CHOLÆMIA.

A Clinical Study of the Nervous Symptoms in Liver Atrophy.

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The idea of a relationship between diseases of the liver and nervous symptoms is long established, as is suggested by the origin and use of the adjective 'choleric.' Wilson's discovery of a group of cases in which cirrhosis of the liver is associated with progressive degeneration of the lenticular nucleus of the brain and striking nervous symptoms, received the immediate attention it deserved, largely because it offered concrete pathological evidence of this relationship. Apart from these we have evidence of the characteristic feelings of depression of a jaundiced patient, and the acute nervous symptoms which may usher in the terminal, or so-called cholæmic, stage of acute liver diseases. Comparatively little has been written on these cases, so that certain observations we have made appear to us worthy of record. These are concerned with nervous signs and symptoms which occurred in two recent cases of liver atrophy in children, and they have been augmented by reference to the clinical records of nineteen other cases of acute or subacute liver atrophy which have come to post-mortem examination in this Hospital since 1913. Of these 21 cases only five were children of the ages, 4, 9, 10, 11 and 14 years. But the subject has a special interest for students of children's diseases because of the greater intensity of the clinical picture in childhood and the resemblance it may bear to that of meningitis.

The first two cases we describe offered good opportunities for the study of the nervous signs, as they ran their courses without the intervention of any terminal complication such as pneumonia or peritonitis to alter the clinical picture. One of the most striking features was the peculiar type of noisy delirium they exhibited. It was more than mere febrile delirium, the peculiar wailing and crying being unlike anything else we have seen in other toxic or delirious states. So distinctive are they that they almost merit the description of 'cholæmic cries.' The first case had an extensor plantar response on one side only, and it would appear that there was also some paralysis of the muscles of accommodation in the eyes. The second case had a paralytic squint. He had also nasal speech and palatal paralysis resembling diphtheritic palsy, yet in the absence of any evidence that it was diphtheritic in origin: a point to be noted, for we shall refer to a case of Bright's described in 1836, which appears to have shown the same disability. Another point to be noted, although its significance cannot be explained, is that the first case had a typical duodenal ulcer, a rare event in a boy of nine.

CASE 1. Boy aged 9 years. Admitted 19.4.26. Died 22.4.26. A very accurate and detailed history was obtained from Dr. Charles, who referred the case to hospital as follows:—A perfectly healthy active boy up to onset of illness 3 weeks before admission. Member of a healthy family with no evidence of syphilis. The first symptoms were lassitude and drowsiness, with some vomiting in the first week. During the second week he was easily tired and peculiarly lethargic and drowsy, and the possibility of encephalitis or meningitis was considered. There were nausea and occasional vomiting with some slight abdominal pain and an attack of diarrhoea for a few days. At this stage his eyesight appears to have become affected in a peculiar way. He was not yet acutely ill, being able to sit about at the fireside, and he is described as being “unable to see things properly and groping for his food at table.” In the third week he became worse and took to his bed. Two days before admission (17.4.26) he was obviously dangerously ill with swollen abdomen, œdema of the feet and delirium. At this time there was no jaundice, and the urine contained no albumen or sugar.

On admission on 19.4.26 the boy was extremely ill and restless. Pulse 112. Respirations 24. Temperature normal. There was obvious recent loss of subcutaneous fat. There was considerable ascites, and the liver was smaller than normal though the edge of the left lobe could be felt high up in the epigastrium and was very hard. Spleen enlarged. The heart and lungs showed nothing to account for the illness. The urine was acid, 1025, no albumen and contained a trace of sugar. Cerebro-spinal fluid was normal. Blood urea 40 mgms. per 100 c.c. No jaundice or petechiæ present. Occult blood was present in the stools.

On this day the nervous signs were as follows:—He was in a restless state suggesting at first sight tuberculous meningitis, but differing from that in the way he would sit up apparently quite conscious, giving vent to peculiar wails and piercing shrieks, refusing to be comforted. These were not mere complaints of acute pain or the insensate cries of semi-coma. They went on at times for as long as ten or fifteen minutes while he sat up in the corner of his cot, resembling some terror stricken animal in its cage. He would then subside into quieter states of irritability or restlessness, to be followed again by these attacks of active shrieking and plaintive wailing. The pupils were widely dilated, but reacted to light. As far as could be seen there was no reaction to accommodation and the fundi oculi were normal. No squints or ptosis. Both knee-jerks and ankle-jerks were present. On the right side there was a well-marked extensor plantar response, on the left side it was equivocal. There was no stiffness of the neck. During the next three days before death the extensor response on the right side persisted, the left plantar response remained indefinite. Pupils remained widely dilated. The restless state continued, but now the periods of crying and wailing were varied by the intermission of convulsive attacks in which he held himself in a position of opisthotonos, the attacks lasting perhaps half a minute and severe enough to suggest poisoning by strychnine. When these passed, there was no rigidity and no neck stiffness, and he lay for the most part quiet and flaccid with occasional return of the ‘cholæmic crying.’ At this stage the Ward Sister ventured the opinion that in spite of the obvious resemblance to meningitis, she had never seen a case of meningitis behave as this case, in the way he changed from one state to another, nor had she ever heard such peculiar wailing going on as it did at intervals for two days and nights. On 22.4.26 petechiæ appeared on the arms and trunk. He vomited blood, then sank into a weak comatose state and died. Jaundice, though eagerly sought for, was absent throughout the illness until 24 hours before death when it appeared in the conjunctiva. Blood taken for a Van den Bergh test on the last day gave a direct positive reaction. A trace of sugar was present in the urine until the last day.

Post-Mortem examination (by Dr. A. F. B. Shaw): A slight degree of jaundice could be noticed in the conjunctiva and skin. A typical condition of advanced subacute atrophy of the liver was found. The liver weighed 28 ozs. Capsule wrinkled in places. Small areas of nodular hyperplasia, canary yellow in colour, varying in size. Spleen enlarged. Ascites present. Small hæmorrhages on surface of heart, at the cardiac end of the stomach and along the small intestine at the mesenteric junction. The pleural and pericardial cavities contained a few ounces of bile-stained fluid. The heart, lungs, kidneys, suprarenals, and pancreas showed nothing of note. The brain was carefully examined and there was no evidence either naked eye or histological to

account for the nervous signs and symptoms. The stomach and intestines contained altered blood. There were no inflammatory lesions in the bowel. There remains to be described the duodenal ulcer already referred to. This was a typical elliptical peptic ulcer one inch in breadth on the first part of the duodenum; the edges clean cut and vertical; the floor smooth and fibrous. There was no eroded vessel to be seen in the floor.

In the next case it is to be noted that the terminal cholæmic state was ushered in by the same type of wailing and 'cholæmic crying' as in the first case. The resemblance was remarkable and of sufficient significance to enable a clear definition of the prognosis.

CASE 2. Boy aged 4. Admitted 22.4.26, died 27.4.26. *History:* The boy had been vaguely 'out of sorts' for 4 months before admission to Hospital. The only definite illnesses had been tonsillitis 9 months and again 5 months before admission, for which the operation of tonsillectomy was performed 10 weeks before admission. From this he made a good recovery, the throat being free from any apparent diphtheritic infection during the stage of recovery. Three weeks before admission he developed jaundice with vomiting and clay-coloured stools. At the end of the second week he began to recover from this and was 'out and running about' two days before admission to Hospital. Next day he became ill again with weakness and lethargy and he was referred for admission to hospital.

On admission. Temperature and respiration normal. Pulse 120. Looked ill and toxic. Quite conscious and able to respond to instructions, but a tendency to drowsiness. Deeply jaundiced. Liver: no alteration in size, firm edge felt just below costal margin. Spleen not enlarged. No ascites. The chief nervous signs at this stage were as follows:—Pupils widely dilated and unequal, right larger than the left. Both react to light. Paresis of the right external rectus with internal squint. No ptosis. Very distinct nasal speech with palatal paralysis. Other cranial nerves normal. Both knee-jerks absent. Both ankle jerks present but responses very faint. Both plantar responses definitely flexor. There was no neck rigidity. Swabs were taken from the nasopharynx and throat. No K.L.B. found. Blood urea normal (28 mgms.). Blood sugar raised = 0.226%. Urine contained a trace of sugar, bile, acetone, and diacetic acid. Leucin or tyrosin were not found. At this stage a diagnosis of catarrhal jaundice was made, but no explanation could be given for throat and eye symptoms.

Two days after admission (*i.e.*, three days before death), the condition changed rapidly for the worse. He became extremely restless and the peculiar 'cholæmic crying' noted in the first case commenced. He preferred to sit up in bed wailing and shrieking intermittently. There appeared to be some photophobia at this time. This state continued for two days, quite conscious sleeping, at intervals, but generally miserable and refusing to be comforted. For these two days the shrieking and crying continued loud enough to be heard in other parts of the hospital and requiring his removal to a side ward. Twenty-four hours before death the picture changed again. He began to sink into coma, and fits commenced, differing a little from the convulsive attacks seen in the first case. In these he threw himself across the bed with his arms above his head and eyes wide open. There was no definite rigidity in these attacks. The lower jaw was flaccid and there was no neck rigidity. During these attacks urine was passed involuntarily. Intermittently the crying continued in a weaker plaintive tone. He died in deep coma.

While under observation the plantar responses remained definitely flexor. Slight glycosuria persisted until the last two days when insulin and glucose treatment was instituted as an attempt to combat the acidosis. The temperature remained normal or subnormal throughout. The pulse rate which was 120 on admission advanced as the illness progressed.

The *post-mortem* was done 2 hours after death by Dr. A. F. B. Shaw. The findings were those of typical liver atrophy. Weight of the liver 18½ ozs. The surface of the liver consisted in some parts of slightly raised yellowish-green tissue, in others of depressed areas dull red in colour. The quadrate lobe was large and appeared to be composed entirely of regenerated liver tissue. On section the organ was typically greenish-yellow in colour cutting firmly, the appearances being those of a subacute atrophy of the liver. Naso-pharynx was clean without

evidence of diphtheritic membrane. Small hæmorrhages were present beneath the surfaces of the lungs and in the mesentery. There were some actively caseous glands in the omentum. Otherwise all other organs shewed no special change. The liver condition was confirmed by microscopic examination.

DURATION OF SYMPTOMS.

The clinical records of the remaining 19 cases are not complete enough to allow a full comparison of all the details of the nervous signs and symptoms noted in the two cases we have described, as some of the patients were admitted to hospital within a few hours of death. In one the picture was complicated by a terminal rupture of a duodenal ulcer, and in three others by extensive bleeding from the bowel. But when the nervous symptoms had been observed and noted, the chief feature commented on was the supervention of 'noisy delirium,' 'shouting' or 'extreme restlessness' a short time before death. The most frequent sequence of events was a stage of drowsiness or lethargy followed by a period of noisy delirium, and ending in coma. Out of the total 21 cases this sequence, or some slight variation of it, could be traced in 16, including the 5 children.

The duration of the acute nervous symptoms of the terminal phase varied in these cases from 12 days to one day, with an average of 4 days. But this period was difficult to define, for in some cases of the subacute type a history was obtained of transient attacks of coma or drowsiness for several weeks before death. This is exemplified in the following instance of a man who died with typical subacute liver atrophy, who had recurring attacks of coma off and on for 6 weeks before death.

CASE 3. Man aged 35. Admitted 22.3.22; died 1.4.22. History of syphilis and salvarsan injections in 1919. The first symptoms appeared seven weeks before death with swelling of the abdomen and jaundice. A week later he had an attack in which he was drowsy and then comatose for 24 hours, followed by complete recovery of consciousness. A week or two after a second attack of coma occurred lasting two days, and again from this he recovered. During these attacks he could not be roused and there was loss of sphincter control. Admitted 9 days before death there were no nervous symptoms or signs. Two days later he had an attack (the abdomen had been tapped a few hours before) in which he is described as "very noisy for an hour or two, shouting and crying, and with incontinence of urine and fæces." He recovered temporarily from this and later became unconscious and died.

Although the appearance of coma or noisy delirium usually denotes the approach of the terminal stage of the disease, we feel that it is neither necessary nor profitable to attempt to define them too closely as a ready means of foretelling the issue. Stuart M'Donald and Milne⁽¹⁾, in a study of the pathological changes in subacute atrophy of the liver have commented on the difficulty of estimating the duration of the morbid processes. They describe cases in which they judged the liver changes to have been present for varying periods up to 7 months. The same difficulty exists in attempting to assess the significance of some of the vague symptoms such as lassitude and sleepiness which some of the cases show for several months before more definite evidence of liver disease show themselves. Moreover this difficulty is presented more clearly

when we remember that all studies of subacute or acute liver atrophy are based on cases which ultimately die. It seems to be tacitly understood that such a diagnosis is ventured only when the liver disturbances, or jaundice if it be present, are severe enough to kill the patient. Short of that, or if recovery takes place, the diagnosis of catarrhal jaundice or perhaps "acidosis" is given. Apropos of this we have recently heard of a case of which we are not able to give full details, in which the patient had symptoms suggesting encephalitis from which he recovered. For the next six months he had vague abdominal and digestive trouble for which a laparotomy was done. At the operation a 'cirrhotic condition of the liver' was found. This may be a case in which acute or subacute atrophy of the liver was present at the time of the encephalitic symptoms of lethargy and from which a recovery was made to go on later to cirrhosis. Byrom Bramwell's⁽²⁾ suggestion that certain unusual cases of cirrhosis in young people might be a phase of Wilson's disease in which the nervous manifestations had not yet declared themselves, has a bearing on this point.

SUMMARY OF OBSERVATIONS.

Without giving details of the other three cases in children and of the remaining adult cases, some points of interest in the whole series of 21 cases can be summarised for brief discussion.

Of 21 cases of liver atrophy 5 were children of 14 or under. These were traced from a total number of 4958 post-mortems in a period of 13 years, and thus represent only the fatal cases which occurred in this time. The possibility exists that other cases have occurred and have recovered.

The pathological changes in the liver in these cases were as follows: 1 case of acute atrophy (acute yellow atrophy) and 20 cases of subacute yellow atrophy. Or classifying them in the way that Miller and Rutherford⁽³⁾ suggest, in which the subacute group is further subdivided according to the amount of regenerative changes found in the liver: 1 case of acute atrophy with early fibrosis, 5 cases of subacute atrophy with early fibrosis, 15 cases of subacute atrophy with marked nodular hyperplasia.

In all 5 cases of children, and in 11 of the adult cases a certain sequence of nervous symptoms characterised the terminal or 'cholæmic' stage. This was more evident in the children than in the adults and consisted of lethargy or stupor, a period of unusual shrieking and crying, a stage of convulsions, death in coma.

The most characteristic of these stages of nervous symptoms was that of maniacal shrieking and wailing which we have termed 'cholæmic crying.' It was not present in all cases, but when it occurred it was distinctive, differing from mere toxic delirium.

In 8 cases where a systematic examination of the reflexes was recorded extensor plantar responses were present in 3. In one of these it was unilateral.

In one case there was palatal paralysis and nasal speech.

In one case there was a paralytic strabismus due to a 6th nerve paralysis.

In 4 cases cerebro-spinal fluids were examined. In none of these were there increases of cells or of protein.

Jaundice was present in all cases but varied greatly in degree, and the appearance of the nervous cholæmic symptoms can bear no relation to it, when we consider the features of the first case we have described. For there a slight tinge of jaundice appeared only in the last 24 hours, when the boy had already had acute nervous symptoms of cholæmia for 6 days. (We recognise from this the mistaken etymology of the term 'cholæmia' in the sense that we have used it. But the use of it as a clinical term to express the terminal stage is justifiable, just as 'uræmia' is used for the analogous toxic stage in kidney disease, although excess of urea in the blood is not the toxin concerned.)

In 4 of the cases of the subacute type with ascites and jaundice, the acute cholæmic stage was precipitated by tapping the abdomen to relieve abdominal discomfort.

A terminal pyrexia was noted in 5 cases, only two of which had broncho-pneumonia. Thus the nervous symptoms of cholæmia cannot be explained by a sudden accession of fever.

In six cases there was evidence of syphilis and treatment by salvarsan, and in one other case of congenital syphilis without treatment by salvarsan. The clinical picture of the cholæmic stage in this group did not differ from that of the other cases.

DISCUSSION.

A few of these points will need more discussion than the comment we have made on them.

Extensor plantar responses. It has long been established that these may occur in cholæmia. As far as we can find Rolleston⁽⁴⁾ first drew attention to it in describing a case of acute yellow atrophy. Later Willcox in his Lettsomian lectures⁽⁵⁾ described cases of infective jaundice, and Elliott and Walshe⁽⁶⁾ cases of hepatic cirrhosis, which developed extensor plantar responses in the terminal cholæmic stage. These are mentioned again by Walshe⁽⁷⁾ in his review 'The Babinski plantar response in toxic states.' Elliott and Walshe state that the stage of cholæmia may be recognised "by the mental changes of mild delirium or drowsiness, associated with a double extensor response." This suggests that the extensor plantar response characterises the toxic stage of cholæmia and is a necessary sign or accompaniment of it, for they go on to state the converse that other cases of hepatic disease may sink "quietly and slowly to death without acute mental changes and without an extensor response even in the last hours, that is, without cholæmia." We agree that careful and repeated examinations of the plantar reflexes should be made in any suspected case, but we cannot agree that when cholæmia ensues, extensor responses will necessarily be found. In our first case it was present on the right side and indefinite on the left. But in the second the responses remained definitely flexor, for they were tested carefully and repeated by

up to the hour of death. Yet this case had the other classical symptoms of cholæmia; maniacal shrieking, jactitations and fits passing on to coma and death. We must therefore presume that although extensor responses may be a valuable physical sign of cholæmia, they are not necessarily present.

Palatal paralysis. This occurred with well defined nasal speech in one case. It was observed in the early stage for a day or two preceding the maniacal shouting, convulsions or coma, and the lack of movement of the palate was easily demonstrable. Its appearance may have been quite fortuitous in our case. We therefore hesitate to define it as a nervous sign of cholæmia: but on the other hand it may be so. In the case described there was no evidence of any other possible cause such as diphtheria. We have been unable to find any record of it in any previously reported case, unless it be a short note that Richard Bright^(*) made on one of his cases. This was in 1836 in a paper which he wrote in the first volume of the Guy's Hospital Reports on 'Observations on Jaundice more particularly on that form which accompanies the diffused inflammation of the substance of the liver.' In this he describes graphically the clinical picture of the condition we now term acute liver atrophy. The note was made 6 days before death and reads: "She generally prefers the sitting posture in bed. Some sluggishness of speech and a plaintive tone."

Maniacal shouting and convulsions. The maniacal shouting (cholæmic crying) was more evident in the children than in the adults. They gave the appearance of suffering intense pain which they could not explain and it is of interest that we noted that when the shouting and crying went on they "preferred the sitting posture," as Bright describes it. As a reference to other descriptions of the noisiness, restlessness and convulsions we can do no better than quote further from Bright. Of one of his cases he writes: "She had all the appearance of a person sinking from the loss of blood, with constant and distressing jactitations, and delirious though faint exclamations. She continued delirious and sank in the afternoon of the following day." Of another: "Nov. 28th.—She generally prefers the sitting posture in bed. Some sluggishness in her mode of speech, and a plaintive tone. Dec. 1st.—Her pupils are rather dilated: her mode of utterance is dull and indistinct: complains of loss of power in the left hand: the right is already disabled by disease. Dec. 2nd.—Is lying on her right side, drowsy, with her legs drawn up, moving her left hand with a kind of jactitation. Dec. 3rd.—Yesterday evening she was screaming loudly, with her tongue protruded beyond her teeth. Today she is in a state of perfect coma with the eyes turned up." And of another: "She lay in a perfectly torpid state the whole night; but towards the morning became delirious, so that it was with difficulty she could be restrained in her bed. At the time of the visit she was very restless, and seemed to suffer pain; but was unable to answer questions."

Cause of Cholæmia. Of the ultimate cause of the toxic state in liver diseases which we term cholæmia, we can offer no explanation. It would appear that the phrase 'hepatic insufficiency' is inadequate to do this. This implies

that a stage of destruction of liver tissue is reached when the hepatic functions fail altogether and toxæmia ensues. Following the results of the experimental Eck's fistula in animals in which convulsions ensued after administration of protein but not of carbohydrate or fat, it has been held that the symptoms of cholæmia are due to the passage of protein substances through the damaged liver that have not been de-aminised. In three of our cases only were estimations made of the blood urea or urine urea. These were carried out at the height of cholæmia and yet the percentage of urine urea reached 2.4% to 3.0% and the blood urea was normal. This hardly suggests a complete breakdown of the urea-forming function of the liver. Moreover, cholæmia may arise as readily in the subacute cases where rapid regeneration of liver tissue has taken place as in the acute cases with extensive destructive changes. The recent researches of Mann⁽⁹⁾ and others at first sight suggest hypoglycæmia as the cause of the cholæmic convulsions. They found a progressive fall of blood-sugar, ending in convulsions and death, in dogs whose livers they had successfully extirpated. This explanation, however, will not serve in our first two cases. In both, traces of sugar were found in the urine, and in one the blood-sugar was high (0.226%). Another possible explanation that could be offered is the production of some autolytic poison from the liver substance itself at some stage or other of the pathological changes which it undergoes. This is suggested by a case which one of us saw six years ago. It was a boy with lymphadenoma whose enlarged cervical glands were being treated by X-rays. The glands began to decrease in size, but in the course of treatment he developed severe toxic symptoms which lasted 3 to 4 days, and resembled closely the picture we have drawn of cholæmia. This case was fully investigated at the time and a careful post-mortem examination made, but none of the usual causes of terminal toxæmia were found, and we were left to presume that the condition had resulted from the release of some autolytic toxin from the lymphadenomatous glands.

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