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Corticonigral degeneration with neuronal achromasia and basal neurofibrillary tangles

W. Paulus[1] **and M. Selim**[2]

[1] Ludwig-Boltzmann-Institut für Klinische Neurobiologie, Wien, Austria
[2] Neurologisches Krankenhaus Marie-Theresien-Schloessel, Wien, Austria

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Summary. A man, aged 58 years, suffered from progressive dementia, parkinsonism, and gaze paralysis for 30 months. Autopsy revealed severe degeneration of the substantia nigra, numerous swollen chromatolytic neurons within the cerebral cortex, scattered basal neurofibrillary tangles, and gliosis of the cerebral white matter and basal ganglia. Unusual globular inclusions positive for tau protein were detected within neurons of the upper cortical layers. Although the pathological findings were comparable with corticonigral degeneration with neuronal achromasia, several clinical and pathological features characteristic for progressive supranuclear palsy, progressive subcortical gliosis, and Pick's disease in this and the nine previously reported cases hampered the unequivocal nosological placement.

Key words: Corticonigral degeneration with neuronal achromasia – Progressive supranuclear palsy – Progressive subcortical gliosis – Pick's disease – Parkinsonism

Corticodentatonigral degeneration with neuronal achromasia (CND) as a clinicopathological entity was described in three patients by Rebeiz et al. [30, 31]. Since that time, six additional patients were reported in detail [3, 14, 23], and three further patients were incompletely documented [8, 33, 37]. The clinical features are similar to progressive supranuclear palsy (PSP) and include late middle-age onset, parkinsonism, involuntary movements, parietal lobe signs, ataxia, brisk tendon reflexes, gaze paralysis, dementia, and a progressive fatal course of 4 to 8 years duration. The characteristic neuropathological findings are neuronal loss and numerous swollen chromatolytic neurons (SCN; Pick cells, ballooned cells) but no Pick bodies in the cerebral cortex; gliosis of the cerebral white matter; and neuronal loss, scattered SCN, and gliosis in various subcortical nuclei. The case reported here presented clinically as PSP. The neuropathological findings correspond to CND, but lesions characteristic for PSP, progressive subcortical gliosis (PSG) and Pick's disease (PD) were also found. Immunohistochemistry for tau protein revealed globular inclusions in small cortical neurons, which have not been described previously.

Offprint requests to: W. Paulus, Institute für Pathologie, Universität Würzburg, Josef-Schneider-Strasse 2, D-8700 Würzburg, Federal Republic of Germany

Case report

A tailor, aged 57 years, presented with a 2-year history of progressive forgetfulness, apathy, sexual recklessness, and episodic depression. He suffered from unsteady gait and backward falls. Neurological examination disclosed bradykinesia and rigidity of neck and extremities, but no tremor. Dystonia of facial muscles and paralysis of downward gaze were noted. Deep tendon reflexes were exaggerated on the left side, and a left Babinski sign was found. Mild truncal ataxia, reflex grasping and reflex sucking were present. Psychometric tests revealed marked dementia, but no aphasia or apraxia. CT and NMR scans showed moderate diffuse brain atrophy. Electroencephalography revealed bifrontal theta activity. A diagnosis of PSP was suspected. During the following weeks paralysis of horizontal gaze and bulbar dysphagia developed. The patient died from aspiration pneumonia after a 30-months course of illness.

Neuropathological findings

The formalin-fixed brain weighed 1200 g and appeared mildly atrophic with frontal accentuation. The ventricular system was slightly dilated.

For histological examination, paraffin sections were stained with H&E, Kluever-Barrera, cresyl violet, Bodian's stain and methenamine silver nitrate. Mild spongiosis was evident in the molecular layer of the cerebral cortex and focally in deeper cortical layers and the cerebral white matter. Marked bilateral symmetric gliosis was seen in the white matter and deep cortical layers at frontal and parietal but not occipital locations. In these areas, fibrillar and gemistocytic astrocytes were increased, fiber formation was common, and some astrocytic nuclei were enlarged and showed coarse chromatin. Mild neuronal loss was seen in the cerebral cortex. Several neurons of the frontal and parietal cortex showed eccentric

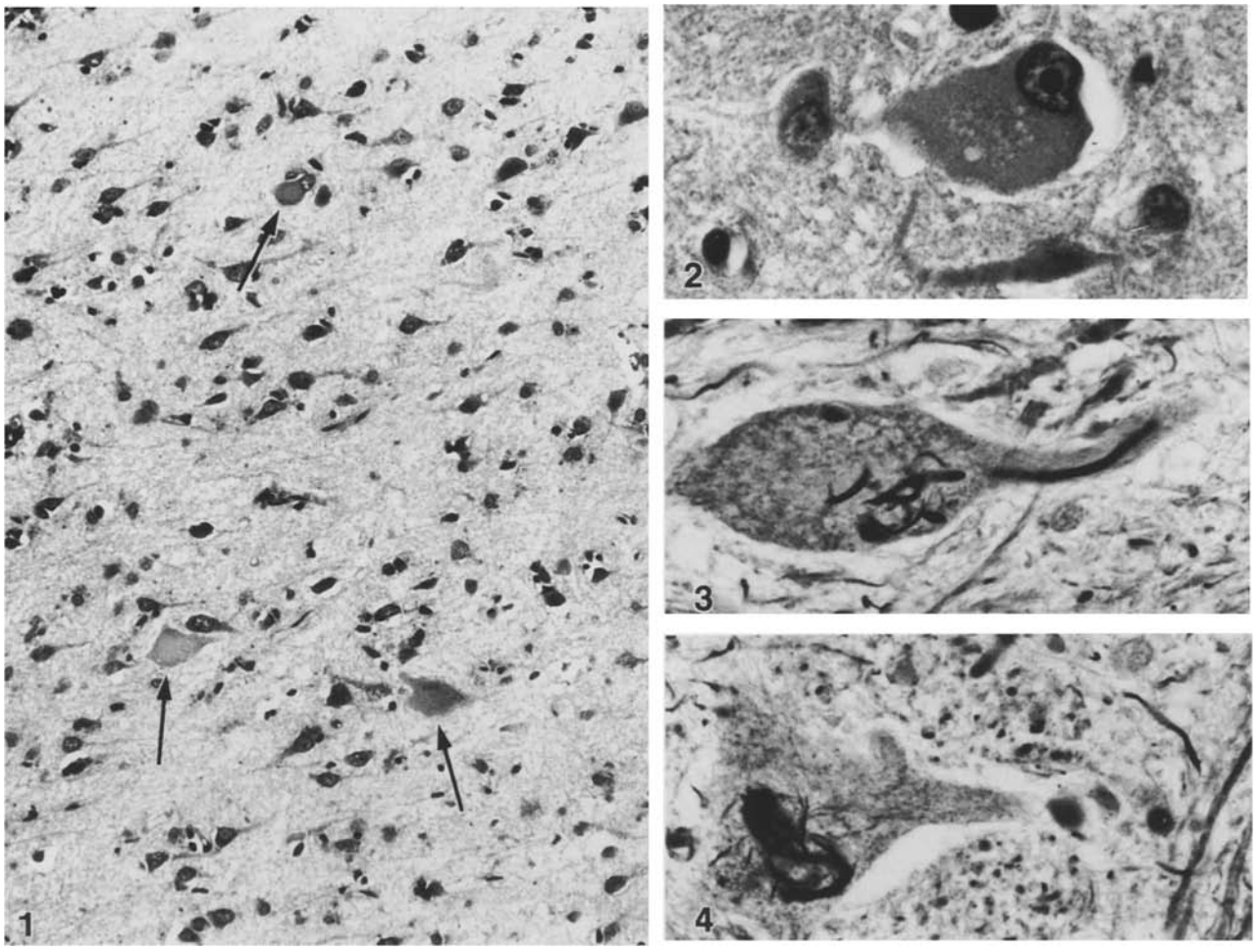

Fig. 1. Frontal cortex showing swollen chromatolytic neurons (*arrows*). Kluever-Barrera, ×170
Fig. 2. Swollen chromatolytic neuron with eccentric nucleus and cytoplasmic vacuolization. Frontal cortex; H&E, ×680
Fig. 3. Neurofibrillary tangle within perikaryon and proximal axon. Nucleus dorsalis raphe; Bodian, ×680
Fig. 4. Neurofibrillary tangle. Nucleus ambiguus; Bodian, ×680

displacement of the nucleus, and an enlarged chromatolytic pale cytoplasm negative with cresyl violet, PAS and Bodian (SCN, Figs. 1, 2); some of the SCN contained a few vacuoles, central lipofuscin or eosinophilic granules, but no Pick bodies or neurofibrillary tangles (NFT). In contrast to chromatolysis due to axonal injury no remnants of Nissl's substance were present at the periphery. Argyrophile plaques, Pick bodies, Lewy bodies and NFT were absent in both the cerebral cortex and hippocampus.

Marked gliosis was also seen in the anterior and medial thalamic nuclei, amygdala, globus pallidus, and moderately in the neostriatum. The myelinated fibers within the globus pallidus were reduced. NFT were observed in the nucleus basalis of Meynert (about 15% of neurons), dorsal raphe nucleus (about 9% of neurons), and in few neurons (less than 5%) of substantia nigra, pallidum, pontine and medullary tegmentum, and cranial nerve nuclei (Figs. 3, 4). Other neurons lacked NFT. Subcortical SCN were absent. Areas with NFT showed mild neuronal cell loss and fibrillar gliosis, but no gemistocytic astrocytes or abnormal nuclei. Subtotal cell loss, intense gliosis, and free melanin was observed in the substantia nigra (see Fig. 8). Here, one neuron in a total of three sections was found to contain a Lewy body. A few neurons of the locus ceruleus harbored Lewy bodies or hyaline inclusion bodies. In the substantia nigra numerous axonal spheroids were found (neuroaxonal dystrophy, see Fig. 8). The cerebellum including dentate nucleus appeared normal without evidence of grumose degeneration. Granulovacuolar degeneration was present in amygdaloid, but not in red nucleus or Ammon's horn neurons. Status cribrosus with perivascular lipophages was evident in the putamen; ischemic necroses were absent.

Table 1. Results of immunohistochemistry for neuronal cytoskeletal components in various pathological structures

	Cortical globules	Lewy bodies	Basal tangles	Achromatic neurons
PHF ubiquitin 5-25	–	(+)	–	–
PHF ubiquitin 3-39	–	(+)	–	–
Tau	+	–	+	(+)
PNF (SMI-31)	–	+	+	+
PNF (SMI-34)	–	+	(+)	+

PHF, Paired helical filament; PNF, phosphorylated neurofilament +, Marked immunostaining of most structures; (+), weak immunostaining or staining of only a few structures; –, absence of immunoreactivity

For immunohistochemistry monoclonal antibodies were used against paired helical filament ubiquitin (PHF 5-25 and 3-39), phosphorylated 150-kDa and 210-kDa neurofilament protein determinants (SMI-31 and SMI-34), and tau protein (Tau-1). Specificities, technical details, sources, and references for these antibodies are described elsewhere [2, 19]. Results are listed in Table 1. The

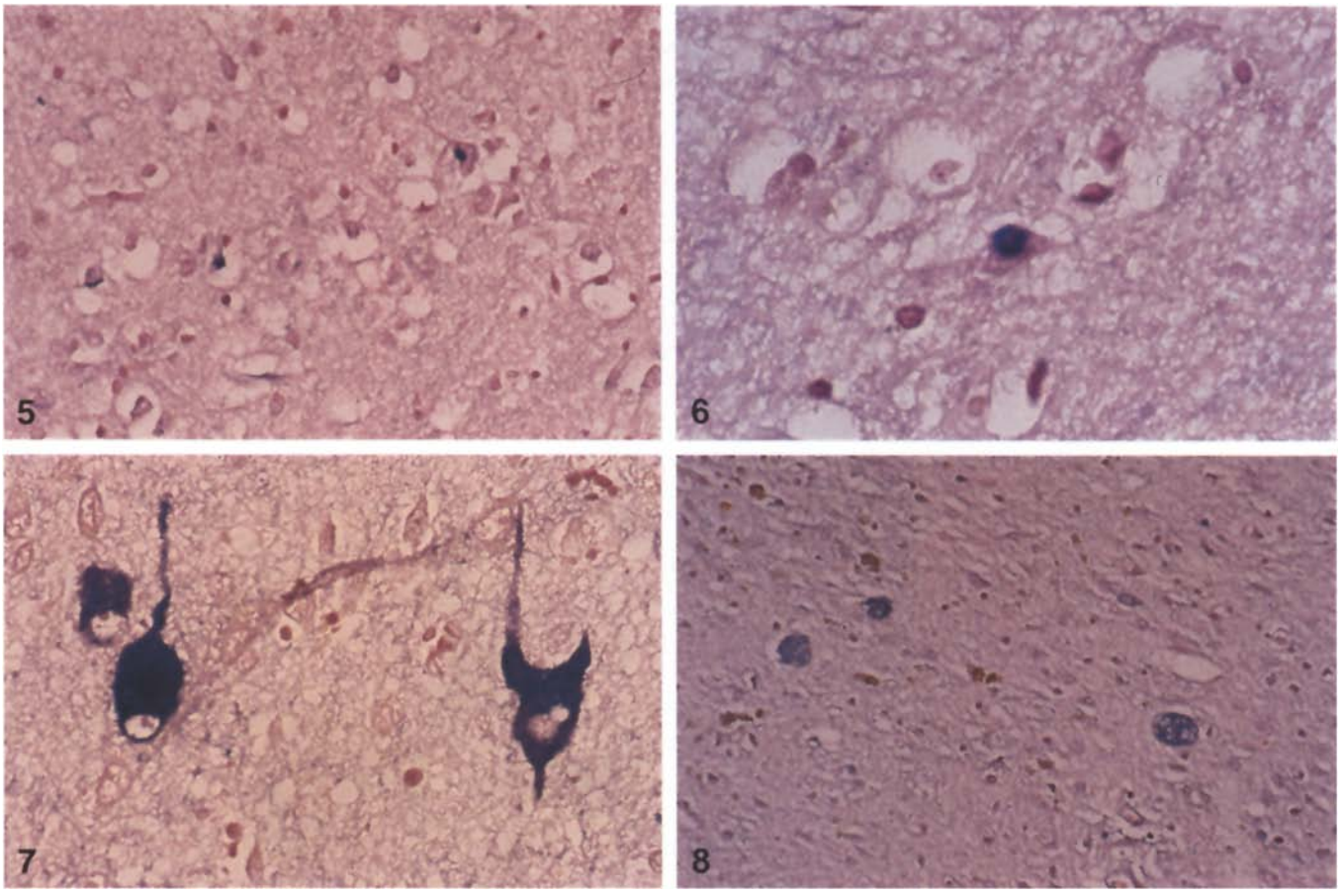

Fig. 5. Several globules within small cortical neurons. Frontal cortex; Tau-1 immunohistochemistry, ×200
Fig. 6. Globule within small neuron. Frontal cortex; Tau-1 immunohistochemistry, ×495
Fig. 7. Swollen chromatolytic neuron containing phosphorylated neurofilament epitopes. Frontal cortex; SMI-31 immunohistochemistry, ×495
Fig. 8. Substantia nigra showing subtotal neuronal loss, marked gliosis, and pigment incontinence. Axonal spheroids are ubiquitinated. PHF 3-39 immunohistochemistry, ×200

chromatolytic neurons contained phosphorylated neurofilament epitopes (Fig. 7). Basal NFT were labeled with tau and phosphorylated neurofilament antibodies, but not with the PHF ubiquitin antibodies. Small globular inclusions intensively positive for tau were found in numerous small neurons of the second and third cortical layer (Figs. 5, 6). They were not seen with any of the other routine or immunohistochemical stainings, and were negative also for chromogranin A. Cortical NFT were not detected. No senile plaques were elucidated. Spheroids within the substantia nigra reticulata contained PHF ubiquitin (Fig. 8).

Discussion

The case presented here is compatible with previous clinicopathological reports of CND (see Table 2). However, since neither clinical nor pathological features are entirely specific for CND and transitions to other entities are common, a spectrum of differential diagnostic possibilities must be considered.

Prominent clinical features of PSP include late middle-age onset, parkinsonism, severe gait difficulty, emotional incontinence, poor response to L-dopa, and a rapid course [17, 34], features that were all seen in the present case. In particular, marked dementia, pseudobulbar signs, and paralysis of downward gaze seen in our patient are more characteristic for PSP than for CND. In the basal ganglia, cerebellum and brain stem nuclei of PSP brains cell loss and NFT composed of 15-nm straight filaments are found [18]. However, the clinical picture of PSP may be associated with different pathological diagnoses, i.e., PSG [39], multi-infarct state due to amyloid angiopathy [10], or CND (as shown here). Furthermore, in the present case some histopathological features of PSP were seen, i.e., NFT in subcortical nuclei, which have been previously described in CND (case 3 in [31]). Gibb et al. [14] found inclusions in neurons of the substantia nigra ("corticobasal inclusions" according to their designation of CND as "corticobasal degeneration") reminiscent of NFT in PSP, but differing in their barely visible filamentous skeins. We were not able to detect light microscopic differences between the present CND NFT and usual PSP NFT. The CND NFT in our case were immunohistochemically more similar to PSP NFT than to Alzheimer's NFT with respect to their positivity for tau protein, but negativity with the anti-PHF ubiquitin monoclonals [1]. On the other hand,

Table 2. Clinicopathological summary of ten cases of corticonigral degeneration with neuronal achromasia

Author:	Rebeiz			MGH	Gibb			Lippa		This
Reference:	[31]			[3]	[14]			[23]		case
Case no.:	1	2	3		1	2	3	1	2	
Age at death	68	67	72	67	71	65	70	78	74	58
Duration of disease (years)	6	8	7	6	4	5	4	6	6	3
Sex	F	M	F	M	M	F	F	M	M	M
Parkinsonism	+	+	+	+	+	+	+	+	+	+
Pyramidal signs	−	+	+	+	−	+	+	+	?	+
Involuntary movements	+	+	+	−	+	+	+	+	?	+
Cerebellar symptoms	+	?	+	−	−	+	−	?	?	−
Gaze paralysis	−	+	+	−	+	+	+	?	?	+
Dementia	−	+	?	+	+	+	−	?	+	+
Asymmetric cerebral atrophy	+	+	−	+	+	−	−	+	−	−
Frontal cerebral atrophy	+	+	+	+	−	+	+	+	+	+
Parietal cerebral atrophy	+	+	−	−	+	+	−	−	−	−
Cortical SCN	+	+	+	+	+	+	+	+	+	+
Subcortical SCN	+	+	+	?	+	+	+	+	+	−
Cerebral spongiosis	?	?	?	+	?	?	?	−	−	+
White matter gliosis	+	+	?	+	+	+	?	+	−	+
Basal ganglia gliosis	+	+	+	+	+	+	?	?	?	+
Neocortical NFT	−	?	−	−	−	−	+	−	−	−
Basal NFT	*	*	+	?	*	*	*	−	−	+
Neuro-axonal dystrophy	?	?	?	?	?	?	?	?	?	+
Senile plaques	−	?	?	+	−	?	−	−	−	−
Degeneration of subst. nigra	+	+	+	+	+	+	+	+	+	+
Lewy bodies/pale inclusions	−	−	−	+	+	+	?	?	?	+
Cerebellar atrophy	−	−	−	−	−	−	−	?	?	−
Dentate atrophy	−	+	+	−	−	+	+	−	−	−

+, Presence; −, absence; ?, presence questionable or not stated; *, "corticobasal" inclusions were detected by Gibb et al. [14], which showed striking resemblance to neurofibrillary tangles
SCN, Swollen chromatolytic neurons; NFT, neurofibrillary tangles

histopathological findings more characteristic for PSP (but seen in just a fraction of PSP cases), i.e., granulovacuolar degeneration of red nucleus neurons or grumose degeneration of dentate nucleus, were absent in the present case. Gliosis, a feature usually seen in CND, has been described in PSP [5, 16]. While the striking feature differentiating CND and PSP are the achromatic neurons (SCN) in the cerebral cortex, brain stem SCN ("ballooned neurons") have been described in PSP [6, 12].

Diffuse Lewy body disease (DLBD) may also present with parkinsonism, gaze paralysis, and dementia, but shows widespread distribution of Lewy bodies, most commonly in cerebral cortex, diencephalon and substantia nigra [9, 20]. We found few Lewy bodies and hyaline inclusions only in the substantia nigra and locus ceruleus, but not enough to diagnose DLBD or Parkinson's disease. Lewy bodies within the substantia nigra have been reported as merely unspecific findings in parkinsonism other than Parkinson's disease, e.g., PSP [15, 26], as well as in brains from patients without parkinsonism in 3.8% in the sixth decade and in 12.8% in the ninth decade [13]. A few pale inclusions and/or Lewy bodies were also detected in some of the previously reported CND cases (see Table 2).

The histological pattern in the cerebral cortex of the present case corresponded to findings in PD. Absence of Pick bodies does not argue against PD since one third of PD cases lacks Pick bodies [7]. Furthermore, PD shows nigral degeneration [29, 35]. Two patients with cortical SCN but only slight nigral and hippocampal degeneration and absence of Pick bodies were classified as variants of PD [4], while PD and CND were differentiated on the basis of involvement of the hippocampus in PD and different involvement of the basal ganglia [14]. According to the latter criteria our case should be classified as CND instead of PD.

PSG, originally named PD Type II [27], presents as progressive dementia and shows subcortical gliosis of white matter, basal ganglia and inferior olivary nucleus as well as slight cortical spongiosis without NFT [28, 36], similar to the present case. A few chromatolytic neurons have been described in one study [28]. The predilection for frontal and temporal sites and age distribution is similar to CND and PD, but the clinical feature usually lacks parkinsonism and ophthalmoparesis [36], although a PSG case with supranuclear ophthalmoparesis (case 2 in [32]) and another with parkinsonism (case 2 in [25]) were recorded. Similar to two patients in the original report of Neumann and Cohn [28], our case presented with Pick-like dementia, which was possibly due to the frontal accentuation of the neuropathological abnormalities. It remains to be determined whether PSG represents a subgroup of CND without SCN and without involvement of the substantia nigra.

Phosphorylated neurofilament epitopes within SCN have been demonstrated in cases of CND [23], PD, Alzheimer's disease [8], motor neuron disease [22] and amyotrophic lateral sclerosis [24]. However, other cytoskeletal components have not been studied in CND so far. Using immunohistochemistry for the microtubule-associated protein tau, we detected small globules within several neurons of the upper cortical layers. These inclusions did not contain PHF ubiquitin and phosphorylated neurofilament epitopes, nor were they visible in routine stainings including Bodian's silver impregnation. The globules differed from Pick bodies and Lewy bodies in their staining characteristics and their localization: Pick bodies are larger argentophilic inclusions, which contain phosphorylated neurofilament epitopes, ubiquitin [11, 29], and chromogranin A [38]. Cortical Lewy bodies are visible in H&E-stained sections, are positive for ubiquitin, negative for tau and are preferentially located within deeper cortical layers [2, 19, 21]. To our knowledge, inclusions similar to the CND globules have not been described previously. It remains to be determined whether these inclusions are characteristic for CND.

In conclusion, there are numerous transitions between CND and PSP, PSG, and PD. Nevertheless, CND can be pathologically separated from these entities. Its exact nosological position must be unravelled by thorough clinicopathological analyses of many cases of CND, PSP, PSG, and PD.

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