TRANSIENT DISTURBANCES OF CONSCIOUSNESS IN HEPATIC CIRRHOSIS

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The occurrence, in hepatic cirrhosis, of transient disturbances of consciousness which cannot be related to cholaemia was mentioned by Osler in 1892. Himsworth (1947) states: "Coma is peculiar in possessing no striking features. The patient seems quietly asleep—limbs have a peculiar 'clasp-knife' rigidity, not unlike that in Parkinson's syndrome, and the plantar reflexes are extensor . . . the majority then quietly die, but recovery sometimes occurs even at this stage." Otherwise this syndrome has received scant attention in the medical literature, and it was thought that it might be of value to revive interest in the condition by publishing a brief account of three such cases.

Case 1

A married woman aged 48 was admitted on April 19, 1947. She gave a history of long-standing jaundice and of swelling of the abdomen and ankles, exertional dyspnoea, and intermittent painless diarrhoea for three years. For six months she had been having attacks of unconsciousness, usually lasting about 24 hours. They came on without warning, usually when she was in bed. Between attacks she felt quite normal apart from her diarrhoea, diminished exercise tolerance, ascites, and leg oedema. There was nothing relevant in her previous health, family history, or social background.

Physical examination revealed slight icterus, multiple spider naevi on the face and trunk, and moderate oedema. There was considerable ascites; the liver was palpable, hard, and irregular but not appreciably enlarged; and the spleen could also be felt (grade I). The chest was normal clinically and radiologically (except for a high diaphragm) and there was no cardiovascular abnormality. The urine was free from albumin and sugar, and examination of the central nervous system revealed no abnormal physical signs. A "barium swallow" demonstrated the presence of oesophageal varices. Liver-function tests showed a reversed albumin-globulin ratio (serum albumin 2.4 g.%, serum globulin 3.8 g.%), a high serum alkaline phosphatase (23.7 units, Jenner and Kay), a positive direct and indirect van den Bergh reaction (serum bilirubin 2.5 mg. per 100 ml.), a five-plus cephalin-cholesterol reaction, a thymol turbidity of 5 units, and a colloidal gold of 44310. The blood count showed a slight macrocytic anaemia with 3,860,000 red cells, 82% (11.3 g.%) haemoglobin, 3,600 white cells, and a normal differential distribution. A fat balance showed 81% absorption. Abdominal paracentesis produced a straw-coloured fluid with a specific gravity of 1025 and a protein content of 880 mg. per 100 ml.

Whilst in hospital the patient was afebrile and the ascites and leg oedema subsided. There was, however, considerable diarrhoea, and three attacks of "unconsciousness"

occurred. Each lasted about 24 hours, and, though the patient was stuporous, consciousness was not completely lost. In one attack she got out of bed and passed urine on the floor. During the attacks no abnormality could be found on examination of the cardiovascular or central nervous systems, and between the attacks she was mentally alert and normal. Blood-sugar estimations during the attacks were within the normal range, and a glucose-tolerance test was completely normal. An x-ray film of the skull was normal, but electro-encephalography carried out during two of the episodes of coma showed grossly abnormal records with a continuous dominant rhythm of 3-6 cycles a second and phase reversal at the parietal and temporal electrodes on both sides. She was discharged at the end of May, 1947.

The patient was readmitted in October, 1947, when her physical condition and liver-function tests had not materially altered. She continued to have attacks of unconsciousness, and ultimately died in Warwick Hospital on February 25, 1948.

Necropsy confirmed the presence of gross multilobular hepatic cirrhosis with splenomegaly and oesophageal varices. The stomach contained blood, there was haemorrhage into the liver substance, and a large haemorrhage from the left middle cerebral artery had destroyed the greater part of the left cerebral hemisphere.

Case 2

A married woman aged 66 was first seen on October 17, 1950. She gave a history of a lifelong tendency to bouts of diarrhoea, and of intermittent soreness of the tongue for many years. In 1940-1 she had been investigated at the Lincoln County Hospital because of abdominal pain and vomiting. A barium meal, cholecystography, and intravenous pyelography at that time showed no abnormality, but gastric analysis revealed achlorhydria.

She was again admitted to Lincoln County Hospital in 1945, when her liver and spleen were both enlarged three fingerbreadths below the costal margin, her blood pressure was raised (175/100), and her heart slightly enlarged both clinically and radiologically. A barium meal and an intravenous pyelogram again showed no evidence of disease. A blood count was normal, and a fractional test meal on this occasion was within the normal range. When first seen her chief complaint was of pain in the left side of the abdomen. There was a generalized brownish discoloration of the skin, the liver was a little enlarged and hard, and the spleen could also be felt (grade I). Her heart was enlarged to the left, her blood pressure was 220/130, and there were frequent extrasystoles. The urine was free from albumin and sugar and the chest was clear. Examination of the central nervous system revealed no abnormal physical signs. She had recently developed attacks of unconsciousness lasting for hours or days. In one of these her doctor diagnosed a "stroke," but there were no neurological abnormalities. She recovered from this and all her other attacks spontaneously and was quite normal, carrying out her full household duties during the intervals between attacks.

She was next seen on January 12, 1951, when she was completely unconscious, febrile (temperature 102° F.—38.9° C.), and grossly oedematous, with ascites and a right pleural effusion. She recovered consciousness and her mental state was normal, but her oedema and ascites increased, her pleural effusions became bilateral, and jaundice developed. She was transferred to this hospital on February 5, and, though bright, alert, and communicative on admission, the following day she became drowsy and incontinent, could be roused only by painful stimuli, and had to be fed through a Ryle's tube. She had recovered completely by the next day, but then again became stuporous for 48 hours, and after one more day of comparative normality gradually lapsed into coma with increasing oedema and jaundice and died on February 20.

During all the observed phases of unconsciousness no change in the cardiovascular state could be detected, and there were no abnormal neurological signs. Electrocardiography between and during attacks was normal apart from a left preponderance, a skull x-ray film was normal, and lumbar puncture showed normal hydrodynamics, chemistry, and cytology. The fasting blood sugar was normal, and during an attack it was 164 mg. per 100 ml. The serum sodium, potassium, calcium, phosphorus, and chlorides and the blood pH were all within the normal range, and the blood urea was 44 mg. per 100 ml. The Wassermann reaction was negative in the blood and cerebrospinal fluid.

Electroencephalography carried out during two of the periods of coma showed grossly abnormal records, with high-voltage delta discharges in all leads and phase reversal in the temporal lobes on both sides. Throughout the records there were periods of low-voltage fast activity and also runs of 9 cycles a second alpha rhythm.

Liver-function tests showed a reversed albumin/globulin ratio (serum albumin 2.39 g.%, serum globulin 3.1 g.%), a high serum alkaline phosphatase (19.5 units, Jenner and Kay), a positive direct and indirect van den Bergh (serum bilirubin 5.4 mg. per 100 ml.), a four-plus cephalin-cholesterol reaction, a thymol turbidity of 7 units, and a colloidal gold of 55321. The blood showed an incipient macrocytic anaemia with 4,370,000 red cells, 96% haemoglobin, and a mean corpuscular volume of $102.9 \mu^3$. The total white cell count was 11,800, 87% of which were polymorphonuclears.

Necropsy confirmed the presence of gross atrophic multilobular cirrhosis of the liver, the whole organ weighing 700 g. The portal vein was dilated, thickened, and atheromatous; the spleen was enlarged (345 g.), with numerous adhesions around it; while the oesophagus showed varices extending up to the bifurcation of the trachea. A suppurative cholecystitis and a solitary gall-stone, the presence of which had not been suspected during life, were also found. The heart showed moderate left ventricular hypertrophy. The brain appeared normal except for a depressed scar on the upper surface of the left cerebral hemisphere in the region of the post-Rolandic gyrus. In particular, the basal ganglia showed no macroscopic abnormality and the cerebral arteries were strikingly free from atheroma. Histological examination of the cortex, basal ganglia, hypothalamus, mid-brain, pons, and medulla revealed nothing that could be regarded as abnormal in a patient of this age.

Case 3

An unmarried woman aged 20 gave a history of chorea when 8 and of never having menstruated. There was no history of any illness suggestive of infective hepatitis. When 16 she had a tonsillectomy for recurrent sore throat, and thereafter had bouts of diarrhoea, with loose pale frothy stools, accompanied by ankle oedema. The oedema was worse at the end of the day, particularly when the weather was hot, and subsided completely with rest. Some two years later she noticed that the oedema involved the face, the arms, and the abdomen, as well as the legs, and that when it was developing she was thirsty and when it was subsiding there was polyuria. The attacks, which lasted up to three weeks, seemed to follow upper respiratory tract infections, and the bowels moved up to 15 times daily during these episodes. She was investigated in two hospitals, and the only treatment found to be effective was mersalyl injections.

She was seen in January, 1951, and was admitted for investigation. Physical examination showed finger-clubbing, "liver palms," multiple spider naevi on the face and arms, and considerable acne. Otherwise there were no abnormalities; the secondary sex characteristics were normally developed, the liver and spleen could not be felt, there was no ascites, and the urinary cardiovascular and central nervous systems were normal. The chest was clear clinically

and radiologically. The electrocardiogram was normal, and the blood Wassermann reaction was negative.

She remained in hospital for 10 weeks, and during this time the occurrence of coincident bouts of diarrhoea and water storage was confirmed. The stools were loose, pale, and frothy, and microscopically showed an excess of fatty-acid crystals. Repeated fat balances showed a fat absorption varying from 87% to 90%. Sigmoidoscopy was normal, but a barium enema showed a lack of colonic haustration, while a barium series showed a suggestion of oesophageal varices and irregular filling and a "snowstorm" effect in the jejunum. A glucose-tolerance test was normal. Repeated liver-function tests all showed evidence of hepatic dysfunction with a reversed albumin/globulin ratio (albumin 2-2.7 g.%, globulin 2.8-3.3 g.%), a cholesterol of 74-166 mg. per 100 ml., an alkaline phosphatase of 15.8-18.4 units (Jenner and Kay), and an invariably positive direct and indirect van den Berg reaction, with serum bilirubin levels of 1.3-3.1 mg. per 100 ml. The flocculation tests were always strongly positive—a four-plus cephalin-cholesterol reaction, a thymol turbidity of 4-6 units, and a colloidal gold of 44321 or higher being present on each occasion.

Needle biopsy of the liver revealed destruction of the liver parenchyma and replacement by granulation tissue, the liver cells showing vacuolation of the cytoplasm. The blood count while she was in hospital always showed evidence of a slightly macrocytic anaemia, with red cells from 3,260,000 to 3,890,000 and haemoglobin from 68 to 82%. The total and differential white cell count and the reticulocytes were always within the normal range, and the mean corpuscular volume varied from 86.6 to $102.5 \mu^3$. Hess's test was negative and the prothrombin was 53%.

The patient was regarded as suffering from hepatic cirrhosis, and the alimentary defects were thought to be secondary to this, though they may have been the primary cause of the liver disease, for which no other cause was evident. She was discharged from hospital on April 21, and shortly afterwards entered into a phase of water retention and diarrhoea lasting five days. Though this episode resolved in the usual way, she did not recover her normal health; her appetite was poor, she was depressed, irritable, and intolerant of noise, and at times restless and excitable. Her parents stated that she seemed tired and drowsy and often sat with a vacant stare, whilst at other times she seemed confused and disorientated and kept repeating phrases and questions. They also said that she slept badly, and they had noticed restlessness and jerking and twitching of the limbs at night. Epistaxis occurred on three or four occasions. On May 19 she again developed thirst, diarrhoea, and increasing oedema, and vomiting also occurred. Three days later she seemed very drowsy, and at 10 a.m. went to bed. During the day she became quite unconscious and was readmitted to this hospital on that evening.

On admission she was comatose but restless, and there were frequent jerky movements of the arms and legs, which exhibited clasp-knife rigidity. She was grossly oedematous, the liver and spleen were still impalpable, and liver dullness was absent. She remained in coma of varying depth for three days and then with the subsidence of oedema recovered full consciousness. During this attack she showed some pyrexia (up to 100.6°F .— 38.1°C .), was incontinent, and had to be fed through a Ryle's tube. There were some athetotic movements and much twitching of the limbs, and she yawned frequently; her face was expressionless, and her speech slow and monotonous. For a few hours the right plantar response was extensor. During this phase of unconsciousness the blood urea, blood sugar, serum sodium, and serum potassium were all within the normal range, but the chlorides were high (407-413 mg. per 100 ml.), and the carbon dioxide combining power was only 40 volumes %. After recovery of consciousness, however, the chloride level was still approximately the same. Electroencephalography, carried out during the unconscious phase, showed a large

dominant slow rhythm in all leads, with phase reversal at both temporal electrodes, but when full consciousness was restored the electroencephalographic pattern reverted to normal.

She remained in hospital for 12 weeks, during which one further brief episode of thirst, diarrhoea, increased oedema, pyrexia, and drowsiness occurred, and throughout her stay intermittent twitchings of the feet were noticed. There were no other neurological abnormalities, and Mr. Jameson Evans reported no Kayser-Fleischer rings. Fat balances, liver-function tests, and haematological investigations were substantially the same as during her previous period in hospital except that her anaemia was more severe. After a large blood transfusion she was discharged to her home subjectively well, and so far no further episodes of unconsciousness have occurred.

Discussion

A relationship between hepatic cirrhosis and degenerative changes in the brain has been well recognized since Kinnier Wilson (1912) published his classic description of six cases of progressive lenticular degeneration in which hepatic cirrhosis was associated with symmetrical degeneration of the putamen, globus pallidus, and caudate nucleus evidenced in life by tremor, muscular rigidity, dysarthria, dysphagia, and emotionalism, and he pointed out the strong hereditary and familial bias in this condition. Hadfield (1923) described a similar case in which necropsy revealed degenerative changes in the cortex (particularly the frontal cortex) and the dentate nucleus as well as the basal ganglia. Greenfield, Poynton, and Walshe (1924) described a further case and pointed out that pseudosclerosis and torsion spasm were variants of the same condition. Barnes and Hurst (1925) recorded a family of eight, five of whom were afflicted with hepato-lenticular degeneration. Their necropsy findings confirmed that degenerative changes occur in the cortex and cerebellum as well as the basal ganglia.

Later, Scherer (1933), in a study of 41 patients dying from cirrhosis and other forms of liver disease, found evidence of degeneration in the brain in over 90%. This consisted of changes in the oligodendroglia and the occasional presence of Alzheimer cells, and showed no predilection for the basal ganglia.

Crandall and Weil (1933) produced liver atrophy in dogs and rats by common-bile-duct ligation. They found that degenerative changes rapidly supervened in the corpus striatum, cerebral cortex, mid-brain, and cerebellum.

Brouwer (1935-6), in a review of the relationship between liver disease and the brain, mentioned two cases of hepato-lenticular degeneration in which, in addition to the symmetrical lesions in the corpus striatum, the cerebral cortex, particularly in the frontal area, showed cavitation and gliosis. He also described a case of haemochromatosis in which there occurred attacks of mental confusion, restlessness, urinary incontinence, and somnolence lasting two or three days. Later, emotionalism, dysarthria, dysphagia, tremor, and ataxia developed, and a necropsy showed parenchymal degeneration with gliosis, cavitation, and Alzheimer cells in the corpus striatum and frontal cortex.

Rabiner, Joachim, and Freiman (1944) recorded two cases of hepato-lenticular degeneration in which splenectomy appeared to have aggravated the nervous symptoms and hastened the fatal issue.

The association of hepatic disease with degenerative changes in the brain therefore seems well established.

In the first two cases here described there was, however, no evidence of any neurological abnormality during life, apart from the episodes of coma, and no structural change was found in the brain except the terminal cerebral haemorrhage in Case 1. No histological examination of the brain was made in this case, but in the second case the brain showed nothing that could be regarded as abnormal at the age of 66, either macroscopically or histologically. The third case, however, has shown objective evidence suggestive of striatal disturbance.

Though no precise explanation of the attacks of unconsciousness is offered, the third case does suggest that they may arise from factors similar to those which operate in Wilson's disease, and Brouwer's above-mentioned case of haemochromatosis supports this hypothesis.

Though the attacks, of themselves, do not appear to be in any way dangerous or to require any particular treatment, and though they cannot be regarded as cholaemic in the ordinary sense in which that term is used, their occurrence probably portends, like the development of ascites, a fatal termination within a period of months. Death occurred in the first case sixteen months and in the second only four months after the first attack of unconsciousness.

In each of the three cases ascites and oedema were present when the attacks occurred, and it is possible that fluid retention may in some way be responsible, though the second and third cases suggest that this is not related to sodium retention, as the serum sodium was within the normal range in both subjects. Certainly in each case there was abundant evidence of gross parenchymatous liver disease.

The electroencephalographic abnormalities observed during the periods of unconsciousness are probably non-specific and simply the result of coma, as the third case reverted to a normal electroencephalographic pattern between her episodes of unconsciousness.

Summary

Transient attacks of unconsciousness are described in three cases of hepatic cirrhosis.

Death in cholaemia followed within a period of months in two of the cases.

The attacks were associated with fluid retention, but the precise mechanism of their causation is not understood.

We are greatly indebted to Professor P. C. P. Cloake for the electroencephalographic studies, to Dr. A. P. Prior for the necropsy report on Case 1, to Professor J. M. Orr for the necropsy and histology of Case 2, to Dr. J. V. S. A. Davies for details of the previous history of Case 3, and to Dr. Trevor Cooke for his help in the care of Case 3.

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