Central pontine myelinolysis

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A demyelinating disease limited to the central portion of the pons was first described in 1959 by Adams, Victor, and Mancall. The absence of this condition from their earlier post-mortem material and from the neuropathological literature led the authors to suggest that this was a new disease, which they associated with alcoholism and/or malnutrition. Since then 16 additional instances have been recorded (Adams, 1962; Aki, Miyazaki, Takeuchi, Shimamine, and Aisawa, 1961; Aleu and Terry, 1963; Bailey, Bruno, and Ober, 1960; Berry and Olszewski, 1963; Girard, Plauchu, Tommasi, and Bourrat, 1959; Green, Sung, and Wolf, 1962; Klavins, 1963; Lapresle and Clay, 1959; Lapresle and Milhaud, 1962; Mathieson and Olszewski, 1960), bringing the total to 20.

The unusually high frequency of alcoholism and/or malnutrition in the population from which our post-mortem material is derived led us, in 1952, to begin a careful examination of the nervous system for evidence of related lesions. The first two patients with central pontine myelinolysis, however, were not seen until 1958, the third was discovered in 1959, and the remaining 13 since September 1960.

The purposes of this paper are to document the 16 new instances of this disease, to stress the frequency of small subclinical lesions, and to discuss its pathogenesis and its relationship to other conditions, particularly alcoholism.

With the exception of two, the patients forming this study died in Detroit Receiving Hospital, the major adult emergency hospital for this city, and the Dearborn Veterans Administration Hospital. Approximately 1,000 necropsies per year are performed in these two institutions; examination of the nervous system, including brain, spinal cord, lumbar dorsal root ganglia, and adjoining peripheral nerves, is done in more than 90%.

REPORT OF CASES

CASE 1 E.B. (DRH 58-1100) A 56-year-old white woman was admitted with haematemesis and in shock. She was said, by her inebriated daughter, to have drunk 'only an occasional beer'.

The blood pressure was unobtainable. She was disoriented, with dilated and unreactive pupils. The remainder of the neurological examination was within normal limits.

No laboratory studies were obtained.

The patient died 24 hours after admission.

General necropsy findings were severe fatty portal cirrhosis, acute gastric ulcers with haemorrhage, and early bronchopneumonia.

CASE 2 E.Z. (WCGH 58-A-499) A 40-year-old white woman was admitted with jaundice, abdominal enlargement, dark urine, weakness of the legs, and loss of appetite for four weeks. She had been a severe alcoholic for 15 to 20 years, taking little food during frequent alcoholic bouts.

She was described as well developed, well nourished, alert, oriented and icteric, with foetor hepaticus. The blood pressure was 130/80 mm. Hg, pulse 90, and respirations 18. There was marked hepatosplenomegaly and palmar erythema. No neurological abnormalities were noted.

Significant laboratory findings included: haemoglobin, 10.6g; serum bilirubin, 27.5 mg./100 ml.; prothrombin time, 25 seconds (control, 12 seconds); total serum protein, 7.3 g./100 ml. (albumin 3.1 and globulin 4.2); serum alkaline phosphatase, 16.1 units (normal 2.9); serum cholesterol, 270 mg./100 ml. (esters, 30%); serum glutamic oxaloacetic transaminase, 150 S-F units.

Treatment consisted of a variety of antibiotics, steroid hormones, and brewer's yeast. Her condition remained essentially unchanged for two weeks, when she began to bleed from the gastrointestinal tract, the ears, and terminally from the vagina. She died on the 38th hospital day.

At necropsy, she did not appear to be malnourished. The general necropsy findings were portal cirrhosis with bleeding oesophageal varices, haematometra, and suppurative bronchopneumonia.

CASE 3 A.W. (DRH 59-1363) A 43-year-old white man complained of progressive dyspnoea and ankle oedema for two weeks, and severe weakness of the legs for one day. There was a long history of alcoholism with two episodes of delirium tremens.

The patient was well developed, well nourished, alert, cooperative, jaundiced, and tachypnoeic. The blood pressure was 94/64 mm. Hg, temperature 100.2°F. (rectally), pulse 120, and respirations 36. The pupils

reacted slowly and slightly to light. The tongue was smooth. The heart was enlarged, with a systolic murmur along the left sternal border. Crepitant rales were heard in both lung bases. The liver extended 7 cm. below the right costal margin. Pitting oedema of the legs and cyanosis of the hands and feet were present. There was generalized weakness. Sensation to pinprick was decreased in both legs distal to the mid-thigh level, with diminution of vibratory sense and preservation of position sense. The deep tendon reflexes were symmetrically hypoactive. The abdominal and cremasteric reflexes were absent.

Laboratory examinations gave the following results: haemoglobin, 11.4 g.; leucocyte count, 4,900; serum protein, 7.7 g./100 ml. (albumin 4.7 and globulin 3.0); serum bilirubin 5.2 direct, 9.2 total, mg./100 ml.; thymol turbidity, 8 Shank-Hoagland units; cephalin-cholesterol flocculation, 4 plus in 24 hours; serum alkaline phosphatase, 4.3 Bodansky units; serum glutamic oxaloacetic transaminase, 1,300 S-F units; prothrombin time, 21.5 seconds (control, 11.4 seconds); urine: 2 + albumin, hyalin, and granular casts, 15 to 20 white blood cells and 10 to 20 red cells per high-power field.

A chest radiograph disclosed cardiac enlargement, the heart returning to normal size on later examinations.

Treatment consisted of high dosages of vitamins (thiamin, 500 mg. per day, niacin, riboflavin, ascorbic acid, 'Berrocca-C' parenterally, and vitamin K), chlorpromazine, intravenous glucose, and antibiotics.

On the second hospital day the patient became confused and later had hallucinations. Later, his confusion cleared partially, but jaundice and oedema persisted to his death on the tenth hospital day.

The findings at necropsy were: advanced and active portal cirrhosis, with superimposed severe passive hyperaemia beriberi; and heart disease with failure.

CASE 4 D.J.H. (DVAH A-60-243) A 55-year-old white man was admitted in congestive heart failure, with loss of 10 to 15 lb. weight in the preceding two months. He had been a severe alcoholic.

He appeared chronically ill and thin, but was alert and cooperative. Neurological examination revealed no abnormalities. The remainder of the physical examination indicated congestive cardiac failure due to rheumatic heart disease with mitral stenosis.

All laboratory examinations were normal with the exception of minimally elevated urinary urobilinogen (positive in dilution of 1:40).

He was given the usual treatment for cardiac failure, and multiple vitamins for 41 days. His condition progressively deteriorated, with death on the 80th hospital day.

The general necropsy findings consisted of rheumatic heart disease with mitral stenosis and insufficiency, and severe passive congestion of all organs.

CASE 5 E.S. (DRH 60-1528) A 51-year-old Negro woman was admitted deeply jaundiced and obtunded. No history was obtainable except that of chronic alcoholism.

She was well developed, well nourished, deeply

jaundiced and extremely lethargic, with foetor hepaticus. Blood pressure was 110/70 mm. Hg, temperature 100.4°F., pulse 120, and respirations 28. Neurological examination revealed flapping tremor, extensor rigidity of the extremities, symmetrically hyperactive deep tendon reflexes, bilateral sucking and grasp reflexes, and bilateral extensor plantar reflexes. Inconstant nuchal rigidity was also noted. The pupils were round, regular and equal, and reacted sluggishly to light and in accommodation. Cranial nerves appeared intact. The remainder of the physical examination showed abdominal distension with shifting dullness, and hepatomegaly.

Significant laboratory results were as follows: haemoglobin, 13.8 g., falling to 9.8 g.; leucocyte count, 27,700; platelet count, 84,000; total serum protein, 6.5 g./100 ml. (albumin 2.8 and globulin 3.7); serum bilirubin, 11.2 direct, 17.6 total, mg./100 ml.; prothrombin time, 24.9 seconds (control, 13.5 seconds); cerebrospinal fluid (opening pressure 150 and closing pressure 50, mm. of water), clear and xanthochromic, with 6 lymphocytes, protein, 40, and glucose, 90, mg./100 ml.

The patient was treated with intravenous glucose, multiple parenteral vitamins, adrenal cortical steroids, antibiotics, and blood transfusions. Rectal bleeding was noted two days after admission. Although she became slightly more responsive for short periods, she remained deeply jaundiced, and died on the ninth hospital day.

General necropsy findings were those of advanced active portal cirrhosis, oesophageal and gastric varices and superficial ulcers in the stomach and ileum with haemorrhage.

CASE 6 P.K. (DRH 60-162 1) A 32-year-old white woman was admitted with a history of dark urine for one month, pale stools and jaundice for four days, and a loss of 25 lb. in weight in the preceding two months. She drank large quantities of beer and whisky daily for 10 years.

She was well developed, slightly obese, alert, oriented and icteric. Neurological examination disclosed no abnormalities except flapping tremors of the hands. Hepatomegaly and vascular 'spiders' were the only other abnormal findings.

Laboratory examinations gave the following significant results: haemoglobin 11.4g, falling to 8.6 g.; leucocyte count 9,950, rising to 21,570; total serum protein 7.2 g./100 ml. (albumin 3.3 and globulin 3.9); serum bilirubin, 8.8 direct, 12.8 total, mg./100 ml.; thymol turbidity, 13 Shank-Hoagland units; serum alkaline phosphatase, 7.0 Bodansky units; serum glutamic oxaloacetic transaminase 125, rising to 250, S-F units; prothrombin times, 14.3 seconds (control, 13.3 seconds) rising to 22.5 seconds (control, 13.6 seconds); serum sodium, 135, potassium, 1.3 (rising to 2.5), chloride, 101 and carbon dioxide content, 14.3, all in mEq./l.; urine, 2 + albumin, 4 + bile, 6 to 8 white blood cells per high-power field.

Treatment initially consisted of a high-protein high-carbohydrate diet, later changed to a low-protein low-salt diet; multiple vitamins (plus thiamin 100 mg. niacin 100 mg., and riboflavin 10 mg. per day); antibiotics; and potassium chloride. She gradually became

obtunded, developed fever, ascites, and peripheral oedema, and died on the 27th hospital day.

Necropsy revealed advanced and active portal cirrhosis with oesophageal varices, jaundice and ascites, and a marked vacuolar nephropathy suggestive of potassium deficiency.

CASE 7 S.O. (DVAH A-61-3) A 38-year-old white man was admitted with a bimalleolar fracture of the left ankle, suffered from a fall while intoxicated. There was a history of heavy drinking for at least eight years.

He was well developed, well nourished, confused, tremulous, and perspiring. Blood pressure was 130/70 mm. Hg, temperature 98.6°F., and pulse 74. The pupils were round, regular and equal, reacted to light and in accommodation, and ocular movements were full. No other neurological examination was recorded. The remainder of the examination was negative except for a fracture of the left ankle.

No laboratory studies were done.

Treatment, in addition to that for the fracture, consisted of promazine, whisky (1 oz. four times a day), multiple vitamins and thiamin.

On the second hospital day, the patient was confused, arose and began walking, then fell to the floor and had a seizure consisting of drawing up of the hands and twitching of the left side of the face, following which he became unconscious. He was found dead in bed the evening of the same day.

General necropsy findings were those of very early fatty cirrhosis, pulmonary oedema and early pneumonia, and the aforementioned fracture. Although minimal amounts of fat were present in pulmonary capillaries, none could be demonstrated in the brain.

CASE 8 F.J.D. (DVAH A-61-36) A 67-year-old white man was admitted with a five-day history of gradual onset of jaundice, preceded by darkening of the urine. A cholecystojejunostomy had been done one year previously for obstruction of the common bile duct by a carcinoma of the head of the pancreas. Because of anorexia with vomiting, a gastrojejunal bypass for gastric obstruction was done four months before the last admission.

He was described as well developed, well nourished (despite a 60-pound weight loss), alert, cooperative, and oriented. Blood pressure was 120/80 mm. Hg, and pulse 118. Neurological examination was recorded as negative. The only abnormal findings were jaundice, an enlarged spleen, and an irregular mass in the right upper abdominal quadrant.

Significant results of laboratory examinations were as follows: haemoglobin, 10.1 g.; leucocyte count, 11,800; serum bilirubin, 4.4 direct, 7.8 total, mg./100 ml.; total serum protein, 6.1 g./100 ml. (albumin 3.9 and globulin 3.2); serum alkaline phosphatase, 34.5 Bodansky units; urine, positive for bile.

Treatment included multiple vitamins continuously for the year following the first admission, as well as several whole blood transfusions, chloromycetin, and analgesics.

During his terminal period in hospital, he developed auricular fibrillation and later became lethargic and weak, and, during a 45-minute period of shock immedi-

ately preceding death, confused and incoherent. He died on the eleventh hospital day.

The general necropsy findings were: adenocarcinoma of the head of the pancreas with obstruction of the common bile duct and metastases to regional lymph nodes and liver; hydrohepatosis; marked cachexia; ascites; jaundice; inactive rheumatic mitral and aortic valvulitis with cardiac hypertrophy; pulmonary oedema and bilateral pleural effusion.

CASE 9 P.P. (DRH 61-A-1284) A 40-year-old white man was admitted tremulous, disoriented and confabulating.

He was known to be a chronic alcoholic, and had been treated elsewhere for cirrhosis with jaundice and for hypertensive heart disease with congestive failure.

He appeared well-nourished; the blood pressure was 130/80 mm. Hg, temperature 99.8°F. rectally, pulse 78, and respirations 16. Except for symmetrically hyperactive tendon reflexes, the physical examination was negative.

Three days later he became stuporous; temperature was 104.4°F. rectally, blood pressure 95/60 mm. Hg, pulse 96, and respirations 24. There were moist rales in the right lower lung field, and the tendon reflexes were symmetrically depressed. On the seventh hospital day he began vomiting coffee-ground material, and died two days later.

Laboratory findings, including the examination of cerebrospinal fluid, were within normal limits except for the haemoglobin, which fell from 15.8 to 9.8 g.

Treatment consisted of parenteral fluids with glucose and multiple vitamins, various antibiotics, digoxin, chlorpromazine, and chlorthalidoxepoxide.

The general necropsy findings were: portal cirrhosis with oesophageal varices; bleeding duodenal ulcer; hypertensive cardiovascular disease; and confluent bronchopneumonia of the right lung.

CASE 10 L.B. (DRH 61-A-1596) A 30-year-old white woman was admitted with a history of jaundice for two weeks and melaena for one day. She had been admitted to hospital three times previously for the treatment of alcoholism and cirrhosis.

She was obese, stuporous, and deeply jaundiced. Blood pressure was 126/68 mm. Hg, temperature 99.6°F. pulse 108, and respirations 24. There were vascular 'spiders' of the skin, blood in the nose and mouth, ascites, splenomegaly, and pretibial oedema. No neurological abnormalities were recorded except for moderate nuchal rigidity and bilateral extensor plantar responses.

Laboratory findings indicated anaemia (haemoglobin, 8.5 g.), thrombocytopenia (75,000), and marked impairment of liver function. The cerebrospinal fluid was within normal limits.

She was treated with parenteral fluids containing glucose and multiple vitamins, but failed to respond and died on the second hospital day.

The general necropsy findings were: portal cirrhosis with jaundice, ascites and splenomegaly; slight cardiomegaly of unknown cause; and pulmonary oedema.

CASE 11 O.K. (DRH 62-A-1176) A 65-year-old alcoholic white man was admitted nervous and tremulous after a

drinking bout. He had been admitted to hospital previously for treatment of delirium tremens.

He was obese and slightly dehydrated. Blood pressure was 100/70 mm. Hg, temperature 99°F., pulse 92, and respirations 24. The remainder of the examination, including the neurological evaluation, was negative except for slight hepatomegaly.

Shortly following admission, he developed pneumonia. Despite treatment, which included tracheostomy, multiple antibiotics, parenteral fluids with glucose and vitamins, and steroids, his condition steadily worsened, with death on the 36th hospital day. Terminally, there was marked bleeding from the tracheostomy site.

The pertinent laboratory findings included leucocytosis during the period of pneumonia, *Klebsiella pneumoniae* in sputum and blood cultures, and evidence of moderate impairment of liver function. The remainder of the laboratory findings, including cerebrospinal fluid, were within normal limits.

The general necropsy findings indicated early, active portal cirrhosis, chronic interstitial pancreatitis, bilateral bronchopneumonia, and massive aspiration of blood from the tracheostomy site.

CASE 12 R.C. (DRH 62-A-1350) A 36-year-old white man, an alcoholic for 15 years, was admitted, after a three-day drinking bout, because of haematemesis. He had been admitted to hospital six months previously for treatment of delirium tremens and pneumonia. During his initial period in hospital, he was found to have cirrhosis, with moderate impairment of liver function, a tremor of the tongue and hands, and decreased sensation for pain in the feet and legs.

At the time of his final admission, he was restless, with a tremor of the hands. Blood pressure was 80/50 mm. Hg, pulse 120, and temperature 101.8°F. rectally. The only other abnormality described was scattered rhonchi over both lung fields.

A chest radiograph showed a right middle and upper lobe pneumonitis. There were no significant laboratory findings (except for an absence of leucocytosis).

He was treated with penicillin, chlorthalidopoxide, and parenteral fluids. Because of severe dyspnoea, a tracheostomy was done, and blood aspirated from the trachea. He developed severe hypotension, and died on the morning following admission.

General necropsy findings were: lobar pneumonia involving the right upper and middle lobes; complete occlusion of the trachea by clotted blood, apparently originating from the tracheostomy site; and moderately advanced portal cirrhosis.

CASE 13 W.D. (DRH 62-A-1534) A 67-year-old white man, a chronic alcoholic, was admitted complaining of epigastric pain and haematemesis for one day. He had been admitted to hospital once, 10 months previously, for 'impending delirium tremens', at which time he was found to have anasarca and hypoalbuminaemia, thought to be the result of cirrhosis.

At the time of final admission, he was pale, with a blood pressure of 118/60 mm. Hg, and pulse of 116. There was abdominal distension, and fresh blood in the rectum.

The haemoglobin level on admission was 5 g., rising to 12 g. after numerous transfusions; white blood count was 14,500, with a left shift; there was slight prolongation of both bleeding and clotting times; the bromsulphalein retention was 31% in 45 minutes; the serum alkaline phosphatase was 17.8 Bodansky units; and the serum glutamic oxaloacetic transaminase was 63 S-F units.

After receiving 32 units of whole blood, and parenteral fluids with added vitamins, he was operated upon for a bleeding duodenal ulcer. The ulcer was oversewn, the gastroduodenal artery ligated, and a vagotomy and gastroenterostomy done; however, he developed a reversible shock and died on the fourth hospital day.

The general necropsy findings were: duodenal ulcer; haematoperitoneum; slight left ventricular myocardial hypertrophy, with focal fibrosis; and acute passive congestion of the liver. There was no evidence of cirrhosis.

CASE 14 M.H. (DVAH A-62-388) A 56-year-old white man was admitted because of haematemesis for two days. A chronic alcoholic, he had been admitted many times previously for gastritis, cirrhosis, malnutrition, chronic bronchitis, and emphysema.

He was acutely ill and appeared intoxicated. Blood pressure was 80/70 mm. Hg, temperature 98°F., pulse 100, and respirations 22. There were rhonchi and basal rales over the lung fields; the abdomen was distended with fluid. No neurological abnormalities were recorded.

Haemoglobin was 12.6 g., and the blood urea nitrogen 62 mg./100 ml.

Shortly after admission, he aspirated vomitus and died. General necropsy findings were: bronchopneumonia with terminal aspiration of gastric contents; chronic gastric ulcer; portal cirrhosis; cardiac hypertrophy of undetermined cause; and hydronephrosis on the right due to stricture at the uretero-pelvic junction.

CASE 15 J.B. (DVAH A-63-33) A 69-year-old white man, a chronic alcoholic, was admitted because of confusion, faecal and urinary incontinence, and severe anaemia. Eight years previously, he had had a gastrectomy for a peptic ulcer. He was treated subsequently for fractures of the left tibia, femur, and a lumbar vertebra. His condition had deteriorated slowly over the past three years, associated with anorexia, nausea, vomiting, weakness, and confusion. During his penultimate period in hospital, one year before death, at another hospital, he was considered to have hypochromic microcytic anaemia, malnutrition, and portal cirrhosis.

At the time of final admission, he was dehydrated, confused, pale, and appeared chronically ill. Blood pressure was 110/60 mm. Hg, temperature 97.4°F., and pulse 116. He was confused and disoriented. There was a resting tremor of the arms, with a suggestion of cogwheel rigidity. The remainder of the neurological examination was within normal limits, although sensory evaluation was difficult.

The significant laboratory data included: haemoglobin 6.5 g.; blood urea nitrogen, 57 mg./100 ml.; transient elevation of serum glutamic oxaloacetic transaminase (to 99 S-F units); alkaline phosphatase, 9.8 Bodansky units; cephalin cholesterol flocculation, 4 +; stools

positive (4+) for occult blood. The cerebrospinal fluid was normal on two occasions.

He was given whole blood, antibiotics, and multiple vitamins. After initial transient improvement, he developed staphylococcal pneumonia and died on the 18th hospital day.

General necropsy findings were: bronchogenic carcinoma with metastasis to regional lymph nodes and adrenals; bronchopneumonia; and benign nephrosclerosis. The liver showed mild fatty change, but no evidence of cirrhosis.

CASE 16 S.M. (W.B.H. A-63-250) A 36-year-old white woman, who admitted to being a moderately heavy drinker, entered the hospital complaining of anorexia, fatigue, jaundice, and pruritus for a week.

She was well developed and well nourished, alert, oriented and deeply jaundiced. Temperature was 98°F., pulse 80, and respirations 20. Dullness and decreased breath sounds were noted in the right lung base; the abdomen was distended, and the liver was enlarged, firm, and slightly tender.

Laboratory data indicated slight anaemia, leucocytosis, marked hyperbilirubinaemia, and moderate impairment of liver function. A liver biopsy was interpreted as showing portal cirrhosis.

She developed obvious and increasing ascites, deepening jaundice, and confusion progressing to complete disorientation; she died on the 17th hospital day.

General necropsy findings were: severe, active portal cirrhosis; acute and chronic pancreatitis; pseudo-membranous enteritis; and bronchopneumonia.

NEUROPATHOLOGICAL FINDINGS

In Table I, the dimensions of the 16 pontine lesions are indicated. In all instances, they were located in the base of the pons, were midline, usually symmetrical, and approximately equidistant from the floor of the fourth ventricle and the ventral pontine surface. In 13 instances, they were on cross section roughly triangular, with the base dorsal

TABLE I

SIZES OF LESIONS

Case No.	Diameters (mm.)		
	Transverse	Dorso-ventral	Cephalo-caudal
1	10	4	Not recorded
2	5	3	Not recorded
3	5	5	Not recorded
4	4	4	Not recorded
5	5	5	Not recorded
6	5	3	Not recorded
7	2	4	'Nearly entire pons'
8	2	5	Not recorded
9	4	10	Not recorded
10	5	3	Upper half of pons
11	18	11	'Nearly entire pons'
12	6	6	Not recorded
13	7	10	10
14	5	4	Not recorded
15	8	10	20
16	4	10	Not recorded

FIG. 1. Case 13. The lesion is somewhat asymmetrical, roughly triangular, and shows slight central cavitation.

FIG. 2. Case 12. The triangular shape and somewhat granular appearance are well shown.

and apex ventral (Figs. 1 and 2); in the remaining three, the cross-sectional shape was approximately oval. In all but one, the maximum cross-sectional area of the lesion was at the level of the external origin of the trigeminal nerve, tapering rostrally and caudally. In the one exception, case 3, the extension was in a rostral direction only.

In the 12 instances in which the lesions were

FIG. 3

FIG. 3. Case 2. Myelin loss abrupt and complete. Mahon $\times 14$.

FIG. 4

FIG. 4. Case 4. Within the demyelinated area, some fibre bundles have retained their myelin sheaths. Mahon $\times 35$.

recognized grossly, they were granular and slightly depressed. In 10, they were gray to brown; in two, occurring in jaundiced patients (cases 8 and 10), they were faintly but distinctly green.

The microscopic findings are based upon examination of formalin-fixed, paraffin-embedded tissue, using the following stains: haematoxylin and eosin,

Mahon, luxol fast blue-silver nitrate, phosphotungstic acid-haematoxylin, periodic acid-Schiff, and Wilder's reticulin.

Sudan IV stains were done on frozen sections in four instances (cases 5, 13, 14, and 15); this was supplemented, in case 13, with Nile blue sulphate and Sudan black B stains.

FIG. 5. Case 2. Macrophages within the lesions are filled with P.A.S.-positive granules. Periodic acid-Schiff $\times 400$.

FIG. 6

FIG. 6. Case 5. Numerous bulbous swellings of axis cylinders are shown. The black fibres in the upper left corner represent myelinated axons at one edge of the lesion. Luxol fast blue-silver nitrate $\times 90$.

With the haematoxylin and eosin stain, as well as in sections stained for myelin, the lesions were sharply demarcated and pale, with loosening of the tissues, and slight central cavitation in three instances. In eight, myelin loss was complete in this area (Fig. 3). In seven others, scattered small fibre bundles within the area retained their myelin sheaths (Fig. 4). In the remaining case, myelin loss was diffuse but incomplete (similar to a 'shadow plaque' of multiple sclerosis).

Macrophages containing myelin in various stages of breakdown were seen in variable, but usually moderate, numbers. They were scattered throughout each lesion, but were often concentrated about blood vessels. In the conversion of myelin to neutral fat, there was a stage during which the intra- and extracellular material was P.A.S.-positive (Fig. 5); however, no consistent spatial arrangement of these stages was recognized. A few lymphocytes were occasionally seen about blood vessels within and at the periphery of the demyelinated area.

Oligodendrocytes were markedly reduced to absent in the areas of demyelination. They appeared unaltered in the surrounding pons, and also in the myelinated bundles persisting within the lesions.

Few significant changes were noted in axis cylinders. There was slight numerical reduction in five cases, and focal axonal swellings in three (Fig. 6).

Except for two instances in which there was marked reduction in numbers in the centres of the lesions, the nerve cells exhibited few changes.

There were no significant alterations of astrocytes or blood vessels, except for occasional very slight reactive astrocytosis at the periphery.

In none of the patients was there significant atherosclerosis of the basilar artery or its branches, and in none did these vessels contain thrombi or emboli.

No other demyelinating lesions were seen elsewhere in the nervous systems of any of the patients in this group. The additional pathological findings in each patient are included in Table II.

DISCUSSION

As with other demyelinating diseases, the pathological process in central pontine myelinolysis is one of destruction of myelin with (relative) preservation of the axis cylinders. It can be differentiated from multiple sclerosis only by its symmetry, unique position in the central portion of the basis pontis and, in our experience, its singularity. The lesion can often, but not always, be recognized grossly by its characteristic brown or grey granular appearance. In two severely jaundiced patients, the lesions were

TABLE II

Case	Age	Sex	Race	ASSOCIATED CONDITIONS OR DISEASES				Other
				Other Central Nervous System Lesions of Alcoholism or Malnutrition	Cirrhosis	Alcoholism or Malnutrition (History)		
1	56	F	W	None	+	Probable alcoholic		Bronchopneumonia, acute bleeding, gastric ulcers
2	40	F	W	Minimal cerebellar atrophy	+	Both		Hepatic insufficiency, bleeding oesophageal varices, bronchopneumonia.
3	43	M	W	Wernicke's disease, subacute	+	Alcoholic		Beriberi, heart disease, pulmonary anthraco-silicosis
4	55	M	W	None	0	Alcoholic		Rheumatic heart disease, old temporo-parietal cerebral infarct
5	51	F	N	Wernicke's disease, subacute	+	Alcoholic		Hepatic insufficiency
6	32	F	W	None	+	Alcoholic		Hepatic insufficiency, bronchopneumonia.
7	38	M	W	Moderate cerebellar atrophy	+	Alcoholic		Delirium tremens, bimalleolar fracture, pulmonary oedema with early pneumonia
8	67	M	W	None	0 (Biliary obstruction)	Malnutrition, not alcoholic		Carcinoma pancreas with common bile duct obstruction, rheumatic heart disease
9	40	M	W	Wernicke's disease, acute	+	Alcoholic		Hypertensive heart disease, bleeding duodenal ulcer, bronchopneumonia
10	30	F	W	Wernicke's disease, chronic	+	Alcoholic		Hepatic insufficiency, cardiomegaly, cause undetermined
11	65	M	W	None	+	Alcoholic		Klebsiella pneumonia, chronic pancreatitis
12	36	M	W	None	+	Alcoholic		Lobar pneumonia
13	67	M	W	None	0	Alcoholic		Bleeding duodenal ulcer
14	56	M	W	None	+	Alcoholic		Bronchopneumonia, bleeding gastric ulcer, cardiomegaly, cause undetermined
15	69	M	W	Wernicke's disease, chronic	0	Alcoholic		Bronchogenic carcinoma with metastasis, bronchopneumonia
16	35	F	W	None	+	Alcoholic		Hepatic insufficiency, acute and chronic pancreatitis, pseudomembranous enteritis, bronchopneumonia

bile-stained, indicating local breakdown of the blood-brain barrier.

The destruction of myelin appeared to proceed in the same fashion as in Wallerian degeneration and in most demyelinating diseases.

Disappearance of myelin and oligodendrocytes appeared to be concomitant, with no indication that one preceded the other.

From the invariable singularity of the lesions and the occasional presence of central cavitation, it seems evident that they do not arise from coalescence of multiple foci. In our material, there is no clear-cut evidence to confirm or refute the assumption that the lesions begin as a small focus and enlarge peripherally.

These lesions can be differentiated from infarcts by the lack of characteristic ischaemic changes in the nerve cells included in the area, and the absence of any occlusive lesions in the basilar artery or its branches. The possibility that anoxia, without vascular occlusion, may be a causative factor cannot easily be dismissed, since it is well known

that anoxia may produce demyelination (Meyer 1958). However, the total lack of ischaemic changes in any of the numerous nerve cells included within these lesions, as well as the absence of other lesions characteristic of anoxia in these 16 patients, argued strongly against anoxia as a significant factor.

In Table II are summarized the associated findings in our 16 patients. Similar data for the previously recorded cases have been well summarized in the recent publications of Klavins (1963) and of Berry and Olszewski (1963), and will not be repeated here. So far as we are able to determine, there is no single factor which is common to all of the reported cases. The association of alcoholism, however, although not constant, is certainly impressive. Fourteen of our 16 patients were known to be chronic alcoholics, and this was almost certainly true of the fifteenth (case 1). Of the 20 reported cases, alcoholism was recorded in 10 cases. (It is true that in two (Berry and Olszewski, 1963; Klavins, 1963) alcoholism was said to have ceased several years before death; our experience of the reliability

of the history in chronic alcoholics leads us to question this.) Thus, in 25 of the 36 patients, alcoholism was either known or highly probable.

The second striking and unexpected finding in our series was the total absence of Negro males afflicted with this condition. Unfortunately, race is not recorded in most of the previous reports. Figures are not available in our institutions for the proportion of Negroes in the necropsy population; it is certain, however, that they represent a significantly large proportion of that population, and it is equally certain that a history of alcoholism is common in the Negro patients in these hospitals. Whether the absence of this condition in Negro males in our material reflects a genetically determined metabolic difference, or a different set of environmental factors, or is purely fortuitous, cannot, of course, be answered. In this regard, it is of interest that clinical experience at both hospitals has indicated comparative infrequency of delirium tremens and of alcoholic cirrhosis in Negro males.

The possible causes of this disorder have been the subject of considerable speculation. It seems particularly important to us, however: (1) that the lesion is strongly, although inconstantly, related to excessive alcohol ingestion; and, (2) that it has appeared only within recent years, while alcoholism and malnutrition have been prevalent for centuries. This suggests to us, as to others (Aleu and Terry, 1963), the likelihood that central pontine myelinolysis is caused by a toxic substance, exposure to which is

not peculiar to alcoholics, but is more prevalent in this group.

SUMMARY

Sixteen new examples of central pontine myelinolysis, a demyelinating disease involving the base of the pons, are described. The pathological process is one of destruction of myelin sheaths and oligodendrocytes, with relative preservation of axis cylinders and nerve cells. The association of this lesion with other conditions, especially alcoholism, is indicated, and reasons are given for suspecting an as yet unidentified toxin as the cause. The absence of this lesion in alcoholic Negro males remains unexplained.

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