VIRAL HEPATITIS WITH HAEMOLYTIC ANAEMIA DUE TO GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

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It is well known that liver disease can give rise to various haematological changes viz. anaemia, leucopenia, thrombocytopenia and coagulation defects. These changes depend on types of liver disease. Anaemia in chronic liver disease can be due to multiple factors such as bleeding from oesophageal varices, hypersplenism, pulmonary infection, malnutrition, marrow suppression and haemolysis. Haemolysis in chronic liver disease has been extensively studied. Hyman and Southworth (1951) reported the association of haemolytic anaemia and liver disease in 21 cases, of which 8 were histologically proven chronic liver disease. On the other hand, the association of haemolytic anaemia with acute viral hepatitis is not common. Raffensperger (1958) reported 3 cases of acute haemolytic anaemia associated with viral hepatitis. One case ended fatally and the diagnosis of viral hepatitis was confirmed at autopsy. Kivel (1961) reported 2 cases of viral hepatitis with transient pancytopenia, and congenital non-spherocytic haemolytic anaemia. The association of haemolytic anaemia due to glucose-6-phosphate dehydrogenase deficiency in viral hepatitis is also not well known. Wong (1965) and Choremis et al (1966) described this condition in children and recently Salen et al (1966) described three cases in adult Negroes in America. As viral hepatitis and glucose-6-phosphate dehydrogenase deficiency are not uncommon in the adult population of this country it is therefore the purpose of this paper to describe 11 patients with viral hepatitis and haemolytic anaemia due to glucose-6-phosphate dehydrogenase deficiency, who were admitted into Medical Unit One of the Outram Road General Hospital, Singapore.

Case 1

This Chinese school boy aged 15 complained of fever, abdominal pain and passing tea coloured urine for 5 days. Two days later developed jaundice. At the same time his appetite was poor although there was no nausea or vomiting. He had no past history of jaundice. Two or three months prior to admission, he received 5 injections from a private practitioner. Three years ago he had haemorrhagic dengue without any jaundice.

On examination, he was very yellow. He had a temperature of 102° which lasted for 10 days. The temperature subsided without any specific therapy. The other significant finding was that his liver was enlarged and tender.

Investigations revealed: Hb. 12. T.W. 5,00; P 76%, L 18%, M 3%, and E 1%, Retic 1.5, Serum bilirubin 33.0 mg%. Alk. phosphatase 21.6. Alb. 3.3, Glob. 2.3. S.G.P.T. more than 400 Kings units (Normal 35 - 110). S.G.O.T. 390 units (Normal 30 - 125). Thymol turbidity 8. Blood urea 34 mg%. Three days after admission the reticulocyte count was 4. Urine showed presence of bile, urobilin and urobilinogen. Bleeding time 3 minutes, clotting time 3 minutes and prothrombin time 19 seconds compared to control 16 seconds. X'ray chest—normal and X'ray abdomen showed enlarged liver. G-6-P-D was absent. No abnormal haemoglobin was detected. Blood for leptospira was negative. It was noted that the reticulocytes increased as the serum bilirubin fell, as is shown in Fig. 1.

Liver biopsy showed changes characteristic of viral hepatitis (Figs. 2(a) & (b)).

Case 2

This Chinese school boy aged 14 was admitted into hospital with the complaints of fever and yellow eyes for 3 days. He went to see a private doctor, who gave him oral penicillin tablets and the A.P.C. mixture. At the same time, he noticed that his urine became more darkly coloured. He lost his appetite and experienced aches all over the body. One of his brothers had viral hepatitis a month before this episode.

On examination he had a temperature of 99°F and was very yellow. He also appeared to be pale. There was no scratch mark, or any stigmata of liver disease. The other findings were normal except for hepatomegaly, which was smooth, soft and tender.

Investigations showed haemoglobin 10 gm%, white cell count 6,100 with the differential count of polymorphs 69%, lymphocytes 25%, monocytes 3%, eosinophils 3%, and atypical mono-

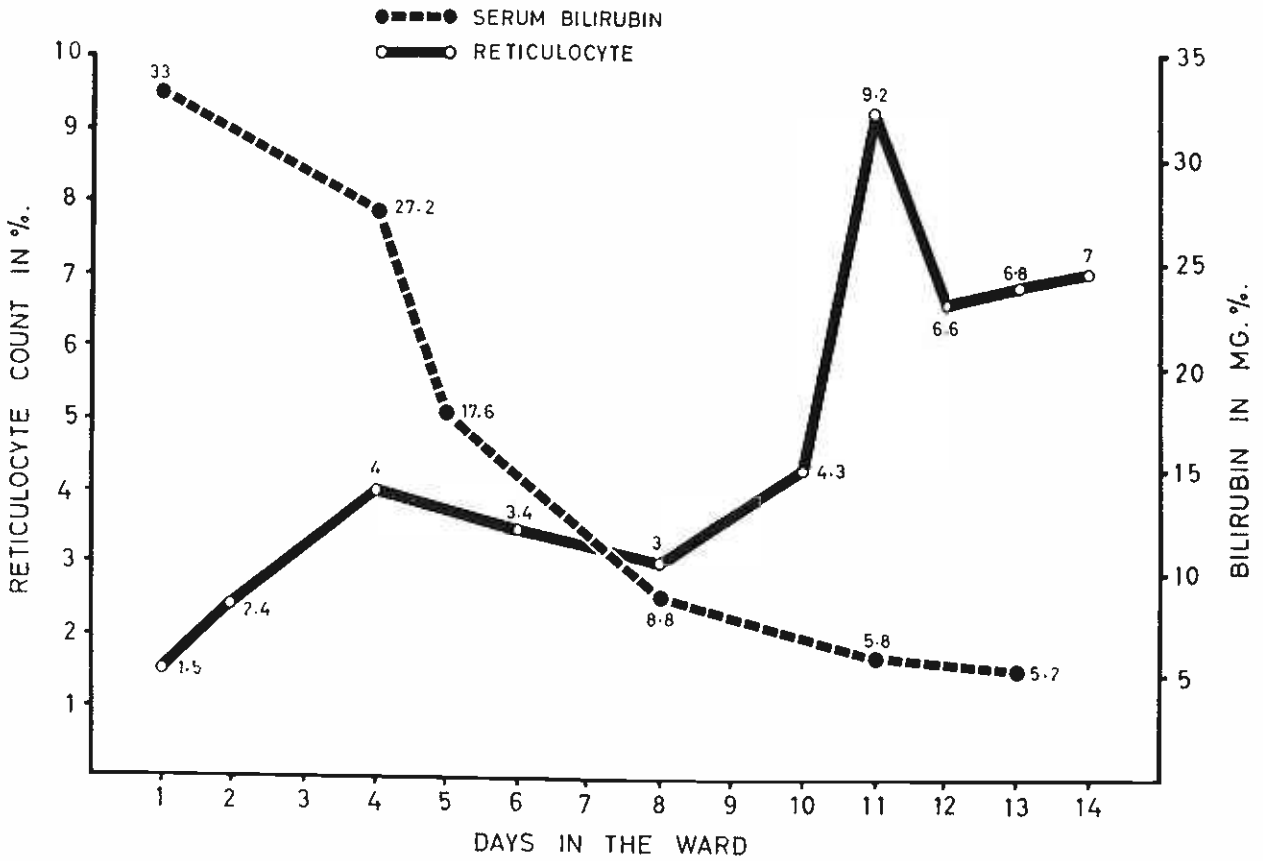

Fig. 1. Shows the reticulocyte counts and the serum bilirubin levels in Case 1 during the course of the disease.

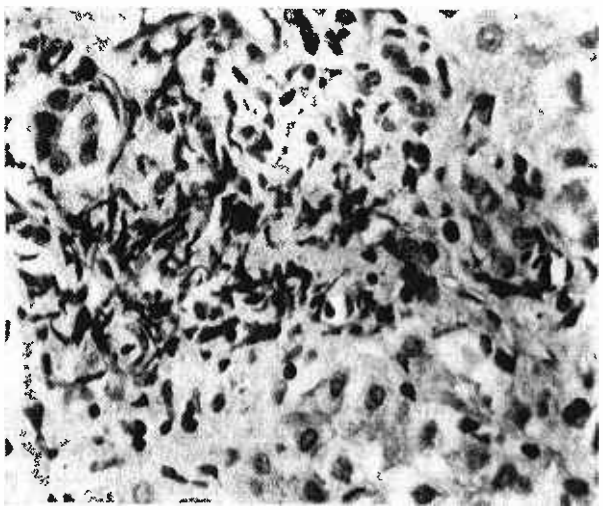

Fig. 2(a). Case 1. Liver biopsy showing portal tract cellular infiltration. H. & E. × 500.

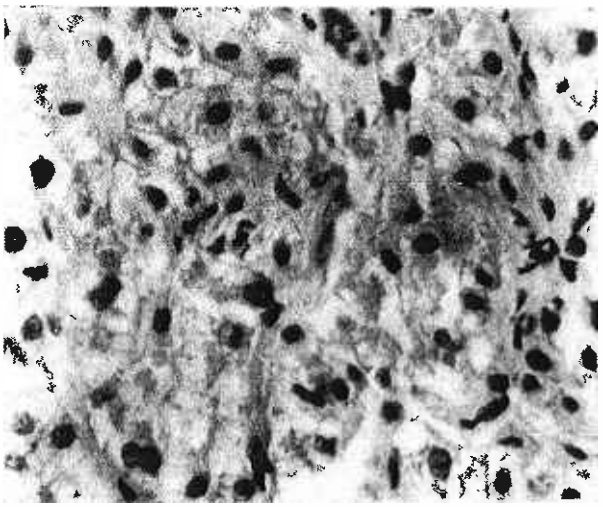

Fig. 2(b). Case 1. Liver section shows cellular degeneration. H. & E. × 500.

nuclears 7%. Reticulocytes 3%, E.S.R.: 51mm/hour. Total serum bilirubin 31.2 mg% with the direct bilirubin of 12 mg%, thymol turbidity 10 units, alkaline phosphatase 25.9 King-Armstrong units. Albumin 4.8 gm%; globulin 2.7 gm%. Latex fixation test and L.E. cells were negative, glucose-6-phosphate dehydrogenase absent. Urine bile 3+, urobilin, urobilinogen and Coomb's test were negative.

Clinically he looked rather sick, so he was given prednisolone and 2 days later jaundice became less and his appetite returned. The liver remained enlarged. 7 days after admission no bile, or urobilinogen could be detected in the urine and the serum bilirubin fell to 5.6 mg%, thymol turbidity 6 units and alkaline phosphatase 23.5 K.A. units.

When his condition improved, a liver biopsy with Vim-Silverman needle was carried out, and it was reported by the pathologist as follows:—

"Section shows strips of liver tissue with ballooning and vacuolation of liver cells. There are areas of degeneration and bile stasis was also present. There is moderate histiocytic infiltration in the portal areas (Fig. 3).

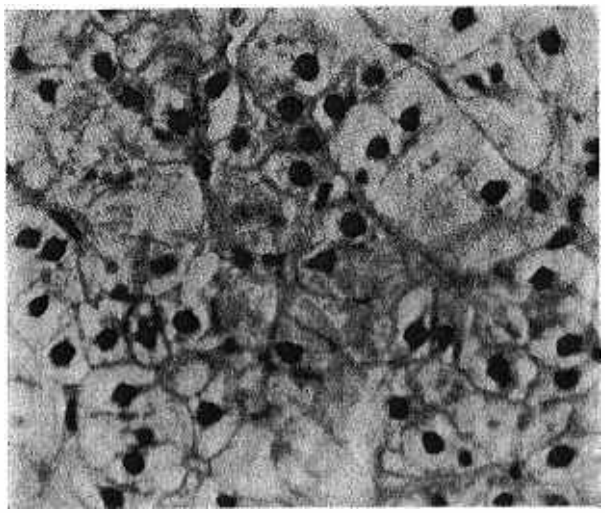

Fig. 3. Case 2. Liver cells showing vacuolation and degeneration. H. & E. × 500.

Case 3

This patient, a Chinese boy aged 11 was admitted to the hospital because of fever and abdominal pain for 5 days, yellow eyes, loss of appetite, vomiting and passing tea coloured urine for 4 days. He was brought to see a private doctor who gave him antacids and B12 injection. The doctor at that time had also noticed that this boy was jaundiced. The colour of the stool was normal.

There was no history of taking other drugs and the past history was not relevant to the present illness.

Examination showed that he had a temperature of 100°F and was deeply icteric. He was conscious and rational and there were neither signs of hepatic failure nor any stigmata of chronic liver disease. The other significant finding was that the liver was enlarged, soft, smooth and tender. The spleen was not palpable.

Investigations: Haemoglobin 10.8 gm%, W.B.C. 7,300 with a differential of 80% polymorphs, 14% lymphocytes, 3% monocytes, 3% eosinophils, Reticulocytes 2.5%, E.S.R.: 43, serum bilirubin direct 9.7 mg%, total 25.6 mg%, thymol turbidity 12 units, alkaline phosphatase 33.6 King-Armstrong units, albumin 4 gm%, globulin 2.7 gm%, Coomb's test negative, glucose-6-phosphatase dehydrogenase absent, urine bile 2+, urobilin +, urobilinogen +.

After 5 days stay in the hospital his appetite returned and he became less jaundiced, serum bilirubin being total 7.7. mg%, direct 3.5 mg%. Two weeks later he completely recovered and there was no jaundice and the liver was not palpable.

Case 4

A 38 year old Chinese male patient was noticed by his relatives to be yellow in the eyes two weeks prior to admission. One week after he started to have nausea, vomiting and anorexia. He went to consult his own doctor, who gave him multivitamins and prochlorperazine (Stemetil—May & Baker, London). He denied taking alcohol or having had jaundice before.

Physical examination revealed that he was febrile with a temperature of 100°F and was icteric, but without any other signs of chronic liver disease. The liver was enlarged, soft, smooth and tender.

Investigations: Haemoglobin 12.3 gm%, W.B.C. 7,000 cu. mm., differential count 78% polymorphs, 16% lymphocytes, 3% monocytes and 3% eosinophils, reticulocytes less than 1%. Serum bilirubin total 15.6 mg%, direct 5 mg%, thymol turbidity 7 units, alkaline phosphatase 16.2%, albumen 4.9 gm%, globulin 2.8 gm%, urine + for bile, urobilin and urobilinogen. Glucose-6-phosphatase dehydrogenase absent.

One week after admission jaundice began to clear up and 3 weeks later serum bilirubin was 3 mg%. He was discharged and was not seen subsequently.

Case 5

An 11 year old female complained of fever, passing dark urine, and yellow eyes for 9-10 days,

and jaundice. She also had vomiting and nausea. No history of taking drugs.

On examination the main findings were jaundice and 3 finger breadth enlarged liver. Spleen was just palpable.

Investigations: Haemoglobin 9.5 gm%, Reticulocytes 10%, Platelets 300,000 Coomb's test negative, S.G.P.T. 450 King's units, S.G.O.T. 410 King's units. Serum bilirubin 31 mg%, thymol turbidity 7 units, alkaline phosphatase 18.9%, albumen 4.3 mg%, globulin 3.8 mg%; total white count 17,100; differential count 68% polymorphs 24% lymphocytes, 3% monocytes, 5% eosinophils. Urine bile ++, urobilin +. Glucose-6-phosphate dehydrogenase absent. Four weeks later the haemoglobin was 14.3 gm%, reticulocyte count 1% and jaundice cleared up completely.

Case 6

An 18 year old Chinese male patient was hospitalized because of fever for 5 days prior to admission, chills, loss of appetite and generalised body aches for 4 days. There was no history of his exposure to hepatotoxic agents or alcohol. He denied taking drugs prior to admission.

Clinical examination indicated that he had a temperature of 99°F and was deeply jaundiced. The only other significant physical sign was hepatomegaly, which was soft, smooth and tender.

Investigations: Haemoglobin 12.3 gm%, white blood count 8,500 cu. mm. differential count 77% polymorphs, 19% lymphocytes, 1% monocytes and 1% eosinophils. Reticulocyte count 1%, E.S.R. 25 mm/hour, Coomb's test negative, L.E. cells negative, serum bilirubin direct 13 mg%, total 34.3 mg%, thymol turbidity 6 units, alkaline phosphatase 16.7 K.A. units, albumen 4.9 gm%, globulin 3 gm%. No abnormal haemoglobin on electrophoretic study, S.G.O.T. 400 King's units and S.G.P.T. 535 King's units. G-6-PD absent.

One week after admission he improved a great deal, the liver became smaller and he was less icteric and by one month he had no further clinical jaundice though the serum bilirubin was 1.4 mg% and the liver was not palpable. Other liver function tests also returned to normal.

Case 7

A 10 year old male Chinese complained of yellow eyes, passing tea coloured urine and anorexia for 1 week. He lost his appetite for all types of food. He also had slight fever. At 6 months he had intussusception. No history of taking drugs was obtained.

On examination, he was jaundiced and the temperature was 99°F. Liver was 3 finger breadth.

Investigations revealed E.S.R. 41 mm. Haemoglobin 11.2 gm%, total white count 4,800 cu. mm.; differential count 83% polymorphs, 14% lymphocytes, 1% monocytes, 2% eosinophils. Reticulocyte count 3%. Urine bile +, urobilin nil, urobilinogen trace. S.G.P.T. more than 400 King's units. Serum bilirubin 9.6 mg%, thymol turbidity 9 units, albumen 3.7 gm%, globulin 3.9 gm%, alkaline phosphatase 31.6%, glucose-6-phosphate dehydrogenase negative. X-ray of abdomen showed liver enlarged, no calculi seen. Four weeks later—serum bilirubin 0.5 mg%, thymol turbidity 3 units, albumen 4.7 gm%, globulin 3.1 gm%. No liver biopsy done. After 7 days patient less icteric.

Case 8

A 31 year old Chinese female was admitted with the complaints of pain in right hypochondrium for 1 day; fever, jaundice and vomiting for 1 week. She also noticed passing dark coloured urine. She felt better after being given some pills by a private doctor.

On examination she was jaundiced but afebrile. The liver was 2 finger breadth enlarged.

Investigations showed haemoglobin 13 gm%, white blood count 7,800 cu. mm. differential count 79% polymorphs, 13% lymphocytes, 4% monocytes, 4% eosinophils. Reticulocytes count 2%, platelets 285,000. Urine bile ++, urobilin+, glucose-6-phosphatase-dehydrogenase absent. S.G.P.T. more than 400 King's units, thymol turbidity 8 units. Serum bilirubin 8.7 mg%, alkaline phosphatase 16.4%, Coombs' test negative, blood urea 32 mg%. Three weeks later no jaundice could be detected clinically.

Case 9

A 21 year old Chinese male was admitted to hospital for generalised weakness and malaise, loss of appetite and yellow eyes for 1 week. He went to see a private doctor and was advised admission. No drug was administered by the doctor. He had no history of taking alcohol or past history of jaundice.

Physical examination revealed that he was afebrile and looked well, but he was icteric and pale. The liver was enlarged, soft and tender.

Investigations: Haemoglobin 12.8 gm%, white blood count 11,400 cu. mm. with a differential count of polymorphs 78%, lymphocytes

18%, monocytes 2%, eosinophil 2%. Reticulocytes 1%. Urine bile+, urobilin and urobilinogen+. Serum bilirubin total 9.4 mg%, thymol turbidity 5 units, alkaline phosphatase 18.2 King-Armstrong units, albumen 5.2 gm%, globulin 3.2 gm%. L.E. cells negative. S.G.O.T. 171 King's units, S.G.P.T. 456 King's units.

Three weeks after admission, the jaundice became very faint with serum bilirubin of 2 mg% and the liver was no longer palpable.

Case 10

A twenty year old Chinese male was first seen in this unit on 5.2. 1960 with the history of 3 days fever and pain in the right hypochondrium for 2 days and jaundice for 1 day. He lost his appetite and noticed that the urine became darkly coloured.

On examination he was febrile with temperature of 100°F and very marked jaundice. The liver was 2 fingers breadth and tender. He was then diagnosed as viral hepatitis.

Investigations: Haemoglobin 13.5 gm%. E.S.R. 3, urine bile+, urobilin+, urobilinogen+, Total white count 6,100 differential count 52% polymorphs, 23% lymphocytes, 10% monocytes, 1 eosinophils. Reticulocyte count 1%. Thymol turbidity 5 units, serum bilirubin 27.8 mg% rising to 34.8 mg%, alkaline phosphatase 12 K.A. units, albumen 5.61 gm%, globulin 2.43 gm%. By the 6th week, his serum bilirubin was 4.2 mg and 3 months later it was 1.8 mg. Liver biopsy done and was reported as showing changes consistent with viral hepatitis (Fig. 4).

He was admitted again on 19.3.1964 with the complaint of yellow eyes for 4 days and no other complaint.

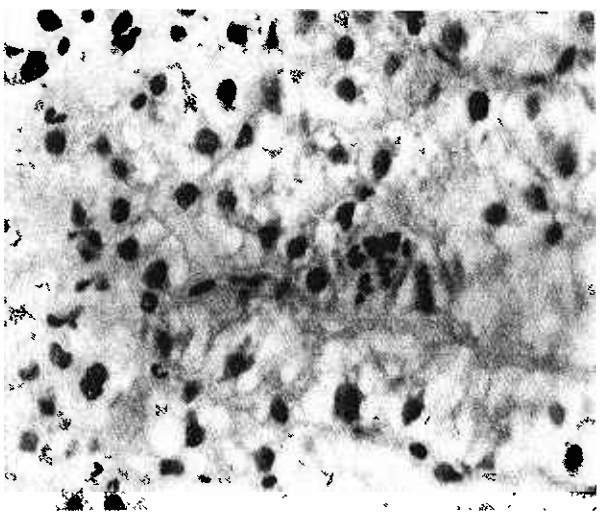

Fig. 4. Case 10. There is vacuolation of liver cells. Near the centre of the field, there is a small focus of polymorphonuclear infiltration. H. & E. × 500.

On examination he was jaundice and the liver was just palpable.

Investigations: Haemoglobin 10.9 gm%, total white count 11,200 cu. mm. differential count polymorphs 88%, lymphocytes 9%, monocytes 0%. eosinophils 3%. Urine bile nil, urobilin+, urobilinogen+. Serum bilirubin 11.8 mg%, alkaline phosphatase 9.9 K.A. units, thymol turbidity 3 units, albumen 4.6 gm%, globulin 2.9 gm%. G-6-P-D absent.

Case 11

This patient a Chinese female aged 46 complained of heaviness of head, fever, loss of appetite, passing dark coloured urine and paleness of face for 3-4 days. No history of taking drugs or having had previous transfusion was obtainable. On examination, she was found to have a temperature of 99.4°F with jaundice and pallor. The main findings were liver was enlarged and tender. The other systems were normal. Investigations revealed Hb. 12 gm%, T.W. 7,200, Polymorphs 70%, lymphocytes 23%, monocytes 2%, eosinophils 1% and 4% atypical mononuclears. Urine bile+, urobilin+, urobilinogen+. Serum bilirubin 10 mg%, direct 5.5 mg. Alkaline phosphatase 26.4. Thymol turbidity 7. Serum protein—albumen 3.2, globulin 3. R.A. Factor negative. S.G.P.T. more than 400 units. Glucose-6-phosphate-dehydrogenase absent.

Within 3 weeks the jaundice subsided with almost negligible tinge of yellowness. The liver was not palpable. Serum bilirubin 1.4 mg; Alkaline phosphatase 9.2. Thymol turbidity 5. S.G. P.T. 140.

COMMENTS

In order to accept that viral hepatitis associated with haemolytic anaemia due to G-6-P-D deficiency occurred in all these cases, there must be evidence to indicate that there was viral hepatitis and haemolytic anaemia and absence of glucose-6-phosphate dehydrogenase. As long as the virus of viral hepatitis cannot be isolated and also there is no specific laboratory test, its diagnosis will have to depend on the classical clinical and laboratory features of the disease. All these cases had the characteristic features of the disease viz, anorexia, fever, vomiting, jaundice, hepatomegaly, relative lymphocytosis and abnormal liver function tests. Three cases, 1, 2, and 10 had liver biopsies which showed characteristic changes of viral hepatitis such as ballooning of the liver cells and chronic inflammatory cells in the portal triad. The biochemical

functions which support the diagnosis of viral hepatitis in these cases were raised serum bilirubin, thymol turbidity, raised alkaline phosphatase and transaminases. As there was also presence of haemolytic anaemia, serum glutamic oxaloacetic transaminase could not be considered as specific to hepatitis because it is also raised in haemolytic anaemia. However, serum glutamic pyruvic transaminase (alanine transaminase) is more specific as it is not increased in haemolytic anaemia (Baron-1964).

Fig. 5 gives the summary of the laboratory findings in these 11 cases. One interesting feature that stood out prominently in all these cases was that hyperbilirubinaemia was totally out of proportion to the clinical state of the patient and to the other battery of liver function tests. Unlike ordinary viral hepatitis cases when such a degree of hyperbilirubinaemia would have been ominous. Case 1 was diagnosed by other physicians who were not familiar with this condition as a case of viral hepatitis with subacute liver necrosis. During our initial experience with such a case as in case 2 we started him on prednisolone therapy thinking that such a severe jaundice was probably due to severe hepatitis. It turned out that hyperbilirubinaemia was mainly due to haemolysis and therefore subsequently no steroid was used in treating such cases.

All these cases were Chinese and they all had no glucose-6-phosphate dehydrogenase enzyme activity in their sera. It is well known that G-6-P-D deficiency can occur in Chinese. As 85% of the population in Singapore are Chinese, it cannot be interpreted as Chinese being more susceptible to viral hepatitis. According to Beutler (1967), cases with mild reduction of glucose-6-phosphate dehydrogenase activity, where 25 to 75% of normal enzyme activity are present and their capacity to survive normally in the circulation is not impaired, there appears to be no consequences. This occurs in the mild Italian (Barbieri) type, mild Greek type, Tel-Hashomer variant or the Austin 1 and 2 variants. The African (Negro) type with 7 to 15% of normal enzyme activity, form the intermediate group. They are clinically normal unless subjected to stress or infection, ingestion of drugs or diabetic acidosis. It was the study of the effect of primaquin on Negro subjects that led to the discovery of glucose-6-phosphate dehydrogenase polymorphism. A more severe grade of glucose-6-phosphate dehydrogenase deficiency occurs among Mediterranean subjects and has been observed in Sardinians, Greeks and Sephardic Jews. The Mediterranean subjects are not only susceptible to drugs and infection but also to favism and haemolytic disease of the new born. The glucose-

		Hbg%	T.W.	Ret.%	S.B.	T.T.	Alk. Phos.	Serum Alb. Glob.	S.G.O.T.[1]	S.G.P.T.[2]	G 6 P D.[3]	URINE Bile	Urobilin	Urobilinogen	Liver Biopsy
1.	F P.W.	12	5,000	1·5	33	8	21·6	3·3 : 2·3	390	>400	absent	+	+	+	+
2.	Y.N.C.	10	6,100	3	31·2	10	25·9	4·8 : 2·7	—	—	"	+++	+	+	+
3	O H.C.	10·8	7,300	2·5	25.6	12	33·6	4 : 2·7	—	—	"	+	+	+	—
4.	L C.M.	12·3	7,000	1	15.6	7	16·2	4·9 : 2·8	171	161	"	+	+	+	—
5	L.A H	9·5	17,000	10	31·0	7	18·9	4·3 : 3·8	450	410	"	++	+	+	—
6	N.K M.	12·3	8,500	1	34·2	6	16·7	4·9 : 3	400	535	"	++	+	+	—
7.	N.S A.	12·2	4,800	3	9·6	9	31·6	3·7 : 3·9	—	400	"	+	+	+	—
8.	L.C.E.	13	7,800	2	8·7	8	16·4	—	—	400	"	++	+	+	—
9	Y.Y.K.	12·8	11,400	1	9·4	5	18·2	5·2 : 3·2	171	456	"	+	+	+	—
10.	G.K S.	13.5	6,100	1	34·8	5	12	5.6 : 2·4	—	—	not done	+	+	+	+
2nd admission		10·9	11,200	3	11·8	3	9·9	4·6 : 2·9	—	—	absent	—	+	+	—
11.	C.S.Y.	12	7,200	1	10	7	26.4	3·2 : 3	—	>400	"	+	+	+	—

1. NORMAL VALUES – 35 – 125 KING'S UNITS (KING. J. (1960) J MED. LAB. TECH 17.1).
2. " " – 30 – 110 " " (——— IBID ———)
3 BERNSTEINS METHOD (BERNSTEIN R.E. (1962) NATURE 194.192)

Fig. 5. Summary of laboratory findings in 11 cases.

6-phosphate dehydrogenase deficiency in Chinese is described as the Canton variant and occupies the position between the Negro type and the Mediterranean type in severity. The most functionally severe type of glucose-6-phosphate deficiency is that observed in connection with nonspherocytic congenital haemolytic anaemia. These variants include Oklahoma 1 and Chicago 1 variants. In this group the enzyme is of such inferior quality that red cell life span is markedly shortened even in the absence of drug challenge. This is usually noted in infancy or early childhood and results in a moderate haemolytic anaemia. All the above cases were Chinese and they are therefore in the "Canton" variety, in whom haemolysis can arise from drug or infection. They showed evidence of haemolysis namely, urobilinogen in the urine, leucocytosis and reticulocytosis, though in 3 cases the reticulocyte was only 1% on admission. Salen's three cases also initially had low reticulocyte count during the acute stage. It was unfortunate that reticulocyte count was not repeated in the course of the disease in other cases; however, in Case 1 when this was done it revealed that when the serum bilirubin fell, the reticulocytes increased in number (Fig. 1). Normally in a typical case of viral hepatitis the jaundice clears slowly, but in these cases inspite of such severe hyperbilirubinaemia, the level of serum bilirubin returned to normal fairly rapidly. In all these cases the jaundice disappeared between 3-4 weeks.

According to Ivanyi and Gall-Horvath (1960) haemolysis occurred to a certain degree in the acute stage of viral hepatitis, but no explanation was given for this phenomenon. Keiderling et al (1958) using radiochromium to study red blood cell survival time observed that in six out of ten cases of viral hepatitis, there was shortened red cell survival time. Hyman and Southworth (1951) in their reports on the association of haemolytic anaemia and chronic liver disease speculated that the liver may be damaged in such a way that its normal capacity to degrade or detoxify haemolytic factors may be impaired to an extent that haemolysis results, which in turn causes hepatic impairment thus establishing a vicious cycle. The other possibility put forth by them was that some abnormal metabolite secondary to liver injury acting as an antigen might cause the production of abnormal antibodies which were responsible for red cell haemolysis. The evidence to support this latter hypothesis was the response to steroid therapy and the occurrence of positive Coomb's test in some of their cases. Raffensperger (1958) speculated on the possibility that the virus might alter the resistance of human red blood cell to haemolysis or the abnormal destruction of erythrocytes could be due to spleen or the presence of some unknown haemolysin. Kivel (1961) considered such factors as intrinsic red cell defect, erythrocyte and immunological consequences of viral infection, the effects of liver damage and the splenomegaly to be important in the causation of haemolysis. So far no postulation has been made as to the importance of glucose-6-phosphate dehydrogenase deficiency in inducing haemolysis in viral hepatitis. The negative Coomb's test that was done in 5 cases, and the absence of splenomegaly in all these cases indicate that the immunological factor and splenomegaly were not responsible for haemolysis. It is possible that the damaged liver from viral hepatitis might release an erythrotoxic factor of some unknown substance to act on the erythrocytes which were already deficient in glucose-6-phosphate dehydrogenase to cause haemolysis, in the same manner that drug causes hemolysis in this type of cases. Although it is quite difficult to exclude completely the possibility that the drugs could be responsible for haemolysis because they were given to these patients in cases 1,2,3,4,8, it is likely that these drugs could have aggravated the haemolysis. On the other hand, haemolysis in these cases could have been induced in the way that haemolytic crisis occurs in the sickle cell anaemia. The other possibility was that viral hepatitis per se acted as an exogenic trigger mechanism to induce haemolysis, as in typhoid cases reported by C. Hersue et al (1967). Although Kivel (1961) attributed that his second case was due to congenital non-spherocytic anaemia, it was possible that it could have been due to glucose-6-phosphate deficiency because it has been noted that abnormal glucose-6-phosphate dehydrogenase activity may be present in some of these cases Newton and Bass (1958), Newton and Frajola (1958), Shahidi and Diamond (1959), Zinkhan and Lenhard (1959). Further Berry and Vietti (1965) had shown how easily this condition can be missed if the possibility of this condition is not borne in mind as shown by the fact that 7 out of 14 of his cases were not diagnosed until years later. In this series, case 10 is an example.

Before concluding that these cases were viral hepatitis associated with haemolytic anaemia due to the absence of glucose-6-phosphate dehydrogenase, it is important to consider whether cases of haemolytic anaemia due to absent glucose-6-phosphate dehydrogenase could present with features simulating viral hepatitis. Berry

and Vietti (1965) observed the clinical features of 14 Negro children and found them to be variable; Ben-Ishay and Izak (1964) gave a description of 4 adults with clinical and laboratory evidence of increased haemolysis associated with glucose-6-phosphate dehydrogenase deficiency. In the case of the latter authors, the liver function tests were normal except for the rise in indirect bilirubin in the serum. In addition, two of their cases had liver biopsies, which revealed normal hepatic architecture and fine lipofuschsin granules in the liver cells. Chew (1967 unpublished observation) also found that liver biopsy in G-6-P-D cases which presented with haemolysis only was also normal. None of the above cases described had the features similar to those described by those workers. Moreover, the histology in cases, 1,2 and 10 showed definite changes consistent with viral hepatitis. It can therefore be concluded that these cases are without doubt viral hepatitis with haemolytic anaemia due to glucose-6-phosphate dehydrogenase deficiency.

SUMMARY AND CONCLUSIONS

Eleven cases of viral hepatitis with haemolysis due to glucose-6-phosphate dehydrogenase deficiency were reported in Chinese in Singapore. They all had absence of glucose-6-phosphate dehydrogenase. There was clinical and biochemical evidence to suggest that they had viral hepatitis and hemolysis. Two characteristic features were that the hyperbilirubinaemia was completely out of proportion to the clinical state and that reticulocytes tended to rise as serum bilirubin fell. Therefore in the initial stages of the disease, reliance can not be placed only on reticulocytosis. Further, it is important to test for G-6-P-D in Chinese patients who have evidence of viral hepatitis with severe hyperbilirubinaemia.

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