Importance of cardiomyopathy and cerebral ischaemia in the diagnosis of fatal coma in pregnancy

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SYNOPSIS A case of cardiomyopathy of pregnancy where death was due to profound cerebral ischaemia is reported. Two other similar cases are mentioned. Awareness of this syndrome may help the pathologist to establish the cause of coma and death in pregnancy when clinical studies have failed to indicate the cause. It is suggested that electrocardiography should be carried out in all cases of apparent cerebrovascular accidents that occur during pregnancy or the puerperium as there may be an underlying cardiomyopathy. The nature and the possible aetiology of cardiomyopathy of pregnancy are briefly discussed.

Sudden coma and death in pregnancy is fortunately rare, and when it occurs the clinician and pathologist may be faced with a difficult diagnostic problem. A known cause of sudden death is cardiomyopathy and, as no fatal case of cardiomyopathy of pregnancy has been described in the United Kingdom, we report the following case in which death was due to cerebral ischaemia.

MATERIALS AND METHODS

Numerous blocks from the viscera were embedded in paraffin wax and sections were stained by haemalum and eosin. The myocardium was also stained by haemalum and van Gieson's fluid, by the periodic-acid-Schiff method before and after treatment with diastase, by Masson's trichrome method, and by the acid-fuchsin method of Bajusz (1963) which demonstrates selectively 'pre-necrotic' changes in myocardial fibres (Poley, Fobes, and Hall, 1964; Connor, 1964). Frozen sections were stained for fat with Sudan III and IV. The brain and spinal cord were fixed intact for three weeks in 10% neutral formal saline. After transecting the mid-brain, the cerebral hemispheres were cut into coronal slices 1 cm. thick. Large blocks of frontal, parietal, temporal (two levels from each hemisphere) and occipital lobes, cerebellum, brain-stem, and spinal cord were embedded in nitro-cellulose. Sections were stained by Nissl's method using cresyl violet, Woelke's modification of Heidenhain's method for myelin, phosphotungstic acid haematoxylin (Lieb's), and Holzer's method for glial fibrils.

CASE REPORT

A woman (J.B., K137/62), aged 27, with four living children was well until the 20th week of her fifth preg-

Received for publication 1 November 1965.

nancy when she began to experience abdominal pain and a day later she was found unconscious in the bath. On admission to hospital she was still unconscious and was cyanosed. She vomited and was doubly incontinent. Her temperature was 96°F., blood pressure 140/65 mm. Hg. and pulse rate 120 per minute. Physical examination revealed some crepitations in the lungs but there were no other signs of heart disease. The pupils were normal and there was no papilloedema. There was a right hemiparesis involving face, arm, and leg, all tendon reflexes were brisk, there was bilateral ankle clonus, and both plantar responses were extensor. The uterus was enlarged to size consistent with a 20-week pregnancy.

The next day coma was deeper, the pupils were dilated and the eyes deviated to the right. She was transferred to the Regional Neurosurgical Unit at Killearn Hospital where the neurological state was found to be essentially unchanged. Lumbar puncture produced clear, colourless cerebrospinal fluid under a pressure of 65 mm./cerebrospinal fluid containing 264 mg. protein per 100 ml. and 103 mg. sugar per 100 ml.; the cell count was normal. Serum electrolytes were normal. The haemoglobin was 12.1 g. per 100 ml. (83%) and the white blood count was 10,600 per c. mm. Electrocardiographic and neuroradiological studies were not carried out.

Throughout the entire illness the patient's pulse remained above 130 per minute and on two occasions reached 164 per minute. The blood pressure was recorded frequently but was never below a normal level. There was no improvement in the conscious state, and the patient died on the seventh day of her illness.

NECROPSY There was a slight excess of serous fluid in the pericardial sac but careful examination of the heart (340 g.) revealed no macroscopic abnormalities in the pericardium, myocardium, endocardium, or valves. No mural thrombus was found. The coronary arteries were widely patent. Examination of the lungs showed an early

FIG. 1. There is a wedge-shaped focally haemorrhagic infarct in the left middle front gyrus, i.e., in the boundary zone between the anterior and middle cerebral arterial territories. $\times \frac{1}{2}$.

bronchopneumonia. The uterus contained a normal male foetus of a size consistent with a 20-week pregnancy. There were no abnormalities in the alimentary, urinary, endocrine, or reticulo-endothelial systems.

The brain weighed 1,270 g. The surfaces of the cerebral hemispheres were of normal appearance but the posterior two-thirds of the left middle frontal gyrus was soft. At the base and in the Sylvian fissures, the arteries were normal, and there was no evidence of a tentorial or of a tonsillar hernia. Coronal sections through the cerebral hemispheres showed symmetrical ventricles of normal size. In the left superior and middle frontal gyri posteriorly

FIG. 2. Myocardium: there are multiple areas of muscle fibre loss. Masson trichrome $\times 44$.

there was a well-defined, wedge-shaped infarct (Fig. 1) involving the cortex and white matter with a maximum depth of 6 cm. The central part of the infarct was soft and haemorrhagic. A smaller similar infarct was seen in the lateral part of the right occipital lobe. In the cerebellum there was haemorrhagic infarction of the tips of the folia at the dorsal angle of the right hemisphere. The brain-stem and spinal cord appeared normal.

HISTOLOGY In the myocardium there were multiple foci of muscle fibre loss in which the outlines of some fibres could still be seen (Fig. 2). Many of the latter were represented by large spaces surrounded by a sarcolemmal sheath and other less severely affected fibres had coarsely vacuolated cytoplasm (Fig. 3). At the edges of the lesions

FIG. 3. Myocardium: at the edge of this lesion there are vacuolated muscle fibres. 'Empty' sarcolemmal sheaths are clearly seen at the foot of the picture. There are no inflammatory cells. Masson trichrome $\times 525$.

the muscle fibres were shredded and vacuolated. The muscle nuclei round the damaged areas tended to be large and vesicular but some were hyperchromatic. Perinuclear vacuolation was clearly seen in some fibres. None of the abnormal fibres contained fat or glycogen but collections of granular material in the lesions and in adjacent abnormal and apparently normal fibres gave a positive staining reaction with the periodic-acid-Schiff and acid-fuchsin methods (Fig. 4). Within the abnormal areas there was no increase of collagen and there were no lymphocytes, plasma cells, or polymorphonuclear leucocytes. Nuclei were more numerous than in normal myocardium and while some of these were apparently derived

from muscle fibres, many were histiocytic. The small vessels in the myocardium were normal.

The only other significant abnormality was broncho-pneumonia.

Central nervous system Alterations in the cerebral hemispheres were much more widespread and severe than naked-eye examination had suggested. In addition to the large softenings observed in the left frontal and right occipital lobes, well-defined areas of ischaemic necrosis were seen in the cortex and white matter in the inferior temporal gyri, in the left occipital lobe laterally, and in the right middle frontal gyrus (Fig. 5). In these lesions neuronal destruction was complete and there were marked reactive changes in astrocytes and microglia. In

FIG. 4. Myocardium: normal muscle fibres are seen at the foot of the picture. At the edge of the lesion, a recognizable fibre is deeply fuchsinophilic, and scattered throughout the abnormal area there are collections of fuchsinophilic material. Acid-fuchsin $\times 525$.

the basal ganglia abnormalities were restricted to slight patchy neuronal necrosis in the anterior parts of the caudate nuclei. There were no severe abnormalities in the Ammon's horns.

The principal abnormality in the cerebellum was the haemorrhagic softening referred to above in the posterior part of the right hemisphere but there was a similar smaller, non-haemorrhagic softening in a corresponding position in the left hemisphere (Fig. 6).

The brain-stem was normal. In the spinal cord there were small discrete foci of necrosis in the white matter in the lower thoracic region.

FIG. 5. Right frontal cortex: there are numerous sharply defined foci of necrosis and reactive proliferation of glial cells and capillaries in the cortex and adjacent white matter. Nissl $\times 4$.

FIG. 6. Left cerebellar hemisphere: the vascular and microglial proliferation can be seen clearly in the molecular layer and in the white matter at the sites of infarction. Nissl $\times 4$.

DISCUSSION

The histological appearances of the myocardium in this case were those of cardiomyopathy of pregnancy (Gouley, McMillan, and Bellet, 1937). As the association between cardiomyopathy of pregnancy and fatal coma has not been reported previously from the United Kingdom, we believe that other cases have escaped recognition because of lack of awareness of the condition and consequent incomplete study of the cases. This possibility is illustrated by our experience with two other recently encountered cases which were essentially similar although in neither has it been possible fully to substantiate the diagnosis because of incomplete examination.

The patients were young women, aged 35 and 21 respectively, who were found unconscious in the second trimester of pregnancy. In the heart of the

first case there was an area of pallor surrounded by a zone of discoloration in the interventricular septum but the myocardium was not studied histologically. The brain even after three weeks' fixation showed only ill-defined areas of pallor in the caudate nuclei and cortical ribbon which would certainly not have been noticed had the brain been cut in the unfixed state. A detailed neuropathological study of this brain showed severe and widespread ischaemic damage in the cortex, basal ganglia, and cerebellum (Figs. 7 and 8). The lesions were of the type and in the distribution seen after an episode of severe hypotension (Brierley and Cooper, 1962; Adams, Brierley, Connor, and Treip, 1966). In the second patient, who was admitted to hospital with focal neurological signs and marked tachycardia, there was clinical and necropsy evidence of acute heart failure and myocardial degeneration. The necropsy was carried out at another hospital on behalf of the

FIG. 7. Right temporal cortex: severe neuronal necrosis affecting the full thickness of the cortex in the depths of the sulcus. Nissl $\times 4$.

FIG. 8. Cerebellum: there is almost complete loss of Purkinje cells and the increased cellularity of the molecular layer is due to microglial proliferation. Nissl $\times 44$.

procurator fiscal and the brain was cut in the fresh state. No abnormalities were found in it or in the one small block of cortex examined histologically.

Our experience of the naked-eye appearances of the heart and brain in these two cases and of the heart of the case reported in detail indicate the difficulties that may be encountered in establishing the diagnosis of cardiomyopathy of pregnancy as a cause of cerebral ischaemia.

The term 'cardiomyopathy of pregnancy' implies only the existence of heart disease in pregnancy in the absence of any known cause. This name and the probably synonymous titles 'puerperal' and 'post-partal cardiomyopathy' have been used by writers who thought that there was an aetiological relationship to these states (Meadows, 1957), but, while Reid (1961) has never seen the disease in nulliparous females, he has seen a clinically indistinguishable condition in older males. There are about 140 clinical descriptions in the literature (Gouley *et al.*, 1937; Hull and Hafkesbring, 1937; von Bonsdorff, 1939; Meadows, 1957; Brigden, 1957; Rosen, 1959; Reid, 1961; Becker and Taube, 1962; Gilchrist, 1963). Seventeen of these are from the United Kingdom (Brigden, 1957; Rosen, 1959; Gilchrist, 1963). Other cases of similar nature are almost certainly reported under other names (Szekely and Snaith, 1947; Tweed, 1960). Of the 21 necropsy cases reported none is from Great Britain.

The pathological use of the term 'cardiomyopathy' should be restricted to cases with muscle fibre damage and little or no inflammatory reaction. Such lesions, described as 'focal myocytolysis'¹ by Schlesinger and Reiner (1955) and reported by Gouley *et al.* (1937), Meadows (1957), and Becker and Taube (1962) in cases of pregnancy cardiomyopathy, were seen in the present case. Barclay (1961) described similar lesions in the myocardium of patients with ischaemic heart disease or left ventricular hypertrophy. He was of the opinion that these lesions represented an intermediate stage between acute hypoxic myocardial degeneration and actual myocardial infarction, and that the absence of inflammatory exudate was possibly due to the small size of the lesions and their slow evolution.

Similar histological features are seen in alcoholic cardiomyopathy (Brigden, 1957) and in the cardiomyopathy associated with toxoplasmosis (Paulley, Jones, Green, and Kane, 1956). Toxoplasma organisms were sought unsuccessfully in our three cases and none of the patients was alcoholic.

The cause of cardiomyopathy of pregnancy is unknown. Meadows (1957) thought that anoxia caused the lesions and Barclay's work (1961) supports this contention. 'Intermittent or chronic

spasm of the coronary arteries' was thought to be an aetiological factor by Becker and Taube (1962). Whatever the immediate cause, we feel that the experimental work of Bajusz (1963) is possibly of aetiological significance. This author produced focal myocardial degeneration by 'conditioning' rats with steroids and subjecting them to stress or the administration of vasopressin. The lesions illustrated are identical with those seen in the present case, and as the serum levels of both cortisol (Doe, Zinneman, Flink, and Ulstrom, 1960) and vasopressin (Paterson, 1958) may be increased in pregnant women, there could exist during pregnancy a pharmacological state similar to that which existed in Bajusz' experimental animals.

The cerebral pathology was clearly that of widespread and severe ischaemic damage. There were large wedge-shaped zones of necrosis involving cortex and white matter in the boundary zones ('watersheds') between the main arterial territories in the cerebral and cerebellar hemispheres. There were also small discrete foci of neuronal necrosis in the cerebral cortex and in the caudate nuclei. It has been firmly established that the decreased cerebral blood flow consequent on an episode of severe hypotension can cause widespread neuronal necrosis in the brain (Brierley and Cooper, 1962) and that, if the hypotensive episode is particularly severe but transient, cerebral abnormalities are most severe in the 'watershed' territories (Zülch and Behrend, 1964; Adams, 1964, 1965; Romanul and Abramowicz, 1964; Adams *et al.*, 1966). In the absence of evidence of occlusive arterial disease or of embolism it would appear that the cerebral pathology must be attributed to a transient reduction in cerebral blood flow below the critical level required to maintain an adequate supply of oxygen to the brain. Although the blood pressure was normal by the time the patient was admitted to hospital, we believe that there was a period of profound hypotension due either to heart block or cardiac arrhythmia, both of which are common in cardiomyopathy.

Cardiomyopathy of pregnancy is apparently not often associated with acute cerebral damage (Becker and Taube (1962) could find only two recorded cases), but there have been no detailed neuropathological studies in fatal cases of cardiomyopathy of pregnancy and the association may therefore be more common than published findings would suggest. In this context it is interesting to recall that it is often difficult to account for 'strokes' that occur during pregnancy or in the puerperium, particularly when cerebral angiography fails to reveal any abnormality. These strokes therefore might be a complication of an unsuspected cardiomyopathy of pregnancy, particularly as this is a condition which may be

¹See Addendum

clinically silent until death (Brigden, 1957) or may go unsuspected and be followed by complete recovery. In such cases, electrocardiographic studies might establish the diagnosis during life, while, in fatal cases, diagnosis will depend on histological study of the myocardium, including methods to show pre-necrotic damage, and detailed neuropathological study of the nervous system. These should be undertaken even if both heart and brain appear normal.

ADDENDUM

Since this paper was prepared for publication, it has become clear that focal myocytolysis can be secondary to brain damage, as one of us has now observed focal myocytolysis in the myocardium of seven patients dying six or seven days after severe cerebral damage (Connor, 1965). Five cases had ruptured intracranial aneurysms, one had a massive intracerebral haematoma, and one had suffered a severe head injury.

However, we feel that the patients described in this paper were suffering from primary heart damage, rather than heart damage caused by the brain lesions because all had marked tachycardia on admission, two had early clinical and necropsy evidence of heart failure, and none had evidence of a primary intracranial lesion.

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