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EPISODIC HEPATIC ENCEPHALOPATHY: A PROBLEM OF ALL SPECIALTIES

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COMA is a well-recognized and much-feared complication of hepatic disease, especially of cirrhosis. In recent years the spectrum of neuropsychiatric symptoms due to hepatic disease, varying from subtle personality change, episodic stupor, and transient coma, to chronic dementia, has been more fully appreciated.[1] We are reporting four cases of hepatic encephalopathy which were not suspected either by the referring physicians or by the clinicians here who first examined the patients. The first patient was admitted to the vascular service for study of edema of the lower half of the body and suspected "thromboembolic strokes." The second patient was admitted to the proctologic service because of severe rectal hemorrhage associated with possible small strokes. The third patient was admitted to the gastrointestinal service because of jaundice, splenomegaly, and recurrent anemia after several gastrointestinal hemorrhages. The fourth patient was admitted to the neurosurgical service because of stupor thought to be the result of a cerebral injury incurred in an automobile accident. In each of these patients the elevation of the blood ammonium nitrogen (hereinafter designated as B.A.N.) was of decisive importance in the diagnosis. The normal range was from 36 μg. to 75μg. per 100 ml. The blood was drawn into syringes containing heparin, and the determinations

were performed within 20 minutes. The method was a modification (by W. R. F.) of the Conway Method.

Subtle personality change may escape notice for long periods, and its relationship to known hepatic disease may not be recognized or the mental disorder may progress to a dementia and the established hepatic disorder may be forgotten. Instances of chronic dementia have been described in which hepatic disease was present, and the relatively simple treatment of reducing or temporarily withdrawing dietary protein has effected a return to a normal mental state.[2] Since increased protein intake is necessary to combat the underlying hepatic disorder, other therapeutic measures to permit this are necessary; these will be described.

The current concept of the mechanism of episodic stupor is that in hepatic disease the products of accelerated bacterial action on ingested proteins in the digestive tract not only are poorly detoxified by the abnormal liver, but also bypass the liver, by the collateral circulation, to exert a harmful effect on the central nervous system. Although other toxic substances may be involved, ammonia is the only toxic product demonstrable in most patients, and measurable with reasonable accuracy by standard methods.

After portacaval anastomosis the blood, and consequently ammonia, can bypass the liver more readily. Thus, episodes of stupor may occur more readily with an overload of dietary protein with only minor impairment of hepatic function; however, patients can adjust to a higher systemic concentration of ammonia so that such episodes may not recur frequently. Gastrointestinal hemorrhage in, and the administration of ammonium compounds to, patients with hepatic disease may impose an excessive load of ammonia on the liver, and result in coma. Some diuretic agents such as chlorothiazide* and acetazolamide† may also precipitate hepatic coma.

There are two possible mechanisms by which excessive ammonia and other possible toxic agents can reach the general circulation from the intestine. These are through a severely diseased liver as in severe hepatitis, and through various collateral vessels that bypass the hepatic parenchyma as in cirrhosis. The path through collateral vessels is the mechanism involved in most clinical instances of hepatic encephalopathy; thus Sherlock, Summerskill, White, and Phear[2] have termed this "portal-systemic encephalopathy."

Our four cases illustrate some of the variations of the syndrome of hepatic encephalopathy. Three patients had demonstrable collateral circulation and may therefore be considered to have had portal-systemic encephalopathy. In one patient collateral circulation was not demonstrated although it may have been present.

Case Reports

Case 1. A 46-year-old white man was admitted to the Cleveland Clinic Hospital, on

**Diuril (chlorothiazide), Merck Sharp & Dohme.*
†Diamox (acetazolamide), Lederle Laboratories.

December 17, 1957, to the peripheral vascular disease service with a history of recurrent swelling of the legs, a transient cerebrovascular disorder, thrombophlebitis, and of having had ligations of the saphenous and of the femoral vein. Twenty-six months previously (October, 1955) he had swelling of one leg and the scrotum, and was hospitalized for one month for thrombophlebitis, and for hepatic and renal diseases. Alcoholic beverages, used to "excess" up to that time, had been discontinued because of a hepatic disorder. Sixteen months later, ten months before examination here, swelling of the legs and of the scrotum recurred, but responded to mercurial diuretics. Three months later an episode of stupor, slurred speech, and incoordination was diagnosed as cerebral thrombosis without residual neurologic deficit. The next month another episode was more intensively investigated with pneumoencephalography; the diagnosis was the same. In the next month, superficial thrombophlebitis was treated by ligations of the bilateral saphenous and right femoral veins because of the above-described episodes of slurred speech and incoordination which were considered "small strokes from emboli." For the next five months the patient continued to have swelling of the legs and of the scrotum, and to receive mercurial diuretics. There was only slight response to treatment, and the patient was unable to return to work.

At physical examination here he weighed 232 pounds, and his blood pressure was 140/86 mm. of Hg. The patient was alert and cooperative. There were no spider nevi or icterus. The heart and lungs were normal. The abdominal wall was edematous and the abdominal organs were not palpable. There was severe edema of the penis, the scrotum, and the legs. After the loss of edema fluid following intensive treatment, examination disclosed a descent of the liver one fingerbreadth below the right costal margin, and of the spleen four fingerbreadths below the left costal margin. There were no signs of neurologic disorder.

Roentgen findings of the skull and chest were normal. An esophogram showed no evidence of varices. An electrocardiogram showed no abnormality.

According to initial laboratory studies: the hemoglobin was 10 gm. per 100 ml., with 4,000 leukocytes and a normal differential count. Urinalysis showed a trace of albumin and many erythrocytes. The culture of the urine showed no organisms. Fasting blood sugar was 83 mg., blood urea 33 mg., plasma creatinine 0.5 mg., serum cholesterol 174 mg., serum albumin 1 gm., serum globulin 4.5 gm. per 100 ml.; serum bilirubin, direct was 0.3 mg., and indirect was 1.5 mg. per 100 ml. Bromsulphalein retention was 9 per cent in 45 minutes. The serologic test for syphilis was negative. Thymol turbidity was 10 units. The prothrombin time was 18 seconds (68 per cent of normal). The cephalin-cholesterol flocculation test was 4 plus in 24 hours. The zinc sulfate turbidity test was 21 units.

Progress laboratory findings showed a striking increase in Bromsulphalein retention after the first month, but no other notable change. The cephalin-cholesterol flocculation test continued to be 4 plus and remained so three months after the patient was discharged. Serum proteins were temporarily increased by parenteral injections of albumin, subsequently declined, and later increased slightly. The number of blood platelets was decreased, the count being from 30,000 to 90,000 per cubic millimeter, which was ascribed to probable hypersplenism.

On the third day in the hospital a venogram showed evidence of a normal inferior vena cava.

The patient was treated with mercurial diuretics and in one week lost 22 pounds in weight; he became confused and stuporous. A gross tremor was noted and also fetor hepaticus. He was given a low-protein (from 20 to 30 gm.), low-sodium (0.5 gm.), high-carbohydrate diet; orally neomycin sulfate tablets* (500 mg.), four times daily; sodium glutamate (25 gm. in 500 ml. of 10 per cent dextrose solution) and arginine hydrochloride (25 gm. in 500 ml. of 10 per cent dextrose solution) intravenously daily. He gradually improved. Arginine glutamate† (25 gm. in 500 ml. of 10 per cent dextrose) was sometimes substituted for sodium glutamate and arginine hydrochloride. Administration of mercurial diuretics was continued. He was also given albumin (25 gm.) daily intravenously for several days and two units of whole blood. After two weeks he was mentally clear and his weight had decreased 25 pounds more (a total loss of 47 pounds of edema fluid). During a period of 10 days the protein intake was again gradually increased to 110 gm. daily and neomycin was omitted. The patient again lapsed into a semicomatose condition; a program similar to that described above was reinstated.

These episodes were characterized by mental confusion, incoordination, tremor of the body, flapping tremor of the hand, presence of Babinski's sign (variably right or left foot), hyperactive deep-tendon reflexes, and bilateral sustained clonus of the ankles. A significant feature of these episodes was the transient nature of the neurologic manifestations. Although neurologic examination showed definite abnormality at the time of each episode of stupor, a few days after each episode findings were equivocal or normal. The electroencephalograms likewise showed a striking change *(Fig. 1)*.

The patient again recovered. He was discharged and was directed to follow a 120-gm. protein diet with neomycin (0.5 gm.) four times daily. He returned in four days, stuporous and tremulous; laboratory findings were similar to those described above; the B.A.N. was 264 μg. per 100 ml.

A low-protein (30-gm.) diet, neomycin orally (1 gm.) every three hours, and arginine hydrochloride intravenously were given. Later, 25,000 units of bacitracin was administered orally every six hours. The patient made rapid symptomatic progress and became normally alert. The B.A.N. decreased to 183 μg. per 100 ml., and the patient was discharged on the fifth day, with the advice to follow an 80-gm. protein diet, neomycin (0.5 gm.) four times daily, and bacitracin (25,000 units) orally four times daily.

In the out-patient department he made satisfactory progress. The B.A.N. concentration remained abnormally high in the first month, but the electroencephalogram was normal. Later the concentration of B.A.N. declined, although it remained elevated. Lymphedema of the legs and thighs, which persisted in spite of diuresis and loss in weight, was successfully controlled by pneumatic massage and full-length elastic stockings. After one month the patient returned to work for the first time in almost two years. In two months the patient started full-time work, and although requiring regular treatment, including a neomycin sulfate tablet (0.5 gm.) four times daily, a tablet of neomycin (25 gm.) and bacitracin (2,500 units) ‡ four times daily, he is much improved, and has continued so to the last follow-up examination in October, 1958. The B.A.N.

**Mycifradin (neomycin) sulfate tablets, The Upjohn Company.*

†Modumate (arginine glutamate) was provided through the courtesy of Abbott Laboratories.

‡Neobacin (neomycin 25 mg., and bacitracin 2,500 units) tablets were supplied through the courtesy of Reed & Carnrick.

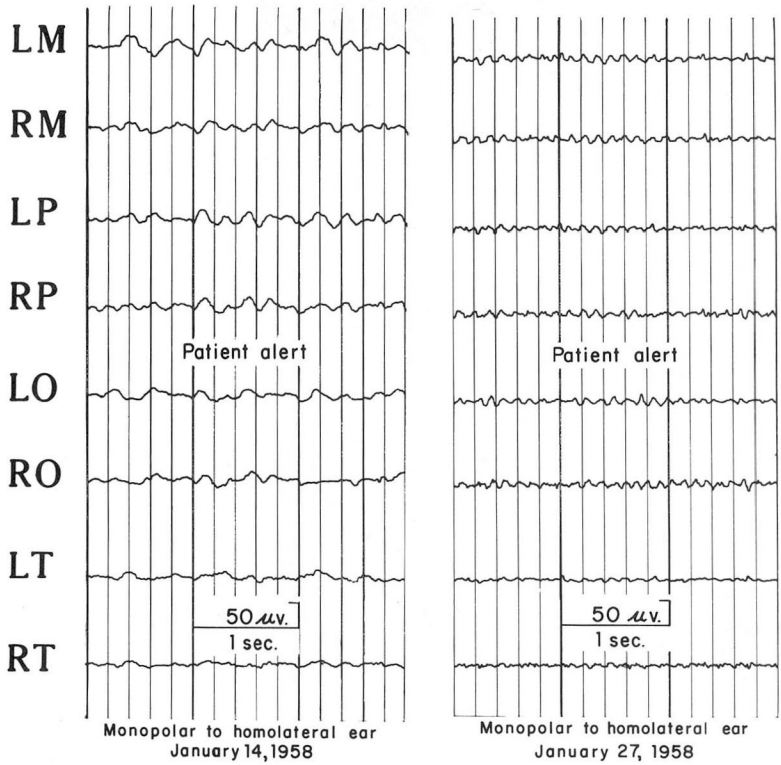

Fig. 1. Case 1. Electroencephalograms before and after treatment for episodic stupor.

has remained at about 140 μg. per 100 ml. despite clinical improvement.

Comment. This case emphasizes the importance of recognizing the syndrome of episodic stupor. The description of the previous episodes, which were considered recurrent cerebral thromboses without residual effects, was identical with that of the episodes of portal-systemic stupor that we observed. The two recurrences of these episodes after the institution of a high-protein diet suggest the probability that previously the patient had an intermittent type of high-protein intake with episodes of stupor following periods of increased intake, with these in turn being relieved by the decreased protein intake attendant upon such stupor. The striking change in the electroencephalogram after treatment is noteworthy. The triphasic waves that have been considered most typical of hyperammoniemia[3, 4] are not present, but the diffuse, abnormal changes are definite, and the complete disappearance after treatment is dramatic.

The chronic renal disorder present in this patient had no apparent relationship to the episodic stupor. There were no significant variations in renal function, electrolyte imbalance, azotemia, or other evidence of renal failure.

Case 2. A 53-year-old white woman was transferred on December 26, 1957, to the

proctologic service of the Cleveland Clinic Hospital from another hospital where she had been for one month because of weakness, loss of weight, recurrent rectal bleeding, and a brief episode of hepatic coma that was said to have responded to cortisone treatment. Two years previously a large liver was noted.

On admission to the Cleveland Clinic Hospital, the patient had a temperature of 99° F., a pulse of 80, and a blood pressure of 120/70 mm. of Hg. Mild icterus was present, but no spider nevi were seen. The liver was nodular and descended 10 cm. below the right costal margin, and the spleen descended 6 cm. below the left costal margin. Neither edema nor ascites was present.

Laboratory findings included: bromsulfalein retention 15 per cent in 45 minutes; cephalin-cholesterol flocculation 4 plus; thymol turbidity 14 units; bilirubin, direct, 0.3 mg., indirect, 0.8 mg.; serum albumin 2.4 gm., and serum globulin 4.6 gm. per 100 ml. Prothrombin time was 68 per cent of normal (18 seconds; normal, 14 seconds); bleeding time 1½ minutes; coagulation time 16 minutes. After a barium meal, roentgenograms of the esophagus and stomach showed no evidence of varices, barium enema showed only diverticula. Esophagoscopy revealed no varices. Proctoscopy showed greatly dilated mucosal veins well above the rectal ampulla. Histologic study of specimens of a needle biopsy of the liver showed severe hepatic cirrhosis with features of both the postnecrotic and nutritional types.

The patient was discharged and was advised to follow a program of treatment for hepatic cirrhosis. She was readmitted two months later; she had gained 14 pounds in weight and had slight edema of the ankles. Additional history from relatives disclosed that two years previously she had undergone certain changes, among which slow, deliberate speech, slow motions and actions, and prolonged reading time were noted. Six months before admission the patient had deep stupor after rectal bleeding, had fallen and fractured some ribs, but had no recollection of doing so. At re-examination the B.A.N. was 210 μg. per 100 ml.; serum albumin had increased to 3.2 gm., and serum globulin was about the same at 4.5 gm. per 100 ml.; bromsulfalein retention value also was higher, 29 per cent in 45 minutes. An electroencephalogram showed abnormal, diffuse changes with slow activity more pronounced on the left than on the right side.

The patient was started on a course of treatment that included neomycin (0.5 gm.) four times daily for three days, then neomycin (50 mg.) and bacitracin (5,000 units) four times daily in a special tablet. A high-protein diet and intravenous injections of albumin were also instituted. In four days the B.A.N. decreased to 104 μg. per 100 ml. and the patient became much more alert; the examinations and her progress under treatment indicated that prolonged hepatic encephalopathy had existed.

A portacaval shunt and a cholecystectomy were performed. The diagnosis of postnecrotic cirrhosis with portal hypertension was confirmed. At discharge the patient was advised to follow a high-protein diet and to take a small daily dose of neomycin. The neomycin was discontinued after one month, after which time the diet was not followed carefully. She made satisfactory progress for two months, and then was reported to have become gradually weaker and more lethargic. During this period of increasing weakness and lethargy she had eaten larger quantities of meat than usual.

She was readmitted to the hospital after three months. Memory deficit, psychic apraxia, presence of Verpus (snout) reflex and left Babinski's sign, and a grossly asym-

metric electroencephalogram all suggested to the neurologist the presence of a chronic cerebral disease. The patient was given neomycin (0.5 gm.) four times daily, and daily infusions of arginine hydrochloride (25 gm.). Within a few days she improved greatly, although dietary protein was not restricted. The B.A.N. varied from 142 μg. to 274 μg. per 100 ml. and gave no evidence of an over-all decrease.

Two months later the patient was asymptomatic, although the B.A.N. was 160 μg. per 100 ml.; four months later the B.A.N. was 110 μg. She was taking 120 gm. of protein daily, Neobacin tablets three times a day, and was alert and well.

Comment. This case demonstrates a chronic disorder of the personality with definite decrease in intellectual function and altered affect. A special aspect of the problem was the striking collateral circulation provided by the dilated sigmoidal veins. After a portacaval shunt, increasing stupor developed. The interesting point was that because she knew she was not doing well the patient herself increased the consumption of meat. The immediate response to treatment was especially noteworthy, although the neurologist considered the symptoms indistinguishable from chronic cerebral disease.

Case 3. A 35-year-old white man was admitted on October 14, 1957, to the Cleveland Clinic Hospital, to the gastroenterologic service, because of recurrent jaundice and anemia following recent hematemesis and melena. Four years previously, at another hospital, he had a cholecystoduodenostomy performed for obstruction of the common bile duct. At physical examination, splenomegaly, and jaundice without hepatomegaly were noteworthy. Studies of specimens of a needle biopsy of the liver showed the presence of moderate posthepatitic cirrhosis. Esophograms showed definite evidence of varices *(Fig. 2)*. While studies were in progress the patient had a recurrent severe upper

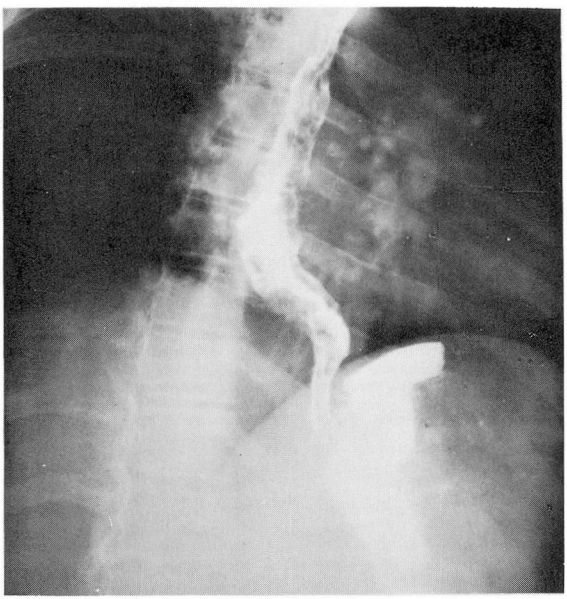

Fig. 2. Case 3. Esophogram showing evidence of extensive varices in a patient who had episodic stupor.

gastrointestinal hemorrhage that was controlled by balloon tamponade using a Sengstaken-Blakemore tube. With satisfactory hepatic function and repeated hemorrhages, surgical management of portal hypertension was elected. Splenoportography showed marked dilatation of the portal vein with extensive esophageal and gastric varices. An end-to-side portacaval shunt was constructed; immediately, portal pressure as well as the size of the varices decreased. The postoperative course was satisfactory, and 20 days after operation the patient was discharged with the advice to follow a program for treatment of cirrhosis, including a 120-gm. protein diet daily.

The patient returned about three months later, reporting a steady gain in weight and strength, but with an increasing inability to concentrate, and soreness and stiffness of the muscles in walking. His family physician had noted some loss of affect. Examination showed a masklike facies, rigidity of the head and arms while walking, and a generalized, fine, intermittent tremor. Administration of prochlorperazine* tablets, which had been given in a dosage of 5 mg. four times daily, was discontinued, but there was no change within 24 hours. At that time the arterial B.A.N. was 167 μg. Neomycin tablets were given in a dosage of 2 gm. four times daily, and in 24 hours the patient improved dramatically; he was alert, without tremor, and with less soreness of muscles. The B.A.N. decreased to 85 μg. during the one day. A few days later the patient was discharged with the advice to follow the same high-protein diet, but with 0.5 gm. of neomycin for a week, then two Neobacin tablets with meals and at bedtime. Thereafter he resumed full-time work without difficulty and in four months was able to discontinue the taking of antibiotics.

Comment. This case likewise demonstrates the gradual onset of a personality change after portacaval shunt, and then a striking response to therapy. The esophageal varices were well demonstrated in the roentgen study of the esophagus, indicating the extent of collateral circulation present before the portacaval shunt, when there was no evidence of hepatic encephalopathy.

Case 4. A 55-year-old white man was transferred on March 5, 1958, to the Cleveland Clinic Hospital for neurosurgical care because of stupor occurring the day after a splenectomy that was performed at another hospital for traumatic laceration of the spleen sustained in an automobile accident. There had been no initial period of unconsciousness. It was learned (sometime later) that the history included excessive use of alcoholic beverages, a tendency to fall asleep "too easily," and an episode of jaundice in childhood.

Although not alert at the time of admission here, the patient was able to cooperate for examination. The blood pressure was 120/80 mm. of Hg. A mild fetor, and a flapping tremor of the outstretched hands were present. The liver descended 6 cm. on inspiration. Laboratory findings included: B.A.N. 121 μg. per 100 ml.; bromsulfalein retention 12 per cent in 45 minutes; serum albumin 4.1 gm.; serum globulin 2.9 gm.; serum bilirubin, direct none, indirect 0.8 mg.; and blood urea 101 mg. per 100 ml. At lumbar puncture, normal cerebrospinal fluid was found and the dynamics were normal. An electroencephalogram showed abnormally slow waves without dominant rhythmi-

**Compazine (prochlorperazine), Smith, Kline & French.*

city, waves of varying frequency (from 4 to 6 per second), and rhythmicity on a varying base line.

The patient was given arginine hydrochloride (25 gm. in 500 ml. of 10 per cent dextrose in distilled water) intravenously every six hours for one day, and then once daily for five days. He became much clearer mentally after one day of treatment. The flapping tremor and the fetor disappeared.

The patient subsequently showed gradual decline in blood hemoglobin content, and the symptoms and signs of abdominal sepsis developed. At operation, multiple "stress" ulcers of the stomach and cecum were found along with a perforation of the cecum. A hemigastrectomy, closure of the perforation of the cecum, and a tube cecostomy were performed. Thereafter the patient's course was rather stormy, but he gradually improved. Eventually the degree of improvement permitted needle biopsy of the liver. The histopathologic diagnosis was slight fatty change and chronic inflammation in the portal areas. Two months later the patient had completely recovered and had resumed full activity.

Comment. This case demonstrates the effect of a combination of gastrointestinal bleeding, shock, and abdominal trauma on a mildly diseased liver. The ammonia formed in the intestinal tract was undoubtedly not metabolized by the liver because of its temporarily depressed function.

Although the patient was referred to the Cleveland Clinic originally because of the possibility of cerebral injury, none was found.

Uremia must be considered in the differential diagnosis of disease in this patient, since the blood urea was increased. The flapping tremor may occur in uremia, but hyperammoniemia does not. The response to arginine also favors the diagnosis of hyperammoniemic (hepatic) encephalopathy.

Diagnosis

The diagnosis of hepatic encephalopathy necessitates a greater awareness of its varied symptoms, and more understanding of the multiple neurologic and personality changes that can occur. The lack of recognition of this syndrome is dramatically illustrated by the experience of Sherlock and associates[2] who described several patients having "episodic stupor" who had been placed in mental institutions. As the patients became stuporous they stopped eating, thus decreasing the dietary protein intake. With a decrease in protein intake, the patients regained their mental faculties, only to lapse into stupor again as they again ate more protein; hence the term "episodic stupor."

This condition occurs after operations for portacaval shunt, and in patients with portal hypertension in whom venous shunts and collateral circulation have developed. The encephalopathy is episodic, frequently being precipitated by gastrointestinal hemorrhage, trauma, infection, or excess dietary protein intake.

Episodic hepatic encephalopathy, as well as many instances of acute hepatic coma such as those precipitated by massive gastrointestinal hemorrhages, differs clinically from hepatic coma that develops spontaneously in the late stages of chronic hepatic disease, as in Laennec's cirrhosis. The prognosis in episodic hepatic

encephalopathy is good, *provided the condition is recognized and treatment is instituted.* Repeated episodes can occur with the patient recovering and being left with no residual cerebral or neurologic damage. The prognosis of hepatic coma occurring in the late stages of chronic hepatic disease usually is poor and the episode is fatal. However, ammonia intoxication may be a factor and treatment should be attempted.[5]

Bizarre and shifting abnormal neurologic changes, personality disorders, loss of affect, loss of memory, and stupor in a patient with hepatic disease should suggest the diagnosis of episodic hepatic encephalopathy. These changes are almost pathognomonic in any patient with portal hypertension, or in a patient who has had a portacaval shunt. According to current concepts, the diagnosis is confirmed by the finding of an abnormally increased amount of B.A.N.. The concentration of B.A.N. usually approaches normal as the patient improves with treatment. Electroencephalographic changes also can be of diagnostic help.

Treatment

Until the cause of hepatic encephalopathy is more clearly understood, treatment will continue to be largely supportive and nonspecific. At present, in selected cases, some specific measures seem applicable. Details of treatment are presented fully in other reports[5, 6] and will be reviewed only briefly here.

Episodic stupor or suspected chronic "hepatic" dementia may be treated by temporary withdrawal of protein from the diet. Neomycin, 1 or 2 gm. every six hours, is given by mouth to suppress intestinal bacteria, thereby preventing enzymatic degradation of protein and the formation of ammonia. Vitamin supplements, particularly vitamins B, C, G, and K are administered. The patient is sustained with carbohydrate foods and, after improvement is noted, protein is added to the diet slowly in increasing amounts. Many patients will tolerate a high-protein diet as long as neomycin is continued. Later, moderate protein intake may be tolerated without neomycin. Prevention of recurrence of episodic stupor involves adjustment of the protein in the diet to the tolerance of the patient, along with the general measures for the chronic hepatic disease present. Neomycin may be necessary indefinitely to permit satisfactory protein intake.

In deepening or severe stupor, or in those cases in which a flapping tremor of the hands with the arms outstretched heralds the onset of coma, arginine or glutamic acid should be administered intravenously, arginine hydrochloride (25 gm.), arginine glutamate or sodium glutamate (23 gm. in 500 ml. of 10 per cent dextrose in water) may be given as often as every six hours. Arginine and glutamic acid combine with ammonia and facilitate its excretion. Acidosis from the arginine hydrochloride, or edema from the sodium glutamate may limit such therapy. Thus, arginine glutamate, may prove to be preferable.

Hepatic coma as a complication of bleeding esophageal varices demands comprehensive treatment.[6] The blood must be quickly removed from the gastroin-

testinal tract. Since the Sengstaken-Blakemore tube usually will be inserted for esophageal tamponade in such cases, aspiration of blood pooled in the stomach, and administration of medications, are readily accomplished. Castor oil or magnesium sulfate should be given through the tube and, later, administration of neomycin should be started. The colon should be emptied by means of cleansing enemas. Other aspects of treatment include supportive measures, surgical treatment, and the therapy of hepatic disease per se.[5, 7]

Summary

Encephalopathy due to hepatic disease may be manifested by episodic stupor or chronic change in the personality as well as by coma. Since these various manifestations of encephalopathy may appear as complications of other diseases, especially of acute, severe disorders, all physicians ought to be aware of their significance. Episodic stupor, unlike many instances of terminal hepatic coma, may be reversible. Specific measures to diminish formation of ammonia in the intestinal tract and to lower excessive amounts in the blood are utilized along with general measures for hepatic disease.

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