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Does Haptoglobin Phenotype Impact Infection Mortality?

Akissi Joelle Koffi, Hugues Thierno Ahiboh, Philémond By, Delphine Gabillard, Roseline Affi, Francisk Kouakou, André Inwoley

Département de Biochimie et Biologie Moléculaire, UFR SPB, Université Félix Houphouet, Boigny, Ivory Coast
Email: akissijoelle@gmail.com

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Abstract

Introduction: The physiological status of a subject and the pathophysiology in some diseases might be under the influence of haptoglobin phenotype. The objective of this work was to determine the relationship between mortality from HIV/AIDS infection and haptoglobin phenotype in a black population in Côte d'Ivoire. **Methods:** The study was conducted from a retrospective panel of 933 sera/plasma from the previous workup of the ANRS 12136 TEMPRANO trial at month 0 of patients in deferred-ART arms. For each subject, we determined the serum haptoglobin concentration, haptoglobin phenotype, and other variables from patient files from the TEMPRANO trial database. Statistical tests used were Chi-2, Fischer, and Kruskal-Wallis tests for non-gaussian distribution. We used the Kaplan-Meier method for survival analysis. **Results:** The distributions of the haptoglobin phenotypes were 32.3% for Hp 1-1, 39.5% for Hp 2-1 and 27.2% for Hp 2-2. The blood haptoglobin concentration seemed to be associated with haptoglobin phenotypes (p-value > 5%). The survival rate at M30 and for an extended follow-up up to 6 years was independent of haptoglobin phenotype (p-value > 5%). Besides, the haptoglobin phenotypes do not appear to be associated with CD4+ T-cell count and with hemoglobin concentration. **Conclusion:** Haptoglobin phenotype seems to not impact the mortality of HIV/AIDS infection. However, given the antioxidant and immunomodulatory properties of some haptoglobin phenotypes, it would be relevant to seek out possible confounding factors indirectly associated with haptoglobin phenotypes and clinical or biological infection variables.

Keywords

HIV/AIDS Infection, Phenotype of Haptoglobin, CD4+ Cell Counts, Hemoglobin, Mortality

1. Introduction

Haptoglobin (Hp) is a glycoprotein endowed with three main phenotypes polymorphism: Hp 1-1, Hp 2-1, and Hp 2-2 [1]. Each phenotype has specific antioxidant and immunomodulatory properties [1]. These properties are more or less powerful depending on the concerned phenotype [1]. Due to its antioxidant property, haptoglobin inhibits the toxic activity of plasma hemoglobin (Hb) [1]. Studies have shown that haptoglobin phenotypes have different impacts on the production of pro-inflammatory and anti-inflammatory cytokines [1] [2].

Thus, the physiological status of a subject and pathophysiology in some diseases and infections may be influenced by the haptoglobin phenotype and genotype [3] [4] [5] [6]. Few studies have been done to determine the trend and intensity of the relationship between haptoglobin phenotypes of black populations and infections in a highly infectious endemic environment. Particularly in Côte d'Ivoire, no study on the haptoglobin phenotype relationship and infectious disease has been undertaken on a large population [7].

The objective of this work was to determine the relationship between mortality from HIV/AIDS infection and haptoglobin phenotype in a black population in Côte d'Ivoire. In a specific way, the aim was to determine the distribution of haptoglobin phenotypes in the population and to identify the relationship between these phenotypes and mortality during HIV infection.

2. Materials and Methods

This retrospective descriptive and analytical study took place at the Centre de Diagnostic et de Recherche sur le Sida et les autres Maladies infectieuses (CeDReS) of the university teaching hospital (CHU) of Treichville in Abidjan, Côte d'Ivoire from July to September 2016. It was conducted on a retrospective panel of 933 sera/plasma from the initial workup at month 0 (M0) of patients in groups 1 and 2 of the ANRS 12136 TEMPRANO trial cohort [8]. This multicenter randomized controlled trial was conducted in Abidjan, Côte d'Ivoire from March 2008 to January 2015. Subjects eligible for the trial were 18 years old and older, with positive serology for HIV 1 or for HIV 1 & 2. All patients had a CD4+ count at the inclusion of fewer than 800 cells/mm^3 and did not meet any criteria for starting antiretroviral (ARV) therapy according to World Health Organization (WHO) guidelines at this moment [9]. All the subjects gave their informed written consent.

For patients in group 1 (late ARVs) antiretroviral treatment was deferred until the WHO criteria for starting antiretrovirals (ARVs) were met. Those in group 2 (late ARV plus isoniazid), in addition to the group 1 criteria, received isoniazid for 6 months, as prevention of tuberculosis, a month after their inclusion in the TEMPRANO ANRS 12136 study [8]. In our study, for each subject, we determined the serum haptoglobin concentration by immunoturbidimetry on the Cobas C311 (ROCHE Diagnostic). Patients' haptoglobin phenotype was determined by native polyacrylamide gel electrophoresis (native-PAGE) [10] [11]. Other variables

such as gender, HIV serology, hemoglobin concentration, CD4+ count, HIV viral load, and number of deaths during follow-up were obtained from the subject records filed in the TEMPRANO ANRS 12136 trial database.

Statistical Analysis

Statistical analyses were performed with SAS ®9.4 software. Quantitative variables are described in terms of median and interquartile range. The comparisons were made using Chi-2 or exact Fisher tests for qualitative variables (comparison of proportions), and Kruskal-Wallis for quantitative variables (comparison of distribution of the variable). We used the Kaplan-Meier method to determine the survival trends and comparisons were done using Log-rank test. All comparison test and correlation were considered statistically significant for a p-value inferior to 0.05.

3. Results

1) Demographics

The average age of our patients was 36 years (±9 years). The number of women was 722 (77.4%) and 211(22.6%) for men, *i.e.* a sex ratio of 0.29. The difference between percentages is significant (p-value < 0.05).

2) Distribution of haptoglobin phenotypes in our study population

The three major haptoglobin phenotypes (Hp 1-1, Hp 2-1, and Hp 2-2) were found in the proportions of 32.3% (CI: 29.2% - 35.5%), 39.5% (CI: 36.2% - 42.8%), and 27.2% (CI: 24.2% - 30.2%), respectively.

The Hp 0-0 phenotype was found in a proportion of 1% (CI: 0.3% - 1.6%).

3) Relationship between haptoglobin phenotype and serum hemoglobin and haptoglobin concentration

The average hemoglobin and haptoglobin concentration in our patients' population at inclusion was respectively 113 g/l (CI: 111,986 - 114,014).

4) Relationship between haptoglobin phenotype and haptoglobin concentration

Haptoglobin concentrations of the 1-1 phenotype were less dispersed than those of the 2-1 and 2-2 phenotypes. The highest haptoglobin concentrations were found in the 2-1 and 2-2 phenotypes (**Figure 1**). The haptoglobin concentration of our patients appeared to be related to the haptoglobin phenotypes (p-value = 0.008) (**Figure 1**).

5) Relationship between HIV serotype and haptoglobin phenotype

The HIV serotype most frequently encountered in the studied population was HIV 1. Statistical analysis showed no relationship between HIV serotype and haptoglobin phenotype (**Table 1**).

6) Relationship between average lymphocyte count and haptoglobin phenotype

We found no relationship between CD4+ T-cell count at inclusion and the haptoglobin phenotype. Likewise, there was no relationship between lymphocyte count and haptoglobin phenotype (p-value = 0.89) (**Table 2**).

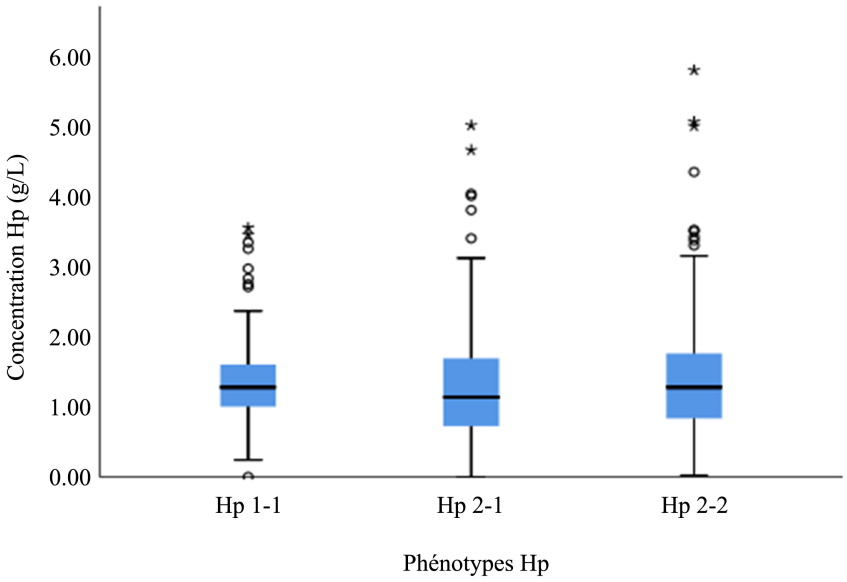

Figure 1. Distribution of haptoglobin concentration at inclusion by haptoglobin phenotype (p-value = 0.008).

Table 1. Distribution of haptoglobin phenotype by HIV serotypes.

Hp phenotype	HIV 1		HIV 1 & 2		Total	p-value (fisher)
	N	Lig %	N	Lig %		
1-1	266	98.5	4	1.5	270	0.875
2-1	323	97.9	7	2.1	330	
2-2	222	97.8	5	2.2	227	
0-0	8	100	-	-	8	
Total	819	98.1	16	1.9	835	

Table 2. Average number of CD4+ cells per mm^3 at inclusion by haptoglobin phenotype.

Hp phenotypes	N	Average ($cells/mm^3$)	Standard deviation	p-value (Kruskal-Wallis)
1-1	270	471	144	0.89
2-1	330	470	149	
2-2	227	469	149	
0-0	8	450	208	
Total	835	465	147	

7) Survival trends according to haptoglobin phenotype

Survival at M30 and at extended follow-up on 6 years did not vary with haptoglobin phenotype (Log-rank test p-value = 0.48 and p-value = 0.28 respectively) (**Figure 2**).

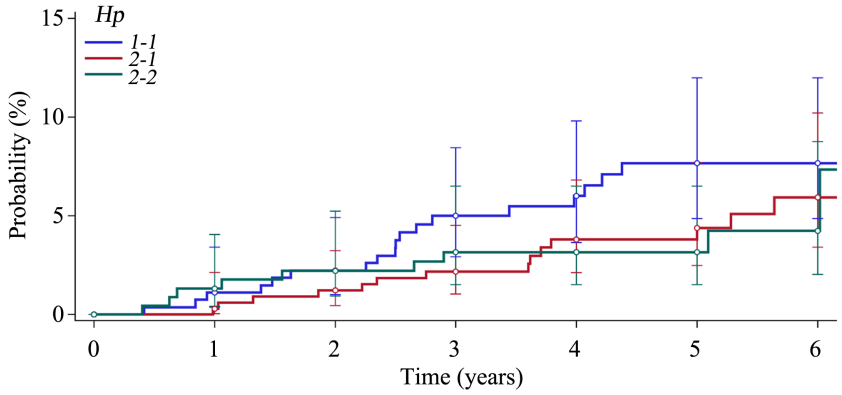

Figure 2. Survival curve in extended follow-up according to Hp phenotype.

4. Discussion

The progression of HIV infection is influenced by various host genetic factors [12]. The haptoglobin phenotype, according to several studies, may be among these factors [3]. Thus, the objective of our work was to determine the influence of the haptoglobin phenotype on the HIV evolution in black subjects followed in Ivory Coast.

The sex ratio in our study was 0.29. The difference in collection center attendance between men and women was not due to random sampling. This difference is due to socio-economic and cultural factors. Therefore the risk of seroconversion is twice higher in women [13]. The anatomo-physiological specificity of the female sexual system compared to the male sexual system, the easier access of the cervico-vaginal mucosa, facilitating infections and inflammations, the socio-economic conditions of women and the fact that they attend more often health centers than men, are all important determinants that explain this high number of HIV-positive women [13] [14] [15].

The three major haptoglobin phenotypes were found in our population. The genotypes are distributed differently according to the geographical area with a higher frequency of Hp^1 allele in Africa and South America [16]. Our results were similar with this geographical distribution.

The susceptibility to be infected with HIV serotype 1 or HIV dual did not appear to be influenced by haptoglobin phenotype in our study; similar fact was observed in a brazilian HIV 1 seropositive population [17].

Hemoglobin concentration was not related to haptoglobin phenotype. Haptoglobin, which role is to bind free toxic hemoglobin for plasma clearance, appears to not be involved in the trigger of hematopoiesis. The synthesis of haptoglobin takes place mainly in the liver and secondarily in the lungs, skin, spleen, kidneys and adipose tissue [4]. Generally, the increase of haptoglobin is induced not only by the presence of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor α (TNF-α) [18] [19] [20], but also induced by growth hormone, insulin, bacterial endotoxin, glucocorticoids, catecholamines, and hypoxia [21] [22]. In our population, haptoglobin concentrations differed

significantly depending on the haptoglobin phenotype. Our results reveal that the expression of haptoglobin in the blood could be related to the haptoglobin phenotype of the subject.

There was no significant variation in CD4+ T-cell counts according to haptoglobin phenotype. These results were similar to Delanghe *et al.* results which found similar average CD4+ numbers between the three haptoglobin phenotypes [23]. The variable anti-oxidant and immunomodulatory properties of the haptoglobin according to their respective phenotypes did not influence the probabilities of death either in the short term or in a long term.

5. Conclusions

Our study concerned a population of black PLHIV living in West Africa. Although present in our population, major haptoglobin phenotypes seemed to not impact the mortality of HIV/AIDS infection.

However, this study showed that the expression of haptoglobin in the blood could be influenced by the patient's phenotype. Given the antioxidant and immunomodulatory properties of certain haptoglobin phenotypes, it would be relevant to look for possible confounding factors indirectly associated with haptoglobin phenotypes and clinical-biological expressions of HIV/AIDS infection.

Conflicts of Interest

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

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