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Uncommon Extensive Juxtacortical Necrosis of the Brain

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Summary. A previously healthy woman in middle age, vacationing in Spain, is treated with a massive dose of insulin for minimal hyperglycemia following an apparent gastrointestinal disease. This results in rapid coma and, 20 days later, in death. At autopsy, the main finding consists in a remarkable and uncommon ribbon-like juxtacortical necrosis of the white matter in both hemispheres of the telencephalon. There is also a microscopic focal necrosis in the pons cerebri. The grey matter of cortex and basal nuclei, and the subcortical arcuate fibers are spared. The detailed autopsy fails to reveal other essential changes. We have not been able to find reports on an identical case. Hypoglycemic coma usually causes cerebral lesions different from those seen in the present case. A brief analysis of the differential diagnosis is made. In the absence of unequivocal signs of infection, vascular disease or degenerative marks, the findings are tentatively related to complex interactions between fluid loss, hypoglycemic coma, hypoxia and other metabolic disturbances.

Key words: Brain-necrosis – Juxtacortical – Coma – Brain death – Hyperinsulinism – Dehydration – Acidosis – Adult female

Presentation of Case

A 48-year-old Caucasian woman was spending her summer holidays in Spain. With the exception of slight arterial hypotension, there were no prior illnesses or medical treatments. She was well until she suffered from nausea, repeated vomiting and diarrhea after a party. Two days later she was admitted in a private hospital. The information about her stay, however, is very fragmentary. On the day of admission, the patient was weak, but able to walk, slightly apathetic and fully conscious. The blood glucose was reportedly 208 mg/dl (11.6 mmol/l). Potassium and sodium levels in the serum were elevated, and the blood pH 7.14. The white-cell count in the blood was 14,000. An infusion was given and 235 units of insulin were administered within 4 h. This led to a deep coma. Four hours later the patient was transferred to a district hospital. The comatose woman did not respond to painful stimuli. There were no signs indicating a focal neurologic process. The body temperature was 34° C, the blood glucose 40 mg/dl

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(2.22 mmol/l), the serum potassium 2.3 mval/l (=mmol/l). The arterial blood-gas analysis revealed hypoxemia and considerable metabolic acidosis. The cerebrospinal fluid was normal. Electroencephalographic findings were compatible with metabolic brain damage. An X-ray film of the chest showed parahilar infiltrations. A diagnosis of bronchopneumonia was made, and a treatment with penicillin, gentamycin and clindamycin was instituted. A tracheal intubation was performed with subsequent assisted ventilation. Diuresis was normal. The respiratory and metabolic problems mentioned above were resolved within half a day following admission to the district hospital. Two days later, the patient was flown back to Switzerland and hospitalized at the Kantonsspital Luzern. She was still comatose, with a spontaneous respiratory frequence of 28/min., a blood pressure of 150/90 mm Hg (20/6.7 kPa), and a regular pulse of 96/min. Painful stimuli elicited scant, aimless movements of the spastic extremities. Ciliar, corneal and deep tendon reflexes were normal. The pupils were equal and reactive. The ophthalmoscopic findings were normal. Later Babinski's sign developed bilaterally. The cerebrospinal fluid was clear, with 1 mononuclear cell/µl, 41 mg/dl protein, 123 mval/l chlorides, and 70 mg/dl (3.89 mmol/l) glucose. The pressure was 120 mm water (1.18 kPa). Queckenstedt's sign was positive. Electroencephalographic examination disclosed marked general alterations particularly of the anterior region, compatible with generalized hypoxic brain damage. The hemoglobin was 12.4 g/dl (7.69 mmol/l), the white blood cell count 11,200/µl. The blood electrolytes, the blood glucose and the results of urinanalysis were normal, as was the electrocardiogram. Pneumonic signs were no longer detectable. Anticoagulants were given by gastric tube. The tracheal tube was removed 5 days after transfer. The patient died 13 days later without having regained consciousness.

Anatomical Findings

Leptomeningeal and cerebral blood vessels are acutely congested. The brain is voluminous and heavy (1,467 g) with flattened gyri and partial herniation

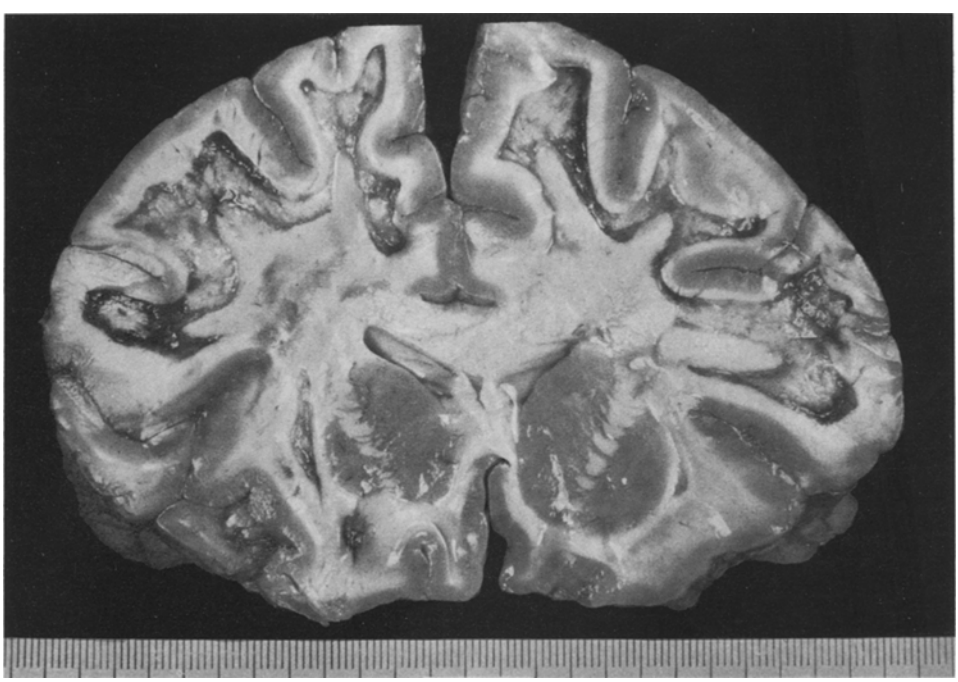

Fig. 1. Frontal section of the brain at the plane of the anterior portion of the septum pellucidum, metric scale (one division 1 mm). The ribbon-like zone of subcortical necrosis is sharply demarcated. There is focal hemorrhage in the marginal area. Cortex and basal ganglia appear normal

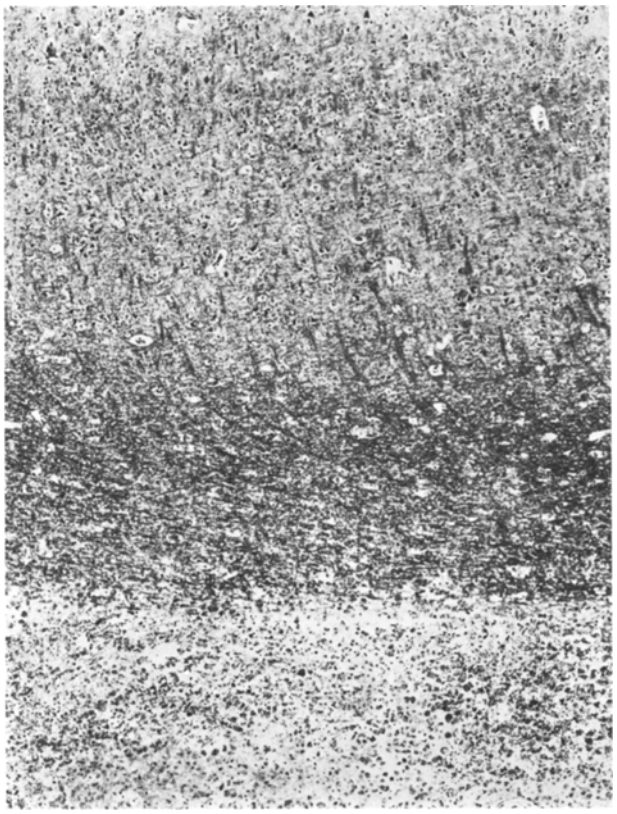

Fig. 2. Survey of the cortico-medullary junction in the telencephalic occipital lobe. There is an organizing necrotic zone at the bottom. In the center, the darker subcortical area appears well preserved, as does the cortex on the top (Klüver, original magnification × 25)

of the cerebellar tonsils. There is an extensive and continuous juxtacortical necrosis of the white matter in the centrum semi-ovale of the telencephalon, also involving deeper layers (Figs. 1, 2 and 3). In the vicinity of the slightly liquefied necrotic areas, there are small hemorrhages and signs of organisation with numerous lipid-laden macrophages (Figs. 1 and 3). Cortical gray matter and subcortical arcuate fibers are spared (Fig. 2); neocortex, the Sommer sector of Ammon's horn, basal ganglia, and cerebellar cortex appear normal; there is minor and probably artificial neuronal shrinkage in the telencephalic cortex. Further, there is a microscopic focal necrosis in the pons cerebri. Vascular occlusion, necrotizing vasculitis, perivascular leukocytic infiltrates or cuffs, microglial nodules, intranuclear or intracytoplasmic inclusions, and concentric demyelination cannot be detected.

A complete and detailed autopsy fails to disclose other essential changes. There are minor bronchopneumonic residues in the right upper lobe, and occlusion of rare small pulmonar arteries with fresh thrombotic material. The cardiovascular system is normal, with the exception of a slight endocardial fibrosis of the left atrium and the aortic cusps. Atherosclerosis is

Fig. 3. Organizing juxtacortical necrosis with numerous lipid-laden macrophages and focal hemorrhage (hematoxylin and eosin, original magnification × 100)

minimal. The thyroid is small (11 g), with several calcified nodules measuring up to 8 mm. The liver displays a slight diffuse fatty change with small droplets, and the proximal convoluted tubules of the kidney are vacuolated. Pituitary, adrenals and pancreas are normal.

Discussion

A previously healthy woman in middle age, vacationing in Spain, is treated with a massive dose of insulin for an apparently minor illness accompanied by a minimal hyperglycemia. This results in rapid coma and, 20 days later, in death. At autopsy, the main remarkable finding consists in an uncommon juxtacortical necrosis of the white telencephalic matter. We have not been able to find an identical case in the literature, nor were distinguished neuropathologists to whom slides of the gross findings and histologic sections were submitted (see acknowledgements). The history points to an insulin overdose as prime pathogenetic factor. Hypoglycemic coma, however, usually causes quite specific cerebral lesions in man and in experimental animals, which differ from those seen in the present case [Escourolle and Poirier 1978; Greenfield 1976; Finley 1941; Hicks 1950; Hoff et al. 1945; Baker 1939; Liebaldt and Schleip 1977; Grünthal 1941; Krämer and Ostertag 1971; Vital et al. 1967; Lawrence 1942]. The lesions of hypoglycemia are comparable to those seen in cerebral anoxia: the involvement is primarily cortical, with necrosis of cortical layers or even the whole cortical ribbon

[Escourolle and Poirier 1978]; Ammon's horn – particularly the Sommer sector – displays neuronal loss, as do the caudate nucleus and putamen. An unusual marked medullary demyelination of both hemispheres with sparing of cortex and adjacent white matter has been reported in a 38-year-old man following 65 treatments with insulin, a total of 71 hours spent in hypoglycemic coma, and 43 electroconvulsions administered within 6 years [Pentschew 1958].

History and structural findings of our case are not suggestive of a cardiac arrest encephalopathy [Amann et al. 1971; Janzer and Friede 1980], nor of subcortical arteriosclerotic encephalopathy [Rosenberg et al. 1979; Escourolle and Poirier 1978]. The arteries of the patient were virtually normal, and there were no indications of arterial hypertension.

There have been few reports on advanced necrosis of the brain, presumably related to edema and/or to vascular factors [Jakob 1931; Beckmann 1947; Orthner 1953]. The changes, however, were not comparable to those described in the present study: The necrosis comprised not only the white matter, but also cortex and corpus callosum [Jakob 1931]; the deep white matter necrosis, attributed to edema ("Oedemnekrose"), involved the centrum semi-ovale of one hemisphere only in a 29-year-old man suffering from glomerulonephritis [Beckmann 1947]. Necrosis of the white matter of both telencephalic and cerebellar hemispheres of a 53-year-old man poisoned by methanol was also imputed to edema [Orthner 1953].

Symmetric bilateral demyelinative lesions – but not necrosis – have been found in the lateral hemispheres of rats following a rapid rise in serum sodium, with anoxia and ischemia as possible contributors [Kleinschmidt-de Masters and Norenberg 1981]. Vasogenic brain edema, seen after osmotic stress [Neuwelt et al. 1980], may also cause demyelination [Greenfield 1976]. Necrosis of the white matter could be a consequence of interactions between cerebral edema and moderate hypoxia above all in the deep, less well vascularated layers [Feigin et al. 1973].

The present history is not suggestive of fat embolism. The latter tends to result in more focal damage of the brain, and to involve the white matter, possibly also deeper cortical layers [Greenfield 1976]. The few reports on air embolism in patients who did not die within minutes stress cortical lesions, whereas the white matter remains unchanged [Greenfield 1976].

Progressive demyelination which spares the cortical fibers has been observed mainly in the telencephalon following exposure to toxic doses of carbon monoxide, cyanides or ether [Hicks 1950; Hurst 1942]. However, the juxtacortical zone was clearly necrotic in our case; further, history and symptoms lend no support to this etiology. The rare encephalopathy of Marchiafava-Bignami has been observed only in severe chronic alcoholism of long duration [Lechevalier et al. 1977; Escourolle and Poirier 1978].

The possibility of cerebral lesions related to viral disease should also be considered, such as the acute hemorrhagic leukoencephalitis [Hurst 1941; Crawford 1954; Greenfield 1976]. However, necrosis of blood vessels was not seen in the present case nor was there perivascular cell accumulation. The cerebrospinal fluid of our patient did not display elevated numbers

of polymorphonuclear neutrophilic granulocytes, nor elevated protein levels. Thus, major criteria are not fulfilled for this diagnosis.

Diseases of the white matter with genetic character and inflammatory features usually occur in age groups different from that of our patient, and run a more protracted and continuous course [Escourolle and Poirier 1978].

The pathogenesis of the lesions mentioned in this report is obscure. Similar, although less pronounced changes have been reported in patients suffering from an acute illness or intoxication with rapid progression to coma, and with a concomitant, rapid deterioration of homeostatic mechanisms. In the absence of unequivocal infections, cardiovascular disturbances or degenerative processes, it seems reasonable to relate the present unusual morphologic findings to complex interactions between circulatory and metabolic events, such as arterial hypotension, hypoxia, hypoglycemia, electrolyte imbalance and cerebral edema [Burger and Vogel 1977; de Reuck and van der Eecken 1978; Ginsberg et al. 1976].

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