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Risk Factors of Liver Cirrhosis in Chad: Large Proportion of Cases without Clear Etiology

Ali Mahamat Moussa[1*], Pascal Pineau[2], Mayanna Habkreo[1], Moussa Hassan Elefi[1], Tahir Mahamat Saleh[3], Maire Dehainsala[1], Mahamat Ali Hachim[1], Adama Ahmed N'Gare[1], Adoum Abderrazak Fouda[4], Bessimbaye Nadlaou[5], Adawaye Chatté[4]

[1]Service de Médecine Interne et Gastroentérologie, Centre Hospitalier Universitaire La Référence Nationale, Ndjamena, Tchad
[2]Unité "Organisation Nucléaire et Oncogenèse", Institut National de la Santé et de la Recherche Médicale U993, Paris, France
[3]Service de Medecine Interne, Centre Hospitalier Universitaire La Renaissance, N'Djamena, Tchad
[4]Programme de Lutte Contre le VIH et SIDA, Hépatites et Infectins Sexuellement Transmissibles, Ministère de la Santé Publique, N'Djamena, Tchad
[5]Service de Laboratoire, Centre Hospitalier Universitaire La Reference Nationale, N'Djamena, Tchad
Email: *alimahamatmoussa@hotmail.com

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Abstract

Background: In comparison to other forms of chronic liver diseases, cirrhosis is generally poorly studied in sub Saharan Africa. In Chad, more particularly, no data are available despite the burden of liver diseases considered as the first cause of hospitalizations in the country. **Methods:** We conducted a retrospective analysis of 268 patients with liver cirrhosis attending care at the University Reference Hospital between 2007 and 2016. **Results:** This series of liver cirrhoses was characterized by a weak mal predominance (M:F = 1.7). The age of onset occurs significantly earlier in women than in men (40.6 ± 12.0 *vs.* 44.4 ± 13.4, $p = 0.0171$). The principal risk factor was persistent infection with hepatitis B virus (49% of cases) followed distantly by infection with hepatitis C virus (13%) and excessive alcohol consumption (10%). Men were more frequently carrying HBV surface antigen than women (65.6% *vs* 35.9% $p = 0.0019$). HBV-associated liver cirrhosis was overall more severe than diseases from other causes. A large proportion of cirrhosis (30%), observed primarily in women (48.1% *vs* 24.1%, $p = 0.0036$), was considered are cryptogenic. **Conclusions:** The etiological spectrum of liver cirrhosis remains to be properly defined in Chad. This lack of knowledge prevents the implementation of an efficient policy of prevention. A significant effort should be secured to characterize hitherto neglected infectious, lifestyle or genetic risk factors responsible of this form of terminal disease and improve subsequently liver health of local populations.

Keywords

Chad, Liver Cirrhosis, Hepatitis Viruses, Alcohol, Cryptogenic

1. Introduction

Liver health is a major concern in most countries located south of the Sahara. Many worries are, understandably, focused on hepatocellular carcinoma (HCC) that often represents the first or second malignancy in men and the third of fourth in women [1]. Persistent infections with hepatitis B, C and Delta viruses are major risk factors of terminal liver diseases and represent heavy burdens of chronic diseases in sub Saharan Africa (SSA) [2]. Comparatively to HCC, much fewer works have been dedicated to liver cirrhosis (LC) in SSA although it remains with a major killing disease in the region as anywhere else [3]. Actually, with more than one million deaths yearly, it ranks 12th position for causes of death worldwide. Its incidence is presumably underestimated due to a protracted asymptomatic phase that keeps LC undiagnosed. It has been shown recently that mortality from LC increased substantially in all regions of SSA during the last period with as outcome a doubled incidence of death in three decades [4] [5] [6]. This increase even surpasses that of HCC. In Africa, infection with hepatitis B (34%) or hepatitis C (17%) viruses as well as heavy alcohol intake (18%) represent the three main causes of LC. Amazingly, the risk factors underlying almost one third (31%) of LC affecting Africans south of the Sahara are poorly defined [4].

Chad is a country of 15 million habitants that occupies a landlocked and central position in Middle Africa and extends from the Sahara in the North to the great savanna in the South. Its gross domestic product per capita places Chad in the lower median half in Africa. Data concerning liver health in the country are still very scarce particularly concerning chronic liver diseases. Recent hospital inquiries conducted in Ndjamena, the national capital, indicated, however, that severe liver diseases represent the first causes of hospitalizations in the city. Regarding hepatitis, Chad has been mostly studied for hepatitis E, regularly responsible of outbreaks throughout the country [7]. The situation of hepatitis B (HBV) our hepatitis C (HCV) viruses has been only partially described but available data suggest that endemicity of both viruses could be very high in multiple regions of the country [8] [9]. Controversial reports concerning alcohol consumption in Chad, a predominantly Muslim society, have been published making of this particular risk factor of LC another serious public health issue locally [10] [11]. Additional etiological agents of liver fibrosis or even cirrhosis affect most probably Chadian populations despite a conspicuous lack of data about them. It is notably the case of type 2 diabetes and obesity prevalent in various segments of local populations and it is the case of endemic diseases present in Chad such as sickle cell anemia or schistosomiasis [12] [13] [14] [15] [16]. The role of visceral leishmaniasis (Kala-Azar), iron overload, auto-immunity, or herbal remedies involved in subsets of chronic liver diseases throughout Africa is currently unknown in Chad.

Both clinical presentation and biological features of LC have never been described in Chad. Furthermore, and despite the recent progress made in the field of non-invasive appraisal of liver fibrosis, very few reports have been published

from Middle Africa. In the present study, we retrospectively analyzed records from 268 patients with LC attending care in the reference hospital of Ndjamena. We intend to describe thereafter the etiological spectrum as well as the clinical and biological settings of the local form taken the disease.

2. Patients and Methods

2.1. Patients and Liver Cirrhosis Diagnosis

A series of 268 records from patients attending healthcare between April 2007 and August 2016 were analyzed. Data were collected from the clinical records of patients hospitalized in the department during the study period. The risk factors investigated were hepatitis B and C serology status, alcohol consumption, clinical signs of cirrhosis decompensation, liver and kidney function tests, and the socio-demographic profile of each patient included in the study. The diagnosis of LC was established on the basis of several elements of evidence, including heterogeneity of the liver with an irregular contour on ultrasound with the presence of at least one of the clinical signs of decompensation of cirrhosis such as the presence of ascites fluid, esophageal or gastric varices with or without rupture, signs of encephalopathy. Exclusion was decided in case of homogeneous liver at ultrasound or in case of suspicion of hepatocellular carcinoma (219 cases of primary liver cancer were excluded. Ultrasound was performed either with a LOGIQ 400 cc (General Electric Healthcare, Waukesha, WI, USA) or a MINDRAY 40C (Mindray Biomedical electronics, Shenzhen, PR China) apparatus. No Fibroscan© was available in Ndjamena during the period of the study. This research received the approval of the Ethics committee of the Ndjamena School of Medicine. Due to the retrospective nature of this research no informed consent was obtained.

2.2. Serological Tests

Viral serologies targeting HBV surface antigen (HBsAg) and immunoglobulins directed against HCV (anti-HCV) were performed a VIDAS® apparatus (bioMérieux, Craponne, France). Clinical biochemistry parameters including alpha-foetoprotein were also determined on a VIDAS automat.

2.3. Statistical Analyses

Statistical analyses were performed using a Prism 8.0.2 statistical package (GraphPad, USA). Numerical variables were summarized by their median, mean, and range according to their types of distribution (normal or not). They were compared either by a Student's t-test, ANOVA or by a Mann-Whitney test as appropriate. Categorical variables were summarized as frequencies that were compared by Fischer's exact test. All tests were univariate and two-sided. Level of significance was set at $p < 0.05$.

3. Results

A series of 268 cases of patients with liver cirrhosis were recovered from the arc-

hives of Ndjamena General Hospital in the period extending between 2007 and 2016. A large majority of patients were living in Ndjamena (75.6%), the national capital that counts around one million habitants. The second region of provenance was Chari-Baguirmi (6.7%) that immediately surrounds Ndjamena.

The mean age of patients was 43.0 ± 13.0 years (range 16 - 90) (see Table 1). The sex ratio indicates a mild predominance of male sex (M:F = 1.7). Major risk factors were persistent mono-infection with HBV (48.8%) followed distantly by heavy alcohol intake (>30 g/24h in men, >20 g/24h in women, 10.1%). The dual infection with HBV and HCV was found in 8.5% of cases whereas mono-infection with HCV was retrieved in another 5.7% of the records. It was concluded to an absence of clear infectious or lifestyle risk factor in 30.7% of patients. Both viral

Table 1. Demographical and clinical characteristics of the patients studied.

Demography and Clinical Features (n = 268)	
	Values
Demography	
Age (years)	43.0 ± 13.0
Sex-ratio M:F	1.7 (161:95)
Risk Factors	**n (%)**
HBsAg (+)	131 (48.8)
Anti-HCV	15 (5.7)
Co-infection HBV + HCV	23 (8.5)
Non HBV, non HCV	87 (32.6)
Alcohol intake	27 (10.1)
Clinical Symptoms	**n (%)**
Signs of decompensation	208 (77.6)
Ascites	54 (26%)
Severity of ascites	
I	5 (9.7)
II	32 (58.4)
III	17 (31.8)
Variceal bleeding	20 (9.7)
Encephalopathy	121 (58.4)
Splenomegaly	82 (39.4)
Jaunice	43 (20.9)
Edema	43 (20.7)
Hepato-renal syndrome	29 (14.2)
Collateral venous circulation	15 (7.4)

serologies were unavailable in 78 cases. Signs of decompensation were observable at diagnosis for the great majority of cases (77.6%). The most frequent symptom of decompensated liver cirrhosis was ascites (72.3%), followed by variceal bleeding (9.7%), and severe encephalopathy (3.0%). Ascites was already severe at presentation in almost one third of cases (31.8%). **Table 1** summarized the demographical and clinical characteristics of the patients studied.

The performances of non invasive fibrosis assessment scores are, overall, poorly known in SSA. We used, therefore, some of them to get a better clinical assessment of this series of Chadian patients. Age-to-Platelets index (API) was reaching the diagnostic threshold of F4 fibrosis (≥6) in 38.6% whereas it was the case for 43.4% of patients with FIB-4 (>3.3), 23.5% with APRI (AST to platelets ratio index, >2.0), 87.5% with de Ritis ratio (AST to ALT ratio, AAR, >1.0), and 34.4% with GPRI (gamma-glutamyltransferase-to-platelet ratio, >0.74) [17] [18] [19] [20] [21].

We subsequently tried to better characterize the patients by proceeding to a systematic search for correlation between clinical and biological variables. Overall, age of patients was not strongly influencing disease presentation. Blood urea concentrations (median value 0.4 mg/mL *vs* 0.28 mg/ml, p = 9.1E−04) and API fibrosis score (5.5 ± 2.1 *vs* 3.7 ± 2.3, p = 1.5 E−07) were the only two variables significantly worsening in the upper median for age (>43 years). But the presence of API was expected as age is one of the two parameters used to calculate this score.

By contrast, the sex of patients was strongly structuring this series. Male patients were four years older than women (44.4 ± 13.4 *vs* 40.6 ± 12.0, p = 0.0171, and more often affected from jaundice (19.2% *vs* 9.4%, OR = 2.2, 95% CI: 1.02 - 5.5, p = 0.0496). Risk factors were different according to sex. As expected, men were more often carriers of HBsAg (65.6% *vs* 35.9%, OR = 2.8, 95% CI: 1.4 - 5.9, p = 0.0019) while women were more often affected with an idiopathic form of liver cirrhosis (48.1% *vs* 24.1%, OR = 2.9, 95% CI: 1.3 - 6.3, p = 0.0036). Regarding biological variables, men were presenting with significantly degraded values for amino-transferases and total bilirubin when compared to women.

Risk factors of disease were potent modulators of presentation at clinical or biological levels. Patients with persistent HBV infection tend, albeit not significantly, to be younger than others (42.4 ± 11.9 *vs* 46.5 ± 15.0, p = 0.0730). Fibrosis scores such as APRI, FIB-4 and GPRI were all significantly worsened in case of infection with HBV and it was of course the case as well for biological features used to build these scores but not exclusively to them (aminotransferases, GGT, urea, total bilirubin, or platelets count). Overall, sero-reactivity for HBsAg was associated at the biological level with a more severe disease in Chadian patients. Clinical signs of decompensation tended, albeit non significantly to be more frequent at diagnosis in HBsAg (+) patients than in others (62.5 *vs* 47.3, p = 0.0633, ns). **Table 2** summarized the biological features and the scores of non-invasives fibrosis of patients studied.

Table 2. Biologicals features and scores and predictors non-invasives fibrosis of the patients studied.

Biological Features (n = 268) Values		
Clinical biochemistry and Platelet	**Mean ± SD**	**Median**
AST (IU/mL)	94.9 ± 145.5	48.5
ALT (IU/mL)	51.2 ± 78.2	30.0
Gamma GT (IU/mL)	124.9 ± 148.2	71.0
Creatinine (mg/L)	13.9 ± 13.1	9.8
Urea (g/L)	0.76 ± 2.7	0.3
Total bilirubin (mg/L)	27.2 ± 46.	14.4
Albumin (g/L)	23.1 ± 9.3	23.0
Prothrombin time (%)	52.1 ± 23.8	49
AFP (ng/mL)	9.3 ± 16.1	1.9
Platelets (G/L)	203 ± 143	165.0
Scores and Predictors		
API (n = 194)	4.6 ± 2.5	5.0
Fibrosis Index score (n = 18)	4.1 ± 1.8	4.6
Fibro Alpha (n = 23)	1.6 ± 0.3	1.6
FIB-4 (n = 161)	5.6 ± 27.6	2.5
APRI (n = 167)	1.7 ± 2.1	0.83
De Ritis ratio (AAR)	2.3 ± 3.8	1.8
GPRI	1.0 ± 1.4	0.47

Infection with HCV was less evocative plausibly due to the fact that the number of patients concerned was low compared with HBsAg (+) (n = 19 *vs* n = 90). Anti-HCV carriers developing liver cirrhosis in Chad were more often heavy alcohol drinkers (25.0% *vs* 5.8%, OR = 5.2, 95% CI: 1.05 - 26.2, $p = 0.0284$). Degraded values of De Ritis ratio was the only non-invasive fibrosis assessment system to be worsened in anti-HCV (+) patients (2.2 ± 0.7 *vs* 1.7 ± 1.0, $p = 0.0052$). Heavy alcohol drinkers were more often affected from jaundice than other patients (42.3% *vs* 13.2%, OR = 4.7, 95% CI: 1.8 - 12.2, $p = 6.6$ E-04) but lack any obvious biological alterations. The reverse was true for NonB-nonC patients who were characterized at the biological level by better parameters than other subjects. Remarkably, these patients displayed significantly better scores than other patients for all fibrosis assessment indices (API, FIB-4, APRI and GPRI). Accordingly, signs of decompensation tended to be less frequent (48.0 *vs* 64.0 %, OR = 0.5, 95% CI: 0.2-1.0), albeit without reaching the level of significance ($p = 0.0794$, ns). Interestingly, this subset of patients was more often affected with digestive symptoms (flatulence, nausea and vomiting, diarrhea, constipation) than others patients (32.2 *vs* 10.6%, OR = 3.9, 95% CI: 1.2 - 13.9, $p =$

0.0192).

With regards to the major clinical outcomes of the disease, signs of decompensation were significantly associated with lowered platelets counts (186 ± 130 g/L *vs.* 225 ± 155 g/L). Patients who unfortunately died during their hospitalization were more often heavy alcohol drinkers (30.4% *vs* 11.4 %, OR = 3.3, 95% CI = 0.8 - 12.4, $p = 0.0479$). Urea (1.1 ± 1.4 *vs* 0.4 ± 0.5, $p = 0.0372$) and even more so total bilirubin (85 ± 122 *vs* 11 ± 9, $p = 7.2$ E−04) were significantly increased in patients who will ultimately deceased during hospitalization.

4. Discussion

With regards to the presentation of liver cirrhosis in Chad, we observed that disease has some peculiarities when compared with others countries of the region. The mean age of the patients affected by liver cirrhosis in N'Djamena (43.0 ± 13.0 years) was in keeping albeit somewhat lower than those observed in Ghana (45.0 ± 12.3 years), Nigeria (46.4 ± 15.6), in Ivory Coast (47.5 ± 14.4 years) or in Sudan (48.7 ± 15.1 years) [22] [23] [24] [25] [26]. The sex-ratio was much lower in Chad than in other African counties (1.7 *vs* 3.5 in Ghana, 2.3 in Ivory Coast, 3.3 in Nigeria and 5.4 in Sudan) [22] [23] [24] [25].

As in most locations in SSA, persistent infection with HBV is the primary causes of LC in Chad (48.8%) in accordance with observation from West African countries as Ghana (48%) but at a level much lower than in Nigeria (65%), or Ivory Coast (87%) [23] [24] [25]. HBsAg is, however, more prevalent in LC from Chad than in Eastern African countries such as Uganda (27%) or Sudan (35%) [22] [27]. We can assume, therefore, that Chad occupies in this regard an intermediate position between West and East Africa. Anti-HCV (13.2%) was more prevalent in Chad than in Ghana (6.7%), in Ivory Coast (5.7%) or Uganda (3.5%) but similar (12.4%) to an observation made on a small series of Sudanese patients [22] [24] [25] [27]. In contrast, heavy alcohol intake (10.1%) was a less frequent RF of LC than in Ghana (39.5%) or in Uganda (55%) but in keeping with observation made in Ivory Coast (7.5%) [24] [25].

Symptoms at admission, such as ascites (72.3% *vs* 74.2%) or upper gastrointestinal bleeding due to variceal esophageal rupture (9.7% *vs* 12.6%) were similar to those identified in Ivory Coast or Uganda [25] [27]. By contrast, encephalopathy (3.0%) was much less frequent in Chad than selected series of Ivory Coast (34%) but similar to other surveys from the same country (3.8%) [26]. Median values of biological parameters were often slightly better at admission than those measured in corresponding patients from Ivory Coast [25]. This observation is presumably due to the higher percentage of patients with cryptogenic cirrhosis who generally displayed better biological features than HBsAg carriers. There is a lack of data about cut-off values of non-invasive fibrosis assessment tests such as FIB-4, GPRI, APRI, *etc*, in patients south of the Sahara. Mean and median values observed in the current study are higher than those observed in Ethiopian patients with LC [28].

A remarkable feature of our work is the large proportion (30.7%) of patients with a cryptogenic disease ie neither HBV, HCV nor alcohol-related. This observation is not unprecedented though. Worldwide, it has been shown that around one-fifth of liver cirrhosis are not linked to any of the major causes mentioned above [29]. In some West Africa countries, however, the share taken by cryptogenic cirrhosis appears as reduced when compared to Chad (10.2% in Ghana) [24]. By contrast, LC without identified etiology was observed in 21 and 27% of recent series of Ivorian and Ugandan subjects [27] [30]. This proportion was increased to an even higher level in Sudan (>50%), a country that neighbors Chad on the East side [22]. As shown recently in Eastern Ethiopia, where a majority of chronic liver diseases are neither associated with hepatitis viruses infections nor excessive alcohol intake, severe liver diseases could be triggered by the use herbal remedies or vegetal psychostimulants usage (such as khat, *Catha edulis, Celastraceae*) [31] [32]. Similar risk factors have not been suspected so far in Chad. However, other affections that include genetic (sickle cell anemia, thalassemias) or parasitic (hepatic schistosomiasis, visceral leishmaniasis) diseases are known to have in some circumstances deleterious consequences for the liver and to contribute probably in association with other risk factors to LC [33] [34] [35]. Some of these diseases are particularly relevant in the Chadian context [36] [37]. Although the role of non-alcoholic fatty liver disease (NAFLD) was not properly assessed in the present work, we consider it as presumably still low in sub Saharan Africa as multi-ethnic surveys have clearly shown that subjects with African ancestry are less susceptible to develop abnormal fat liver storage [38]. However, due to the large genetic diversity of Africans, this assumption deserves, however, further confirmation in various places of the continents [39]. Finally, the molecular testing for HBV DNA might reveal occult B infection, alone or in association, represents a significant RF of LC in Chad [40].

Our study suffers of course from several shortcomings inherent to the lack of resources in SSA. Firstly, and at variance with most developed countries, we did not dispose from a transient elastography measurement tool, and assessment of the degree of fibrosis was therefore inaccurate. In addition, the panel of serological methods employed to characterize the patients was rather rudimentary as only two markers have been used. Notably, the anti-HBc and the anti-delta status were unknown, even though we reported in another study that the prevalence of anti-Delta in chronic HBV carrier [41]. Likewise, no molecular methods were used to characterize viral loads, virus genotypes or occult B infections. Finally, the Child-Pugh stages of the disease were not determined.

In conclusion, we observed that in Chad, the onset of LC symptoms occurs early (43 years) and even more so in women (around 40 years) than in men (44 years). HBV ranks in first position of etiological agents, but a sizeable proportion (>30%) of LC is not due to *bona fide* persistent infections with hepatitis viruses or to an excessive consumption of alcoholic beverages. These idiopathic forms of LC concern mostly women and represent an important field of future

investigations. Patients seropositive for HBsAg present with the most severe forms of the diseases both at the clinical and biological levels. We suggest that, as suggested by other investigators elsewhere in SSA, a significant effort should be engaged now to improve diagnostic facilities and in particular, nucleic acid testing in N'Djamena [32].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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