	–	++
Subthalamic nucleus	+++	–	–	+++
Thalamic fasciculus	–	++	–	+++
Red nucleus	+	+	–	++
Substantia nigra	+++	+	–	++
Oculomotor complex	+	–	–	+
Midbrain tectum	++	+	+	+++
Locus ceruleus	+++	–	–	++
Pontine tegmentum	++	–	–	++
Pontine base	++	–	–	++
Medullary tegmentum	+++	–	–	++
Inferior olive	+	+	–	+
Dentate nucleus	+	–	–	+
Cerebellar white matter	–	+	–	–

– = absent; + = occasional; ++ = mild; +++ = frequent; NFT = neurofibrillary tangle.

white matter. The tau immunostain showed many neurons with granular cytoplasmic staining consistent with pretangles (Fig. 3D–F). Neuronal tau deposits in the substantia nigra and locus ceruleus formed so-called corticobasal bodies, also visible in HE stain (Fig. 3G–I). The lower brainstem was remarkable for tau positive thread-like cell processes, as well as pretangles (Fig. 3J). There were also many astrocytic plaques (Fig. 3K) and variable numbers of oligodendroglial coiled bodies (Fig. 3L). Detailed distribution of neuronal and glial tau deposits is presented in Table I.

## Discussion

Clinically and pathologically our patient fulfilled the currently proposed CBD criteria.

The symptoms of CBD usually begin in the sixth to eighth decade and the typical disease duration is between 5 and 10 years [19]. Surprisingly, our patient’s age at onset (63 years) and disease duration (8 years) are identical to the mean values for the series of fourteen definite CBD cases reported by Wenning et al. [24]. During the course of his illness our patient developed all cardinal features of CBD such as asymmetric parkinsonism, dementia,

balance problems and myoclonus. However, he never developed alien limb phenomenon. His parkinsonism did not respond to dopaminergic challenge, which is typical for CBD. Epileptic fits have not been reported in CBD. The single occurrence of grand-mal seizure in our patient could be attributed to the treatment with escitalopram in an attempt to treat his depression. The structural (MRI) and functional (SPECT) brain examinations demonstrated typical for CBD asymmetry of cortical atrophy and hypoperfusion, which in our patient were more pronounced on the left side and corresponded well with clinical findings. Atrophy of the left hippocampus was seen on MRI, but evident neuropathological correlates of this finding were not observed. Stimulation of the right median nerve in order to obtain the somatosensory cortical evoked potentials revealed a significant reduction of left N20 (1.39 vs. 3.31) and left N35 (-0.74 vs. 2.64) evoked potential amplitude. On a review of literature, we were not able to find similar observations. Therefore, further studies of somatosensory evoked potentials performed prospectively and longitudinally with comparison groups containing patients with other parkinsonian syndromes may be warranted. If such observation could be confirmed, somatosensory evoked potential testing may be an important diagnostic tool in differentiating parkinsonian conditions.

CBD should be differentiated from other forms of four-repeat tauopathies, particularly from progressive supranuclear palsy (PSP). This is difficult in PSP cases associated with apraxia. Frequent falls and severe postural instability, symmetric parkinsonism and absence of cortical signs would be suggestive of PSP. In the later stages, PSP and CBD, both unresponsive to levodopa challenge, can be differentiated by downward gaze paralysis and persistent symmetry of symptoms in PSP, and alien limb phenomenon, focal dystonia and apraxia in CBD [14]. Supranuclear gaze palsy can be seen in 1/3 of CBD patients; however, impairment of downward gaze is thought to be specific for PSP [12]. Nevertheless, our patient developed vertical gaze palsy including downward eye movements, postural instability and falls in the late stage of the disease. In contrast, asymmetric parkinsonian and cortical signs, without a history of falls at the first neurological visit in our patient, all pointed from the beginning to the diagnosis of CBD. Differential diagnosis of CBD also includes Alzheimer's disease

(AD) and frontotemporal dementia (FTD). Cases with clinical features of FTD, who were diagnosed pathologically as CBD, have been reported [16]. Dementia was observed in an early stage of disease in nine of thirteen pathologically proven CBD cases [9]. Patients with rapidly progressing dementia are usually diagnosed as AD, and those with severe speech impairment as FTD. Thus, we cannot exclude that patients meeting classic diagnostic criteria (i.e. without dementia) might be a minority of all CBD patients. Neuropsychological examination did not reveal dominant memory dysfunction, which characterizes AD and frontal lobe syndrome with behavioural disturbances typical for FTD.

The pathology of our case is that of typical corticobasal degeneration [2]. Gross findings consistent with CBD include asymmetric atrophy of temporo-parietal cortex, thinning of the corpus callosum, flattening of the head of the caudate, rust-like colour of the globus pallidus and depigmentation of SN. The histologic picture of our case included neuronal loss, superficial spongiosis and ballooned neurons, all characteristic features of CBD. The most diagnostic microscopic findings were widely diffused tau-positive neuronal and glial deposits, i.e. thread-like cell processes, pretangles, astrocytic plaques and oligodendroglial coiled bodies in the cortex, basal ganglia, thalamus and brainstem [2,3,6,20].

Neuropathologic differential diagnosis of CBD includes other sporadic tauopathies – PSP and Pick's disease. Gross midbrain atrophy is much more common in PSP than in CBD, with atrophy of the superior cerebellar peduncles being a useful biomarker of PSP [22]. The most distinctive microscopic feature of PSP is widespread neurofibrillary degeneration (globose NFT), and tufted astrocytes, as opposed to astrocytic plaques in CBD [20]. Structures more frequently and severely affected in PSP than in CBD include the subthalamic nucleus, red nucleus, midbrain tectum and dentate nucleus [2]. Pick's disease (PiD) is grossly characterized by a sharply circumscribed cortical atrophy. The peri-Rolandic sensorimotor cortex in PiD, unlike in CBD, is frequently spared [4]. Microscopically, there is severe neuronal loss, ballooned neurons and Pick bodies. Neuronal tau pathology is more pronounced than glial. In contrast to CBD, tau lesions in PiD are negative with Gallyas silver staining [17]. This can be explained by preferential affinity of Gallyas staining to four-repeat tau [23], which is a predominant tau isoform in CBD

[6], but not to three-repeat tau, characteristic for PiD. Neuropathologic differentiation of CBD from frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), which is an autosomal dominant hereditary tauopathy, is often impossible without family history and genetic studies [25].

In summary, we present the first pathologically proven Polish case of CBD and highlight the spectrum of clinicopathological observations. Hopefully, advances in ancillary diagnostic testing along with its greater availability, and founding the national brain bank will contribute to the further development of research studies on this rare neurodegenerative disorder in Poland.

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