Diffuse degeneration of cerebral white matter resembling so-called Binswanger’s disease and symmetrical necrosis of the globus pallidus associated with acute porphyria and cerebral atherosclerosis

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SYNOPSIS A 59-year-old woman admitted to hospital in coma also showed generalized muscular rigidity and porphyria. After two days she became fully conscious but the muscular rigidity increased and persisted until death occurred 12 weeks later. The brain showed diffuse degeneration of the white matter; symmetrical necrosis of the globus pallidus was associated with severe localized atherosclerosis. The lesions probably resulted from the combined effects of porphyria and atherosclerosis. It is suggested that in later life unusual cerebral lesions may occur with porphyria because of associated atherosclerosis. The porphyria may be overlooked clinically.

CASE REPORT

A spinster of 59 who had previously been in good health complained of feeling drowsy one evening and was found unconscious in bed the next morning. She was admitted to hospital in coma with striking rigidity affecting the muscles of the neck, both arms, and both legs. Deep reflexes were increased. Plantar reflexes were extensor. Blood pressure was 125/80 mm. Hg. Lumbar puncture showed clear fluid under normal pressure containing less than 2 cells per ml. and protein 30 mg./100 ml. The urine was very dark, containing large quantities of porphobilinogen and porphyrins when examined by the methods described by Whittaker and Whitehead (1956). Liver function tests were normal. Barbiturates were not detected in the blood. The blood urea level was 66 mg./100 ml. The Wassermann reaction was negative.

During the next two days the patient became fully conscious but the rigidity in her arms became even more marked and it was impossible to straighten them at the elbow joints. Rigidity also developed in the facial muscles and tube feeding was necessary. An electroencephalogram showed generalized irregular slow waves completely replacing any basic rhythmic activity. A muscle biopsy (taken from the right deltoid by Dr. A. L. Woolf) showed definite, though slight, involvement of the lower motor neurone.

The patient remained in this curious state of rigidity and akinesia, but eventually developed a urinary tract infection and bedsores and she died from bronchopneumonia 12 weeks after the onset of the illness. During the whole period she passed porphobilinogen in the urine but the amount became substantially less after the first four weeks. Her mind remained clear, she was able to speak, and she gave no history of any previous illness or family history suggestive of acute porphyria.

NECROPSY FINDINGS

Coronal sections of the brain after fixation showed slight symmetrical dilatation of the lateral ventricles, and small areas of necrosis in the medial parts of both pallida, which on the right side also involved the adjacent part of the internal capsule. There was mild atheroma of the basal arteries.

The spinal cord and the peripheral nerves and muscles showed nothing of note. The lungs showed patchy bronchopneumonia. No other relevant abnormalities were seen.

HISTOLOGY

CENTRAL NERVOUS SYSTEM Sections from blocks doubly embedded in celluloid-paraffin wax and also
frozen sections were examined with routine general and neurohistological stains.

Throughout the white matter of both cerebral hemispheres myelin stains show numerous ill-defined, pale areas of degeneration, which vary in size from 0.5 to 10 mm. in cross section, and in many places coalesce to involve much larger areas (Fig. 1). In a few of the smaller areas there is complete demyelinination, although variable numbers of swollen and fragmented myelin sheaths are usually seen, especially at the periphery of the lesions. The myelin of the optic nerves, cerebellum, pons, medulla, and spinal cord appears normal. A consistent feature is an irregular, narrow band of normally stained myelin immediately beneath the cerebral cortex (Figs. 1 and 2). Higher magnification of the white matter between the degenerated areas shows swelling and beading of the myelin sheaths but no definite reduction in their number.

In frozen sections the areas of degeneration contain abundant, rounded, granular masses of lipid material which is sudanophilic and Marchi positive (Fig. 2) and P.A.S., negative. Some of these lipid masses represent bloated microglial phagocytes although many appear to be extracellular. The majority are unstained in embedded sections and appear as clear spaces, sometimes related to a small round or elongated nucleus (Fig. 3). There is diffuse stippling with free-lying sudanophilic particles, both in the degenerated areas and in the intervening white matter, where occasional rounded lipophages are also noted. Short lengths of beaded, myelinated fibres, which are sudanophilic and Marchi positive, are seen in the areas of degeneration, where there is also swelling, fragmentation, and reduction in the number of axons. The axonal degeneration is quantitatively less severe than the myelin degeneration.

There is astrocytic hypertrophy throughout the white matter, especially within or adjacent to the degenerating zones (Fig. 3). Glial fibres are scanty except in the small foci of complete demyelination and giant multinucleated astrocytes are not seen. The oligodendrocytes show cytoplasmic swelling and are reduced in number; in some areas of degeneration they have completely disappeared. There are no inclusion bodies. The perivascular spaces are frequently dilated and contain eosinophilic fluid and variable numbers of lymphocytes and phagocytes.

In the grey matter of the hemispheres there is chromatolysis of occasional nerve cells in the pyramidal layers of the cerebral cortex and hippocampus, and in the cranial nerve nuclei. Other nerve cells appear shrunken and chromophilic but vacuolation is not seen. In the cerebral cortex small groups of neurones in the middle layers stain poorly, and in the inner layer there is patchy loss of nerve cells, perineuronal...
show fibrous thickening which is not exceptional for
the age of the patient. There is adventitial and medial
fibrosis of the small arteries traversing the subarachnoid
space. The main arteries of the circle of Willis show
similar fibrosis, together with mild non-
occlusive intimal atheroma and thickening of their
internal elastic lamellae.

Peripheral nerves were not available for histological
examination. Bronchopneumonia was confirmed. In
the muscles and other organs there were no relevant
changes.

**DISCUSSION**

Degeneration of the subcortical white matter
associated with symmetrical pallidal necrosis has
very occasionally followed on a period of coma
resulting from anoxia due to inhalation of coal gas,
carbon monoxide, nitrous oxide, or other noxious
gases (Courville, 1957; Denny-Brown, 1962; Plum,
Posner, and Hain, 1962). This mechanism did not
account for the onset of coma in the present case,
neither was there evidence of anoxia during the
period of coma.

Although demyelination of the peripheral nerves is
a well-known complication of acute porphyria, cere-
bral demyelination has been described in only a few
cases and has then been focal in type and usually
perivascular in distribution (Baker and Watson,
1945; Denny-Brown and Sciarra, 1945; Abbott and
Evans, 1946; Gibson and Goldberg, 1956). Accord-
ing to Goldberg (1959) the most frequent age of onset
of acute porphyria in women is in the third decade
and in his series of 50 cases in only five (four women
and one man) did it first occur over the age of 40 years.
Because of this early age incidence it is unlikely that
cerebral atherosclerosis was a significant factor in the
pathogenesis of the cerebral lesions hitherto recorded
in this condition. In the present case of late onset,
however, it is likely that the widespread degeneration
of cerebral white matter resulted from the combined
effects of cerebral atherosclerosis and porphyria.

We were unable to find any precipitating factor for
the attack of porphyria or any incident in the past
medical history indicating a previous attack. As the
patient recovered consciousness while still excreting
large amounts of porphobilinogen, and as this only
lessened after about four weeks, the initial coma
cannot be entirely attributed to the porphyria. We
have not found a previous record of a similar clinical
picture in porphyria; the nearest example is case 3 of
Schwarz and Moulton (1954), in which there was
tonic contraction of shoulder, facial, and thigh
adductor muscles. The absence of mental changes
throughout our patient’s illness was a surprising
feature in view of the considerable interruption of

**FIG. 3.** Occipital region. Clear spaces containing granular
material indicate sites of lipid masses. Astrocytic hyper-
trophy. Phosphotungstic acid-haematoxylin. × 620.

satellitosis, and astrocytic hypertrophy. Both thalami
show similar but more extensive neuronal degenera-
tion, maximal in the lateral nuclei. Many neurones
throughout the brain contain an excess of lipofuscin
pigment. In the cerebellum random Purkinje cells
and nerve cells in the dentate nuclei show either
chromatolysis or atrophy and homogeneous staining,
together with related astrocytic hypertrophy. The
anterior horn cells in the spinal cord showed central
chromatolysis.

Both pallida show clearly defined areas of necrosis
involving their dorso-medial segments and the adja-
cent margins of the internal capsules. On both sides
the lesions are bordered by a thin zone of hyper-
trophied astrocytes, amongst which there is a mesh-
work of glial fibres. Within the lesions are irregular
masses and strands of necrotic debris, separating and
also infiltrated by foamy and granular phagocytes.
Small arteries traversing the necrotic areas show
perivascular fibrosis, pronounced medial fibrosis,
calcification and siderosis, and fibro-fatty intimal
proliferation resulting in narrowing and in places
obliteration of their lumina. There is evidence of
recanalization in several occluded vessels. Elsewhere
in the lentiform nuclei the small arteries show much
less severe degeneration and their perivascular spaces
are dilated. Within the rest of the brain the arterioles

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*References cited in the text are not included in this snippet.*
cortical association and projection systems. Strich (1956) described spastic quadriaparesis in patients showing diffuse cerebral demyelination after head injury but severe dementia was also present. Rigidity is a frequent finding with symmetrical pallidal necrosis due to asphyxic anoxia (Denny-Brown, 1962).

Focal necrotic cerebral lesions have been found before with porphyria and attributed to vasospasm (Hierons, 1957), and Denny-Brown and Sciarr (1945) held that the clinical manifestations might result from vasoconstriction during phases of hypertension. Degeneration of the white matter resembling that found in our case has not previously been reported with porphyria. Similar degeneration occurs in the condition commonly known as Binswanger’s disease, attributed to Binswanger (1894), and subsequently discussed by Alzheimer (1905), Farnell and Globus (1932), Davison (1942), Neumann (1947), and Olszewski (1962); the cause has been held to be ‘arteriosclerosis’ of the deep penetrating arteries supplying the white matter. The differential histological diagnosis includes diffuse sclerosis (Schilder’s disease) and the recently described progressive multifocal leucoencephalopathy which is most commonly associated with malignant reticulosises (Richardson, 1961). In the case of Binswanger’s disease reported by Farnell and Globus (1932) there was widespread muscular rigidity similar to that shown by our patient. Wertham and Wertham (1934) and Neumann (1947) suggested that the lesions of Binswanger’s disease would be found more often if ‘arteriosclerosis’ alone was the cause. Our findings support the view that encephalopathy of the Binswanger type can result from many causes, including cerebral atherosclerosis, which may act alone or in various combinations. Olszewski (1962) suggested that obscure examples of subcortical demyelination which are not clearly related to ‘arteriosclerosis’ should not be associated with the name of Binswanger, and our case falls into this category.

From the practical point of view this case is instructive because it indicates that in later life cerebral lesions complicating porphyria may be unusual in type due to associated atherosclerosis. The porphyria in such a case may not be noticed clinically.

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REFERENCES


