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TRANSAMINASE AND LIVER-FUNCTION STUDIES IN INFECTIOUS MONONUCLEOSIS

BY

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Clinical manifestations of hepatitis are infrequent in infectious mononucleosis, though subclinical hepatitis is believed to be common because liver-function tests are usually abnormal. However, the tests most often used to demonstrate impaired liver function, the thymol turbidity and the cephalin-cholesterol flocculation, are those which reflect alterations in serum proteins, alterations for which antibody production might be in part responsible; caution has therefore been exercised in regarding abnormal flocculation tests as evidence of liver damage. Nevertheless, Leibowitz (1953) in a review of clinical, chemical, biopsy, and post-mortem studies concluded that hepatitis was an integral feature of most, if not at all, cases of infectious mononucleosis, a conclusion confirmed by the almost invariable finding of inflammatory changes in the liver in the biopsy studies of Nelson and Darragh (1956) and Sullivan *et al.* (1957).

Wróblewski and LaDue (1956) have shown that the levels of the serum glutamic-oxaloacetic and serum glutamic-pyruvic transaminases (S.G.O.T. and S.G.P.T.) are increased in liver-cell injury, the enzymes being liberated from the damaged liver cells into the bloodstream. They also showed that determinations of these enzymes (though not actually measuring liver-cell function) more sensitively reflect liver-cell damage than do conventional liver-function tests.

Rennie and Wróblewski (1957) studied serum transaminase levels in hepatitis associated with infectious mononucleosis and concluded that most patients with infectious mononucleosis have laboratory evidence of complicating hepatitis, but in a later article Wróblewski (1958) states that infectious mononucleosis usually is accompanied by normal S.G.O.T. and S.G.P.T. activity.

A study of liver function in infectious mononucleosis using serum transaminases and conventional liver-function tests has been in progress since the beginning of 1958, and our observations and conclusions are presented below.

Materials and Methods

Twenty-three consecutive patients presenting with infectious mononucleosis during a period of 12 months were studied. These comprised 15 nurses, 1 medical student, and 3 female and 4 male patients referred by local practitioners. All but three of the patients were hospitalized, two were confined to bed at home, and one patient (Case 18) remained ambulant throughout the course of her illness.

The minimum diagnostic requirements for inclusion in the study were the presence of fever, sore throat, and lymphadenopathy, accompanied at some stage by a blood picture in which at least 50% of the total white cells were lymphocytes, and at least 10% of the total white cells were atypical lymphocytes of the type described by Downey and McKinlay (1923).

The serum heterophil antibody titre (H.A.T.) was determined in all patients and differential absorption performed, using ox red-blood-cell and guinea-pig-kidney suspension (Davidsohn, 1937). An H.A.T. of 1:28 or more, provided that absorption occurred with ox red cells but not guinea-pig kidney, was taken as a diagnostic titre (sero-positive) in this laboratory.

Sera were obtained from all patients as soon as possible after the start of illness and at intervals of three to seven days during its course: 10 patients were followed up at least three months after its onset. The start of illness was defined as the day of onset of sore throat, fever, lymph-node swelling, or gastro-intestinal symptoms.

The following chemical estimations were made: S.G.O.T. (Karmen *et al.*, 1955), S.G.P.T. (Wróblewski and LaDue, 1956), thymol turbidity and flocculation (MacLagan, 1944), colloidal gold flocculation (MacLagan, 1946), zinc sulphate turbidity (Kunkel, 1947), mercuric chloride turbidity (MacLagan *et al.*, 1957), alkaline phosphatase (King and Armstrong, 1934), total bilirubin (Malloy and Evelyn, 1937), and total protein (Van Slyke *et al.*, 1950). The normal values of these tests in the laboratory are given in Table II.

Paper electrophoresis by the hanging-strip method was also performed. 10 μ l. of serum was applied to Whatman No. 3 MM filter paper saturated with barbitone buffer (pH 8.6, μ 0.05), subjected to a potential difference of 110 v. for 15 hours, and the strips were dried, stained with light green, and scanned, using an EEL scanner.

Clinical Findings

All patients had an illness with fever, sore throat, and lymph-node enlargement always affecting the posterior cervical and sometimes the axillary and inguinal nodes. The illness was in all cases of short duration; the average stay in hospital was 19 days, and all patients

made a complete clinical recovery. Sensitivity to alcohol for at least three months after their illness was noted by three patients (Cases 4, 5, and 6); nausea and dizziness followed the ingestion of a quantity of alcohol which prior to illness had no such effect. The illness was judged to be severe in three patients, and in two of these and in one further patient a diagnosis of accompanying hepatitis was made on clinical grounds because of the severity of gastro-intestinal symptoms. Only one patient was clinically jaundiced; four patients had a palpable liver. Antibiotics, usually penicillin, were administered to patients with severe oropharyngeal inflammation; otherwise treatment was symptomatic, and consisted of gargles, aspirin, and rest in bed until one week after fever had subsided.

Important clinical data of these cases, together with their maximal H.A.T. and haematological findings, are listed in Table I.

Chemical Findings

Table II lists the maximal laboratory findings for each patient. The serum transaminases were elevated in 18 of the 19 sero-positive cases. Sera were obtained from 12 of these within seven days of the start of the illness and raised levels were found in all. Except in one case transaminases were maximal during the second week of illness. Raised levels had usually reverted to normal by the fifth week from the start of the illness. The S.G.O.T. and S.G.P.T. values ran roughly parallel, the S.G.P.T. exceeding the S.G.O.T. in approximately two-thirds.

No correlation was observed between the transaminase activities and the H.A.T., the lymphocyte percentage, or the percentage of atypical lymphocytes in the blood. Like Rennie and Wróblewski (1957) we found that in individual patients fluctuations in clinical condition were reflected in alterations of transaminase levels, but the level of activity could not be related from patient to patient to the severity of the accompanying illness. The illness in Case 6, for instance, was much milder than that in Case 9, though the serum possessed at least double the transaminase activity.

Conventional liver-function tests were positive less often in these sero-positive cases, the thymol turbidity, for example, being raised in 12, the zinc sulphate

TABLE II.—Maximal Chemical Data on 23 Cases of Infectious Mononucleosis

Case No.	S.G.O.T. (Units/ml.)	S.G.P.T. (Units/ml.)	Thymol Turbidity (Units)	Thymol Flocculation	Colloidal Gold	Zinc Sulphate Turbidity (Units)	Mercuric Chloride Turbidity (Units)	Alkaline Phosphatase (Units)	Total Bilirubin (mg./100 ml.)
Normal:	5-35	5-25	0-4	0-1	0	0-4	0-4	3-13	0-1
1	130	140	8	3	4	7	9	16.0	0.8
2	167	242	4	1	3	10	—	11.5	0.1
3	428	535	5	2	2	6	6	15.5	1.6
4	38	81	8	3	5	—	5	19.0	0.6
5	32	42	5	2	1	3	5	6.5	—
6	740	600	11	4	3	10	7	14.0	0.6
7	112	65	4	0	1	4	4	10.0	0.5
8	43	22	5	2	3	6	4	6.0	0.5
9	370	184	14	4	3	12	13	64.0	2.4
10	28	9	3	0	2	5	5	5.5	0.6
11	225	175	3	0	0	5	2	10.5	0.4
12	37	33	4	0	0	7	4	7.5	0.5
13	111	148	8	2	4	12	9	12.5	0.6
14	140	162	6	0	2	8	6	11.5	0.5
15	225	310	6	2	2	6	8	24.0	1.5
16	128	163	3	0	2	3	5	9.0	0.4
17	128	132	5	0	1	5	6	35.0	0.3
18	67	62	6	2	1	2	2	6.0	0.1
19	82	126	3	1	2	5	6	14.0	0.5
20	32	10	2	0	0	2	1	8.0	0.1
21	30	18	4	0	2	7	4	8.5	0.6
22	33	45	6	0	4	8	7	9.5	0.1
23	413	180	8	3	2	5	8	14.0	0.4

turbidity in 14, the alkaline phosphatase in 9, and the serum bilirubin in 3. Flocculation tests were generally maximal towards the end of the second week of illness and, with the exception of the zinc sulphate turbidity, had usually returned to normal by the fifth week. They were commonly normal early in the disease, the thymol turbidity and the zinc sulphate turbidity being raised in three and six respectively of the 12 patients tested during the first week of illness. Changes in these tests could not be related to the clinical, serological, or haematological state of the patient.

Moderate elevation of the transaminases and abnormal liver-function tests were present in two of the four cases of infectious mononucleosis in which no H.A.T. could be demonstrated.

Paper electrophoresis was performed on sera taken at the height of illness from 19 of the 23 patients, and was abnormal in all, the commonest abnormality being increase of the α_2 - and γ -globulins.

TABLE I.—Clinical and Maximal Haematological Findings on 23 Cases of Infectious Mononucleosis

Case No.	Age	Sex	Anorexia	Nausea	Vomiting	Jaundice	Palpable Liver	Palpable Spleen	Severity of Illness	Hepatitis Diagnosed Clinically?	Treatment	Maximal H.A.T.	Maximal W.B.C. per c.mm.	Maximal % Lymphocytes	Maximal % Atypical Lymphocytes
1	18	F	Moderate	Moderate	Mild	Absent	Present	Present	Severe	Yes	Symptomatic	1: 896	8,000	52	20
2	24	F	Absent	Mild	Absent	Present	Absent	Absent	Moderate	No	Penicillin	1: 28	13,100	52	15
3	24	F	Mild	Absent	Present	Present	Present	Present	Severe	Yes	Symptomatic	1: 1,792	20,500	80	30
4	21	M	Moderate	Mild	Mild	Absent	Present	Present	Severe	Yes	Penicillin	1: 3,584	13,400	60	36
5	20	F	Absent	Mild	Absent	Present	Present	Present	Mild	No	Symptomatic	1: 112	17,400	50	12
6	20	F	Present	Mild	Absent	Present	Present	Present	Moderate	Yes	Penicillin	1: 224	10,000	86	80
7	20	F	Present	Absent	Present	Present	Present	Present	Mild	Yes	Symptomatic	1: 112	13,100	77	52
8	20	F	Present	Present	Present	Present	Present	Present	Severe	Yes	Penicillin	1: 224	9,000	51	26
9	23	F	Present	Present	Mild	Present	Present	Absent	Severe	Yes	Symptomatic	1: 224	11,200	60	40
10	27	F	Present	Present	Absent	Present	Present	Present	Moderate	Yes	Symptomatic	Negative	8,500	79	52
11	21	F	Present	Present	Present	Present	Present	Present	Mild	Yes	Symptomatic	1: 224	4,500	67	45
12	20	F	Present	Present	Present	Present	Present	Present	Severe	Yes	Symptomatic	1: 28	8,300	68	56
13	20	F	Present	Present	Present	Present	Present	Present	Severe	Yes	Symptomatic	1: 1,792	17,200	88	72
14	20	F	Present	Present	Present	Present	Present	Present	Severe	Yes	Symptomatic	1: 448	10,000	67	17
15	21	F	Mild	Mild	Mild	Present	Present	Present	Moderate	Yes	Penicillin	1: 224	5,500	77	60
16	28	F	Absent	Absent	Absent	Present	Present	Present	Severe	Yes	Penicillin, tetracycline	1: 448	10,900	67	47
17	24	M	Present	Mild	Present	Present	Present	Present	Mild	Yes	Symptomatic	1: 56	10,400	76	52
18	19	F	Moderate	Absent	Present	Present	Present	Present	Moderate	Yes	Penicillin	Negative	8,500	68	60
19	23	M	Present	Present	Present	Present	Present	Present	Moderate	Yes	Penicillin, tetracycline	1: 224	14,800	80	40
20	20	F	Absent	Present	Present	Present	Present	Present	Mild	Yes	Symptomatic	1: 56	11,700	54	25
21	19	M	Mild	Present	Present	Present	Present	Present	Severe	Yes	Symptomatic	Negative	14,000	61	52
22	19	F	Present	Present	Present	Present	Present	Present	Severe	Yes	Symptomatic	1: 448	12,400	82	55
23	23	M	Present	Mild	Mild	Present	Present	Present	Moderate	Yes	Penicillin	1: 114,688	9,400	59	35

Elution of heterophil antibody was accomplished from paper electrophoretograms of the serum of four sero-positive cases, and the antibody was found to move with the γ -globulin.

Table III shows the laboratory findings on 10 patients tested at least three months after their illness. All had normal transaminases, but half had a raised zinc sulphate turbidity, minor disturbances of other flocculation tests, and increased γ -globulin on electrophoresis. The zinc sulphate turbidity chiefly measures γ -globulin; that its elevation might be related to persisting antibody was supported by the higher titres of heterophil antibody in these patients' sera.

Ten patients confined to bed with upper respiratory illness other than infectious mononucleosis, but in whom a diagnosis of infectious mononucleosis had been considered on clinical grounds, had normal transaminases and normal liver-function tests. Five cases of reticulosis (three of lymphosarcoma and two of Hodgkin's disease) which presented with fever, lymph-node enlargement, and abnormal cells in the peripheral blood had normal values for these tests.

Discussion

Increased S.G.O.T. and S.G.P.T. activity in infectious mononucleosis indicates liver involvement, for though S.G.O.T. activity may be increased in both myocardial and liver-cell injury, S.G.P.T. activity is not significantly increased in the former (Wróblewski and LaDue, 1956). The superiority of the transaminases over conventional liver-function tests in their sensitivity to liver injury and ability to reflect the patient's clinical state indicates that where transaminase determination is available other tests of liver function may be unnecessary. Like Sullivan *et al.* (1957) we found that flocculation tests gave little information about the extent or duration of liver involvement, whereas transaminase determination would seem the ideal laboratory test for following the course of illness, the effect of treatment, and the duration of liver damage. The early elevation of the transaminases was helpful in the diagnosis of cases with negative serology and an equivocal blood picture. By finding raised transaminase levels we were occasionally able to predict that the serological or haematological findings would become positive. Normal transaminase levels were found in the 10 patients with upper respiratory illness and the five with reticulosis in whom a diagnosis of infectious mononucleosis was considered but not confirmed.

Clinical (Mason and Adams, 1958), liver-function (Berk *et al.*, 1948; Sullivan *et al.*, 1957), and liver-biopsy (Nelson and Darragh, 1956; Sullivan *et al.*, 1957)

studies have indicated differences between the hepatitis of infectious mononucleosis and that of infective hepatitis. The transaminase pattern also differs from that found in infective hepatitis, since the levels are lower (they exceeded 500 units per ml. in only two of our cases) and are usually maximal in the second week of illness, whereas in infective hepatitis the peak of S.G.O.T. and S.G.P.T. activity is usually in excess of 500 units per ml. and occurs in the early phase of the disease (Pryse-Davies and Wilkinson, 1958).

It has been suggested (Cohn and Lidman, 1946; Bennett *et al.*, 1950; Hsia and Gellis, 1952) that, to prevent permanent liver damage, patients with infectious mononucleosis should be treated with a regime of high-carbohydrate, high-protein, and low-fat diet, vitamin supplements, parenteral fluids if there is anorexia, and protracted rest. This treatment has been recommended because of the belief that the hepatitis of infectious mononucleosis may become chronic (Cohn and Lidman, 1946; Bennett *et al.*, 1950) or proceed to cirrhosis (Jordan and Albright, 1950; Leibowitz and Brody, 1950). The incidence of these hepatic sequelae is not accurately known, nor has the value of the proposed therapy been established. Increased serum transaminase activity in the first week of illness, and the frequency of biochemical evidence of liver damage even when symptoms and signs of liver involvement are absent, suggests that treatment considered useful in preventing liver damage should be instituted in all cases and begun as soon as the diagnosis is established. Such treatment should perhaps be continued until transaminase activities return to normal.

Our four sero-negative cases failed to reveal heterophil antibody despite repeated testing. Two of these had normal transaminase levels and two had slightly raised levels: it may be that liver injury is milder or less common in sero-negative disease.

The presence of hepatitis so frequently in the course of infectious mononucleosis suggests the possibility that the infective agent of the disease, if present in the liver, might pass from damaged liver cells via the bile into the faeces, and that ingestion of contaminated material might be responsible for some cases.

Summary

Serum glutamic-oxaloacetic transaminase (S.G.O.T.), glutamic-pyruvic transaminase (S.G.P.T.), and liver-function studies were carried out on 23 patients with infectious mononucleosis.

Raised transaminase values were observed in 18 out of 19 sero-positive cases and in two out of four sero-negative cases. The levels of activity of both enzymes

TABLE III.—*Follow-up Findings on 10 Cases of Infectious Mononucleosis*

Case No.	Days after Start of Illness	H.A.T.	S.G.O.T.	S.G.P.T.	Thymol Turbidity (Units)	Thymol Flocculation	Colloidal Gold	Zinc Sulphate Turbidity (Units)	Mercuric Chloride Turbidity (Units)	Alkaline Phosphatase (Units)	Total Bilirubin (mg./100 ml.)	Total Protein (g./100 ml.)	Serum Electro-phoresis
			Units/ml.										
4	317	1:56	27	14	4	1	1	6	3	7.0	0.1	7.4	Increased γ -globulin Normal Increased γ -globulin Normal
5	334	1:28	9	8	2	0	1	2	1	4.5	0.6	7.1	
6	95	1:56	19	8	3	1	2	6	4	3.5	0.4	7.7	
7	181	1:28	13	9	2	0	0	1	2	6.5	0.4	6.9	Normal " " " Increased γ -globulin Normal
8	158	Negative	13	9	2	1	1	5	3	4.5	0.1	7.5	
11	118	1:28	19	12	1	0	0	1	2	—	—	6.4	
13	102	1:224	20	15	3	1	1	6	3	8.0	0.1	7.7	Increased γ -globulin Normal " " "
12	144	Negative	16	8	1	0	0	3	3	3.5	0.6	6.7	
15	91	1:56	20	9	2	0	0	5	3	6.5	0.1	7.5	
16	99	1:28	16	9	1	0	1	1	2	3.0	0.4	5.5	

were increased in the first week of illness, were usually maximal during the second week, and returned to normal about five weeks from its commencement. The S.G.O.T. and S.G.P.T. levels ran roughly parallel, the S.G.P.T. exceeding the S.G.O.T. in about two-thirds of the cases.

Transaminase values were below 500 units per ml. in all but two patients; high levels were not necessarily associated with severe illness. Variations in individual patients' clinical state were reflected in alterations of their transaminase levels.

Conventional liver-function tests were less often abnormal and were not affected so early. The zinc sulphate turbidity and serum γ -globulin were sometimes raised some months after recovery, when other tests were normal; this was thought to be related to persisting antibody.

Transaminase determination was helpful in early diagnosis and differential diagnosis, and may assist case management. Our findings confirm that liver involvement is a usual feature of the disease.

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GASTRO-DUODENAL HAEMORRHAGE AS A SURGICAL EMERGENCY

BY

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From this hospital, Bohn (1949) reported his experience of 150 cases of gastro-duodenal haemorrhage treated under his personal care in surgical wards. 135 were of acute or chronic peptic ulcers, 33 (25%) underwent emergency surgery, and the overall mortality was 7.4%.

Since that time changes in policy and organization have taken place, and it seemed timely to survey the situation again. The five years 1953 to 1957 are reviewed in this report. Over this period all cases of gastro-duodenal haemorrhage were admitted as routine surgical emergencies under the care of the surgeon on duty. As a result four consultant surgeons and various registrars have been responsible for the treatment of the patients, in contrast to the earlier series, in which all the cases received the individual attention of a single surgeon specially interested in the problem.

In these five years 551 patients were admitted with gastro-duodenal haemorrhage, but 11 are now excluded because the evidence concerning the haemorrhage was doubtful. Of the remaining 540 cases, 488 were due to acute or chronic ulceration; 97 of these underwent emergency surgery, and the overall mortality was 5.9%. This paper is concerned with an analysis of these statistics, and reviews some aspects of the whole period of 11 years from 1946, during which time 861 cases of haemorrhage from peptic ulcers have been treated.

Statistical Analyses

Of the 540 cases of definite haemorrhage, 488 were diagnosed as due to ulceration. The other cases were diagnosed as follows: hiatus hernia 30, oesophageal varices 10, gastric carcinoma 7, purpura 2, and ulcerated gastric polyp, leiomyoma of stomach, and haemophilia 1 each. The diagnosis of hiatus hernia needs some comment. The high incidence in this compared with earlier series is probably due to increased knowledge of the lesion, and in consequence a routine radiological search is made for it. These cases, like nearly all the others, received medical treatment, and later, when bleeding had ceased, a barium-meal examination was made. The hiatus hernia was not firmly diagnosed, therefore, until some days after bleeding had ceased. In many cases oesophagoscopy was done at this stage, but few were found to have oesophagitis. Whether this indicated that oesophagitis had settled on medical treatment, or that the hernia was a coincidental accompaniment of an acute ulcer, it is not possible to say.

The major problem in all series of this sort is, however, the haemorrhage from peptic ulceration (including both acute and chronic ulcers), and the following tables give data concerning the 488 patients in this group.

Table I shows how the group is divided according to diagnosis and sex, and gives numbers treated surgically, with the mortality rates. The "peptic ulcer" group, in which the site of the ulcer was not known, is a rather unsatisfactory one, especially so because it had a high mortality rate. In all there was a history of chronic ulceration, but the site remained in doubt