CONSTITUTIONAL HEPATIC DYSFUNCTION

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Constitutional hepatic dysfunction is a rare condition in which there is hyperbilirubinaemia without evidence of liver disease. This bilirubin gives an indirect van den Bergh reaction and the disorder is completely benign. Long-continued mild jaundice in a young person is usually considered to be due to chronic viral hepatitis if haemolytic disease can be excluded, but it is important to bear constitutional hepatic dysfunction in mind in the differential diagnosis. This is particularly so because bed rest features prominently in the management of viral hepatitis. These problems are illustrated by the case now presented.

CASE REPORT

In October 1956 a 29-year-old European University lecturer noted considerable fatigue and was exhausted at the end of each of his lectures, when there was some discomfort in the right side of the chest. This troubled him for another 6 weeks, when he developed a pyrexial illness that lasted a few days. His practitioner, noting that his urine was dark, found that he had mild jaundice, and made a diagnosis of infective hepatitis. It was after this that the patient became slightly nauseated—though he retained his appetite—and developed intermittent discomfort in the right upper quadrant. The stools were normal in colour and the urine was dark only for a few days, while the temperature was elevated. To the patient the illness was no different from attacks of influenza from which he had suffered in the past. The serum bilirubin was noted to be 2·2 mg.% (direct 1·3) at this time and 1·4 (direct 0·9) 2 weeks later.

In spite of spending 6 weeks in bed his symptoms persisted, and in February 1957 he again saw his practitioner, when the bilirubin was 2·0 (direct 0·7). Another 6 weeks in bed did not produce much improvement, but the symptoms were at no time severe.

He presented himself at Groote Schuur Hospital on 16 April 1957. Physical examination was quite negative, save for extensive lower-motor-neurone paralysis of the left arm, the result of an attack of poliomyelitis in 1947. Icterus was not detected clinically, and the urine was free of bile and urobilin, but the serum bilirubin was 4·0 mg.% with a negative van den Bergh reaction. Accordingly he was admitted for further study. Again physical examination was negative; in particular, the liver and spleen were not enlarged and there was no hepatic tenderness. These signs were unchanged after strenous exercise lasting 2 hours. The results of urine analysis were negative. Examination of the blood revealed: Hb. 13·5 g.%; VPC 48%; WBC 10,000 per c.mm. with 76% polymorphs, 22% lymphocytes and 2% eosinophils. The erythrocyte sedimentation rate was 4 mm. in the first hour (Westergren). A blood smear was normal; there was no microspherocytosis.

Three further estimations of serum bilirubin were made over the next 5 days, with a negative van den Bergh reaction and levels of 1·4, 1·7 and 1·5 mg.%. The last 2 figures were obtained before and after 2 hours of exercise. The serum proteins were albumin 5·6 and globulin 2·7 g.%; alkaline phosphatase 3·5 King-Armstrong units; cholesterol 200 mg. A bromsulfalein test showed no retention of dye at 45 minutes. The prothrombin index was 100. Osmotic fragility of the red cells was normal. The reticulocyte count was 1·2%. Shumm's test for methaemalbuminaemia[5] was negative. The direct Coombs test was negative. An oral cholecystogram showed good function of the gall bladder; there were no calculi. Liver biopsy was essentially normal.

The patient's symptoms responded well to reassurance and the information that the tests performed had been normal.

DISCUSSION

On reviewing the data in this case it becomes apparent that there are no good reasons for confirming the original diagnosis of viral hepatitis. In retrospect it seems that he had chronic fatigue (see below) and a non-specific pyrexial

illness, at which time mild icterus was discovered. His urine had not been tested for bile or urobilin; the dark colour may well have been due to concentration associated with his fever. Only when that diagnosis was suggested did he develop symptoms of 'hepatitis.'

Throughout these studies there has been a preponderance of indirect-reacting bilirubin, the total figures now being not much lower than at the start of the 'illness', with a rather higher level just before admission. The investigations failed to reveal any evidence of liver dysfunction other than the hyperbilirubinaemia. It is noteworthy that severe exercise did not aggravate the clinical or biochemical situation; this also inclines the diagnosis against viral hepatitis—it will be remembered how, in the army, vigorous activity often led to a relapse.[4] The other studies completely excluded haemolysis as a cause of the jaundice.

The normal liver biopsy must be stressed. Smetana[11] considers that biopsy is the single most reliable laboratory test in the diagnosis of viral hepatitis. Six months after an acute attack one might not have expected degeneration and necrosis of liver cells, or periportal and intralobular cellular infiltration—although these might have been evident with continuing jaundice—but there should have been evidence of parenchymal regeneration. Smetana mentions that one lesion in particular persists for months in viral hepatitis—lipochrome pigment in the Kupffer cells, due to the phagocytosis of dead liver cells; this change was absent in the present case.

Watson[12] has stressed the importance of the one-minute direct-reacting bilirubin (1′)—corresponding to a prompt positive van den Bergh—in indicating actual liver disease or obstructive jaundice. His figures suggest that jaundice due to liver damage should be accompanied by a high 1′ level.

Recently Reichman and Davis[8] discussed their experience with American servicemen diagnosed as having suffered. from viral hepatitis. In particular they analyzed a number of cases in whom jaundice had apparently persisted after an attack, and have discovered that some of their patients had actually not had hepatitis at all. In 6 patients persistent elevation of the indirect fraction of the serum bilirubin was found. In only 1 of these was the diagnosis of hepatitis upheld—2 liver biopsies showed evidence of continuing inflammation. Another 2 patients were found to suffer from acholuric family jaundice, for which splenectomy was successfully performed; in neither of these had anaemia been significant. The remaining 3 cases had normal liver function tests and biopsies and fell into the group of constitutional hepatic dysfunction.

In 1902-1907 Gilbert and Lereboullet (quoted by Dameshek and Singer[2]) described cases of mild hyperbilirubinaemia in the absence of liver disease; it is now felt[2] that their familial cases were probably examples of mild haemolytic anaemia. In 1918 A. A. H. van den Bergh (quoted by Meulengracht[7]) stated that he had often encountered healthy people with 'physiological hyperbilirubinaemia.' Meulengracht[6, 7] collected 35 cases whom he labelled as having 'chronic intermittent juvenile jaundice' as most of his patients were diagnosed when aged 15-25 years. Apart from jaundice the only complaint was of periodic lassitude. In many cases he could trace hereditary occurrence, but this was not always obvious. Certain factors were found to precipitate lassitude and exacerbations of jaundice—'alcohol, convivial evenings, lack of sleep, sorrow and anxiety' and gastro-intestinal disturbances. The present patient complained first of fatigue, and he sometimes drank to excess; perhaps a 'convivial evening' had preceded his out-patient attendance at which the serum bilirubin was found to be 4·0 mg.%!

Dameshek and Singer[2] presented 3 families with this condition. They found no abnormalities other than an inability of the liver to handle bilirubin adequately; there was a greatly delayed excretion of injected bilirubin from the blood. There was no family history of jaundice in my patient, but his relatives live in Germany and communication with them has been scant.

It should be noted that the serum bilirubin level in constitutional hepatic dysfunction can be quite high—Sherlock[10] says it is rarely higher than 5 mg.%, but Watson[12] records a case with a 1′ level of 0·96 and a total of 8·8 mg.%.

Recent work by Cole and Lathe[1] and Rudi Schmid[9] has thrown much light on the chemistry of the bilirubins and the mechanism of the van den Bergh reaction—and, incidentally, on the nature of the defect in constitutional hepatic dysfunction. It has been shown that the indirect-reacting pigment is free crystalline bilirubin, which is insoluble. In the liver this is conjugated with glucuronide to form soluble direct-reacting bilirubin. *In vitro*, crystalline bilirubin can be rendered soluble by various means, as when alcohol is added in the second part of the van den Bergh test.

The implications of these facts in relation to constitutional hepatic dysfunction were discussed by Schmid at a meeting at the Massachusetts General Hospital in December 1956. He feels that the probable pathogenesis of this condition is the absence, on an hereditary basis, of the enzyme responsible for glucuronide conjugation of free bilirubin. He thinks that this is the heterozygous expression of the deficiency; the homozygous condition may be the rare 'congenital non-haemolytic jaundice with kernicterus' of infants. The features of this latter illness are as follows: High serum bilirubin (15-30 mg.%—all free bilirubin—but clinically they do not appear to be grossly jaundiced); no bilirubin in the bile, which is a pale yellow fluid; normally-coloured stools; death within the first year of life in most cases, after the development of severe basal ganglia signs, which are due to the deposition of insoluble free bilirubin.

This 'Gilbert' type of constitutional hepatic dysfunction is not the only form of constitutional hyperbilirubinaemia;

TABLE I. DISTINCTION BETWEEN 'GILBERT' AND 'DUBIN-JOHNSON' HYPERBILIRUBINAEMIA

	'Gilbert'	*'Dubin-Johnson'*
Urine colour	Light	Dark
Van den Bergh reaction	Indirect	Direct
Thymol and zinc turbidity	Normal	Abnormal
Bromsulfalein retention	Normal	Abnormal
Oral cholecystography ..	Good function	No excretion of dye
Pigment in liver cells ..	Absent	Present

another variety has recently been described by Dubin and Johnson.[3] Its distinction from the Gilbert group is shown in Table I. It, too, has an excellent prognosis. An important feature is the presence of an abnormal lipochrome pigment in the parenchymal cells of the liver.

SUMMARY

A case of constitutional hepatic dysfunction is presented, with a differential diagnosis of the causes of indirect-reacting hyperbilirubinaemia. It is of great importance to distinguish this condition from viral hepatitis. Recent discoveries in the field of bilirubin chemistry, and their clinical significance, are discussed.

I wish to thank Dr. Louis Mirvish for permission to report this case and for much useful advice about its presentation.

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TORN CONGENITAL DISCOID MENISCUS OF THE KNEE

CASE REPORT AND REVIEW

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Torn meniscus of the knee joint in young children appears to be a rare injury, even if an associated congenital anomaly of the cartilage is present. A case of congenital discoid cartilage presenting as an 'internal derangement of the knee', and proving at operation to be a torn cartilage is described.

CASE HISTORY

A female child R.V. aged 6 years and 9 months, was seen at the orthopaedic outpatients department on 16 April 1957. Six days previously, whilst playing, she was pushed and fell against a large stone, twisting her knee as she fell. The left knee became swollen and, although this had now almost subsided, it was still painful. Because of the pain she was unable to walk or extend the leg fully. Nothing of note in the previous history.

Pulse rate 90 per minute. Temperature 98·4°F. No abnormalities detected on general examination.

The right knee was normal on examination. The left knee was slightly swollen, there was no erythema; skin temperatures were equal on the two legs. The knee was held in 10° flexion; flexion-extension movements caused pain at the lateral aspect of the knee joint; there was a block to full extension. Movement was painful and only possible between 170°-90°. A tense, slightly tender swelling was palpable on the joint line antero-laterally, about half an inch in diameter, and this was not attached to the skin.

A diagnosis of internal derangement of the knee, possibly with a cyst of the lateral meniscus, was made and the child was admitted to the ward.

The patient did not improve on skin traction and on 29 April arthrotomy of the knee joint under general anaesthesia and a bloodless field was performed through a lateral vertical incision between the ilio-tibial tract and the patellar tendon with the knee in 90° flexion. The interior of the knee revealed a thickened disc-shaped, lateral cartilage with a transverse tear in the middle of the central portion and the meniscus was removed *in toto.* The post-operative period was uneventful and the child was discharged on 11 May 1957.

DISCUSSION

In view of the rarity of internal derangements of the knee in children of this age a review of the literature is presented.

Although discoid cartilages of the knee had been noted previously in anatomical dissections, the first clinical case was described by F. Kroiss in 1910. It was associated with a tear of the pathological cartilage. Since then 50 cases have been described. A list of such cases appears below, showing those with a definite history of trauma:

1910..	F. Kroiss	1 case with superadded tear.
1928..	A. Schulz	2 cases (1 traumatic).
1934..	J. G. Finder	3 cases (1 traumatic).
1935..	E. Bell-Jones	14 cases (8 traumatic).
1935..	W. Jaroschy	3 cases (1 traumatic).
1936..	A. G. Timbrell-Fisher	2 cases (1 traumatic).
1936..	D. Stewart Middleton	4 cases (1 traumatic).
1945 and previously	E. Cave and O. Staples	7 cases (6 traumatic).
1948..	I. S. Smillie	29 cases.
1957..	E. B. Kaplan	6 cases.

Incidence

Of all meniscal injuries reported, only a small fraction is associated with intrinsic abnormality of the cartilage itself. Cave and Staples in a series of 164 cases requiring meniscectomy described only 4 as having the congenital discoid pathology; less than half of such cases in the literature were associated with trauma. In the series of 1,300 cases of menisectomy reviewed by Smillie only 29 congenital discoid menisci were found.

Age and Sex

The writers on all series of cases requiring operation for damaged menisci agree that the tear is seen most commonly in active sporting enthusiasts between the ages of 20 and 30. In his review of 256 cases Melville Henderson tabulated the age incidence as follows:

Age in Years	*No. of Patients*
10–19	27
20–29	116
30–39	66
40–49	37
50–59	9
60–69	1