

FOCAL NEUROLOGICAL SYNDROMES IN HEPATIC FAILURE

JOHN M. S. PEARCE, M.B.(Leeds), M.R.C.P.

Department of Neurology, Regional Neurological Centre, Newcastle upon Tyne

THE neuropsychiatric disturbances occurring in patients with liver disease have been recognized since the time of the Babylonians (Sherlock, 1958). Only in the last ten years, however, have their clinical and biochemical significances been appreciated (Walshe, 1951) (Adams and Foley, 1953).

The clinical and EEG findings have been described in detail by Sherlock (1955), Davidson and Summerskill (1956) and Parsons Smith, Summerskill, Dawson and Sherlock (1957). These are characterized by:—

1. *Mental symptoms:* lack of awareness, euphoria and apathy, associated with inversion of sleep-rhythm and drowsiness which may lead to delirium and coma. In the precoma stage, childish and inappropriate behaviour, as well as defects of recent memory, are common.

2. *Motor signs.* the most characteristic is a coarse irregular flapping tremor with frequency of 6-9/sec. Other signs include a rigidity of 'cog wheel' or 'lead-piping' type, masking of the facies, dysarthria and increased tendon jerks. Agnosia, usually spatial or visual, is seen less commonly, and constructional apraxia is another manifestation commonly seen. In the coma stage, bilateral clonus and extensor plantar responses may occur.

3. *Electroencephalographic (EEG) findings.* indicate diffuse cerebral damage and take the form of bilaterally synchronous and symmetrical high voltage 2-per-second slow waves. (Foley, Watson and Adams, 1950; Read, Laidlaw and Sherlock, 1961, Parsons Smith, and others, 1957. Laidlaw 1959, Laidlaw and Read, 1961). These changes are associated with a high blood and C.S.F. ammonia level and less consistently with an increase in glutamic acid glutamine in the C.S.F. (White, Phear, Summerskill and Sherlock, 1955; Whitehead and Whittaker, 1955; Booth, Swadey, Fiol, Klein and Hall, 1963).

The neurological findings are usually of a generalized nature, with a notable absence of focal signs, as indeed would be expected in a diffuse metabolic disorder. The following cases are reported because they show that occasionally focal signs may occur in patients with hepatic precoma or coma, and although their mechanism

is obscure, their recognition at the bedside is important.

Methods and Results

To assess the incidence of hepatic encephalopathy, and in particular of the occurrence of focal signs, the records of all cases with hepatocellular disease, admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, in the last five years, were studied. The findings recorded in Tables I to IV are from the 33 patients with porto-systemic encephalopathy. All of these patients had gross biochemical abnormalities of liver function and many had histological proof of cirrhosis or chronic hepatitis.

One hundred and seventy cases were studied, of which 33 (20%) had neuropsychiatric clinical features. In five cases focal neurological features were evident, an incidence of 3%.

TABLE I
FOCAL NEUROLOGICAL FEATURES IN HEPATIC FAILURE

Focal Features		Trans- ient	Per- manent
Hemiplegia	1	—	+
Unilateral increase in reflexes	3	+	—
Cortical blindness and agnosia	1	—	+
Focal seizures	1*	+	—

* In-patient with hemiplegia.

It will be seen that the occurrence of focal syndromes is uncommon, and that in three out of five patients the signs observed consisted of a definite unilateral increase in tendon reflexes which recovered completely when the metabolic disturbance was reversed. The age of the patients varied from 16 to 76, with a mean of 63 years at the time of the last admission to hospital. The incidence in the various age groups is shown in Table 2.

TABLE 2
AGE INCIDENCE OF PATIENTS WITH NEUROPSYCHIATRIC FEATURES OF HEPATIC FAILURE

0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
0	1	1	1	6	12	7	5

The aetiology of the liver disease, and the occurrence of portal hypertension is shown in Table 3.

TABLE 3
THE AETIOLOGY OF LIVER DISEASE AND THE OCCURRENCE OF PORTAL HYPERTENSION

Aetiology	Infective	Alcoholic	Idiopathic	Others	Total
Number ..	11	12	8	2	33
Portal hypertension ..	7	8	6	1	22

A definite past history of an illness compatible with virus hepatitis was taken as evidence of the cause being post-infective. Alcohol was accepted as the cause in patients with a definite history of prolonged and heavy intake of alcohol, and almost all such patients showed other evidence of chronic alcoholism. In the absence of a history of alcohol, or of an episode of hepatitis, the patient was placed in the Idiopathic Group. Two other cases were included both with histological proof of the aetiology; one patient was suffering from acute cholangiohepatitis, the other was a case of hepatic vein thrombosis (Budd-Chiari syndrome).

The incidence of portal hypertension is shown in Table 3. The presence of ascites and bleeding varices, or splenomegaly and varices, or splenomegaly and ascites, were taken as evidence of portal hypertension.

Table 4 is a summary of the relevant features of the 33 patients with neuropsychiatric manifestations.

The major factors precipitating hepatic coma or precoma, in these cases, were gastrointestinal bleeding, paracentesis abdominis, hypokalaemia induced by diuretics, and surgery. Often, multiple factors were operative and included an acute alcoholic debauch, administration of morphine, the ingestion of a high protein diet and infection. These factors are very similar to those described by Sherlock (1958). The neuropsychiatric syndrome may complicate liver disease of almost all types. In this series it was most common in chronic cirrhosis precipitated by an acute insult to liver function by one of the factors recorded above. The syndrome was also common in the 'Acute type of cirrhosis' (Sherlock, 1958) in which it appeared spontaneously, or with some other known precipitant.

The role of portacaval anastomosis in precipitating hepatic coma has been described by Read and others (1961) and by Gütgemann, Schreiber, Schriefers and Penin, (1961).

It will be seen that main clinical features were those of impairment of consciousness, associated with variable confusion and disordered behaviour. In this setting occurred neurological signs, the

most frequent being a flapping tremor. In cases of hepatic coma, hypertonus and hyperreflexia were often observed, usually involving all four limbs symmetrically.

The case reports of patients with focal neurological disturbances are now outlined.

Case reports

Case 1.—S. A., a female, aged 56, was admitted to hospital five days after a transient episode of unconsciousness lasting for three hours. Since this episode she had been drowsy and unable to find her way about her house, bumping into familiar objects, yet with no visual complaints. Examination showed her to be drowsy with no neurological abnormalities, save for a gross cortical blindness affecting the whole of both visual fields, with complete denial of blindness by the patient. Optokinetic responses were negative. There were no clinical stigmata of liver disease. As the possibility of a subdural haematoma could not be ruled out, and as she had bruises on her legs, suggesting a fall at home, bilateral carotid angiography was performed and was normal. Thereafter she became increasingly confused and lapsed into coma and died.

Autopsy revealed acute yellow atrophy of the liver with subcapsular haemorrhage and gross disruption of liver cells. The rest of the body was normal to the naked eye. The brain and vessels were normal macroscopically but histology revealed enlargement of the protoplasmic astrocytes diffusely throughout the brain; a finding typical of portosystemic encephalopathy. There was no evidence of focal infarction or other pathological lesion.

Comment.—In this case a primary intracranial pathology was sought in life, but autopsy showed the cause of the signs observed to be liver-cell failure, in this case of acute onset. It is surprising that no evidence of liver disease was found in life but it is probable that acute yellow atrophy of this severity would not be reversible.

Case 2.—A. B., a 56-year-old female, was admitted to hospital with a long history of alcoholism. For one week before admission she had become confused and irritable and was disorientated in time and space. Clinical examination showed euphoria and hypomania, and episodes of disorientation and violent behaviour were observed. She was jaundiced and had liver palms; hepatosplenomegaly and ascites were found on abdominal examination. Twenty-four hours later she lapsed into coma, with flapping tremor and hepatic fetor, and she then developed right-sided focal seizures each progressing to a major generalized convulsion. Treatment consisted of an intravenous infusion of dextrose and oral neomycin 4 g. daily. The seizures were controlled with paraldehyde. The fits ceased and she partially recovered consciousness, but was now noticed to have a gross dysphasia and a right spastic hemiparesis. This became more marked as her condition relapsed, as a consequence of bronchopneumonia. This proved resistant to antibiotic therapy. She again became comatose with increased tremor and a marked right hemiplegia. Despite continuing intravenous dextrose and electrolytes, oral neomycin and intramuscular penicillin she died. Biochemical tests during life showed strongly positive flocculation tests, bilirubin 3.4 mg./100 ml., alkaline phosphatase 27 K-A units, serum albumin 3.1 g./100 ml., globulin 4.9 g./100 ml.

Autopsy showed advanced portal cirrhosis and bronchopneumonia. The brain and vessels were normal macroscopically, there was no evidence of tumour or of

TABLE 4
CLINICAL FEATURES OF PATIENTS WITH NEUROPSYCHIATRIC DISTURBANCES

Age	Ætiology	P.H. No.	Drowsy	Stupor	Coma	Irritability	Violence	Delirium	Confusion	Foetor	Flapping tremor	Hypertronus	EEG (Abnormality)	Blood NH ₃ µg./100 ml.	Focal Neurological Signs	Focal	Alive or Dead	
G. C.	41	Infective	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
J. C.	72	"	o	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
E. F.	55	"	o	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
L. M.	41	"	o	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
W. B.	42	"	o	+	+	+	+	—	—	+	+	—	—	75	Parkinsonian syndrome	—	—	A
A. F.	16	"	+	+	+	+	+	—	—	+	+	—	—	—	Right hemiparesis	+	—	A
M. M.	39	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
M. S.	57	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
J. H.	71	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
I. S.	51	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
J. K.	47	"	+	+	+	+	+	—	—	+	+	—	—	—	Left-sided focal signs	+	—	D
E. M.	67	Idiopathic	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
A. R.	61	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
E. B.	55	"	o	+	+	+	+	—	—	+	+	—	—	104	Right-sided focal signs	+	—	D
A. P.	56	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
J. C.	65	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
S. A.	56	"	o	+	+	+	+	—	—	+	+	—	—	—	Cortical blindness	+	—	D
E. M.	76	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
T. B.	58	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
T. O.	71	Alcoholic	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
M. M.	44	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	D
J. K.	64	"	o	+	+	+	+	—	—	+	+	—	—	43	—	—	—	A
J. T.	65	"	o	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
D. A.	55	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
G. J.	61	"	+	+	+	+	+	—	—	+	+	—	—	47	—	—	—	A
F. B.	53	"	+	+	+	+	+	—	—	+	+	—	—	—	—	—	—	A
A. B.	56	"	+	+	+	+	+	—	—	+	+	—	—	—	Right hemiplegia. Dysphasia. Focal fits	+	—	D
T. P.	49	"	o	+	—	—	—	—	—	+	+	—	—	—	—	—	—	A
F. D.	55	"	+	+	—	—	—	+	—	—	—	—	+	100	—	—	—	A
H. P.	58	"	+	+	—	—	—	—	—	+	+	—	—	—	—	—	—	D
S. L.	28	Budd-Chiari	+	—	+	+	+	—	—	+	+	—	—	—	—	—	—	D
J. O'K.	75	Cholangio-hepatitis	o	+	+	—	—	—	+	+	+	—	—	—	—	—	—	D

P.H. = Portal hypertension.

No. = Number of episodes of encephalopathy.

infarction of the left hemisphere. Histological examination showed diffuse changes consistent with porto-systemic encephalopathy.

Comment.—The occurrence of focal seizures and later of hemiparesis in this patient suggested the presence of a focal lesion such as a tumour or a cerebral infarct. Autopsy showed no evidence of any such pathological change and by exclusion we attribute the focal clinical features observed to porto-systemic encephalopathy.

Case 3.—M. M., a 33-year-old female, with a progressive subacute hepatitis, was admitted to hospital in hepatic coma, with flapping tremor, hepatic foetor, jaundice, ascites and splenomegaly. There was markedly increased tone and brisk reflexes in the right arm and leg, the tone and tendon reflexes being normal on the left side. Both plantar responses were extensor. After treatment with intravenous glucose and electrolytes and oral neomycin she recovered consciousness and some weeks later was discharged home. The recovery of the conscious state was paralleled by total regression of her focal neurological signs.

Case 4.—J. K., a 47-year-old male, was suffering from portal cirrhosis secondary to post-necrotic scarring, having had severe hepatitis many years previously. He was admitted to hospital in hepatic precoma, with hepatic foetor, flapping tremor, drowsiness and confusion. This was presumed to be precipitated by gastro-intestinal bleeding from œsophagogastric varices. Whilst in this state of stupor and confusion he was noted to have increased tone and reflexes associated

with a mild paresis of the left leg. Treatment with parenteral glucose and blood transfusion, with oral neomycin, was followed by recovery of his conscious mental state and by reversal of his neurological signs.

Case 5.—E. B., a female, aged 55, with hepatic cirrhosis of unknown cause, was taken into hospital in a drowsy confused state. She had palmar erythema, flapping tremor and foetor hepaticus and was jaundiced. Biochemical investigations confirmed the diagnosis of cirrhosis. Her condition deteriorated a little and she then showed a slight increase in reflexes and tone of the right leg with the right plantar response clearly extensor and the left flexor. At this time the blood ammonia was 104 µg./100 ml. With treatment of the hepatic failure her condition improved and the signs in the limbs disappeared.

Case 6.—W. B., a female, aged 42, had a definite history of recurrent hepatitis, progressing to cirrhosis and her liver biopsy showed advanced cirrhosis with active cellular destruction. Having developed resistant œdema and ascites she was given large doses of thiazide diuretics and spironolactone. Over the course of a few weeks she developed a mask-like facies, hypokinesia, slow monotonous speech and cog-wheel rigidity of all four limbs. Probably as a result of her diuretic therapy, she deteriorated and lapsed into coma. The EEG showed symmetrical changes with dominant delta rhythm mixed with theta activity. The blood ammonia was 75 µg./100 ml. Despite treatment, she deteriorated and died. Permission for autopsy was withheld. This case is included because although it does not demon-

strate abnormal lateralizing signs, it does show that the development of signs of an extrapyramidal disorder can dominate the neurological picture found in liver failure.

Discussion

The clinical, electroencephalographic and pathological changes have been previously described by Walshe (1951); Adams and Foley (1953); by Sherlock (1955) and reviewed by Davidson and Summerskill (1956). The incidence of neuropsychiatric disturbances in patients with liver disease is higher than is generally supposed. Read, Laidlaw and Sherlock (1961) found that of 21 patients with liver disease, 8 had neuropsychiatric disturbances; a further 5 patients with no such clinical features had abnormal EEG's. Summerskill, Davidson, Mallory, Sherlock, Turner and Wolfe (1960) found 15 examples with encephalopathy in 70 patients with liver disease. 20% of a recent series of patients with cirrhosis were found to have abnormal EEG's by Gütgemann and co-workers (1961).

The occurrence of focal neurological signs, however, is rare. Focal signs due to intracerebral hæmorrhage were recorded by Stokes, Owen and Holmes (1945) in acute hepatitis. Inequalities in reflexes sometimes associated with a unilateral extensor plantar response occurred in the patients studied by Adams and Foley; however, none of these cases showed motor paralysis. As this paper points out, this occurrence during semicomatose or coma raises serious difficulties in the differentiation of hepatic coma from subdural hæmatoma and apoplexy. In a detailed review of the subject, Davidson and Summerskill (1956) record several generalized neurological syndromes and also note the occurrence of visual and spatial agnosia and constructional apraxia which indicate a disturbance of parietal lobe function.

The only case recorded by these workers, who had focal signs, was an alcoholic with a hemiparesis, who was subsequently shown to have a subdural hæmatoma.

The findings correspond closely to those of other workers in this field (Sherlock, Summerskill, White and Phear, 1954, Davidson and Summerskill, 1956; Sherlock, 1958; Laidlaw, 1959; Read, Laidlaw and Sherlock, 1961). The main psychiatric signs observed were those of drowsiness, confusion, apathy, with outbursts of violence and disturbance of behaviour. Accompanying this mental state, a flapping tremor almost invariably associated with *fœtus hepaticus* were characteristic signs. In the coma stage generalized hypertonus was sometimes seen in the limbs and was associated with hyperreflexia and occasionally extensor plantar responses. The presence or absence of portal hypertension and the ætiological

group did not seem to be related to the tendency to develop porto-systemic encephalopathy in this series. This may be related to the higher incidence of alcoholic cirrhosis in our cases compared to other recent series.

Attention is drawn to the fact that in the absence of local cerebral disease, clinically localised neurological signs may occur in patients with porto-systemic encephalopathy. This occurrence is, however, uncommon. In 3 cases, a transient increase in tone and reflexes occurred unilaterally. In one case a dense hemiplegia and dysphasia was associated with Jacksonian seizures, the hemiplegia persisting until death. Cortical blindness affecting both visual fields dominated the clinical picture in a further case and this also was present till the patient died.

We would stress the rarity of this finding, and when focal signs do occur in patients with hepatic coma, or precoma, it is wise to bear in mind the possibility of a focal, and perhaps treatable, lesion and to perform the relevant investigations when the patient is well enough. If the investigations prove negative then it is probably safe to assume that the clinical features observed are compatible with the diagnosis of hepatic coma or precoma.

In practice the patient may be too ill to withstand intensive investigation, when the focal signs mask their appearance and it is wise, under these circumstances, to treat the hepatic failure on its own merit and to limit neurological investigations to plain x-rays of the skull and chest and serial EEG recordings.

The present series shows an incidence of neuropsychiatric signs, similar to those of other workers (Summerskill and others 1960; Read, Laidlaw and Sherlock, 1961), but clearly the figures show only the proportion of patients with liver disease who are admitted to hospital who have such signs. It is, therefore, apparent that the true incidence of this complication in patients with chronic liver disease is much lower than that shown by hospital statistics.

It is difficult to explain the occurrence of focal cerebral signs in a generalised metabolic disease and one can only say that this is by no means peculiar to liver disease, as similar signs can occur in patients with hypoglycæmia and in uræmia. The cerebral disorder is a generalized one with a characteristic electroencephalogram and a specific, but generalized, histology. It can only be postulated that some transient disturbance of the dynamic cerebral circulation might precipitate a local disturbance of cerebral function.

Summary

A series of 170 patients with liver disease are

reviewed and the incidence of neuropsychiatric manifestations is assessed. Attention is drawn to the occurrence of focal neurological signs in a small proportion of such patients in the absence of localized pathological changes in the brain. The difficulty of excluding a treatable lesion when the patient is in hepatic failure is stressed, and it is

suggested that, if recovery from the acute illness occurs and the neurological signs persist, detailed investigation is warranted.

I am indebted to the physicians in the Royal Victoria Infirmary, Newcastle upon Tyne, for permission to study case records, and to Dr. D. R. Cameron and Dr. J. N. Walton for guidance in the preparation of this paper.

REFERENCES

- ADAMS, R. D., and FOLEY, J. M. (1953): The Neurological Disorder Associated with Liver Disease, in 'Metabolic and Toxic Diseases of the Nervous System', Vol. XXXII. Baltimore: Williams and Wilkins.
- BOOTH, C. B., SWADEY, J. G., FIOL, R. E., KLEIN, B., and HALL, J. C. (1963): Neurologic Status of Patients with Liver Disease, *Arch. Neurol.*, **8**, 257.
- DAVIDSON, E. A., and SUMMERSKILL, W. H. J. (1956): Psychiatric Aspects of Liver Disease, *Postgrad. med. J.*, **32**, 487.
- FOLEY, J. M., WATSON, C. W., and ADAMS, R. W. (1950): Significance of the Electroencephalographic Changes in Hepatic Coma, *Trans. Amer. Neurol. Ass.*, **75**, 161.
- GÜTGEMANN, A., SCHREIBER, H. W., SCHRIEFERS, K. H., and PENIN, H. (1961): Porto-kavale Anastomose und Sogenannte Enzephalopathie, *Dtsch. med. Wschr.*, **86**, 2370.
- LIDLAW, J. (1959): The Application in General Medical Conditions of a Visual Method of Assessing and Representing Generalized EEG Abnormalities, *J. Neurol. Psychiat.*, **22**, 69.
- , and READ, A. E. (1961): The Electroencephalographic Diagnosis of Manifest and Latent Delirium, with Particular Reference to that Complicating Hepatic Cirrhosis, *Ibid.*, **24**, 58.
- PARSONS SMITH, B. G., SUMMERSKILL, W. H. J., DAWSON, A. M., and SHERLOCK, S. (1957): The Electroencephalogram in Liver Disease, *Lancet*, **ii**, 867.
- READ, A. E., LAIDLAW, J., and SHERLOCK, S. (1961): Neuropsychiatric Complications of Portacaval Anastomosis, *Ibid.*, **i**, 961.
- SHERLOCK, S. (1955): Discussion on Hepatic Coma, *Proc. roy. Soc. Med.*, **48**, 479.
- (1958): 'Diseases of Liver and Biliary System'. Oxford: Blackwell.
- , SUMMERSKILL, W. H. J., WHITE, L. P., and PHEAR, E. A. (1954): Portal Systemic Encephalopathy, *Lancet*, **ii**, 453.
- STOKES, J. F., OWEN, J. R., and HOLMES, E. G. (1945): Neurological Complications of Infective Hepatitis, *Brit. med. J.*, **ii**, 642.
- SUMMERSKILL, W. H. J., DAVIDSON, C. S., DIBLE, J. H., MALLORY, G. K., SHERLOCK, S., TURNER, M. D., and WOLFE, S. J. (1960): Cirrhosis of the Liver, *New Engl. J. Med.*, **262**, 1.
- WALSHE, J. M. (1951): Observations on the Symptomatology and Pathogenesis of Hepatic Coma, *Quart. J. Med.*, **20**, 421.
- WHITE, L. P., PHEAR, E. A., SUMMERSKILL, W. H. J., and SHERLOCK, S. (1955): Ammonium Tolerance in Liver Disease: Observations Based on Catheterization of the Hepatic Veins, *J. clin. Invest.*, **34**, 158.
- WHITEHEAD, T. P., and WHITTAKER, S. R. F. (1955): A Method for the Determination of Glutamine in Cerebrospinal Fluid, and the Results in Hepatic Coma, *J. clin. Path.*, **8**, 81.

ERRATUM

'Influenza as a National Problem', A. T. Roden, October 1963. It is regretted that in this article Fig. 1 and Fig. 2 were transposed, and the caption to Fig. 6 applied to Fig. 7 and vice versa.