

## Subacute diencephalic angioencephalopathy: an entity similar to angiodysgenetic necrotizing encephalopathy and Foix-Alajouanine disease

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**Summary.** A previously healthy 58-year-old man developed neurological illness with progressive dementia, hallucinations, central motor and vegetative impairment which led to death in 14 weeks. Autopsy revealed lesions in a symmetrical centrencephalic distribution. Inner cerebral veins and arteries were surrounded by extravasation of plasma and perivascular haemorrhage and were thickened by fibrous scarring and muscle fibre proliferation. Necrotized blood vessels were also found. The parenchyma was damaged by incomplete to complete necrosis. The age and sex of the patient, the progressive clinical course, the increase of cerebrospinal fluid protein, and the histopathology of the lesion show some similarities to angiodysgenetic necrotizing encephalopathy and spinal Foix-Alajouanine disease.

**Key words:** Angioencephalopathy – Centrencephalic lesion – Angiodysgenetic necrotizing encephalopathy – Foix-Alajouanine disease – Dementia

### Introduction

In 1974, DeGirolami et al. [1] first described subacute diencephalic angioencephalopathy (SDAE) in one case. Differential diagnoses included Creutzfeldt-Jakob disease, Wernicke's encephalopathy and the adult type of Leigh's disease [1]. The pathology consisted of a predominantly diencephalic symmetrical angiopathy and chronic incomplete to complete parenchymal necrosis. In a second case, the characteristic clinical presentation, increase of cerebrospinal fluid (CSF) protein with normal cell count, and predominantly diencephalic necrosis in local association with angiopathy were confirmed [4]. We present here a third case of SDAE and emphasize similarities to angiodysgenetic necrotizing encephalopathy (ANE) and spinal Foix-Alajouanine disease (FAD).

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### Case report

A 58-year-old man developed a relentlessly progressive neurological illness which led to death in 14 weeks.

About 2 months prior to admission, the patient experienced a progressive impairment of short memory, difficulty in calculating, a progressive gait disturbance with small steps, and intermittent disorientation in time and space. Four weeks after onset, excessive dreaming and impaired sleep were noted. A positive snout reflex, slowing of speech, slight rigidity and a propulsive gait disturbance were also found at admission. During the further, continuously progressive, course of illness, optic and acoustic hallucinations, excessive sweating and arterial hypotension occurred. Finally the patient was immobile with rapidly progressing symmetrical spasticity. He lost consciousness 1 week before death. Brain scintigraphy and carotid angiography soon after the onset of clinical signs and symptoms were unremarkable. Six weeks before death, CT showed symmetrical hypodense changes in the basal ganglia without increase of volume or contrast enhancement. CSF 5 weeks and 2 weeks before death had normal cell counts, with protein content increased from 46 mg/100 ml to 75 mg/100 ml. EEG showed alpha-beta-theta activities over both hemispheres without paroxysms. Serum investigations including electrophoresis and tests for neurotropic viruses and *Treponema pallidum* were unremarkable. The patient died from pneumonia.

At autopsy, pulmonary abscesses in both sides and pulmonary oedema were found. The right cardiac ventricle was dilated. Renal angiosclerosis and moderate general arteriosclerosis were also found.

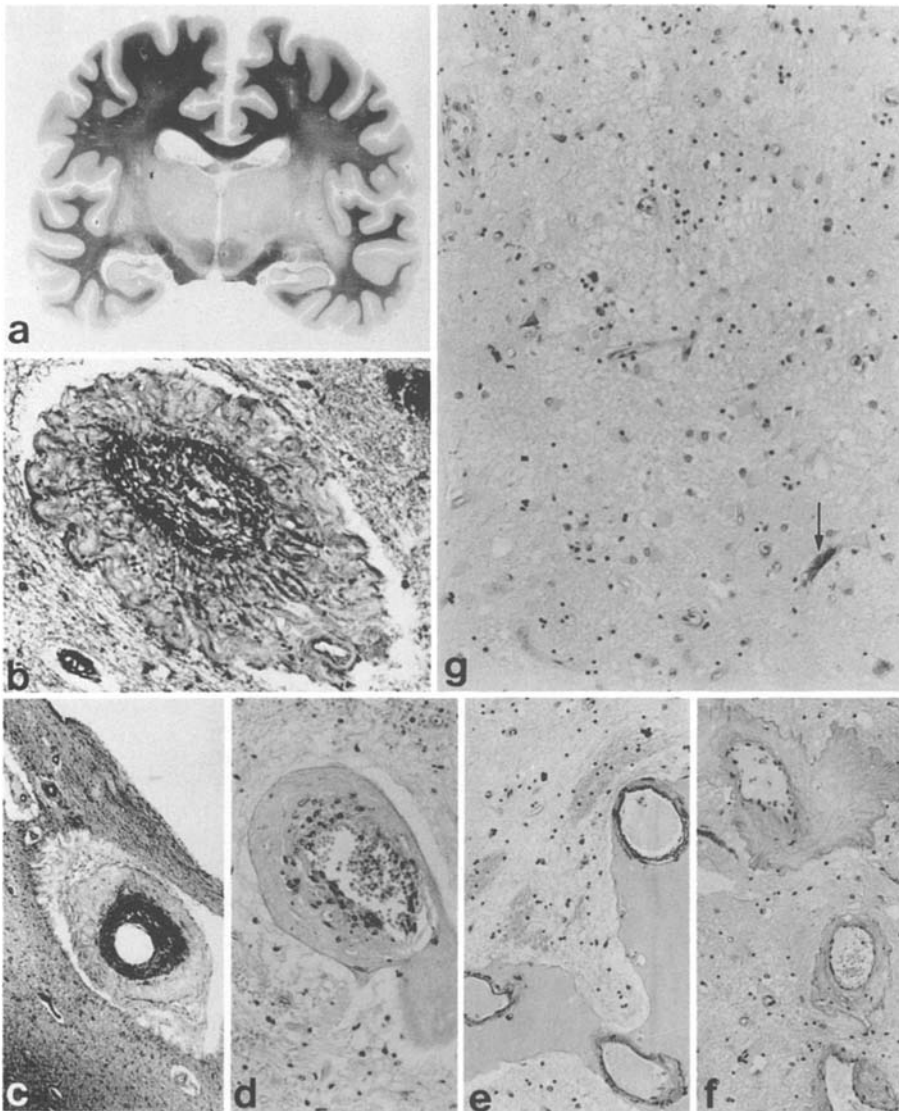
### Neuropathology

#### Macroscopical investigation

The outer surface of the brain was unremarkable. Brain weight after formalin fixation was 1380 g. Coronal sections showed symmetrical brownish softening of the striatum and the thalamus with a recent haemorrhage 2 cm in diameter in the left ventral thalamus.

#### Histopathology

Nearly symmetrical vascular and parenchymal changes were found in the diencephalon and telencephalon (Fig. 1a).



**Fig. 1.** **a** Symmetrical pallor due to many complete and incomplete infarcts in the thalamus, the subthalamus, the fornix and the pars reticulata of the capsula interna. Luxol fast blue.  $\times 0.2$ . **b** Ruff-like adventitial fibrosis and concentric occlusion of a large intraparenchymal vein. Van Gieson  $\times 128$ . **c** Fibroblastic proliferation in the adventitia and intima and muscle fibre proliferation in the media. Periventricular subependymal veins of the thalamo-striata system. Van Gieson  $\times 62$ . **d** Fibrinoid vessel wall necrosis. H & E,  $\times 128$ . **e** Extensive perivenous plasma extravasates. H & E,  $\times 128$ . **f** Ruff-like adventitial fibrosis on small veins. Van Gieson elastin,  $\times 128$ . **g** Fibrin thrombotic occlusion of capillaries (arrow), loss of neurons, astrogliosis, spongy change and attenuation of the neuropil. H & E,  $\times 128$

**Vascular lesions.** The main inner cerebral veins and their large tributaries showed prominent fibroblastic thickening of the intima and adventitia and proliferation of smooth muscle fibres with segmental narrowing or even occlusion of the lumen (Fig. 1b, c). Large intraparenchymal vessels showed necrosis of the wall (Fig. 1d), ectatic widening and recent haemorrhage or thrombotic occlusion. Medium-sized and small intraparenchymal vessels were surrounded by vasogenic oedema (Fig. 1e), or marked thickening of the wall due to fibroblastic proliferation in the adventitia (Fig. 1f), and hyalinosis of the media was found. In centrencephalic capillaries hyperaemia and fibrinoid occlusion (Fig. 1g), often associated with perivascular haemorrhage, were seen.

**Parenchymal lesions.** The striatum, thalamus, caudal hypothalamus and adjacent subthalamus and focal anterior parts of the hippocampus showed incomplete parenchymal necrosis with loss of neurons, astrogliosis and spongy changes (Fig. 1g), or small areas of complete necrosis. These changes were widespread and symmetri-

cal (Fig. 1a). The deep cerebral white matter, particularly the internal capsule, and the fornix showed marked myelin pallor (Fig. 1a) due to confluent oedema and focal complete necrosis.

## Discussion

To our knowledge, this is only the third report on SDAE. Progressive intellectual, behavioural, motor and vegetative impairment in previously healthy male individuals in the fifth to seventh decade, an increase of CSF protein, reflecting blood-brain barrier impairment, and the site of a distinct assembly of vascular and parenchymal, predominantly diencephalic, neuropathology characterize SDAE [1, 4]. Our case shows all these findings, thus supporting the notion that SDAE is a definite clinicopathological entity.

The vascular and parenchymal pathology can explain the continuous progression of the clinical syndrome. Arteries and veins [1, 4] show prominent increase of fibro-

blasts and collagen fibres and proliferation of endothelial cells. The media is often replaced by collagenous connective tissue or shows segmental destruction with homogeneous or fibrillar eosinophilic material [1]. Features reminiscent of hypertensive vascular disease in veins [1] might be the consequence of increased blood pressure common to pathological arteriovenous anastomoses. Some occasional white blood cells are found in the adventitia [1, 4] or in the whole vessel wall [1], but true inflammation is absent. Perivascular haemorrhages are present. All these findings are seen in our case in addition to definite vessel wall necrosis. However, blood vessels with changes of hypertensive angiopathy could not be identified in veins or arteries owing to the advanced pathology. Parenchymal incomplete or complete necrosis [1, 4], is compatible with effects of a primary vascular impairment [4].

A classification of the angiopathy in both previous reports on SDAE, as well as in our case, according to hitherto delineated morphological entities is not possible.

However, the age and sex of patients, a progressive clinical course, the increase in CSF protein in the absence of pleocytosis and particularly the neuropathological changes are similar to spinal FAD [2, 3, 6, 7]. In contrast to FAD, SDAE lacks clear angiodysgenetic (malformative) features.

In 1988, Schmitt et al. [5] described ANE as a symmetrical meningocerebral angiomatous lesion with arteriovenous shunt formation and progressive parenchymal necrosis. ANE may occur as familial or sporadic, as congenital (CANE), infantile (IANE), juvenile (JANE) or adult (AANE) variants and exhibits widespread progressive hypoxic damage in the grey and white matter with or without calcification. Epilepsy and progressive mental deterioration are present in the longer-living patients. The different onset and courses of ANE depend on a varying degree and severity of the diffuse angiomatosis. Owing to its morphological and clinical features ANE should be distinguished from definite phacomatoses like Sturge Weber syndrome which, in contrast, exhibits

facial involvement in the angiomatosis, and a unilateral and circumscribed localization in the parieto-occipital region, while more formal similarities were found to exist between ANE and spinal FAD [5]. SDAE is similar to ANE and FAD with respect to symmetrical non-inflammatory vascular lesions morphologically consistent with arteriovenous shunts and progressive parenchymal necroses. It is different from ANE and FAD with regard to lack of involvement of meningeal blood vessels, and to the non-angiomatous character of the lesion.

Progressive parenchymal ischaemic and exudative changes, regardless of the cause, reflect a stereotyped response of CNS tissue, either of the brain or of the spinal cord [3], to various conditions that promote local pathological arteriovenous blood flow either in phacomatoses like Sturge Weber syndrome, or in angiodysgenetic lesions akin to phacomatoses like FAD and ANE, or in non-angiodysgenetic arteriovenous shunt formation in SDAE.

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