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ORIGINAL ARTICLE

Widespread geographical disparities in chronic hepatitis B virus infection in Algeria

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Abstract Algeria is the largest country of Africa, with a population of 40 million inhabitants living in disparate environments from the Sahara to the large cities of the Mediterranean coast. The molecular epidemiology of hepatitis B virus (HBV) variants has been partially described, but variations in the seroprevalence of HBV surface antigen (HBsAg) throughout the Algerian territories are still poorly described. We analyzed demographic features of new cases of chronic infection collected in 41 administrative regions (covering 92% of the population) in 2013. The mean age of the 1876 HBsAg(+) patients was 36.8 ± 14.2 years, with a slight excess of males (54%). The seroprevalence of HBV early antigen (HBeAg) was 9.3%, and the mean virus load was 3.2 ± 1.8 log IU/ml. A subset of 15.2% of patients was already cirrhotic at disease discovery. An important heterogeneity was observed throughout the country, with nine regions displaying a significant excess of cases. These regions formed four distinct foci located in distant parts of the country: Adrar-Bechar (southwest), El-Oued-Tebessa (east), M'Sila-Sétif (north central) and Oran-Aïn Temouchent (northwest). An excess of cases was found as well in the national capital Algiers. Patients from southern regions with an excess of cases (Bechar, Adrar, El Oued) were significantly younger (32.0 ± 10.7 years), as were patients from the regions of Bejaia and Bouira (32.1 ± 10.6). The southwestern regions were also marked by a significant imbalance of the sex ratio (58 vs 39% of female cases, $P = 4.5$ E-5). The highest HBeAg seroprevalence was observed in Setif (26.4 vs. 7.6%, OR = 4.3, 95% CI 2.6-6.5, $P = 1.1 \times 10^{-11}$) in accordance with the higher virus loads observed in the patients (3.9 ± 2.3 vs. 3.1 ± 1.6, $P = 0.0002$). In conclusion, we observed heterogeneity in HBsAg seroprevalence, demographic traits, and disease evolution in Algeria. Further studies are now warranted to shed light on these differences, which are presumably due to variability in transmission routes or in the infectivity of viral isolates.

Introduction

Persistent infection with hepatitis B virus (HBV) is responsible for a considerable burden of disease affecting almost 350 million individuals worldwide [37]. Chronic hepatitis B virus infection ultimately leads to terminal diseases such as cirrhosis or hepatocellular carcinoma (HCC), which are responsible for more than 1.0 million deaths each year [23]. Remarkably, cirrhosis is the seventh cause of death in countries of the Arabic world, while HCC occupies a rather marginal place except in Egypt [28, 29]. The epidemiological situation regarding hepatitis B is poorly known in Algeria, the largest country of Africa. Algeria is, however, commonly considered to be located in a region of intermediate (2-8% HBV surface antigen

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prevalence) endemicity for chronic hepatitis B virus infection when compared to all other North African countries [31]. The only national survey performed in 1998 yielded an overall HBsAg seroprevalence of 2.15%. In comparable areas of endemicity, the HBV transmission route is thought to be primarily horizontal (familial) *ie.,* depending on contamination modes that remain rather poorly understood. Indeed, in some cases of HBV transmission, contaminated objects and surfaces may behave as fomites, contributing to the spread of the virus [5, 17]. The progressive diminution of HBV circulation is thus considered to be dependent on the global hygiene level and on the availability of key household facilities such as bathrooms, flushing toilets, and, more generally, running water [21, 35].

The HBV strains circulating in Algeria are known to be overwhelmingly dominated by genotype D strains, as is the case in the adjacent Maghribian countries Morocco and Tunisia [4, 11, 20, 22]. Isolates from the southern coast of the Mediterranean are characterized by a very high rate of mutation affecting the basal core promoter (nucleotides 1762 and 1764, 50-63%) and the even more frequent introduction of a premature stop codon in the HBV early antigen (HBeAg) at position 1896 (66-86%) [2, 4, 20].

Algeria is peopled by populations still living according to traditional and even ancestral lifestyles in remote mountains or desert areas as well as by fully urbanized citizens in the largest cities of the country (Algiers, Oran or Constantine), all located on or near the Mediterranean coast [7]. For this reason, HBV transmission routes are predicted to be rather divergent. In an attempt to provide a preliminary map of persistent HBV infection in Algeria, in this report we describe the demographical characteristics of patients from all regions of the country who were confirmed at our institution to be chronically infected.

Patients and methods

Ethics statement

All samples were analyzed according to protocols and quality insurance procedures in use at the Pasteur Institute of Algeria. In conformity with national regulations, all patients were informed and gave their consent both to treatment and to the use, for scientific purposes, of the data produced by analysis of their blood samples.

Patients

This is a population-based retrospective study conducted from January to December 2013. The hepatitis laboratory at the Institute Pasteur in Algiers is the national reference laboratory for hepatitis in Algeria to which samples are sent for confirmation of diagnosis. Once HBsAg seropositivity confirmed at the local-hospital level for two samples taken at a 6-month interval, novel putative cases of chronic HBV infection are referred to our institute for confirmatory serological testing and a pre-therapeutic assessment of the viral load. In 2013, we received positive plasma samples from 41 of the 48 *wilayas*/provinces of Algeria. In total, 2946 samples were tested for HBV load measurement, and among these, 1876 were newly diagnosed chronic HBV infections (see Supplementary Table 1). Samples from patients with previously diagnosed persistent HBV infection (either at the regional level or for which we already had positive clinical records) were excluded from our analysis. Consequently, we focused only on patients for whom the diagnosis of chronic infection was being made for the first time. This report is therefore representative of the current state of evolution of chronic HBV infections in Algeria.

Serological methods

HBsAg, HBeAg, anti-HBc and anti-Hbe serology were performed on an Axsym Abbott PLC system. A second, confirmatory HBsAg test using serum neutralization (HBsAg confirmatory Axsym) was done for all samples for which the HBsAg status was uncertain. Quantification of HBV DNA was performed by real-time PCR using CAP/CTM48 from Roche Diagnostics and *m2000sp/rt* from Abbott, with detection thresholds of 20 and 10 IU/ml, respectively.

Statistical analysis

Comparisons of categorical variables were performed using Fisher's exact test. Continuous variables were analyzed using Student's *t*-test or Mann-Whitney U test as appropriate. Statistical analyses were performed with a risk alpha significance level of 0.05, using the Prism v.6.0d package (Graph Pad Software Inc, San Diego, USA). Mean values are presented with standard deviation (± SD) or standard error of the mean (± SEM).

Results

It is mandatory for Algerian healthcare institutions to get a confirmation of novel cases of chronic HBV infection before implementation of appropriate therapeutics. Samples from confirmed cases of chronic HBV infection (2nd positive sample six months after the first one) are systematically sent to our institution in the frame of a pre-therapeutic assessment for viral load measurement. We

performed a retrospective survey on novel cases of confirmed chronic HBV infection referred to our institution in 2013. The 1876 patients meeting the inclusion criteria were living in 41 of the 48 *wilayas* (administrative regions) of the country. Overall, and according to the last available census (2008), these *wilayas* contain 91.2% of the Algerian population. The mean age of the patients was 36.8 ± 14.2 years with a slight excess of males (53.8%, see Table 1 and Fig. 1). The mean viral load was 3.2 ± 1.8 log IU/ml. Only 9.2% of patients were positive for HBV early antigen (HBeAg), a hallmark of a high level of replication. In 15.2% of the cases, the patient was already affected by liver cirrhosis (Table 1).

Regarding clinico-biological features, we observed that viral loads were slightly higher in males than in females (3.3 ± 0.05 vs. 3.0 ± 0.07 log IU/ml, $P < 0.0001$, see Fig. 2A). The average age of male patients, however, was slightly older than that of females (37.1 ± 0.5 vs. 36.3 ± 0.5, $p = 0.14$ ns, see Fig. 2B), implying that the higher circulating HBV DNA copy number was not due to a higher proportion of recent infections in men. Patients with HBeAg seroreactivity were, as expected, significantly younger than non-carriers (31.8 ± 1.4 vs. 37.6 ± 0.3 years, $P < 0.0001$) and consistently displayed higher viral loads (Fig. 2C-D). Similarly, patients with liver cirrhosis displayed higher virus loads than non-cirrhotic patients (3.56 ± 0.12 vs. 3.10 ± 0.04, $P < 0.0001$), implying poorer control of viral infection in these patients.

We observed significant regional variations in the incidence of chronic HBV infection in Algeria. Using the last available Algerian Republic census (2008), we calculated the expected number of chronic hepatitis B cases for each *wilaya* normalized for the number of inhabitants and subsequently checked whether the expected numbers differed significantly from what was observed. Five clusters composed of nine *wilayas* with a significant excess of referred cases were detected. Odds ratios for *wilayas* affected with an excess of cases are shown in Fig. 3A. In the southwest, the *wilaya* of Bechar (n = 83 cases) and Adrar (n = 61) form a first group covering an immense (585,000-km^2) desert region (See Fig. 3B). In the central eastern part of Algeria, two *wilayas* were affected (El Oued and Tebessa). In the center, a third focus was observed (M'Sila and Setif). Two western coastal *wilayas* displayed an excess of cases as well: Oran and Aïn Temouchent (Fig. 3B). Finally, Algiers, the national capital, also displayed an excess of observed cases. Intriguingly, a lack of consistency was observed within each of the four clusters of *wilaya* regarding the age of the patients, sex ratio or virus loads. This situation suggests that HBV transmission might follow different patterns of transmission in the different communities.

Table 1 Demographic features of the 1876 patients with chronic HBV infection confirmed in 2013 at the Institut Pasteur d'Algérie

Demographic feature	Value
Sex ratio M:F	1.17 (1013:863)
Age (years)	
Mean ± SD	36.8 ± 14.3
Median (IQR)	33 (25-50)
Range	1-84
Virus load	
Mean ± SD (log IU)	3.18 ± 1.77
Median (IQR)	2.79 (2.01-3.61)
Range	1.0-9.0
HBeAg	9.3% (174/1876)
Cirrhosis	15.2% (285/1876)

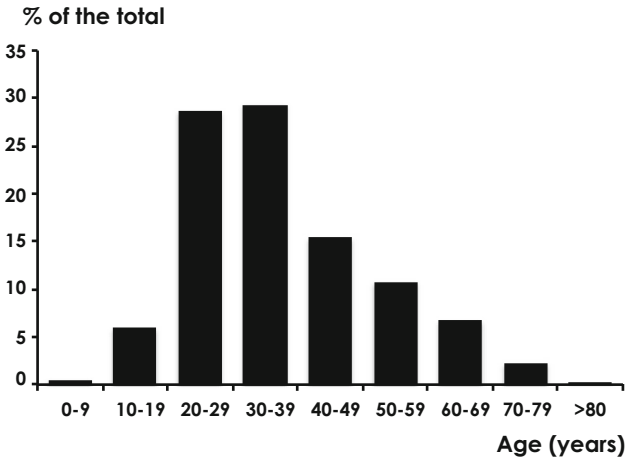

Fig. 1 Age distribution of HBs Ag (+) Algerian patients. Age distribution of all patients with confirmed chronic HBV infection in 2013 (n = 1876)

Clinico-demographic features differed greatly between regions. For example, the proportion of males ranged from 38% (in Adrar) to 78% (in Ghardaia). In these regions, the sex ratio was significantly imbalanced when compared to all other *wilayas* (see Figure 4A). As in Adrar, the proportion of affected men was rather low in Bechar (45.1%), albeit without reaching the level of significance. Taken together, in the southwestern Saharan regions displaying an excess of cases, we observed a significant predominance of women among patients with chronic HBV infection (58.5 vs. 39.4%, OR = 2.0, 95% CI: 1.44-3.0, $P = 4.5$ E-5).

The mean age of HBV carriers in the different *wilayas* ranged from 31.2 ± 8.8 (Bejaia) to 43.4 ± 17.1 (Tiaret). The age of patients was found to be significantly lower than anywhere else in the Adrar-Bechar cluster (31.8 ± 1.9), in El-Oued (32.1 ± 0.9), and in a Bejaia-Bouira cluster in Kabylia (33.1 ± 1.7, see Fig. 4B). The Saharan regions of

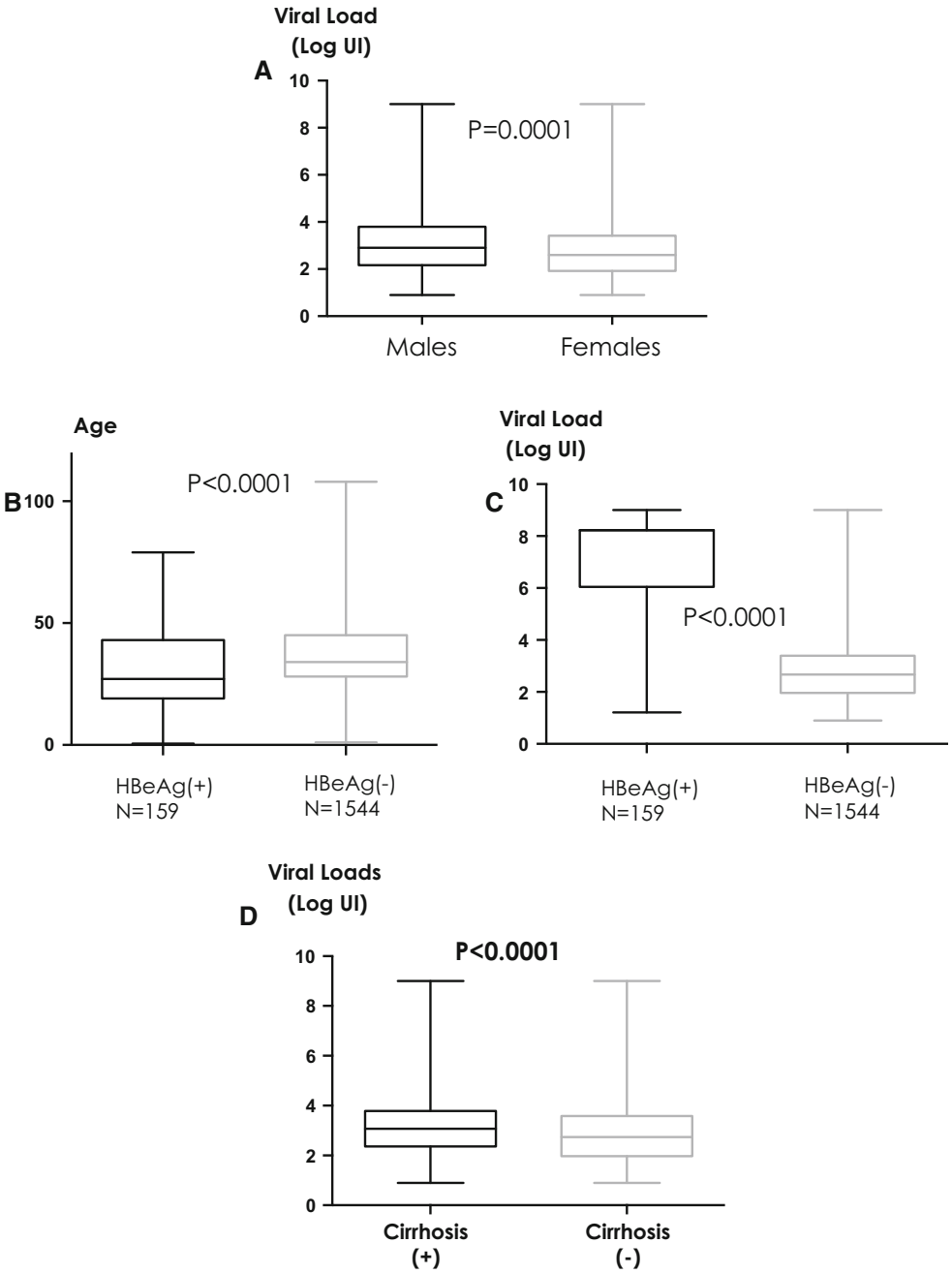

Fig. 2 Clinico-demographic correlations. **A**. Difference in viral loads in Algerian patients according to gender. **B**. Age difference between HBs Ag(+) according to gender. **C.** Age difference between HBe Ag (+) and HBe Ag (-) patients. **D.** Difference in viral load between HBe Ag (+) and (-) patients

Bechar and Adrar display here again their specificity, which suggests early and presumably vertical transmission of the virus.

Among the last parameters at our disposal, HBeAg and virus loads are tightly linked. When examining both parameters, a single region stood out as having abnormal values: Setif. In this *wilaya*, both HBeAg(+) prevalence and virus loads were significantly higher than in other regions of the country (Fig. 5A-B). Finally, we observed an increased prevalence of cirrhosis at diagnosis in patients from Algiers, and especially in patients from M'Sila in the Hodna mounts, Central Algeria (Fig. 5C).

Discussion

Approximately 350 million people worldwide are persistently infected with HBV, which has been classified into eight genotypes (A–H) by means of molecular evolutionary analysis [38]. Algeria is considered a country of intermediate endemicity for persistent HBV infection (2-8%). A previous national survey (1998) found the prevalence of HBsAg to be 2.15% at the national level [6, 12, 19]. Seroprevalence variations throughout the territory, however, are poorly known, although they are suspected to be significant due to extensive differences in the living

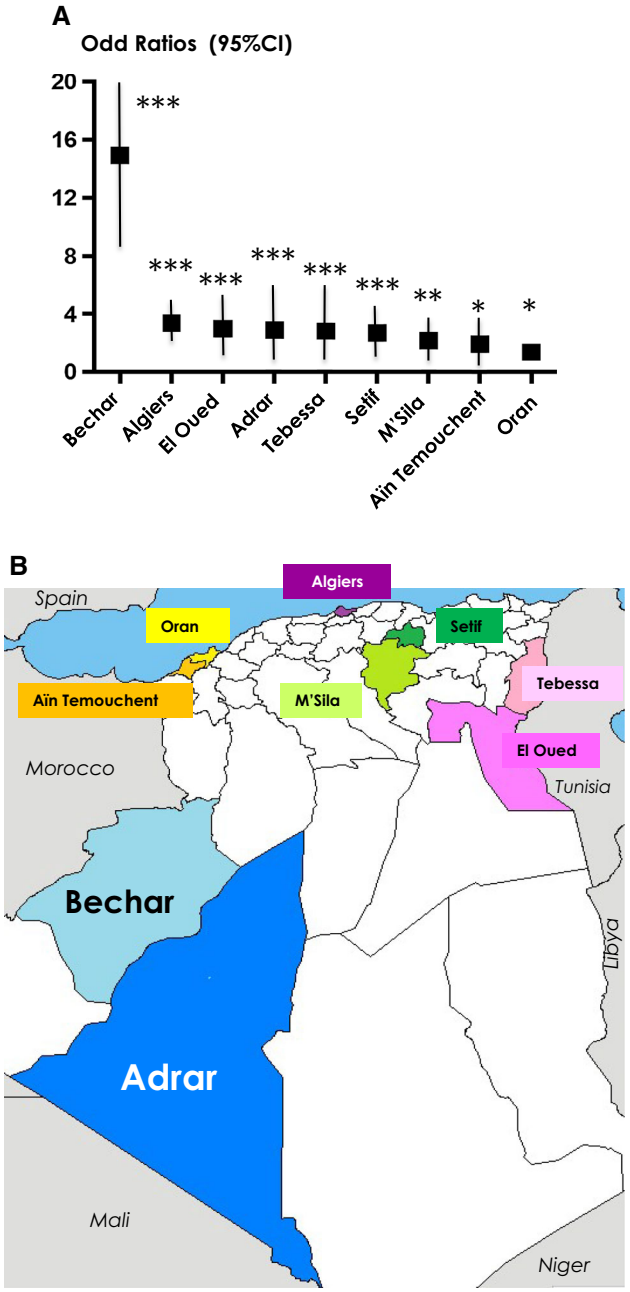

Fig. 3 Foci of chronic hepatitis B in Algeria. **A**. Relative risk (RR) for excess of chronic HBV infections in the different *wilayas* /regions of Algeria. Vertical bars represent the 95% confidence intervals. *, $P < 0.05$; **, $P = 0.0002$; ***, $P < 0.0001$. **B**. Map of Algeria with the four different foci of significantly increased HBs Ag prevalence in 2013

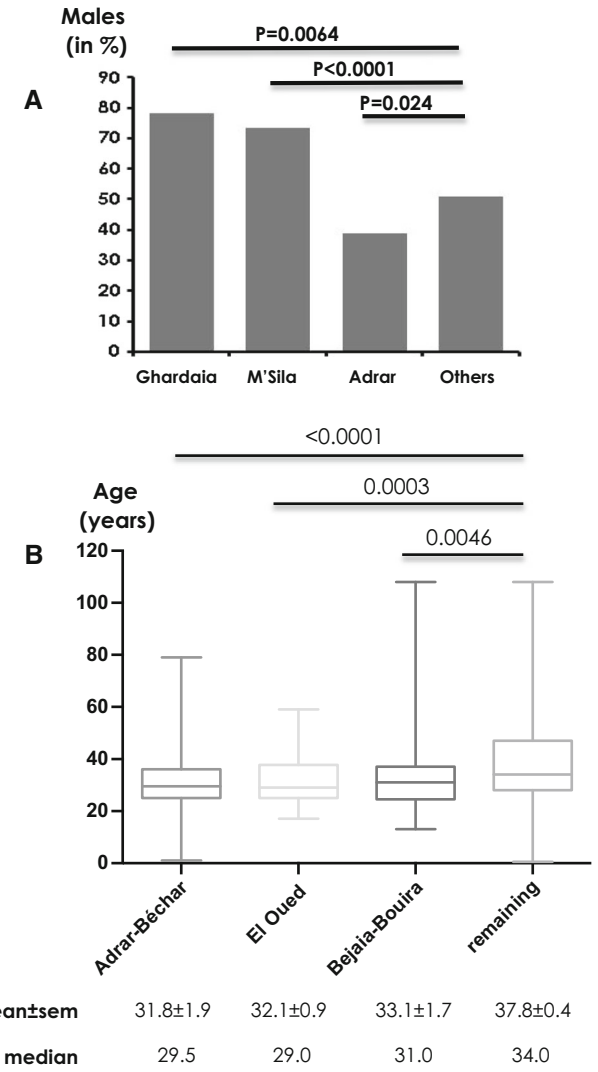

Fig. 4 Clinico-biological features of the three geographical clusters. **A**. Proportion of males in the three regions displaying a significant imbalance in the sex ratio among cases of hepatitis B. **B**. Distribution of the age of patients in the regions with a significantly younger age at diagnosis with regard to the others

conditions of the populations and to the different modes of HBV transmission. To progressively eradicate the hepatitis B burden in the country, vaccination against HBV was introduced into the immunization program calendar for all Algerian children in 2003. In the current study, we reviewed all confirmed cases of chronic infection with HBV received at our institution in 2013.

HBV is a highly infectious agent, ten times more contagious than hepatitis C virus and a hundred times more than HIV. HBV is present in all body fluids (blood, saliva, genital secretions, urine, breast milk) and is transmitted through broken skin or mucous membrane contact with blood or other contaminated body fluids. The possible transmission modes are therefore very diverse, as they could be parenteral (needle stick injury, intravenous drug abuse, acupuncture, tattooing, cupping, scarification), sexual, perinatal, or intra-familial [18, 24]. Indeed, given HBV resistance in the external environment, intra-family transmission is considered fairly common and promoted by circumstances such as exchange of nail clippers, toothbrushes or razors, poor sanitation, or even significant

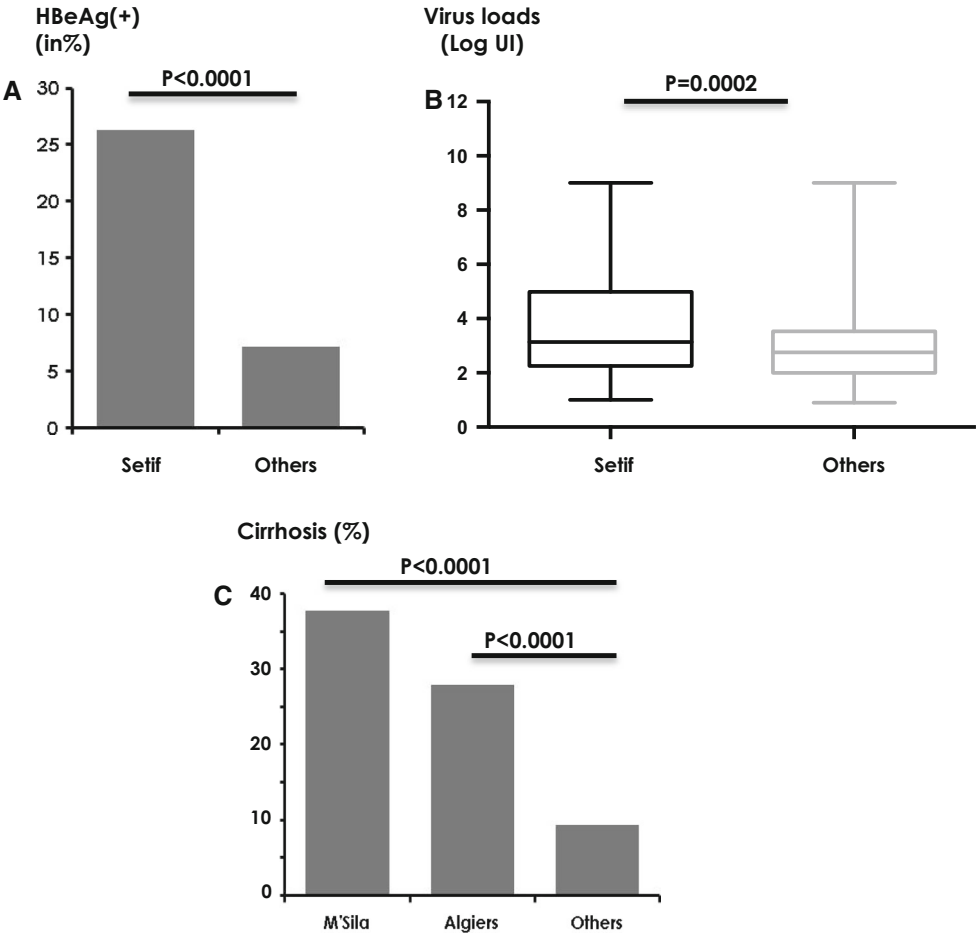

Fig. 5 More active HBV infection in the Wilaya of Setif. **A.** Patients from this region more frequently carry HBe Ag and **B.** display significantly increased virus loads. C. Significant increase in liver cirrhosis prevalence in two regions (Algiers and M'Sila)

overcrowding of the dwelling. In addition, some lifestyle habits and traditions practiced in certain regions of the country such as cupping, scarification, tattooing and piercing can promote the spread of HBV [21, 26].

The mean age of the patients in this study was around 37 years, and the most affected age groups were 20- to 29-year-old and 30- to 39-year-old groups, corresponding to young adults, which are probably the most exposed population, both socially and professionally. Interestingly, in the 0- to 9-year-old group, the frequency was close to nil, suggesting that children who normally received routine immunization are currently well protected in Algeria.

Our results differ slightly from the situation described in neighboring countries. According to a Moroccan study from Sba and co-workers, the most affected age group extended evenly from 30 years to over 50 years. Like in the present work, no cases were documented in patients below 20 years of age by Sba *et al.*, in accordance with the Moroccan universal vaccination program introduced in 1999 [36]. In Libya, a study by Daw et al. indicated a bimodal distribution for age of chronic hepatitis B carriers, with peaks in the 11-20-year-old and 41-50-year-old age groups of the population [9, 27]. In Tunisia, a prevalence of 4-7% was found with an average age of 59 years [1, 3].

The reasons for the differences between Algeria and its closest neighbours (Tunisia, Morocco and Libya) regarding the HBV endemic pattern are currently unknown but may be partly related to the fact that our study focused on confirmed chronic carriers, while the other were essentially prevalence surveys. Considering that fewer than 10% of individuals become chronic carriers of HBV when infected in adulthood, a population screening survey would allow better appreciation of the differences observed throughout the Maghreb countries [3].

Only 9% of the patients were positive for early antigen (HBeAg), a hallmark of significant virus replication. Seropositivity for HBeAg and the viral load are two intertwined parameters in hepatitis B, and HBeAg (+) patients in our series had higher viral loads. However, as frequently observed in the Mediterranean basin, some HBeAg(-) patients nevertheless had high viral loads. This situation, which is frequently observed with genotype D of HBV, which prevails in Algeria, is most probably due to an infection with a so-called "stop pre-core" mutant that

retains high replication without expressing early antigen [8, 10, 25, 33]. As expected, HBeAg carriers were significantly younger than HBe-negative subjects [16, 20, 32, 34, 40].

A subset of 15% of the patients had already developed liver cirrhosis at diagnosis of chronic infection. These patients had higher viral loads than the non-cirrhotic ones. This group of patients was particularly intriguing, as the mean age of these subjects (36.5 ± 0.9 years) was not significantly different from that of non-cirrhotic patients (36.9 ± 0.3 years old). There was a slight but non-significant excess of male patients among cirrhotic cases (59.1 vs 53.0%, OR = 1.2, 95% CI 0.99-1.6, $P = 0.06$, ns). This observation suggests that disease progression is more rapid in these cirrhotic patients, who are poorer HBV controllers than non-cirrhotic subjects. Molecular analyses are now warranted to determine whether such fast progression could be explained by genotypic variations in the HBV genome.

Regarding the geographical distribution of the cases, five clusters composed of eight *wilayas* displayed an excess of novel chronic HBV infection: in the southwest, Bechar and Adrar; in the east, El Oued and Tebessa; in the center, M'sila and Setif; in the north, Algiers; and in the northwest, the Ain Temouchent and Oran regions. A conspicuous lack of correlation was apparent between these areas regarding patients' age, sex and viral loads. This suggests that transmission modes might to some extent differ between each region. Overall, both demographic and clinical characteristics were largely different from one *wilaya* to another. Indeed, there was a predominance of men in the majority of the regions, including M'sila and Ghardaia, where this male predominance reaches 71-78%. By contrast, the percentage of men was only 38% in Adrar. In Bechar, a lower percentage of men was also observed, albeit without reaching the level of significance. This observation indicates that in the southwestern desert region, where a high incidence of chronic HBV infection has been observed, women are more exposed to the virus than men. The reasons for this situation are unknown but are most likely due to some lifestyle practices or traditions specific to this area [13, 30, 31]. This situation is especially worrying and should be tackled in a quick and appropriate manner, as vertical transmission from mother to child represents one of the most efficient ways HBV maintains itself in populations [39]. Regarding the mean age at diagnosis, we observed significant differences between regions. It ranged from 31.2 years in Bejaia on the Mediterranean coast to 43.4 years in Tiaret in the Western high plains of the Tell Atlas. The reasons of such differences are unknown but might be related to social and/or anthropological features such as the mean age of first sexual intercourse, which can vary significantly among Algerian populations [15].

Our observation that viral loads measured in patients from the *wilaya* of Setif are significantly higher than those of patients from other regions is currently unexplained, but several hypotheses could be presented in an attempt to clarify this situation. It is well known that younger patients are more likely to be in the immune-tolerant phase of chronic HBV infection characterized by high viral loads. Regarding age, patients from Setif are exactly positioned on the mean and median values of the whole population studied (mean = 36.7 ± 1.2, median = 33). Similarly, patients from Setif are close to average when considering other features associated with higher viral loads such as male sex (M:F = 1.22 vs. 1.17 for the whole series) or prevalence of liver cirrhosis (17.2 vs. 15.2%). In the absence of clinical features that may explain the high rates of HBeAg(+) patients in Sétif, we can hypothesize either that (i) we are facing the consequences of a recent increase in the amount of contamination with HBV, explaining why so many patients are HBeAg(+), or that (ii) a non-D genotype with molecular features (e.g., a C at position 1858 of HBV genome) that are incompatible with the G1896A mutation (nonsense at codon 28) is circulating in Sétif (a sub-genotype A2 from northern Europe for example, or a rare genotype C from China) [14].

In Algeria, a diagnosis of hepatitis B used to be made late, at the cirrhosis or hepatocellular carcinoma stage. In recent years, however, it is often made in the context of a prenuptial or preoperative assessment. The introduction of anti-hepatitis B vaccination in 2003 was a first step toward reducing and then gradually eradicating HBV infection. Our study clearly shows that the presentation of novel cases of chronic HBV infection is highly variable from one *wilaya* to another, with regions of high incidence, regions of early presentation, and regions with gender imbalance. This situation suggests that there are currently different modes of transmission in Algeria or that viral strains with different biological properties are circulating. A carrier survey for hepatitis B and further analyses of the molecular, clinical, demographic and socio-economic status of the patients should now be considered to shed light on these preliminary results.

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