solution containing 340 mmol/l sucrose, 1 mmol/l ethylenediaminetetra-acetic acid, pH 7·4, and 5 I.U./ml heparin. The cells were adjusted to a concentration of approximately $2{\cdot}0 \times 10^7$ cells ml^{-1} (equivalent to 2 mg protein ml^{-1}) and sonicated. The dithionite difference spectra of the homogenates were determined on a Beckman 24 spectrophotometer. Spectra of all C.G.D. patients resembled those of their normal relatives and controls. There was no evidence of the shift in the myeloperoxidase peak at 474 nm that was found by Segal and others.[8] In A, B, C, and E a shoulder was seen at 445 nm, which apparently was not related to the disease.

Discussion

The finding in the patients D and E (fig. 1) of normal uptake of test particles with abolished intracellular killing, oxygen consumption, glucose-1-C oxidation, N.B.T. reduction, and chemiluminescence establishes that these were cases of C.G.D. The fact that the mother was normal in all tests and that a brother and a sister are affected strongly indicates that this family has the autosomal recessively inherited form of C.G.D.

There have been very few reports of C.G.D. affecting siblings of both sexes. Recently Clark and Klebanoff[10] reported C.G.D. in a brother and a sister, but they detected a chemotactic defect in the neutrophils from these two patients. In contrast to their findings, the only dysfunction we detected in the neutrophils of our cases was in the oxygen-dependent bacterial system.

The fact that cytochrome b was present in the cases of C.G.D. studied by us (both the autosomal recessive and the X-linked form) indicates that absence of cytochrome b is not always the cause of C.G.D. Therefore measurement of cytochrome b cannot be used for diagnosis in the way that oxygen-consumption studies can. Furthermore, this finding invalidates the argument that cytochrome b is part of an oxygen-consuming electron-transport system, since this argument is based on the assumption that cytochrome b is missing when, as in C.G.D., there is no oxygen consumption during phagocytosis. Perhaps other parts of the electron-transport system postulated to be present in the membranes and vacuoles of the neutrophils may be missing in our cases, and this deficiency does not show up in the dithionite difference spectra. This should be investigated.

It now has to be established whether absence of cytochrome b is associated with an abnormality of the neutrophils other than C.G.D., and to see how firmly such an abnormality is associated with C.G.D.

We thank staff and Dr Dirk Roos, Central Laboratory of the Netherlands, Amsterdam, who measured oxygen consumption, glutathione peroxidase, and 6-phosphogluconate dehydrogenase activity. We also thank Dr Anthony W. Segal, Clinical Research Centre, Harrow, who reran the spectra of the patients E and X in his laboratory in collaboration with Dr O. T. G. Jones, Department of Biochemistry, University of Bristol. We thank Mrs Gonna Guldberg, Susanne Overbye, Hanne Tamstorf, and Anna-Lise Poulsen for technical assistance.

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NON-A NON-B HEPATITIS ASSOCIATED WITH CHRONIC LIVER DISEASE IN A HÆMODIALYSIS UNIT

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Summary To clarify the ætiology of an outbreak of HB_sAg-negative acute hepatitis in the renal unit at Fulham Hospital in 1968–70, serological tests for antibody to hepatitis-A virus (anti-H.A.V.) were done retrospectively on serum samples obtained at the time of the outbreak. 7 patients had had two previous episodes of clinical HB_sAg-negative hepatitis. Serum samples were available from 24 of the 29 infected patients, and these were paired in 12 instances. There was a slight increase in the titre of anti-H.A.V. in 1 patient, and a further 2 patients who subsequently developed chronic hepatitis showed a decrease in titre, but no changes in titre were detected in the remaining 21 cases. These findings do not provide evidence for the involvement of hepatitis-A virus in the outbreak of hepatitis and effectively exclude a role for this virus in the chronic liver disease which developed subsequently in 8 (28%) of the patients. This outbreak is therefore probably non-A

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non-B hepatitis, which has not been reported previously in Great Britain in a hæmodialysis unit. The results confirm that this form of hepatitis may be related to a high frequency of persistent hepatic dysfunction.

Introduction

CHRONIC liver disease following acute hepatitis B is well documented both in previously healthy individuals and in patients with renal disease,[1,2] but it has not been detected after serologically confirmed infection with hepatitis-A virus (H.A.V.). Persistent hepatic lesions following two outbreaks of HB_sAg-negative hepatitis thought to be due to hepatitis A have been reported in the renal unit at Fulham Hospital.[3,4] 8 of the 29 patients who had contracted acute hepatitis in 1968–70[4] were subsequently found to have persistently elevated serum-levels of aminotransferase activity. Liver biopsy in 7 of these patients revealed chronic aggressive hepatitis in 3, chronic persistent hepatitis in 2, and non-specific hepatitis in association with massive iron overload in 2.[5] Since that study, serological assays for H.A.V. infection have become available,[6-8] and we have now examined serum samples collected during the outbreak for antibody to H.A.V. (anti-H.A.V.) to determine if that outbreak and the succeeding chronic liver disease were related to infection with hepatitis A virus.

Patients and methods

Two or more serum samples obtained at the time of the outbreak from 24 of the 29 patients were provided by Dr Y. Cossart, Central Public Health Laboratory, London. For each patient, two serum samples were selected. In 12 of the 24 patients (group I), the first sample was obtained before the episode of acute hepatitis and the second 3 to 11 (median 8) months after the acute illness. In 7 cases (group II) the first sample was collected during the acute illness and the second during convalescence 2 to 13 (median 4) months later. In the remaining 5 patients (group III), the exact relationship of samples taken to multiple episodes of elevations in serum-aminotransferase activities was not well defined. Anti-H.A.V. was determined by immune adherence hæmagglutination on serial ten-fold dilutions of heat-inacitvated serum.[9]

Of the 24 patients tested, 5 have since died from causes other than liver disease, 4 have functioning renal transplants, and 15 have been maintained on hæmodialysis. The 5 patients from whom serum samples were unavailable included 2 who had died and 3 who had received successful transplants. The 8 patients who were found to have chronic liver disease are included in the 15 cases remaining on hæmodialysis.

Results

The anti-H.A.V. titres obtained are shown in the table. In group I, no change in titre was apparent between the two samples in 11 of the 12 patients. The remaining patient (no. 7) demonstrated a fall from ≥1000 to <10 and was subsequently found to have chronic active hepatitis (case 3 of the previous report[5]). In group II, differences in titres of anti-H.A.V. between the two samples were detected in 2 cases. In the first (no. 17), the titre increased from <10 to 100, and in the second (no. 15), a decrease from ≥1000 to <10 was observed. Patient 15 was subsequently found to have chronic persistent hepatitis (case 5 of the previous report[5]). No change in titre was found in the 5 patients who comprised group III. Further analysis of the results in the 8 patients who developed chronic liver disease[5] showed no change in anti-H.A.V. titre in 4 of the 5 included in group I (patients 1, 4, 6, 9) or in the 2 cases in group III (patients 23 and 24). As noted above, a significant decrease was observed in the remaining 2 cases (patients 7 and 15).

7 of the 24 patients tested had also developed hepatitis during a previous outbreak at Fulham Hospital in 1966, in which 14 patients contracted HB_sAg-negative hepatitis. Of the 5 included in group I, a fall in anti-H.A.V. titre was observed in 1 (patient 7) as described above. Of the other 4 patients, 2 (nos. 2 and 10) had titres of <10 in both serum samples and 2 (nos. 3 and 9) of ≥1000. The remaining 2 patients, patient 18 (group II) and patient 23 (group III), showed no alteration in titre (≥1000 on both occasions).

Discussion

The possibility that the 1968–70 outbreak was due to hepatitis-B virus (H.B.V.) infection seems remote, for although testing for anti-HB_c was not done, radioimmunoassay for HB_sAg proved consistently negative, and the prevalence of anti-HB_s was no different in patients who had contracted hepatitis from those who had not.[5] Furthermore, in the 7 patients with chronic liver disease in whom liver biopsy was performed, no hepatocytes containing HB_sAg were observed,[5] either by fluorescence microscopy or upon orcein staining.[10] This contrasts strikingly with the ease with which HB_sAg was detected with these procedures in hepatic tissue from renal patients with chronic liver disease related to hepatitis-B infection.[11] The results of retrospective testing in the present study for anti-H.A.V. in 24 of the 29 patients who contracted hepatitis in 1968–70 provide no evidence for the involvement of hepatitis-A virus. Only one

ANTI-H.A.V. IN PATIENTS WITH ONE OR TWO EPISODES OF CLINICAL HB_sAg-NEGATIVE HEPATITIS

Patient no.	No. of episodes	Interval between samples (mo)	Anti-H.A.V. titre	
			Sample 1	Sample 2
Group I:				
1	1	10	100	100
2	2	7	<10	<10
3	2	10	≥1000	≥1000
4*	1	10	≥1000	≥1000
5	1	11	100	100
6*	1	3	≥1000	≥1000
7*	2	10	≥1000	<10
8	1	4	≥1000	≥1000
9*	2	8	≥1000	≥1000
10	2	8	<10	<10
11	1	3	100	100
12	1	6	100	100
Group II:				
13	1	3	<10	<10
14	1	8	<10	<10
15*	1	4	≥1000	<10
16	1	2	<10	<10
17	1	13	<10	100
18	2	2	≥1000	≥1000
19	1	7	≥1000	≥1000
Group III:				
20	1	8	<10	<10
21	1	2	<10	<10
22	1	12	≥1000	<10
23*	2	3	≥1000	≥1000
24*	1	1	≥1000	≥1000

* Persistent elevation of serum-aminotransferase activity.

instance of an increase in anti-H.A.V. titre was observed overall, and this was of minor degree, falling well below the expected levels of 10 to 100 times higher. Thus, this outbreak was unlikely to have been caused by H.A.V. infection.

7 of the 24 patients who were tested had also been infected in the first outbreak of HB_sAg-negative hepatitis which affected 14 patients in the renal unit at Fulham Hospital in 1966–67. Although the anti-H.A.V. titres of samples obtained from these 7 patients 3 years later do not exclude hepatitis-A infection in the first outbreak, this possibility is considerably diminished by the finding of titres <10 in both samples from 2 of these patients. This situation may be comparable to that of intravenous drug addicts who frequently suffer more than one bout of acute hepatitis unrelated to H.A.V. or H.B.V.[12] Analysis of results obtained in the 8 patients who have subsequently developed chronic liver disease revealed no change in titre of anti-H.A.V. in 6, and in the remaining 2 patients titres had decreased in the second sample tested. Thus, it appears unlikely that the fall in antibody titre was causally related to the development of chronic liver disease, particularly since immunoglobulin levels are generally increased in such patients.[13] Other factors which may have contributed to the minor fluctuations in anti-H.A.V. titre observed include blood-transfusions and fluctuations in humoral immunocompetence.[14]

Overall these results must indicate that the development of chronic liver disease was not related to hepatitis-A infection and that this outbreak falls into the category of non-A non-B hepatitis. More and more data point to this as the cause of a substantial proportion of cases of post-transfusion hepatitis negative for HB_sAg[15,16] and to its role in the subsequent development of chronic liver disease.[17-20] Furthermore, 7 patients developed two episodes of clinical hepatitis which was apparently not caused by H.A.V. or H.B.V. These observations support the epidemiological evidence for the existence of more than one agent of non-A non-B hepatitis. Further verification of the nature of the virus involved in this outbreak will require suitable serological tests for non-A non-B hepatitis, and experiments in which the chimpanzee was used as a model for non-A non-B hepatitis[21-23] indicate that the development of such assays may soon be realised.

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DEPENDENCE ON CHLORMETHIAZOLE AND EFFECTS OF ITS WITHDRAWAL

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Summary Five cases of physical dependence on chlormethiazole are reported. Because sudden withdrawal may precipitate an acute "organic psychosis", chlormethiazole should only be used in hospitals and, even then, only for a maximum of 9 days.

Introduction

CHLORMETHIAZOLE ('Heminevrin', 'Hemineurin') was introduced in 1957 and is now widely used in the treatment of delirium tremens and eclampsia. It is also used in the treatment of narcotic withdrawal.[1] Chlormethiazole is chemically related to the thiazole portion of the thiamine (vitamin B_1) molecule, and it acts as a central-nervous-system depressant. The manufacturers recommend[2] its use for "psychomotor agitation, tension and anxiety; daytime sedation in senile psychosis; confusional states; delirium tremens; sleep disturbances; withdrawal symptoms in alcoholism". In the *Data Sheet Compendium*[3] the statement appears "It is seldom recommended in alcoholic withdrawal to administer Heminevrin for more than nine days."

Chlormethiazole is being used frequently in general practice as an alternative to tranquillisers such as diazepam ('Valium'). We wish to draw attention to the serious addictive properties of chlormethiazole and to the considerable problems associated with its withdrawal. In our opinion it should not be recommended or used as a routine sedative or hypnotic. Its chemical relation to vitamin B_1 may have created the erroneous impression that it is quite safe, harmless, and non-addictive.

Reilly[4] noted several references to abuse of chlormethiazole but found only one reported case of physiological dependence.[5] A 31-year-old man developed grand-mal status with confusional delirium, motor restlessness, and visual and auditory hallucinations. This was followed by an "organic psychosis syndrome", with paranoid features and auditory hallucinations with episodic periods

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