Choreoathetosis in porto-systemic encephalopathy

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A disturbing sequel to the operation of portacaval anastomosis for portal hypertension is the high rate of neuropsychiatric complications. Walker, Shaldon, and Vowles (1961) found that 10 of their first 50 patients who had this operation developed these symptoms within five years, and Read, Laidlaw, and Sherlock (1961) reported that seven of their 21 patients had frank neuropsychiatric disorders and a further seven had symptomless electro-encephalographic changes.

The clinical features of porto-systemic encephalopathy in chronic liver disease are extremely varied. The psychiatric manifestations include personality change, intellectual deterioration, and lability of mood, all of which may be episodic in nature. Disturbances of sleep rhythm, bizarre behaviour, and sensory disorders may also be found (Davidson and Summerskill, 1956). The neurological abnormalities which have been described have included flapping tremor of the outstretched hands, increased tone in the limbs with ankle clonus, and in the later stages extensor plantar responses (Sherlock, 1963). Focal neurological signs such as transient hemiplegia, permanent hemiplegia, and epilepsy have been described (Pearce, 1963) and permanent myelopathy with paraplegia has also been recorded (Zieve, Mendelson, and Goepfert, 1960; Liversedge and Rawson, 1966).

A further type of chronic non-familial hepatic encephalopathy was recorded by Victor, Adams, and Cole in 1961. The syndrome was characterized by dementia, dysarthria, cerebellar ataxia, and choreoathetosis, the latter symptom being generalized in half the patients. In a later paper (1965) they gave more details of the syndrome based on 27 cases and recorded an extensive bibliography.

Two more patients are described in whom choreoathetotic movements were the most prominent features of the porto-systemic encephalopathy syndrome.

CASE REPORTS

CASE 1 This patient, a housewife, was born in 1911.

In January 1950 she suffered her first attack of jaundice,

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from which she made an apparently good recovery. This was some months after a series of injections for varicose veins and a deep vein thrombosis. Her first known contact with infective hepatitis was not until early 1951, six weeks before her second attack of jaundice. On this occasion, however, her recovery was much slower.

In the autumn of 1951 she had her first haematemesis, with another in June 1952, requiring transfusion on both occasions. She was investigated in Geneva where she was then living. Her spleen was found to be enlarged. Investigation showed some evidence of hepatic parenchymal damage and thrombocytopenia. A splenectomy was performed.

No haematemeses occurred for the next two and a half years, but between October 1954 and November 1955 she had seven further episodes.

She was first admitted to University College Hospital, in November 1955 under the care of Professor M. L. Rosenheim. She was noted to be slightly anaemic; there were no spider naevi nor was there foetor hepatis. The liver edge was hard and irregular two fingerbreadths below the right costal margin. The serum bilirubin and empirical liver function tests were normal, but there was 8% retention in the bromsulphthalein test. The serum electrophoretic strip showed slightly diminished albumin and some increase of the γ -globulin. Needle biopsy of the liver showed cirrhosis with marked portal fibrosis and some regeneration. A barium swallow demonstrated oesophageal varices.

In view of the repeated haematemeses and good liver function tests a porto-caval anastomosis was performed by Professor R. S. Pilcher on 10 January 1956. The liver was abnormal, being grossly lobulated. The left lobe was represented by a collection of small nodules from 1 cm. to 4 cm. in size. The patient made a good recovery, but it was noted that over the next four weeks she developed a rash over the upper limbs due to generalized spider naevi.

During 1956 she remained well. In particular, her mental state was normal and there was no foetor hepatis.

However, during 1957 she began to have episodes of unsteadiness and slurring of speech. A flapping tremor and foetor hepatis were noted from time to time. A low-protein diet and antibiotics produced only temporary improvement. In September 1957 an E.E.G. showed that there was symmetrical dominant alpha rhythm activity with background low voltage fast activity. After a high-protein diet for four days there had been no change in her clinical state, but the alpha rhythm was now slower.

By January 1959 the tremor, slurring of speech, and movement had become constant, though fluctuating in

severity. It was noted that she was rather vague with emotional lability.

After an attack of bronchopneumonia in February 1962 she was admitted for assessment. The most striking feature was the incessant choreiform movements of her face and head, with protrusion of the tongue interfering with speech. Athetoid movements of her arms made her clumsy and slow. She was not jaundiced. The liver was only palpable across the sternal notch. No Kayser-Fleischer rings were seen.

A year later she suffered an attack of frank hepatic coma precipitated by a respiratory infection, but recovered to her previous state.

In October 1963 she was admitted for the last time. For the previous week she had become increasingly drowsy and the involuntary movements were more severe. Her orientation was poor. The choreo-athetoid movements were even more prominent. They interfered with her speech so much as to render her unintelligible. Spider naevi and liver palms were found as before. Foetor hepatis was also present and a hard liver edge was palpable one fingerbreadth below the right costal margin.

She improved temporarily on a no-protein diet and neomycin with sulphadimidine for a urinary infection. However, even when given only 10 g. protein per day she lapsed into coma and also became oliguric. She recovered spontaneously but passed into coma again a week before her death on 23 November 1963.

The investigations have been summarized in Table I.

General pathological examination The body was that of a moderately nourished woman without jaundice and with well-healed abdominal scars. Acute bronchitis was a contributory cause of death. In the oesophagus a few thin veins were visible in the mucosa of the middle third, but no varices. The liver weighed 680 g., the left lobe being represented by a few nodules only up to 5 cm. diameter and these separated by grey fibrous bands. The right lobe was nodular, the nodules up to 2 cm. diameter, and separated by very thin septa of fibrous tissue, its colour reddish brown. The hepatic artery and its branches were patent. The portal vein was

anastomosed to the inferior vena cava, the opening being patent and 6 cm. in circumference, that is, very wide. Microscopic examination confirmed post-necrotic cirrhosis with fatty change and quite extensive deposition of haemosiderin in parenchymal cells. A section of the pancreas showed no abnormality.

Neuropathological examination A thin brown film of old subdural haemorrhage was present over both hemispheres. The brain weighed 1,440 g. and showed no abnormality of the external surface. Coronal sections of the cerebrum showed slight general congestion and a cystic area 0.5 cm. diameter in the superolateral angle of the left lateral ventricle, as well as a cystic streak 1 cm. long beneath the ependyma over the lower part of the head of the right caudate nucleus. There was slight narrowing of the grey matter in the depths of sulci in scattered areas, *e.g.*, in the left frontal lobe, the right posterior frontal lobe and the posterior ends of both insulae, and in a few parietal gyri. Section of the hindbrain showed a brown streak beneath the ependyma of the right lateral wall of the fourth ventricle which extended into the middle cerebellar peduncle.

Histologically the most conspicuous change was a loss of nerve cells accompanied by gliosis and capillary proliferation in many areas of the cortex of frontal, parietal, and occipital lobes, but sparing most of the temporal lobes. This affected the deeper layers and on the whole the depths and sides of gyri rather than the summits. In a few places a spongy change was apparent in the nervous tissue in these zones, particularly in the occipital lobe, but for the most part was less evident than the capillary proliferation. In one gyrus in the occipital lobe there was telangiectasia in the white matter in the most severely affected area. The number of areas affected in a typical section are shown in Fig. 1 (left frontal lobe at level of caudate nucleus), the typical change in Figs. 2 and 3, the spongy change in Figure 4. A similar change was present to a lesser extent in the dorsal part of the putamen. In the hindbrain there was some loss of neurones in the dentate nucleus of the cerebellum and in the inferior olive. Evidence of old haemorrhage was confirmed in the middle cerebellar

TABLE I

INVESTIGATIONS IN CASE 1

Date	Hb %	Bilirubin (mg.%)		Colloidal Red	Cephalin Cholesterol	Thymol Turbidity	Alkaline Phosphatase	S.G.O.T.	Prothrombin Ratio or Concentration (%)	Plasma Proteins Alb. Glob.	Alb/ Glob. Ratio	B.S.P. Retention (%)
		Direct	Total									
Nov. 1955	74	Negative	0.7	Negative	Negative	1	17.7		83	3.6 2.9	1.2	8
Dec. 1956	82	Negative	1.7	Weak	Negative	4				3.1 2.2	1.4	
Sep. 1957				Positive								
Aug. 1958				Negative	Negative	4				3.3 2.7		
Jan. 1959	88	Negative	2.0	Moderate	Weak	7			49	3.6 2.6	1.4	
Feb. 1960				positive	positive	flocculation						
				Strong	Weak	4				3.4 2.4		
Mar. 1962	80	Weak	0.5	positive	positive	3	13.5		55	Total 5.1		
Feb. 1963	92	Weak	0.9	positive	Weak							
		positive		Positive	Strong	6	18.2	147	46	2.3 3.0	0.77	
Oct. 1963	95	Weak	2.6	positive	positive	8	16.4	29	1.21	Total 4.5		
		positive		Moderate	Strong							
				positive	positive

FIG. 1. Superior half of the left frontal lobe at the level of the caudate nucleus showing number of affected areas (ink marks). $\times 2$.

FIG. 2. Left occipital cortex showing loss of neurones, capillary and glial proliferation in the deeper layers together with microcavitation and dilatation of capillaries in adjacent white matter. Haematoxylin and eosin $\times 175$.

FIG. 3. Insular cortex with changes similar to those in Fig. 2 except for the absence of capillary dilatation. Haematoxylin and eosin $\times 150$.

FIG. 4. Putamen showing spongy change. Haematoxylin and eosin $\times 175$.

peduncle and was accompanied by some gliosis. There was also a mild telangiectasis in the pons without neuronal damage. The glia proliferation involved Alzheimer type II cells in many areas and some of these had small intranuclear P.A.S.-positive inclusions; they were not so large as those illustrated by Victor *et al.* (1965) in their Figure 25. In view of the similarity of the changes in this case to those of Wilson's disease, a particular search was made for Opalski cells which are regarded as a characteristic feature of that disease. No cells were found which could be regarded as abnormally large histiocytes which is the view expressed by Greenfield as to their nature. In scattered areas of the cortex and in the thalamus, however, abnormally swollen degenerate neurones, some with a granular P.A.S.-positive cytoplasm were present comparable to those illustrated by Victor *et al.* (1965) who argue cogently that this cell is indeed a lipid-laden neurone.

CASE 2 J. McG., a storeman, was born on 18 December 1902.

This man was first seen at University College Hospital on 12 June 1961 when he complained of right upper abdominal aching which had been present for two years. Otherwise he had been well, but had been accustomed to drinking 14 pints of beer a day. Examination at that time revealed hepatosplenomegaly, but there were no other stigmata of chronic liver disease. Investigations showed moderately abnormal liver function tests, oesophageal varices were demonstrated at a barium swallow, and a liver biopsy revealed patchy fibrosis.

On 31 January 1962 he was admitted as an emergency following a large haematemesis and melaena to St. Mary's Hospital, London. There was no change in his physical condition at that time and no abnormal neurological signs were noted. A porto-caval anastomosis was carried out on 19 March by Mr. H. H. G. Eastcott and a grossly cirrhotic liver was noted. Post-operatively he had a satisfactory convalescence and was discharged on a low-protein diet with neomycin. It would appear, however, that after a few weeks he returned to a normal diet and stopped taking neomycin.

When seen in the Out-Patients' Department of University College Hospital on 26 May 1964 he was reasonably well and quite alert mentally. On or about 3 June, according to his neighbours, he became confused. He had developed slurred speech and began falling about and was noted to have grotesque writhing movements of the face when admitted as an emergency on

10 June under the care of Professor T. A. J. Pranker. On examination he was moderately confused, although able to give some account of his recent deterioration. He had gross writhing movements of the arms, and to a lesser extent, the legs. He was constantly grimacing, with his tongue being intermittently protruded and being rolled around in his mouth. The reflexes were all equal and normal, but he had bilateral extensor plantar responses. There was no flapping tremor or hepatic foetor. The liver was enlarged, regular and firm, three fingerbreadths below the right costal margin. The spleen was not palpable. He had no ascites or spider naevi. Kayser-Fleischer rings were not seen.

The significant investigations are summarized in Table II. Wilson's disease was considered to have been excluded by the following investigations.

Radio copper studies (Dr. J. M. Walshe) showed that the rate of incorporation of copper into caeruloplasmin (which was given by the ratio of activity in the plasma at 24 hours to that at two hours) was 0.85, which was in the lower limits of normal (range in hepatolenticular degeneration: 0.1 – 0.35). There was a 38% uptake by the liver and the maximum was reached within two hours and thereafter there was a steady decline (normal peak usually reached at 24 to 30 hours with maximum uptake varying from 60 to 90%). During the 15 minutes after the injection of radio copper the uptake by the liver was good and the liver/thigh ratio at 15 min. was 1.8, that is, within the normal range. In Wilson's disease the range varies from 0.6 to 1.2. The caeruloplasmin level was found to be within normal limits.

An E.E.G. two days after his initial admission was unsatisfactory since in order to get a tracing the patient received 200 mg. Seconal an hour before. The dominant rhythm varied between 2 and 6 cycles/second. No high voltage waves were seen. The E.E.G. was repeated later on 4 August when the patient had improved clinically. The dominant rhythms were between 3 and 4 cycles/second and the activity was of higher voltage than previously seen.

Progress On admission he was treated with neomycin 2.0 g. q.d.s. and intravenous dextrose infusions. Later he was put on to a diet containing 20 g. per day protein. During the first five days his mental state improved slowly and the extensor plantar responses noted on admission reverted to flexor after three days. However, his bizarre movements and facial contortions persisted and were only slightly modified by treatment. His constant grimacing with forehead wrinkling, lip smacking,

TABLE II

INVESTIGATIONS IN CASE 2

Date	Hb %	Total Bilirubin (mg.%)	Colloidal Red	Cephalin Cholesterol	Thymol Turbidity	Alkaline Phosphatase	S.G.O.T.	Prothrombin Ratio or Concentration (%)	Total Plasma Proteins	Alb./ Glob. Ratio	B.S.P. Retention (%)
Jun. 1961	113			Positive	Negative			1.04	8.3		
Jan. 1962	69	0.15			Negative	5.0		1.0	6.8	1.1	1
Feb. 1962	99										
Mar. 1962	95	1.16			Negative	9.5		1.0	7.8	0.81	
May 1962		0.95			Negative	21.5	20				
Sep. 1964			Negative	Negative	Negative				5.9		

tongue protrusion, and head rolling remained a constant feature. The athetotic movements of the limbs decreased in severity somewhat. Since that time his clinical state has fluctuated slightly, but he is now able to walk unaided and to feed himself, but is occasionally incontinent of urine and faeces.

DISCUSSION

Of particular interest in these two patients is the presence of choreo-athetotic movements in portosystemic encephalopathy. In both patients the involuntary movements showed a combination of both the choreic and the athetotic components seen in extrapyramidal disorders. Thus the movements of the face, following each other rapidly to give frowning, smiling, and pursing of the lips, all commonly regarded as being choreiform, were combined with more characteristic athetotic movements such as slow protrusion of the tongue, dysarthria, dysphagia, grimacing, and writhing movements of the arms and legs.

Clearly the association of these extrapyramidal signs in a patient with chronic hepatic disease must raise the diagnostic possibility of Wilson's disease (hepatolenticular degeneration). In each case the relatively late onset of the neurological features at the ages of 51 and 62 with negative family histories make this unlikely. Even more suggestive is the fact that the choreo-athetotic movements appeared at 11 and 26 months after a portocaval anastomosis. Detailed copper studies were not considered necessary in case 1, but in case 2 the finding of a normal caeruloplasmin level and normal radio copper studies definitely excluded the diagnosis.

Other causes of choreo-athetotic movements developing for the first time in adult life are few. Although the clinical picture in these cases shows a close similarity to that of Huntington's chorea, the onset soon after surgery and the absence of a family history do not support this diagnosis. Recently dyskinetic movements in and after treatment with phenothiazine derivatives have been reported where the predominant movements have involved the tongue, lips, and face, and the patients had insight into their movements (Heathfield, 1965). In elderly patients, with dementia and sometimes with bilateral pyramidal disease, Rosin and Exton-Smith (1965) have drawn attention to the facial grimacing, complicated movements of the tongue, lip smacking, chewing and blinking movements which may occur.

The association of choreo-athetotic movements with chronic liver disease has been well documented by Victor *et al.* (1965). Of particular interest were two patients who developed the syndrome after portal-systemic shunt in the absence of intrinsic

liver disease. In the majority of their patients they noted that certain symptoms—dementia, dysarthria, cerebellar ataxia, and choreo-athetosis—were persistent and unrelated to attacks of hepatic coma. This occurred in both our patients and the situation was not influenced by low-protein diet and intestinal antibiotics. In five of their patients, as in our cases, a generalized choreo-athetosis indistinguishable from that of Huntington's chorea was present. From examination of the 17 cases which came to necropsy, they considered that the pathological findings in the brain were very similar to those found in Wilson's disease.

The persistence of the neurological signs in our patients is not surprising in view of the histological findings. The changes in the brain in case 1 were maximal in the deeper layers of the cortex, but present to a varying extent in one cerebellar peduncle, the inferior olive, and the basal ganglia. Their distribution is thus essentially similar to that described by Baltzan, Olszewski, and Zervas (1957), Gibson (1963), and Victor *et al.* (1965) in other cases of this syndrome. These reports, however, all emphasize the spongy change in neural tissue. In case 1 this was much less prominent in most areas than capillary proliferation, neuronal damage and loss, which may possibly precede the spongy change.

The distribution of the cortical lesions, maximal in the depths of gyri, as well as their type, suggests at first sight an ischaemic pathogenesis. However, the sparing of the hippocampal gyri is against this. Furthermore, the frequent association of this process with a widely patent portocaval anastomosis is of paramount importance and suggests strongly that the effect of the portal blood on the brain is the essential factor.

Victor *et al.* (1965) have emphasized the similarity of the pathological changes to those of Wilson's disease. The changes in the case recorded here could be accepted as similar to Wilson's disease. Like most of their cases it affected the cortex more severely than the basal ganglia which is unusual but well documented in Wilson's disease.

SUMMARY

The development of choreo-athetosis following portocaval anastomosis for bleeding from oesophageal varices is recorded in two patients with cirrhosis of the liver. The symptoms were not significantly affected by oral neomycin and a low-protein diet. The necropsy findings in one patient showed loss of nerve cells with gliosis and capillary proliferation in the cerebral cortex, with similar though less marked changes in the basal ganglia, dentate nucleus, and inferior olive. Excessive

shunting of portal blood into the systemic circulation through a large anastomosis may be responsible for these changes.

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