

Congophilic Angiopathy with Cerebrospinal Symptoms

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Summary. A patient is reported who developed the first symptoms of spinal motor neuron affection 20 years prior to his death at the age of 79. In the course of the disease dementia and spasticity of the legs occurred. The patient died of metastasizing carcinoma of the colon. The autopsy revealed amyloid angiopathy of the brain and cervical spinal cord, corresponding to the clinical symptomatology. So far, 11 cases of amyloid angiopathy have been reported in which dementia was preceded by dysarthric speech, ataxia and/or spasticity of the legs. We assume that these cases represent a distinct nosological entity, different from a variant course of Alzheimer's disease. The atypical symptomatology may cause problems in the diagnosis of amyloid angiopathy of the CNS.

Key words: Amyloidosis – Cerebrovascular disorders – Dementia – Presenile – Paralysis – Alzheimer's disease – Spinal cord

Congophilic Angiopathy with Cerebrospinal Symptoms

The term “conophilic angiopathy”, or “cerebral amyloid angiopathy” (CAA) (Mandybur 1980; Okazaki et al. 1979) was introduced to describe deposits of amyloid in the walls of meningeal and cortical arteries with penetration into the surrounding parenchyma (Scholz 1938; Schlote 1965; Gerhard et al. 1972; Glenner 1978; Okazaki et al. 1979; Okoye and Watanabe 1982). Congophilic angiopathy is a common finding at autopsy in the brains of aged individuals (Wright et al. 1969; Jellinger 1977; Tomonaga 1981; Mountjoy et al. 1982); its frequency seems to increase with age (Tomonaga 1981). It is often associated with Alzheimer's disease or the senile dementia of Alzheimer type (SDAT) (Mandybur 1975; Glenner et al. 1981; Torack 1983). In the development of SDAT essential pathogenetic importance is attributed to conophilic angiopathy, both for a combined and isolated occurrence (Glenner et al. 1981; Torack 1983). Furthermore it is seen in causal connection with atraumatic, non-hypertensive cerebral haemorrhage (Torack 1975; Jellinger 1977; Ishii et al. 1984). On the other hand, asymptomatic cases are not rare (Wright et al. 1969; Ulrich et al. 1973; Jellinger 1977; Tomonaga 1981; Mountjoy et al. 1982).

The presence of amyloid in the microscopic structures associated with SDAT (senile plaques, Alzheimer's neurofibrillary tangles and the frequently associated but also isolated occurring amyloid angiopathy) was first demonstrated by

Divry (1927, 1934 and 1941). Regarding the vessel wall amyloidosis (*Gefäßwandamyloidose*), Scholz (1938) summarised his findings, i.e. the presence of Congo red staining and birefringence under polarised light giving material in the media and adventitia of cortical and meningeal arteries which shows frequent spreading into the surrounding parenchyma, under the term *drusige Entartung der Hirnarterien und Kapillaren*. Moral and Wildi (1952) introduced the term “dyschoric angiopathy”. Schlote (1965) used the term *drusige Entartung der Hirnarterien*, considering the fibrils radiating beyond the vessel wall to be a sign of penetration of conophilic substances into the tissue. The separation of a variant of the senile vessel wall disease without such signs by Pantelakis (1954) under the name of conophilic angiopathy was inappropriate in Schlote's opinion. At present, amyloid plaques in the vicinity of affected vessels are referred to as atypical plaques by most authors. Due to their morphological appearance and their mostly perivascular localisation, they are distinguished from typical senile plaques (Gerhard et al. 1972; Glenner et al. 1981; Okoye and Watanabe 1982; Griffith et al. 1982). The identity of extracellular fibrils of which both the amyloid of plaques and that of affected vessel walls is composed with those of extracerebral amyloidosis has been demonstrated by electron microscopy (Terry et al. 1964; Schlote 1965). In general, there is no association with other systemic or localized amyloidoses, apart from rare exceptions (e.g. Krüke 1950, 1963; Schwarz 1965). However, immunochemical and cytochemical studies have shown that in spite of the structural similarity, the main fibril protein occurring in cerebral amyloidosis can be differentiated from that of other primarily or secondarily generalised or localised amyloidoses (Torack and Lynch 1981; Powers et al. 1981, 1982; Linke 1982). Furthermore, the amyloid P component can be identified in affected vessels but not in Alzheimer's plaques (Westermarck et al. 1982). As to the pathogenesis of intracerebral amyloid, type and origin of its deposits have at present to be regarded as unknown. The hypotheses of a “leakage” in the blood-brain barrier with penetration of amyloid serum precursors into the vessel wall and the surrounding brain parenchyma (Torack and Lynch 1981; Glenner and Wong 1984), and of localised neuronal degeneration are discussed (Powers et al. 1982). Furthermore, the mutual relationship of different types of cerebral amyloid deposits cannot be clarified at the moment. In summary of the literature, the following statements can be made (cf. Griffith et al. 1982):

1. CAA is frequently, but not always associated with Alzheimer's disease.

2. It is a common finding in the brains of aged individuals; its frequency increases with age.
3. It is in general associated with perivascular amyloid deposits in the cerebral cortex.
4. There is no close relationship to hypertension, arteriosclerosis or generalised primary or secondary amyloidosis.
5. It is frequently the cause of atraumatic, non-hypertensive, intracerebral haemorrhage.
6. The intravital diagnosis is difficult because of the lack of typical symptoms.
7. The pathogenetic mechanism of amyloid deposits in vessel walls is still unknown.

Considering its frequent occurrence in elderly individuals, CAA rarely leads to severe, acute or progressive cerebral disorders with distinct neurological symptoms (Ulrich et al. 1973; Jellinger 1977; Tomonaga 1981; Mountjoy et al. 1982). However, there are exceptions to these general statements leading to the assumption of two distinguishable forms of the disease:

(a) Gudmundssen et al. (1972) reported on 8 patients belonging to four generations of an Icelandic family who suffered from severe, often lethal cerebral haemorrhage, occurring mostly in youth and middle age. In all cases amyloid deposits in cerebral and meningeal arteries were found. There was no generalised amyloidosis. None of the patients showed pathological-anatomical changes characteristic of Alzheimer's disease, i.e. senile plaques, and neurofibrillary tangles. Watten-dorf et al. (1982) reported on a Dutch family observed over two generations, where 11 members suffered from repeated intracerebral haemorrhages, haemorrhagic infarction or ischemic stroke between the ages of 44 and 58 years. Out of 6 autopsies, 5 cases showed morphological changes in the vessel wall as found in CAA. Clinically, dementia symptoms were described, but the morphological criteria of Alzheimer's disease were not fulfilled.

(b) There have been a few reports on another variant of the disease which seems to be of special interest in the present context. In these cases, CAA caused not only numerous vascular lesions – haemorrhages, infarctions, rarefactions – but also multilocular lesions of the parenchyma caused by excessive deposition of perivascular amyloid (atypical plaques). The first detailed case report (Worster-Drought et al. 1940, 1944) described the autopsy findings of 2 siblings. Over three generations, 10 members of this family suffered from progressive muscular weakness and dementia appearing in middle age. The neuropathological findings of these 2 siblings showed extensive vascular changes corresponding to CAA as well as numerous plaques, particularly in Ammon's horn and cerebellar cortex. Compared to the typical senile plaques restricted to Ammon's horn the plaques in the cerebellar cortex showed striking differences in shape and staining properties. In both cases, identical but less pronounced changes were found in the cervical region of the spinal cord. The authors named this syndrome "familial presenile dementia with spastic paralysis" and expressed the opinion that a distinct, so far undescribed disease leading to dementia was involved. In spite of distinct morphological differences, they assumed a relationship to Alzheimer's disease. Other authors who reported on clinically and neuropathologically similar cases (van Bogaert et al. 1940; Luers 1948; Corsellis and Brierley 1954; Neumann 1960; Gerhard et al. 1972; Griffith et al. 1982) expressed essential doubts as to this relationship, since the prevailing neuropathological findings always consisted of a florid CAA as well as of

the so called "atypical plaques". Although senile plaques characteristic of Alzheimer's disease and neurofibrillary tangles could be detected as well in most cases, their scarcity and localisation limited to certain brain regions were different from those found in Alzheimer's disease.

Our own observation of a case induced this report. Based on the clinical symptomatology and characteristic neuropathological findings, this disease can be allotted to CAA with cerebral and spinal symptoms as described under (b) in the previous paragraph. To our knowledge 11 cases of this type have been published to date.

Case Report

In 1963, at the age of 60, the patient who had no history of severe illness or familial occurrence of nervous system disease, first noticed a weakness of his hands. Neurological examination revealed weakness, atrophy and fasciculations of the hand muscles and exaggerated tendon reflexes especially on the right. The CSF showed a slight increase in protein (49.4 mg/100 ml). In the subsequent years, his gait deteriorated, necessitating the use of crutches in 1977 and a wheel chair since 1979. Myelography performed in December 1979 in order to exclude compression of the cervical cord showed normal findings. The CSF showed a pronounced increase in protein (160 mg/100 ml) and a normal cell count. Before and after a prostatectomy in 1980, the patient presented transient states of confusion. In September 1980, he was treated in our medical clinic because of acute-onset respiratory failure. At this time, atrophy and flaccid weakness of both arms, spastic paraplegia and loss of sensitivity to vibration in the lower limbs were found. Electromyography and electroneurography revealed severe neurogenic lesions in the hand muscles. The mental symptoms included desorientation, heavy impairment of memory and apathy. Dysphagia occurred for the first time in January 1983. On 24th January, 1983, the patient was admitted to the surgical clinic because of abdominal symptoms. Sonography of the epigastrium revealed a metastatic liver while the primary tumour remained unknown. The poor condition of the patient did not allow further diagnosis. On 26th January, 1983, the patient was transferred to our clinic. On neurological examination, dysarthria, dysphagia and slight bilateral hypoglossal paralysis were found. Compared with the previous examination, the flaccid paresis and atrophy of arm and hand muscles and the spastic paraplegia were markedly deteriorated. Due to the muscular weakness, disturbances of coordinative motor functions could not be safely examined. Proprioceptive sensation seemed to be absent in the legs and diminished in the arms. The patient was incontinent of faeces and urine, with deteriorated mental status. The EEG showed generalised theta activity. Serum levels of vitamin B₁₂, thyroid hormones, creatine phosphokinase and iron were normal. Cholinesterase (1050 units/l) was pathologically decreased, whereas lactate dehydrogenase (1300 units/l), carcinoembryonic antigen (275 ng/ml), the transaminases and bilirubin were increased. The clinical diagnosis was, besides abdominal malignancy, of a systemic degenerative CNS disease with spinocerebral, particularly cervical anterior horn affection. On 7th February, 1983, the patient died of bronchopneumonia. Autopsy revealed cancer of the sigmoid colon with widespread abdominal metastases and the following impressive findings in the brain and the spinal cord.

Morphological CNS Findings

Macroscopy. Brain reduced in size, weight 1170 g. Numerous, sunken cortical lesions up to 3 by 3 cm in size, especially in the right parietal and left temporal region. Multiple small lesions especially in the frontal lobes of cerebrum (Fig. 1). Asymmet-



Fig. 1. Localized infarction-like lesions in the right frontal lobe, close to the central gyrus (2-fold magnification)



Fig. 2. Numerous double-contoured abnormal blood vessels in the cortical lesion (140-fold magnification) (section of Fig. 1)

rical hydrocephalus ex vacuo with dilatation of the posterior horn of the right lateral ventricle. Asymmetrical atrophy of the spinal cord in the middle and lower cervical regions with dilatation of the central canal up to 3 mm.

Microscopy. Uniform changes were found in the cortical lesions. In some of them, nearly the whole molecular layer was involved with an additional haemorrhagic component but without histological signs of former bleeding. The leptomeninges showed an induration. Neurons were degenerated leaving small glia cell scars. The numerous vessels had a circular cross-section, their walls were penetrated by substances appearing yellow-brown with van Gieson stain. Using Congo red stain, these substances appeared bright red in colour (Fig. 2). Numerous vessels showed distinct double contours of the lumen. The substances deposited in the vessel walls and presented by staining, partly penetrated the surrounding parenchyma with radiating fibrils. This phenomenon was particularly seen using the Gomori silver stain (Fig. 3).

Amyloid plaque-like deposits were found mostly near the vessels. Very few plaques showed the typical structure of senile "Drusen" with amyloid nucleus of concentric layers surrounded by radiating fibrils. Poorly structured amyloid deposits were found mostly around blood vessels. The remaining brain tissue had preserved its structure and showed partial atrophy of neurons and axons. There were no neurofibrillary tangles even in the hippocampus. In the atrophic middle and lower cervical segments of the spinal cord the shape of the grey matter was well preserved. Anterior horn cells were partly atrophic and slightly reduced in number, the axon fascicles were rather thin. The central canal was of normal shape, slightly dilatated. In these sections of the cervical cord, vessels showed the same changes as in the brain with amyloid deposits in vessel walls, occasional penetration into the surrounding parenchyma and double contours of the vessel lumen (Fig. 4). The examined sections of the cerebellum did not reveal any specific changes.

Pathological-Anatomical Diagnosis. Amyloid angiopathy of the cerebrum and the middle and lower cervical cord with typical vessel wall changes and extravasal "atypical" plaques.

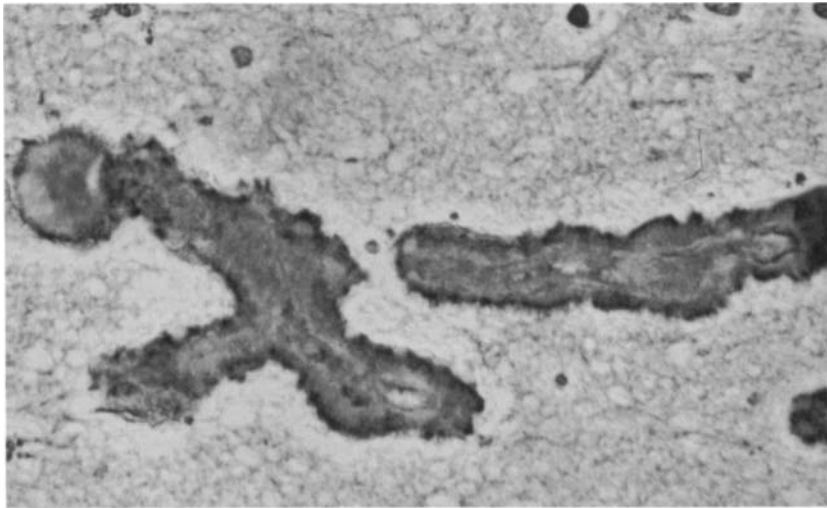


Fig. 3. *Drusige Entartung* of intracerebral small vessels (Gomori silver stain, 350-fold magnification)

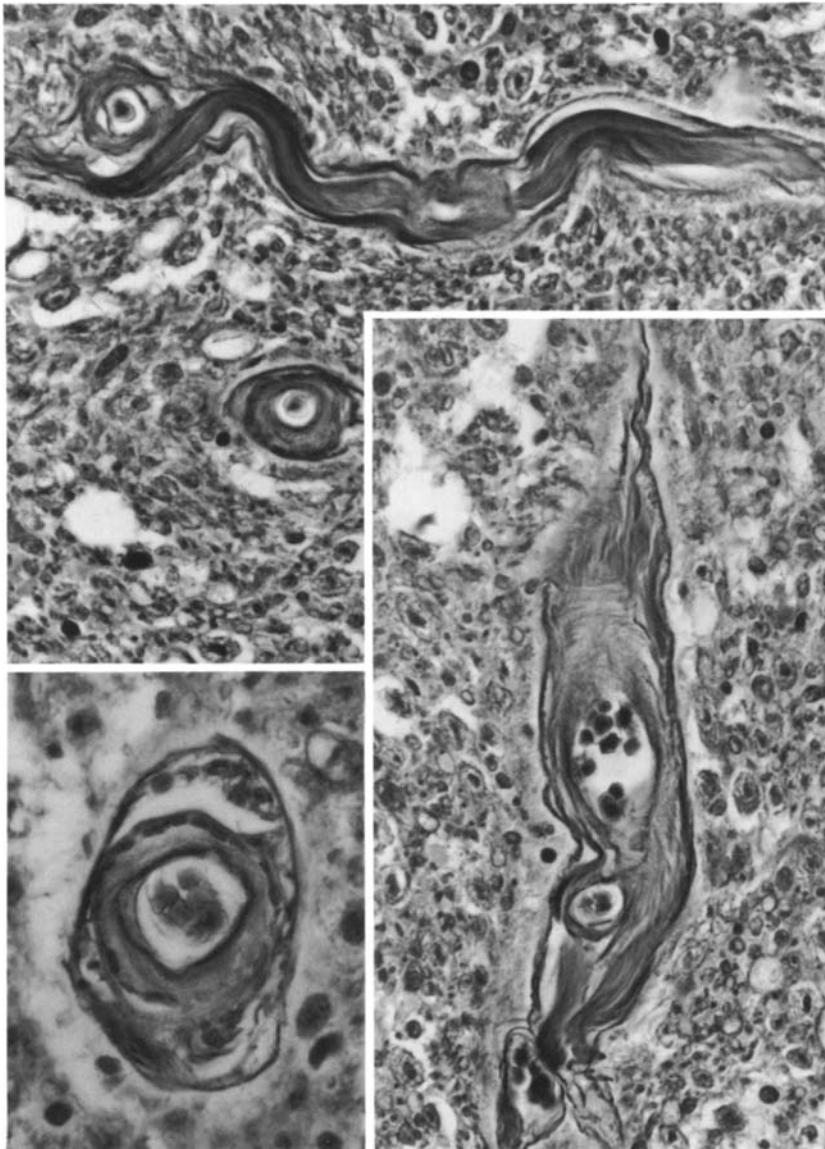


Fig. 4. Abnormally structured blood vessels in spinal cord with characteristic double contours in longitudinal and cross section (140-fold, *inset* 350- or 560-fold magnification)

Table 1. Findings in congophilic angiopathy with cerebrospinal symptoms (referring to Gerhard et al. (1972) and Griffith et al. (1982))

Author	Age at onset	Age at death	Sex	Clinical symptoms	Heredit-ity	Localisation	
						Cerebral	Spinal
van Bogaert et al.	25	39	M	Dysarthria, ataxia, spastic paraplegia, progressive dementia	+	+	
Worster-Drought et al. (1940)	47	54	M	Dysarthria, ataxia, spastic paraplegia, progressive dementia	+	+	+
Worster-Drought et al. (1944)	44	51	F	Dysarthria, ataxia, spastic paresis (arms), progressive dementia	+	+	+
Luers (1948) Case 1	26	41	M	Dysarthria, ataxia, spastic paraplegia, progressive dementia	+	+	
Luers (1948) Case 2	?	43	F	Ataxia, spastic paraplegia, progressive dementia	+	+	
Corsellis and Brierley (1954) Case 1	51	54	F	Epileptic seizures, spastic paresis, progressive dementia	+	+	
Corsellis and Brierley (1954) Case 2	56	66	F	Epileptic seizures, spastic quadriplegia, Progressive dementia	+	+	
Neumann (1960)	45	46	F	Epileptic seizures, ataxia, spastic hemiplegia	-	+	
Gerhard et al. (1972)	40	47	F	Dysarthria, ataxia, hypoglossal paralysis, facial palsy, progressive dementia	+	+	
Griffiths et al. (1982)	54	61	F	Dysarthria, ataxia, spastic paresis, distinct atrophy of hand muscles, progressive dementia	+	+	+
Griffiths et al. (1982)	50	61	M	Dysarthria, facial palsy, hypoglossal plegia, spastic, quadriplegia, progressive dementia	+	+	
Present case	60	79	M	Dysarthria, spastic paraplegia, flaccid arm paralysis, distinct atrophy of hand muscles, progressive dementia	∅	+	+

Typical senile plaques or "Drusen" occurred very rarely. Neurons and axons were changed partly due to senile atrophy and partly to secondary degeneration. Neurofibrillar tangles were not found. Abundant cortical lesions, up to 3 by 3 cm in size, with reactive leptomenigeal fibrosis were considered as a sequel of amyloid angiopathy, due to missing arteriosclerosis of intra- and extracerebral arteries. Reactive systemic (secondary) amyloidosis of other organs was not found.

Summarizing the clinical course and the morphological findings, the first symptoms of an anterior horn affection appeared in the patient at the age of 60. In the further course, spastic paraplegia and progressive dementia developed during the following 19 years. The diagnosis of amyloid angiopathy was made at autopsy, the neuropathological changes being found not only in the brain but also in the middle and lower regions of the cervical cord.

Discussion

To date 11 cases of amyloid angiopathy with cerebrospinal symptoms have been described in the literature. The neurological symptoms, particularly dysarthria, ataxia and spastic paraplegia, developed together with or in some cases preceded dementia (Worster-Drought et al. 1940; van Bogaert et al. 1940; Worster-Drought et al. 1944; Luers 1948 2 cases; Corsellis and Brierley 1954 2 cases; Neumann 1960; Gerhard et al. 1972; Griffith et al. 1982 2 cases, see Table 1). Our own case included, the common feature of all cases is a severe cere-

bral amyloid angiopathy with obligatory presence of atypical plaques with or without relationship to affected blood vessels. The most important clinical features of the disease are: heredity (9 cases), progressive dementia (11 cases), spastic paraplegia (11 cases), ataxia and dysarthria (9 cases). Apart from these symptoms in common, the findings vary from case to case so the assumption of a nosological entity may be doubtful. Though cerebral amyloid angiopathy and atypical plaques were found in all cases, the number and distribution of the lesions within the CNS (cerebellum, brain stem, cervical cord) were subject to considerable variation. The affection of the cervical cord has been described in 3 other patients (Worster-Drought et al. 1940, 1944; Griffith et al. 1982). In 4 cases, neurofibrillary tangles were found to an extent typical of Alzheimer's disease. In 3 other cases, the neurofibrillary tangles were restricted to Ammon's horn. These findings and the severity of dementia in most cases described induced their presumed allocation to Alzheimer's disease. This may have given birth to the terms "juvenile Alzheimer's disease" (van Bogaert et al. 1940; Luers 1948) and "atypical Alzheimer's disease" (Corsellis and Brierley 1954).

In accordance with the conclusions by Gerhard et al. (1972) and Griffith et al. (1982), we do not believe these terms to be appropriate. This opinion is based on the following considerations. As already mentioned, the pathological-anatomical features common to all cases are the distinct cerebral amyloid angiopathy and the obligatory presence of the so-called atypical plaques in varying extent and distribution within the CNS. Due to these changes, additional vascular lesions —

haemorrhages, infarctions and rarefactions – and secondary changes of the parenchyma by the excessive presence of “atypical plaques” resulted.

In previous cases, the clinical symptoms included mainly ataxia, dysarthria, spastic paraplegia and progressive dementia. However, the symptoms of dementia remained unimposing for a long time and neurological symptoms could not be sufficiently explained by a diffuse affection of the brain such as in Alzheimer's disease. The more localized than diffuse lesions and the affection of the cervical cord with corresponding symptoms especially in our case, are the particular features of the disease. Moreover, it frequently occurs at an age which can hardly be regarded as presenile.

These considerations and the complete absence of dementia in one case (Neumann 1960) and of neurofibrillary tangles in our own case and in the case described by Neumann (1960) led to the assumption that the above mentioned cases belong to an independent syndrome that can be distinguished from Alzheimer's disease (Griffith et al. 1982). This opinion is shared by Ulrich et al. (1973) who regarded congophilic angiopathy as a distinguishable disease. Because of its particular character, congophilic angiopathy may not be referred to as a variant of Alzheimer's disease.

Difficulties in differential diagnosis appeared in almost all cases due to the mostly atypical clinical symptoms. In the cases described by Worster-Drought et al. (1940, 1944) it was supposed that a familial type of Jacob-Creutzfeldt's disease could be involved. However, morphological findings ruled out this hypothesis. The cases described by Luers were supposed to suffer from multiple sclerosis. In other cases, disseminated degeneration, demyelinating disorders or motor neuron disease were included in differential diagnosis. With regard to unspecific prodromal signs such as slurred speech, unsteady gait, sensation of dizziness, hypercraesthesia and in some cases headache (Luer 1948; Corsellis and Brierley 1954; Gerhard et al. 1972), the onset of the disease was between 25 and 60 years of age and the duration varied between 1 and 19 years. Regarding our own case which appears to fit well into the series of published case reports because of its clinical symptoms, progression and pathological-anatomical findings it should be mentioned that sporadic cases obviously show a later onset than hereditary ones (Torack 1978). In our patient, who had no familial history, first symptoms appeared at the age of 60.

It should also be mentioned that in our case the autopsy finding of a metastasizing carcinoma of the colon may have led to the assumption of an association between the cerebrospinal symptoms and the tumour. It is known that paraneoplastic neuromyopathy and encephalopathy may precede other symptoms of a tumour by months, rarely by more than a year (Thomas et al. 1972; Reisner 1973; Niederle et al. 1982). Due to the long course of the disease (19 years) a paraneoplastic syndrome as an explanation of the neurological symptoms must be ruled out in our case. Very little doubt is left to the conclusion that tumour-independent congophilic angiopathy with affection of the cervical cord caused the corresponding clinical symptoms. Finally, the following conclusions with particular regard to clinical aspects can be drawn.

(1) Congophilic angiopathy with cerebrospinal symptoms is a rare, diagnostically difficult vascular disease of the brain and the spinal cord. The symptoms are much the same as in primarily degenerative or vascular encephalopathies with associated dementia. In addition, and frequently preceding the de-

mentia, severe cerebrospinal neurological symptoms and signs can be observed.

(2) In patients with unclarified cerebral and spinal disorders, especially if a coincidence of dysarthria, ataxia and spastic paraplegia with dementia is present, “congophilic angiopathy with cerebrospinal symptoms” has to be taken into differential diagnostic consideration.

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