The association of syphilis with cirrhosis: the role of alcohol and serum hepatitis

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Summary

The role of syphilis and alcohol was investigated in a prospective study of patients with cirrhosis of liver in Uganda, and results were correlated with the histological type of cirrhosis, and serological tests for hepatitis B antigen (HB Ag). Eighteen out of eighty (22.5%) patients with histologically-proven cirrhosis had positive serology for syphilis (VDRL and TPI). A high incidence of alcoholism (80%) and syphilis (60%) was found in patients with micronodular cirrhosis who were all negative for HB Ag. By contrast, HB Ag was detected in 37% of patients with macronodular cirrhosis who had a much smaller incidence of syphilis and alcoholism. Although chronic infection with hepatitis B virus related to HB Ag appears to be an important factor in the pathogenesis of cirrhosis in at least 30% of cases, infection acquired during past treatment for syphilis is not an important cause of the association of syphilis with cirrhosis in this population. Subdivision of patients with cirrhosis into those with and those without a history of severe alcohol abuse showed that the difference between the incidence of syphilis in the two groups is significant statistically. However, evidence of syphilis in association with non-alcoholic as well as alcoholic cirrhosis in this and other previously reported series suggests that the association between the two diseases cannot be entirely explained through the common factor of alcoholism, and other factors may also be responsible.

Introduction

There have been numerous reports of the association of syphilis with cirrhosis of liver. Kirmi, Thirkettle and Read (1969), in an extensive review of the literature, found the incidence of syphilis in cirrhosis over the past 100 years to be between 10 and 20%, but could not explain the association. In the past, these two diseases could have occurred together because of syringe-transmitted hepatitis acquired during antisyphilitic treatment (Salaman *et al.*,

1944; Sheehan, 1944). It is known that acute icteric or non-icteric viral hepatitis can on occasions lead to the development of cirrhosis within 5 years (Krarup and Roholm, 1941; Sherlock, 1948; Klatskin, 1958). However, as no specific tests for serum hepatitis were available until now, the role of this virus in the aetiology of cirrhosis could not be studied.

Cirrhosis and syphilis could also occur together through the factor of alcoholism. Several reports (Scheumacher, 1937; Fleming and Snell, 1942; MacDonald and Mallory, 1958; Wells and Lundberg, 1963) give evidence of excessive consumption of alcohol in patients with both diseases, but no data are available from the earlier series that correlate the syphilis with the histological type of cirrhosis associated with it. For example, it is now generally agreed that micronodular cirrhosis is associated with alcoholism, whilst most macronodular types are not (Sherlock, 1968).

With the discovery of hepatitis B antigen (Blumberg, Alter and Visnich, 1965), sensitive tests have been developed for diagnosis of infection with the virus of 'serum' (long-incubation) hepatitis (Shulman, 1970). A study of the association of HB Ag with liver disease has thrown new light on the aetiology of viral hepatitis and cirrhosis in Uganda (Maynard *et al.*, 1970; Anthony *et al.*, 1972; Sadikali, 1972; Sadikali and Barker, 1973). During the course of this prospective study the role of syphilis in patients with cirrhosis was also investigated and an attempt made to correlate the syphilis with the histological type of cirrhosis associated with it, HB Ag and alcohol intake.

Patients and methods

All eighty patients were treated in the medical wards of New Mulago Hospital, Kampala, from June 1970 to June 1972. Most of the patients had advanced liver disease with symptoms and signs of hepatocellular failure and/or portal hypertension. A few were admitted for investigation of hepatomegaly or obstructive jaundice due to gall stones.

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The diagnosis of cirrhosis was confirmed in all by liver biopsy (sixty-eight cases), surgical biopsy (three cases) and at autopsy (nine cases). In addition, in seven of the sixty-eight cases subjected to liver biopsy the diagnosis was confirmed at autopsy. The histological type of cirrhosis was defined as nutritional (micronodular), or macronodular (posthepatic, postnecrotic, and 'mixed' types) according to the criteria of Gall (1960), which have been described in an earlier paper correlating HB Ag with the histopathology of cirrhosis in Uganda (Anthony *et al.*, 1972). Patients were carefully questioned about a past history suggestive of viral hepatitis, genital chancre, treatment for syphilis, and alcohol intake. The standard Venereal Disease Reference Laboratory test (VDRL) was done in all cases and, when positive, Reiter's Protein Complement Fixation test (RPCFT) was also performed. Sera from all patients were frozen and stored at -20°C . The diagnosis of syphilis was confirmed in the VDRL positive sera by the *Treponema pallidum* Immobilization test (TPI). The tests for HB Ag were done on stored sera by the

Complement Fixation and Counterelectrophoretic techniques (Shulman and Barker, 1969; Gocke and Howe, 1970).

Results

Twenty of the eighty (25%) patients had a positive or weakly positive VDRL (Table 1). Eighteen (22.5%) were confirmed as having syphilis by the TPI test. Reiter's test was positive in nine, negative in five and anticomplementary in the rest. Fifteen of the eighty patients had nutritional (micronodular) cirrhosis, the remainder posthepatic, postnecrotic or mixed type of (macronodular) cirrhosis. Results of serological tests for syphilis, HB Ag, and the incidence of alcoholism in the two types of cirrhosis are shown in Table 2. Of the fifteen with micronodular cirrhosis, nine (60%) had positive tests for syphilis (positive VDRL and TPI). In contrast, only nine of sixty-five (14%) with the macronodular type had positive serology. This difference is significant ($P < 0.001$). None of the fifteen with micronodular cirrhosis was positive for HB Ag (positive CF and/or

TABLE 1. Clinical data and serological results in cirrhosis with syphilis

Series no.	Sex	Age (years)	Type of cirrhosis	Past chancre treatment	Past jaundice	Alcohol intake	Syphilis serology			HAA	
							VDRL	RPCFT	TPI	CF	CEP
2	F	28	Nutr.	No	No	+++	weak +	A/C	weak +	A/C	-
9	F	50	Nutr.	No	No	+++	+	A/C	+	A/C	-
12	M	35	Mixed	No	No	+++	+	+	+	A/C	-
18	M	57	Nutr.	Yes	No	+++	+	+	weak +	A/C	-
20	F	49	Mixed	No	Yes	+	+	+	weak +	A/C	-
25	M	60	Mixed	No	No	+++	weak +	+	weak +	80	+
30	M	35	Nutr.	Yes	No	+++	weak +	+	+	-	-
35	M	35	Nutr.	No	No	+	+	+	+	-	-
38	M	27	Postnec.	No	No	No	weak +	-	+	32	+
40	M	45	Nutr.	No	No	+++	+	-	+	-	-
47	M	57	Postnec.	No	Yes	+++	weak +	A/C	+	256	+
49	M	44	Mixed	No	No	+	+	-	+	-	-
52	F	46	Nutr.	Yes	No	No	+	-	+	-	-
55	M	35	Nutr.	No	Yes	+++	+	+	+	-	-
59	M	45	Mixed	No	Yes	No	+	-	Neg.	-	-
61	M	22	Mixed	No	Yes	+	weak +	+	Inc.	-	-
64	M	55	Mixed	Yes	No	+++	weak +	A/C	+	A/C	-
67	F	30	Postnec.	No	No	No	+	A/C	+	4	+
71	M	22	Posthep.	No	No	+++	+	A/C	+	16	+
78	F	35	Nutr.	No	No	+++	+	+	+	-	-

A/C = anticomplementary; Neg. = negative; Inc. = inconclusive; Nutr. = nutritional; Postnec. = postnecrotic; Posthep. = posthepatic; Alcohol intake +++ = chronic alcoholism, + = mild to moderate intake.

TABLE 2. Alcoholism, syphilis and HB Ag in cirrhosis

Type of cirrhosis	No. of cases	Alcoholism		HB Ag positive		VDRL and TPI positive	
		No.	%	No.	%	No.	%
Nutritional (micronodular)	15*	12	80	0	-	9*	60
Macronodular	65*	7	11	24	37	9*	14
Total cirrhosis	80	19	24	24	30	18	22.5

* $P < 0.001$.

CEP), whilst twenty-four of sixty-five (37%) with macronodular cirrhosis were found to be carriers of the antigen. Five patients had positive serological tests for syphilis as well as HB Ag.

Discussion

With few exceptions, previous reports which have suggested the association between syphilis and cirrhosis were based mainly upon a past history of a genital chancre and/or a past history of treatment for syphilis. Even in the few instances where the Wasserman reaction (WR) was used, results of the serological tests were often not recorded. Because of the Biological False-Positive (BFP) phenomenon in patients with abnormal plasma proteins (Moore, 1956), a certain number of positive WRs may be expected to be of this type (Knight and Wilkinson, 1963). It is, therefore, necessary to confirm the diagnosis of syphilis with the more reliable TPI test. Apart from the report by Kirmi *et al.* (1969), this has not been done in any previous studies. The VDRL was used as a screening test in the present work and was found to be a useful indicator of syphilis as TPI was positive in all except two VDRL positive sera. In one of those who had positive VDRL and RPCFT, the TPI was inconclusive but probably positive. The second patient had positive VDRL, but both RPCFT and TPI were negative. Presumably he had a biological false-positive VDRL. Thus, it appears that despite the very high levels of serum globulins the biological false-positive VDRL is not a common finding in cirrhosis. On the other hand, RPCFT proved to be unreliable as a confirmatory test mainly because of anticomplementary reactions, but the test was negative in four out of the eighteen cases who were shown to have positive VDRL and TPI tests. This is not surprising as in syphilis of long duration whether treated or untreated, RPCFT may give false-negative reactions in 50% of cases (Nicholas and Beerman, 1963).

The incidence of treponemal antibodies (22.5%) in cirrhosis in the present series is very much higher than the 1.0% incidence in 14,223 blood donors from an area of 40-mile radius around Kampala, reported by Masawe (1970), who also reviewed the evidence that this truly reflects an incidence of treponemal antibodies in the control population of Uganda of between 1 and 1.3%. The results in this study, therefore, confirm that there is an association between syphilis and cirrhosis in this population. None of the patients with positive serology had any evidence of healed or active cutaneous lesions of yaws or pinta. These conditions are extremely rare in Uganda, and can be excluded as a cause of positive serology. Histological analysis showed that serological evidence of syphilis is found mostly in patients with micronodular cirrhosis (Table 2). No

definite data are available from past reports that correlate syphilis with the type of cirrhosis associated with it. In any case analysis of many of the earlier series is complicated by the inclusion of patients with only a past history and/or treatment for syphilis with no serological or histological confirmation of the diagnosis. Also many of the previous studies were retrospective or based on clinical diagnosis only, so that the type of cirrhosis and alcohol intake were often uncertain (Table 3).

We have previously shown that as in other locations, micronodular cirrhosis in Uganda is associated with alcoholism whilst most macronodular types are not (Anthony *et al.*, 1972). On occasions, however, progression of alcoholic cirrhosis to the post-necrotic (macronodular) variety occurs (Popper *et al.*, 1960). This may partly account for the relatively high incidence of syphilis even in association with macronodular cirrhosis in this and other series (Boles and Clark, 1936; MacDonald and Mallory, 1958; Miyai and Ruebner, 1963; Wells and Lundberg, 1963). At least five of our nine patients with macronodular cirrhosis and syphilis gave a history of chronic alcoholism, and only two denied ever taking alcohol. Subdivision of all cases into those with and those without a history of severe alcohol abuse showed that the incidence of syphilis in the two groups is significantly different (Table 4).

Hepatitis B antigen was not detected in any patient with micronodular cirrhosis (Table 2), which is consistent with the predominant role of alcohol in this type of cirrhosis. By contrast 37% of patients with macronodular cirrhosis had positive tests for HB Ag compared to the 3% incidence in control patients without liver disease, and there is impressive evidence that chronic infection with serum hepatitis virus is an important factor in the pathogenesis of at least 40% of macronodular cirrhosis in Uganda (Maynard *et al.*, 1970; Anthony *et al.*, 1972; Sadikali, 1972). However, the present clinical data do not suggest that the infection was acquired during past treatment for syphilis. Amongst those with syphilis only five were positive for HB Ag and all five denied a past history of treatment for syphilis, injections, or blood transfusions. Three of them did have a history of severe alcohol abuse so that the combined factors of alcoholism and hepatitis were probably responsible for cirrhosis in these three cases. On the other hand, the four patients in this series who had been previously treated for syphilis and had positive VDRL and TPI, were all negative for HB Ag. In the majority of our patients with HB Ag-positive cirrhosis and hepatitis, there was no evidence for transmission of the infection by injection or blood transfusion (Anthony *et al.*, 1972; Sadikali and Barker, 1973). Insect-borne transmission of hepatitis B was suspected from epidemiological data in tropical

TABLE 3. Syphilis and alcoholism in previous series

Authors	No. and type of cirrhosis	Alcoholism (%)	Total % with syphilis
Chapman, Snell and Rowntree (1933)	Fifty-eight, clinical or surgically confirmed	43	17
Rao (1933)	Sixty-five, portal cirrhosis	3	48
Yenikomshian (1934)	Seventy, clinical/non-alcoholic	0	12
Boles and Clark (1936)	243, mixed types at autopsy	30	12
Scheumacher (1937)	Forty-four, diffuse type at autopsy	50	29
Evans and Gray (1938)	217, mixed types at autopsy	27	12
Fleming and Snell (1942)	200, clinical cases	43	16
Ratnoff and Patek (1942)	386, mixed and clinical cases	54	16
MacDonald and Mallory (1958)	221, mixed cases at autopsy	35	23
Miyai and Ruebner (1963)	249, portal type; 177 post-necrotic	65 6	18
Manderson, Patrick and Peters (1965)	Forty-nine, hepatoma with cirrhosis	22	10
Kirmi <i>et al.</i> (1969)	Forty-nine, biopsies (type not stated)	30	13

TABLE 4. Syphilis in cirrhosis with and without alcoholism

	No. of cases	VDRL and TPI positive	
		No.	%
Alcoholism	19*	12*	63
No alcoholism	61*	6*	10
Total cirrhosis	80	18	22.5

* $P < 0.001$

countries (Blumberg *et al.*, 1970), and has been supported by the finding of HB Ag in wild-caught mosquitoes in Kenya and Uganda (Prince *et al.*, 1972). Hepatitis B antigen has also been demonstrated in urine, faeces, and saliva (Blainey *et al.*, 1971; Grob and Jemelka, 1971; Ward *et al.*, 1972) and evidence has also recently been presented for respiratory and sexual transmission (Almeida *et al.*, 1971; Heathcote and Sherlock, 1973).

The importance of serological testing for syphilis, particularly in alcoholic cirrhosis, is again emphasized (Lancet, 1970). None of our eighteen proven cases of syphilis had any clinical signs or symptoms of the disease, and only four had received treatment for it. Liver biopsies from patients with syphilis showed no changes that suggested specific syphilitic involvement. Thus, it appears that regardless of the histological type there is an association of syphilis with cirrhosis in some patients through the common factor of alcoholism, but there are large numbers of patients with syphilis and cirrhosis who have never

taken alcohol (Rao, 1933; Yenikomshian, 1934; Boles and Clark, 1936; Ratnoff and Patek, 1942; Kirmi *et al.*, 1969). In the present series, there were also at least six patients with syphilis and cirrhosis who had no evidence of alcohol abuse (Table 4); there must therefore be a further factor involved, and scarring following severe hepatic secondary syphilis which was untreated does seem a possibility. Studies for syphilis in alcoholics with cirrhosis and a similar control group of alcoholics without cirrhosis are also required to exclude the possibility of syphilis in association with alcoholism predisposing to cirrhosis as suggested by Scheumacher (1937).

Recently the increased titres of antibodies to many viral and bacterial antigens in patients with chronic liver disease (Cross *et al.*, 1971; Protell *et al.*, 1971; Bjorneboe, Prytz and Orskov, 1972) have received considerable attention. However, the statistically different incidence of syphilis in alcoholic and non-alcoholic cirrhosis in the present series indicates that the positive syphilis serology could not be due to this non-specific phenomenon (Triger, Alp and Wright, 1973).

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