Arlet JB et al. J Infect Dis Epidemiol 2016, 2:020
Volume 2 | Issue 3
ISSN: 2474-3658

Journal of
Infectious Diseases and Epidemiology

Research Article: Open Access

Prevalence and Characteristics of Hepatitis C Virus Infection in Adult Sickle Cell Disease Patients Living in France

Jean-Benoît Arlet[1*#], Cloé Comarmond[2#], Anoosha Habibi[3,4], Katia Stankovic[5], Jean-Antoine Ribeil[6], Marilucy Lopez Sublet[7], Louis Affo[8], Christelle Chantalat Auger[9], Marie-Anne Bouldouyre[10], Justine Gellen-Dautremer[3], Sylvain Le Jeune[7], Eléna Foïs[3], Latifatou Boukari[11], Véronique Perronne[12], Denis Vincent[2], Jacques Pouchot[1], Djamal Khimoud[1], François Lionnet[5] and Patrice Cacoub[2*]

[1]*Service de Médecine Interne, Sickle Cell Referral Center, Faculté de médecine Paris Descartes, Sorbonne Paris-Cité et Assistance publique - Hôpitaux de Paris, Hôpital européen Georges Pompidou, 15 rue Leblanc 75908 Paris, France*

[2]*Sorbonne Universités, UPMC University Paris 06, UMR 7211, and Inflammation-Immunopathology- Biotherapy Department (DHU i2B), F-75005, Paris, France; INSERM, UMR_S 959, F-75013, Paris, France; CNRS, FRE3632, F-75005, Paris, France; AP-HP Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France*

[3]*Sickle Cell Referral Center, Unité des Maladies Génétiques du Globule Rouge, Hôpitaux universitaires Henri Mondor-Albert Chenevier, Assistance Publique-Hôpitaux de Paris, Université Paris-Est Créteil, Creteil, France*

[4]*Institut Mondor de Recherche Biomédicale (IMRB), Institut National de la Santé et de le Recherche Médicale (INSERM) U955, DHU A-TVB, F-94010 Créteil, France*

[5]*Service de médecine interne, Sickle Cell Referral Center, hôpital Tenon (AP-HP), 4, rue de la Chine, 75020 Paris, France*

[6]*Département de biothérapie, Sickle Cell Referral Center, Faculté de médecine Paris Descartes, Sorbonne Paris-Cité et Assistance publique - Hôpitaux, hôpital Necker, 160 rue de Sèvre, 75015 Paris, France*

[7]*Service de Médecine Interne et Hypertension Artérielle, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Bobigny, France*

[8]*Service de médecine interne Hôpital Louis Mourier, Assistance Publique-Hôpitaux de Paris, 178 rue des Renouillers 92700 Colombes, France*

[9]*Service de médecine interne et immunologie clinique, hôpitaux universitaires Paris Sud, Assistance publique Hôpitaux de Paris, 94275 Le Kremlin-Bicêtre, France*

[10]*Service de médecine et maladies infectieuses, Centre Hospitalier Intercommunal Robert Ballanger 93602 Aulnay/Bois, France*

[11]*Service de médecine interne hôpital Jean Verdier, Assistance publique-Hôpitaux de Paris, 93143 Bondy, France*

[12]*Service de médecine interne, hôpital de Mantes la Jolie, 78200 Mantes la Jolie, France*

GERMIVIC: Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l'Hépatite C

[#]*Equal contribution*

***Corresponding authors:** *Dr. Jean-Benoît ARLET Service de médecine interne, Hôpital européen Georges Pompidou, 20, rue Leblanc, 75908 PARIS Cedex 15, France, Tel: +33-1-56-09-33-31, E-mail: jean-benoit. arlet@aphp. fr*
Prof. Patrice Cacoub, Department of Internal Medicine and Clinical Immunology, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, Tel: +3301-42-17-80-27, E-mail: patrice. cacoub@aphp. fr

Abstract

Background and aims: The relationship between HCV infection and complications of sickle cell disease SCD has not been reported. To determine prevalence and characteristics of hepatitis C virus (HCV) infection in adult patients with SCD, and to analyze the relationship between HCV infection and SCD complications.

Methods: A total of 267 SCD patients were included. A standardized questionnaire was filled out, including history and complications of SCD, and the status and main characteristics of HCV infection.

Results: 267 SCD patients were included (62.5% women, 69% with homozygous SS genotype, median age 33 years [IQR 25-42]). HCV serology was positive in 17/228 (7.5%) patients in entire cohort,

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Citation: Arlet JB, Comarmond C, Habibi A, Stankovic K, Ribeil JA, et al. (2016) Prevalence and Characteristics of Hepatitis C Virus Infection in Adult Sickle Cell Disease Patients Living in France. J Infect Dis Epidemiol 2:020

Received: June 27, 2016: **Accepted:** November 11, 2016: **Published:** November 14, 2016

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and 17/153 (11.1%) patients with SS form. Major mode of contamination was blood transfusion (n = 16). HCV RNA was positive in 9/17 (53%). HCV genotypes were 4 (4), 1a (2), 1b (2), 2 (1) or unknown (8). Liver fibrosis scores were F0/F1 (6), F3/F4 (5), and unknown (6). Three patients had a sustained virologic response after HCV treatment. HCV-positive compared to HCV-negative SCD patients were significantly older (44 vs. 32 yrs.) and more frequently males (59 vs. 34.5%), with higher rates of hypertension (37.5 vs. 7%) and SS form (100 vs. 69%). In the group of SS form, HCV-positive patients had hypertension (37.5 vs. 4%), leg ulcers (35.5 vs. 13%), and nephropathy (70.5 vs. 46.5%) more frequently. Multivariate analysis limited to SS form showed HCV infection to be positively associated with hypertension (OR = 7.86 [1.83-33.7], p = 0.006) and leg ulcers (OR = 4.42 [1.24-15.77], p = 0.022).

Conclusions: In adult French SCD patients, prevalence of positive HCV serology was high. HCV-positive SCD patients always had a SS form, were older and had hypertension and leg ulcers more frequently.

Keywords

Hepatitis C, Sickle cell disease, Liver fibrosis, Leg ulcer

Sickle cell disease (SCD) is the most prevalent hereditary disorder worldwide. The three most common genotypes are homozygous haemoglobin SS, heterozygous haemoglobin SC, and haemoglobin S/β-thalassemia [1,2]. Polymerization of mutated haemoglobin S results in deformation of red blood cells, which can cause endothelial cell injury and inflammation, and may lead to capillary occlusion and acute or chronic tissue hypoxia. The chronic haemolytic state, which contributes to anaemia and reduces nitric oxide bioavailability, is the other key mechanism that explains the vascular complications of SCD [1]. Chronic haemolytic anaemia, vaso-occlusive crisis and acute chest syndrome are frequent complications of the disease [2]. Other well-defined specific complications of tissue hypoxia include avascular osteonecrosis, priapism, leg ulcers, nephropathy and retinopathy. Although SCD patients are frequently transfused, and therefore represent a high-risk population for hepatitis C virus infection (HCV), the prevalence of HCV has rarely been reported [3-6]. HCV is known to be an important cause of liver disease in SCD patients [3]. In addition, HCV has been recently suspected to be a cardiovascular risk factor for the development of carotid atherosclerosis, heart failure and stroke [7,8]. In France, prevalences of positive HCV serology is around 0.3% in the entire population; prevalence of SCD is around 26,000 patients. While the effect of SCD on liver disease in HCV infected patients had been described [4,9], the impact of HCV infection on complications of SCD has not been reported.

The aims of our study were (1) to determine the prevalence and characteristics of HCV infection in adult patients with SCD in France, and (2) to analyze the relationship between HCV infection and SCD vascular manifestations.

Methods

Patients

All adult SCD patients (≥ 18 years) from eleven centres (including 5 national reference centres) throughout the Paris area (France) were consecutively included over a one-week period in April, 2015 in this observational study. Patients were seen during a routine follow-up outpatient visit or hospitalization. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee. Written informed consent was not required.

Data collection

The investigators completed a questionnaire that included information on demographics (age, gender and geographic origin), risk factors for HCV infection and main clinical features. Other clinical information included the presence or absence of diabetes and hypertension, and history of blood transfusions. Behavioural activity included questions regarding intravenous drug abuse, alcohol abuse and smoking. The history of vaso-occlusive crisis (assessed by the mean annual number of vaso-occlusive crises requiring emergency admission within the last 2 years), acute chest syndrome, chronic complications of SCD, cardiovascular risk factors, and the status and characteristics of HCV infection (mode of contamination, HCV RNA, viral load, genotype, liver fibrosis score and treatment), and hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection were obtained from a retrospective chart review.

No specific blood sample was requested. The more recent biologic findings, at the steady state of SCD disease, included haemolytic parameters (levels of haemoglobin, bilirubin, lactate dehydrogenase, aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and foetal haemoglobin [HbF], using high performance liquid chromatography. The glomerular filtration rate (GFR) was estimated by the CKD-EPI formula without adjustment for race, as recommended in SCD [10]. Pulmonary arterial hypertension was assessed by a Doppler ultrasound and defined as a peak tricuspid regurgitation jet velocity of at least 2.5 m per second. The presence of SCD cardiomyopathy was assessed by an abnormal transthoracic echocardiography (impaired diastolic or systolic function, dilation or hypertrophy) and/or acute episodes of cardiac insufficiency. Cerebral vasculopathy was defined as the presence of Moyamoya, aneurysm or vascular stenosis, with or without episode of stroke.

Statistics

Continuous variables are shown as medians (interquartile ranges, IQR) and compared using the Mann-Whitney test. Categorical variables are expressed as numbers and frequencies (%) and compared using Pearson's chi-squared test or Fisher's exact test. In order to identify factors potentially associated with positive HCV serology, univariate analyses were performed using a logistic regression model. Variables that were significant at *P* values less than 0.10 were included in the multivariate analysis. Multivariate models were selected using backward stepwise procedures on *P* values (5% threshold). *P* values less than 0.05 were considered significant. Calculations were performed using Statview Statistical and SAS statistical software, version 9.2.

Results

A total of 267 patients were included (median age 33 years [IQR: 25-42], 62.5% women). They mainly originated from Sub-Saharan Africa (69.5%). The haemoglobin profile was SS in 70%, SC in 24% and S/β-thalassemia in 6% (Table 1) of these, 228 (85%) had already been screened for HCV infection. The prevalence of positive HCV serology was 7.5% (17/228 patients) in the entire cohort, and 11.1% (17/153 patients) in the homozygous SS subpopulation. Of note is that all the HCV-positive patients exhibited an SS genotype. Concerning HBV infection markers, 65/153 (42.5%) patients had HBc antibodies, and two patients had a profile of chronic active infection (HBs antigen-positive, HBc antibody-positive, HBs antibody-negative). HIV serology was positive in 6 of 205 (3%) patients.

Table 2 shows the main characteristics of SCD patients with positive HCV serology. The mode of contamination was blood transfusion (n = 16) or was unknown (n = 1). The HCV genotypes were 4 (n = 4), 1a (n = 2), 1b (n = 2), 2 (n = 1) or unknown (n = 8). The Metavir liver fibrosis scores [by liver biopsy (n = 5) or elastometry (n = 6)] were F0 (n = 3), F1 (n = 3), F3 (n = 3), F4 (n = 2) and unknown (n = 6). One patient (Patient 1, table 2) had liver failure. HCV RNA was positive in 9/17 (53%) patients. Of the nine, the viral load was above 800, 000 IU/mL in five patients and below this cut-off in four patients. Of the eight HCV RNA negative patients, five had spontaneous HCV clearance, whereas three patients had received a specific HCV treatment and had no detectable HCV RNA at the last screening (sustained virologic response); these included a 59-year-old woman (Patient 5, table 2) after 48 weeks of Peg-IFN/ribavirin, a 49-year-old man (Patient 7, table 2) after 12 weeks of Peg-IFN/ribavirin + telaprevir, and a 60-year-old man (Patient 4, table 2) after 12 weeks of sofosbuvir + daclatasvir.

Table 1: Main characteristics of the entire cohort of sickle cell disease patients.

Characteristics	Total n = 267#	HCV-negative n = 211	HCV-positive n = 17	*P*
Age, years	33 [25-42]	32 [24-40]	44 [38-51.5]	0.001**
Women, n (%)	164/262 (62.5)	135/206 (65.5)	7/17 (41)	0.04*
Origin, n (%)				
Sub-Saharan Africa	177/255 (69.5)	147/200 (73.5)	10/16 (62.5)	0.40
North Africa	5/255 (2)	5/200 (2.5)	0/16 (0)	1.00
West Indies	54/255 (21)	36/200 (18)	6/16 (37.5)	0.10
Caucasian	17/255 (6.5)	10/200 (5)	0/16 (0)	1.00
North America or Brazil	4/255 (1.5)	4/200 (2)	0/6 (0)	1.00
Sickle cell disease genotype, n (%)				
SS	178/253 (70)	136/197 (69)	17/17 (100)	0.004**
SC	60/253 (24)	51/197 (26)	0/17 (0)	0.01*
S/β-thalassemia	15/253 (6)	10/197 (5)	0/17 (0)	1.00
Haemoglobin, g/dL	9.2 [8-10.4]	9.3 [8.1-10.4]	8.7 [7.1-9.5]	0.05
Reticulocytes, 10^9/L	200 [141.5-311.5]	198.5 [137-304.5]	240.5 [178-364]	0.08
History of red blood cell transfusion, n (%)	172/236 (73)	131/184 (71)	16/17 (94)	0.05
Alcohol abuse, n (%)	12/225 (5)	9/175 (5)	2/16 (12.5)	0.20
Intravenous drug abuse, n (%)	2/214 (1)	2/166 (1)	0/16 (0)	1.00
Cardiovascular risk factors:				
Hypertension, n (%)	20/236 (8.5)	13/185 (7)	6/16 (37.5)	0.001**
Body mass index (kg/m²)	21.8 [20.324.5]	21.9 [20-24.9]	22.2 [20.4-25.4]	0.85
Diabetes mellitus, n (%)	5/236 (2)	4/185 (2)	1/16 (6)	0.30
Smokers, n (%)	34/229 (15)	27/181 (15)	1/16 (6)	0.45
Cardiovascular disease events				
Stroke, n (%)	22/241 (9)	19/190 (10)	2/17 (12)	0.70
Myocardial infarction, n (%)	1/239 (0.4)	1/188 (0.5)	0/17 (0)	1.00
Heart failure, n (%)	8/241 (3)	6/190 (3)	1/17 (6)	0.45
Hemochromatosis, n (%)	52/247 (21)	39/195 (20)	8/17 (47)	0.03*
Liver failure, n (%)	2/243 (0.8)	1/190 (0.5)	1/17 (6)	0.16
HBV infection markers, n (%)				
HBc Ab* +, HBs Ag -	63/151 (42)	50/135 (37)	10/13 (77)	0.02*
HBs Ag +	2/204 (1)	1/188 (0.5)	1/16 (6)	0.15
HIV infection, n (%)	6/205 (3)	6/189 (3)	0/16 (0)	1.000

*p < 0.05, **p < 0.01, ***p < 0.001

Continuous variables are expressed in median [IQR]. Ab = antibody; Ag = antigen; #Patients not screened for HCV status: n = 39; *Data for HBc antibodies was not available in 53 patients who had HBV serology screening.

Table 2: Main characteristics of HCV infection in the 17 SCD patients with positive HCV serology.

Patient	Age, gender	Positive HCV RNA	HCV genotype	Mode of contamination	Hb level (g/dL)	ALT (IU/L)	Prothrombin time (%)	Liver fibrosis score**	Treatment
1	51, M	Y*	4	Transfusion	7	157	61	F4	None
2	43, M	Y	4c	Transfusion	6.9	19	79	F3	None
3	44, M	N	ND	NA	7.2	30	81	ND	None
4	60, M	N	1a	Transfusion	6.4	26	61	F4	sofosbuvir + daclatasvir
5	59, F	N	4	Transfusion	9.0	12	95	F0	Peg IFN + ribavirin
6	30, M	N	ND	Transfusion	9.9	31	62	ND	NA
7	49, M	N	1a	Transfusion	8.7	17	89	ND	Peg IFN + ribavirin + telaprevir
8	32, M	Y*	2	Transfusion	11.1	27	92	F1	None
9	42, M	N	ND	Transfusion	9.7	10	73	ND	None
10	46, F	Y	ND	Transfusion	10.2	19	85	F1	None
11	49, F	Y	ND	Transfusion	9.0	43	NA	ND	None
12	34, F	Y*	1b	Transfusion	9.2	35	92	F3	None
13	35, M	Y	ND	Transfusion	7.0	62	97	F0	None
14	43, F	N	ND	Transfusion	9.4	22	90	F0	None
15	52, F	Y*	1b	Transfusion	8.1	21	92	F1	None
16	41, F	N	ND	Transfusion	8.0	36	97	ND	None
17	57, M	Y*	4	Transfusion	8.0	28	79	F3	None

HCV = hepatitis C virus; M = male; F = female; Y = Yes; N = No; Y* = patients with HCV viremia > 800,000 IU/mL at the last screening; ND = not done; NA = not available; Hb = haemoglobin; ALT = alanine aminotransferase; **Metavir fibrosis score; Peg-IFN = pegylated interferon.

In order to explore the possible impact of HCV infection on complications of SCD, we compared the main characteristics of HCV-positive and HCV-negative SCD patients (Table 1). The HCV-positive SCD patients were found to be significantly older (44 vs. 32 yrs, p = 0.001), more often males (59% vs. 34. 5%, p = 0.04) and had a more frequent history of hypertension (37.5% vs. 7%, p = 0.001). There was no significant difference in the rates of alcohol consumption or of other cardiovascular risk factors or major cardiovascular events.

Because all HCV-positive SCD patients had the homozygous SS form, we next compared the characteristics of the 17 HCV-positive with the 136 HCV-negative homozygous SS SCD patients, particularly for specific SCD complications (Table 3). The HCV-positive SCD patients with homozygous SS form showed higher rates of leg ulcers (35.5% vs. 13%, p = 0.03), hypertension (37. 5% vs. 4%, p = 0.0003) and nephropathy (70.5% vs. 46.5%, p = 0.06). The estimated GFR was 108 vs. 121 mL/min/1.73 m² in the HCV-positive vs. HCV-negative group (p = 0.001), and no difference was found with regard to proteinuria. Patients on chronic dialysis were more frequently HCV-positive (2/17; 12%) than HCV-negative (1/136;

Table 3: Comparison of the main characteristics of homozygous (SS) sickle cell disease patients according to their HCV status.

Characteristics[#]	**HCV-negative n = 136**	**HCV-positive n = 17**	***P***
Age, years	30 [24-36]	44 [38-51.5]	< 0.001***
Male, n (%)	46/133 (34.5)	10/17 (59)	0.05
Body mass index (kg/m^2)	21.1 [19.4-23.7]	22.2 [20.4-25.4]	0.85
Hypertension, n (%)	5/120 (4)	6/16 (37.5)	0.0003***
History of red blood cell transfusion, n (%)	103/121 (85)	16/17 (94)	0.47
Origin			
Sub-Saharan Africa	98/130 (75.5)	10/16 (62.5)	0.36
North Africa	3/130 (2.3)	0/16 (0)	1.00
West Indies	21/130 (16)	6/16 (37.5)	0.08
Caucasian	7/130 (5.5)	0/16 (0)	1.00
North America or Brazil	3/130 (2.3)	0/16 (0)	1.00
Haemoglobin, g/dL	8.6 [7.8-9.6]	8.7 [7.1-9.55]	0.51
Foetal haemoglobin, %	6.7 [3.25-12]	5 [1-13]	0.34
Reticulocytes, 10^9/L	244 [183.5-340.4]	240.5 [178-364]	0.62
Lactate dehydrogenase, IU/L	414.5 [305.5-535.5]	485 [348.5-683]	0.09
Total bilirubin, µmol/L	41 [27-57.5]	41 [20-69.5]	0.62
Conjugated bilirubin, µmol/L	10 [7-13]	10.5 [8-15.5]	0.34
AST, IU/L	38 [30-52]	41 [34.5-62]	0.20
ALT, IU/L	25.5 [17-38]	27 [19-35.5]	0.77
Prothrombin time, %	80.5 [70-90]	87 [74.5-92]	0.40
Liver failure, n (%)	0	1 (6)	0.12
GFR, ml/min/1.73m^2	127 [116-141]	108 [74-120.5]	0.001**
Creatinine level, µmol/L	53 [45-63]	63 [53.5-103]	0.005**
Urine albumin-to-creatine ratio, mg/mmol	2.76 [1-9.1]	3.2 [0.8-25.9]	0.71
ratio > 10	22/100 (22)	4/12 (33)	0.47
Acute chest syndrome, n (%)	92/127 (72)	10/17 (59)	0.10
1 episode	21/89 (23.5)	1/9 (11.1)	
2-4 episodes	42/89 (47.3)	8/9 (88.9)	
> 4 episodes	26/89 (29.2)	0	
Vaso-occlusive crisis[*], n (%)	116/125 (93)	15/17 (88)	0.62
1 episode	1/109 (0.9)	4/14 (28.6)	
2 episodes	65/109 (59.6)	7/14 (50)	
> 2 episodes	43/109 (39.5)	3/14 (21.4)	
Chronic complications of SCD:			
- Nephropathy, n (%)	58/125 (46.5)	12/17 (70.5)	0.06
- Retinopathy, n (%)	57/128 (44.5)	8/17 (47)	0.84
- Avascular osteonecrosis, n (%)	42/122 (34.5)	5/17 (29.5)	0.68
- Leg ulcer, n (%)	16/124 (13)	6/17 (35.5)	0.03*
- Priapism, n (%)	11/46 (23.9)	3/10 (30)	0.69
- Pulmonary arterial hypertension, n (%)	20/125 (16)	5/17 (35.5)	0.18
- Cardiomyopathy, n (%)	45/127 (35.5)	6/17 (35.5)	1.00
- Acute heart insufficiency, n (%)	5/121 (4)	1/17 (6)	0.55
- Cerebral vasculopathy[**], n (%)	15/122 (12)	3/17 (17.5)	0.46
- Stroke, n (%)	10/121 (8.5)	2/17 (12)	0.64
Hemochromatosis, n (%)	32/128 (25)	8/17 (47)	0.08
HBV infection markers, n (%)			
HBc Ab +, HBs Ag -	28/89 (31.5)	10/13 (77)	0.008**
HBs Ag +	1/120 (0.8)	1/16 (6)	0.22
HIV infection, n (%)	1/116 (0.9)	0/15 (0)	1.00

*p < 0.05, **p < 0.01, ***p < 0.001

Continuous variables are expressed in median [IQR]. HCV = hepatitis C virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SCD = sickle cell disease; GFR = glomerular filtration rate; HBV = hepatitis B virus; Ab = antibody; Ag = antigen; HIV = human immunodeficiency virus.

[*]Vaso-occlusive crisis requiring hospitalization (mean of the two last years); [**]Cerebral vasculopathy was defined as the presence of Moya-Moya, aneurysm or vascular stenosis, with or without episode of stroke; [#]Homozygous (SS) SCD patients not screened for HCV status were not included in this analysis (n = 25).

0.7%) (p = 0.03). No significant difference was found concerning other classical SCD complications or biological parameters (i.e. levels of haemoglobin, reticulocytes, LDH, AST, ALT, and bilirubin) (Table 3). A multivariate analysis model in the SS form cohort of SCD patients showed HCV infection to be positively associated with hypertension (OR = 7.86 [1.83-33.7], p = 0.006) and leg ulcers (OR = 4.42 [1.24-15.77], p = 0.022).

Discussion

In this large cohort of adult French SCD patients, the prevalence of HCV-positive serology was high, i.e. 7.5% in the entire cohort and 11.1% in the group with SS homozygous form. About one-third of HCV-positive patients had severe liver fibrosis. HCV-positive SCD patients had more frequent extra hepatic vascular complications, i.e. leg ulcers, nephropathy, and hypertension.

The high prevalence of HCV infection found in our SCD cohort should be first compared to the 0.94% (0.6-1.51) prevalence reported in people living in the same area (Paris, France in 2003-2004) [11]. The prevalence of positive HCV serology in SCD patients has been rarely reported, and to our knowledge no data are available in Europe. Two small single-centre studies in the US found positive HCV serology in 10% of 99 SCD patients [4] and 20.7% of 121 SCD patients [3]. These studies also found a significant correlation between the high prevalence of positive HCV serology and the SS genotype of SCD. In two more recent Brazilian single-centre studies (n = 291 and n = 1225), the prevalence of positive HCV serology was about 14% [5,6]. In the study by Torres, et al. [5], 83% of HCV-positive patients were HCV RNA positive, with HCV genotypes 1b (63%), 1a (21%) and 3a (16%). They also found that the HCV-positive population was older (26 vs. 15 years), but there was no attempt to compare biological markers or clinical phenotypes between the HCV-positive and HCV-negative patients.

As expected, blood transfusion appears to be the major mode of HCV contamination in SCD patients. Fortunately, the prevalence

decreased dramatically among patients who received transfusions after the implementation of blood donor screening for HCV in the early 1990's. This probably explains the higher age of the HCV-positive SCD patients. Up to 15% of SCD patients in our cohort had never been screened for HCV infection, although they belonged to a high-risk population. This could be a bias that underestimates the prevalence of HCV infection. Thus, HCV screening should be a part of the management of SCD patients. This is further highlighted by the fact that at least one-third of HCV-positive patients in our cohort of young adults already had severe liver fibrosis, a status known to be associated with a 1-4% annual rate of hepatocellular carcinoma [12]. Recent advances in HCV treatment using interferon-free and ribavirin-free combinations, with very high rates of HCV cure (> 95%) and very good safety profiles, stress the importance of detection campaigns in this high-risk population. Concerning HBV infection markers, patients HBc Ab+ HBs Ag- and those HBs Ag+ were more frequently found in the group of SCD patients HCV positive, probably reflecting the same mode of HBV transmission by blood transfusion.

The second objective of our study was to explore the relationship between HCV infection and SCD complications. It is well known that, compared to patients with other SCD genotypes, patients with a homozygous SS genotype have more severe anaemia, more frequent haemolysis, a higher mortality rate, and different frequencies of acute and chronic SCD complications [2]. We therefore compared SCD complications in the homozygous SS form cohort more in depth, since all HCV-positive patients had the SS genotype. In this cohort, HCV-positive SCD patients had hypertension, nephropathy and leg ulcers more frequently. The high rate of hypertension was unexpected, as SCD patients were reported to have lower blood pressure than the general population [13]. HCV-positive patients had a lower glomerular filtration rate. Hypertension and kidney involvement in this HCV-positive SCD population might reflect the role of HCV as a cardiovascular risk factor, as has been recently emphasized by Domont, et al. [8]. One explanation for the higher rates of leg ulcers in HCV-positive patients may be the presence of mixed cryoglobulinemia, but this hypothesis was not explored in our study. Of note is that the association with leg ulcers was also found in a Brazilian single-centre retrospective study on 1,225 patients (OR = 1.74, 95% CI: 1.06-2.84) [6]. It also found an association between HCV-positive status and a higher risk of stroke (OR = 1.94, 95% CI: 1.15-3.27), painful SCD crisis (OR = 1.61, 95% CI: 1.17-2.22, P = 0.004) and hospitalization (OR = 1.52, 95% CI: 1.07-2.17).

One limitation of our study was the retrospective nature of the chart review for the past medical history of specific SCD complications. On the other hand, a major strength of this study was its multicentre design, including a large number of SCD patients from the same geographic area in Europe.

Conclusions

The prevalence of HCV-positive serology in this large French cohort of SCD patients was high (7.5% in the whole cohort, and 11% in the cohort with the homozygous form). Transfusion was the major mode of contamination. HCV-positive SCD patients, all with a homozygous SS form, were older and presented hypertension and chronic leg ulcers more frequently. The relationship between HCV infection and vascular complications of SCD needs to be further studied.

Conflict of Interest Statement

- Dr. P Cacoub has received consulting and lecturing fees from: Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme.
- All the other authors declare no conflict of interest with this article.

Financial Support Statement

DjamalKhimoud received grants from the French Ministry of Health (rare diseases reference centres). This work was supported by an unrestricted grant provided by Merk Sharp Dohme.

Contributor ship

Study concept and design: JBA, CC, PC.

Acquisition of data: JBA, CC, DV, DK, and PC.

Analysis and interpretation of data: JBA, CC, PC.

Drafting of the manuscript: JBA, CC, and PC.

Critical revision of the manuscript for important intellectual content: JBA, AH, KS, JAR, MLLS, LA, CC, MAB, JGD, SLJ, EF, LB, VP, FL and PC.

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