



Comparison of the clinical course of COVID-19 infection in sickle cell disease patients with healthcare professionals

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Abstract

It is highly expected that COVID-19 infection will have devastating consequences in sickle cell disease (SCD) patients due to endothelial activation and decreased tissue and organ reserve as a result of microvascular ischemia and continuous inflammation. In this study, we aimed to compare the clinical course of COVID-19 in adult SCD patients under the organ injury mitigation and clinical care improvement program (BASCARE) with healthcare professionals without significant comorbid conditions. The study was planned as a retrospective, multicenter and cross-sectional study. Thirty-nine SCD patients, ages 18 to 64 years, and 121 healthcare professionals, ages 21 to 53, were included in the study. The data were collected from the Electronic Health Recording System of PRANA, where SCD patients under the BASCARE program had been registered. The data of other patients were collected from the Electronic Hospital Data Recording System and patient files. In the SCD group, the crude incidence of COVID-19 was 9%, while in healthcare professionals at the same period was 23%. Among the symptoms, besides fever, loss of smell and taste were more prominent in the SCD group than in healthcare professionals. There was a significant difference between the two groups in terms of development of pneumonia, hospitalization, and need for intubation (43 vs 5%, $P < 0.00001$; 26 vs 7%, $P = 0.002$; and 10 vs 1%, $P = 0.002$, respectively). Prophylactic low molecular weight heparin and salicylate were used more in the SCD group than in healthcare professionals group (41 vs 9% and 28 vs 1%; $P < 0.0001$ for both). The 3-month mortality rate was demonstrated as 5% in the SCD group, while 0 in the healthcare professionals group. One patient in the SCD group became continuously dependent on respiratory support. The cause of death was acute chest syndrome in the first case, hepatic necrosis and multi-organ failure in the second case. In conclusion, these observations supported the expectation that the course of COVID-19 in SCD patients will get worse. The BASCARE program applied in SCD patients could not change the poor outcome.

Keywords Sickle cell disease · COVID-19 infection · SARS-CoV-2 · Hemoglobinopathy · Pneumonia · Acute chest syndrome

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Introduction

Sickle cell disease (SCD) is among the most common genetic diseases worldwide characterized by typical painful crises, chronic hemolysis attacks and organ damage as a result of abnormal hemoglobin S (Hgb S) production [1]. Organ damage that develops in SCD patients leads to early mortality. Among the most common factors responsible for mortality are acute chest syndrome and multiple organ failure [2]. The disease is common in Turkey in the Eastern Mediterranean Region. In some regions, the Hgb S carrier rate reaches 30% [3].

Microvascular ischemia, endothelial activation and inflammation resulting from cytokine release play an important role in the pathogenesis of SCD. Sickled erythrocytes lead to the release of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) from monocytes [4–6]. Endothelial activation is responsible for typical vaso-occlusive events by activating complement along with thrombin formation and increasing contact between blood cells and endothelial structure [7–10]. Sickle cell patients are susceptible to infections. Viral infections, mycoplasma and encapsulated microorganisms cause the onset of typical vaso-occlusive attacks in SCD patients [11, 12]. One of the most feared complications during these attacks is acute chest syndrome, which occurs with fever, chest pain, and pulmonary infiltrates [13, 14].

Since March 2020, when the severe acute respiratory failure syndrome (COVID-19) caused by the coronavirus SARS-Cov-2 was declared a global epidemic by the WHO, the infection has also seriously affected SCD patients. Damaged structure and chronic inflammatory process in the endothelium which is the target tissue of COVID-19, may herald cytokine storm and thrombotic events. Inflammation biomarkers (c-reactive protein, d-dimer, IL-6, ferritin, and activated platelet tests), which are almost always active in SCD, may be associated with their ability to precipitate cytokine storm and the rapid deterioration of the clinical situation [12, 15–17]. The emergence of pathological evidence of acute respiratory failure in COVID-19 and the gradual definition of systemic findings of thrombosis susceptibility are also seen to be associated with mortality [17, 18]. Despite all these assumptions, information about the clinical course of COVID-19 in SCD is not clear.

In this study, it is aimed to determine the frequency of COVID-19 infection among SCD patients and to analyze the short-term clinical course of the disease.

Material and methods

Study design and patients

The study was planned as a retrospective, multicenter, and cross-sectional study. The study was conducted with adult

SCD cases with a diagnosis of homozygous Hgb SS disease or compound heterozygosity (Hgb SC, Hgb SD, Hgb SO-Arab, Hgb S β -thalassemia cases) living in the Eastern Mediterranean Region. Patients who were older than 18 years and diagnosed with COVID-19 for the period between June 2020 and January 2021 were included in the study. The crude ratio of COVID-19 infection among the SCD patients registered to the BASCARE system and the healthcare professionals at the same center were determined. The two groups were compared in terms of the clinical course of COVID-19 disease.

Among these patients with known demographic characteristics (Most of them are registered with BASCARE, the Clinical Care Improvement Program of Baskent University), the daily hospital records of SCD patients required hospitalization were examined and/or communication was established with the Pandemic Unit staff doctors [19]. Telemedicine method was used for patients hospitalized in external medical centers or patients being treated in the outpatient clinics. These patients were evaluated by contacting their physicians at least once a week until clinical recovery. In addition, the clinical and laboratory characteristics of the cases followed up in external centers were evaluated using the e-nabiz, which is the National Electronic Central Health Recording System, Turkey (www.enabizgov.tr).

Inclusion criteria

Consecutive patients with SCD over the age of 18 and a weight of 50 kg who were diagnosed COVID-19 by clinical history and positive results for SARS-CoV-2 by Reverse transcription polymerase chain reaction (RT-PCR) analysis were enrolled. On the other hand, healthcare professionals, age between 18 and 50 years, who did not have a distinct comorbid condition and who had COVID-19 infection in the same period with SCD patients were included in the study consecutively.

Exclusion criteria

Patients with unconfirmed COVID-19 diagnosis by a positive RT-PCR test of nasopharyngeal swabs, active secondary infection, renal failure, hepatic necrosis, and pregnancy were excluded from the study.

Ethical approval

An application to the Ministry of Health General Directorate of Health Services, COVID-19 Scientific Research Evaluation Commission (<https://www.bilimselarastirma>.

saglik.gov.tr) was completed. After the approval had been obtained, an application was also made to the Baskent University Institutional Review Board (KA21/17).

Data collection

The study was conducted in 4 centers located in Adana and Mersin provinces in the Eastern Mediterranean Region.

The demographic, clinical, and laboratory data related to the course of the infection were collected from the PRANA Electronic Health Record System used for BASCARE program (Nucleus, version 9.3.39; Monad Software Company, Ankara, Turkey). Data on health-care professionals with COVID-19 were collected from the same hospital who implemented the BASCARE clinical care program. In other centers where the study was conducted, data were collected from patient files. Data on patients receiving treatment in other centers were collected via interview records conducted with the doctor of the patients under the heading of telephone recording. The radiological findings obtained from the national e-nabiz system were used after re-evaluation with a radiologist.

The collected data included demographic characteristics of the patients for two patient cohorts. Clinical data of SCD patient group consisted of current organ damage, vaccination, use of hydroxyurea, angiotensin converting enzyme (ACE) inhibitors, and acetylsalicylic acid (ASA), transfusion/erythrocyte exchange therapy within 3 months before COVID-19 diagnosis, cardiac complications, annual painful crises episodes, neurological attacks, asthma and acute chest syndrome. Among the laboratory data, in addition to steady state hemoglobin, leukocyte, platelet, count, d-dimer, c-reactive protein, biochemical tests for liver and kidney functions were collected. Radiologically, data on chest X-ray and high resolution computerized tomography (HRCT) were evaluated.

Regarding the diagnosis and treatment of COVID-19, symptoms, RT-PCR/or serological test results, treatment agents including convalescent plasma were recorded. Outcomes, including intubation need, complications according to the Common Toxicity Criteria for Adverse Events, Version 4.0 (CTAE) and survival data were also recorded. Patient outcomes were followed up clinically after diagnosis for up to 3 months.

Definitions

Clinical grading of COVID-19 Definitions of the Turkish Ministry of Health compatible with the US National Institute

of Health will be considered. Among the cases that fit the possible case definition, cases that were found to have SARS-CoV-2 by RT-PCR were defined as definite COVID-19 infection. Clinical grading was made for COVID-19, taking into account the symptoms of the patients, development of pneumonia, respiratory failure, and oxygen demand at room air. People with $O_2 < 94\%$ in room air, $PaO_2/FiO_2 < 300$ mm Hg, respiratory frequency $> 30/\text{min}$ or lung infiltrates $> 50\%$ was defined as severe illness. People with respiratory failure, septic shock and/or multiorgan dysfunction fell into the critical disease category.

<https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>

<https://covid19.saglik.gov.tr/TR-66337/genel-bilgiler-epidemioloji-ve-tani.html>

RT PCR analysis RT PCR analysis of nasopharyngeal swabs were carried out by the regional laboratory of MoH, General Directorate of Public Health.

Hypotension with dyspnoea and respiratory distress, respiratory rate $\geq 30/\text{min}$, $PaO_2/FiO_2 < 300$, increased oxygen demand during follow-up, $SpO_2 < 90\%$ or $PaO_2 < 70$ mmHg despite 5 L/min oxygen therapy (systolic blood pressure $<$ Patients with a decrease of 90 mmHg and more than 40 mmHg from the usual SBP and with a mean arterial pressure < 65 mmHg, tachycardia $> 100/\text{min}$, acute kidney injury, acute liver function disorder, confusion, acute bleeding diathesis, and immunosuppression. The presence of troponin elevation and skin disorders such as arrhythmia, lactate > 2 mmol, capillary return disorder and cutis marmoratus will be defined as cases that should be evaluated in terms of intensive care need.

The recovery will be defined as the time in months after infection diagnosis until the patient becomes asymptomatic, signs disappear, and the PCR test becomes negative.

<https://covid19.saglik.gov.tr/Eklenti/39061/0/covid-19rehberieriskinhastatedavisipdf.pdf>.

Definitions of SCD-associated clinical conditions Patients who had not required medication to treat painful conditions for the previous 4 weeks were considered to have steady-state disease. A painful crisis was defined as the need for hospital admission due to pain not related to any cause other than SCD or for the use of parenteral non-steroidal anti-inflammatory drugs, metamizol, or narcotics for SCD-related pain treatment. The crisis frequency was defined as rare if the patient experienced fewer than three painful crises a year and frequent if the number of yearly painful crises was three or more. Microalbuminuria was defined as 30–300 mg microalbumin per day in a spot urine test in an afebrile patient with episodes of pain. Nephropathy was

defined as the presence of at least one indicator of renal dysfunction, such as microalbuminuria and proteinuria, and low creatinine clearance. Pulmonary hypertension was defined as a mean resting pulmonary artery pressure of > 30 mm Hg following exercise and tricuspid regurgitant jet velocity ≥ 2.5 m/s at least 3 weeks after a vaso-occlusive crisis (14). Hydroxyurea use was defined as the regular use of minimum 15 mg hydroxyurea/kg/day for at least 1 month.

Endpoints

Primary endpoints: Disease-free rate at 3 months, overall survival rate at 3 months, intubation rate at 3 months. Secondary endpoint: Rate of infection-related complications (pneumonia, respiratory failure, neurological findings, thrombotic episodes).

Statistical analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS) software, version 17 (SPSS Inc., Chicago, IL, USA). Baseline categorical variables were compared using Fisher's exact test, whereas continuous variables were compared using Mann–Whitney *U* test or two-sample *t* test as appropriate. Comparison between estimates of crude incidence were made by using χ^2 test. A *P* value less than 0.05 was considered statistically significant.

Results

In patients with COVID-19 in two study cohorts diagnosed by RT-PCR of nasopharyngeal swabs, a false-negative rate (0.5%) of testing has been observed in SCD cohorts. In 2 SCD patients who were hospitalized, initial test results were negative but subsequent test results during the same hospitalization were found to be positive. All patients in the health professionals group were positive for RT-PCR test.

Most of the data of the 39 SCD patients diagnosed with COVID-19 infection were collected from the BASCARE registry system, PRANA (31 patients, 79%). Sixty patients who underwent hematopoietic stem cell transplantation among 415 SCD patient data in the BASCARE system were excluded from the study. Among the remaining 355 cases, the crude infection rate was 9% and the mortality rate was 5% for SCD patients who had COVID-19 infection. Of the 2076 healthcare professionals, 486 were infected (crude infection rate 23%). However, of the healthcare professionals who had COVID-19 infection, 365 were excluded from the study due to age and comorbid conditions. No mortality developed in this group. In the same period according to MoH data, COVID-19 infection rate in the general

population in Turkey was 0.3%. The mortality rate was also reported as 1%. (www.worldmetersinfo/coronavirus/).

The SCD cases and healthcare professionals included in the study were found to be similar in terms of age, gender, smoking status, diabetes, hypertension, and chronic obstructive pulmonary findings, except for extra-sickle cell comorbid conditions. Majority of the patients with SCD had homozygous Hgb SS disease (59%). The others (41%) were compound heterozygous cases [15(38%) Hgb S β + thalassemia, 1(3%) Hgb SE]. In terms of organ damage, SCD patients were found to have a history of neurological attack (38%), pulmonary hypertension (10%), and a history of acute chest syndrome (13%). Most of the patients were using hydroxyurea, ACE inhibitor, and acetyl salicylic acid (64, 33, and 46%, respectively) (Table 1).

Given the symptoms associated with COVID-19, loss of sense of smell and taste occurred more frequently in SCD patients than in the healthcare professionals group (31 vs 5%; *P* < 0.00001). A similar situation was also valid for fever (54 vs 20%; *P* = 0.0004) (Table 2).

Although there was no significant difference between the groups in terms of the occurrence of severe pneumonia, SCD patients were more likely to develop mild/ moderate pneumonia (43 vs 5%; *P* = 0.002). This was also evident on radiological examinations (49 vs 15% for positive HRCT; *P* = 0.00001) (Table 3).

When the laboratory findings were evaluated, it was observed that the inflammation markers ferritin and D-dimer values were higher in SCD patients compared to healthcare workers (*P* < 0.00001) (Table 4). In steady state, D-dimer and ferritin levels were found to be higher than normal limits. With the COVID-19 infection, these values increased even more, but the difference was found to be statistically significant (Table 5).

The vast majority of the patients in both patient groups received antiviral therapy (76 or 88%, respectively). While prophylactic low molecular weight heparin (LMWH) was prescribed in 41% of the SCD group, for the healthcare staff, LMWH was required in only 9% of cases (*P* < 0.0001). Salicylate use was also found to be higher in the SCD group compared to the healthcare workers (*P* < 0.0001). The use of corticosteroids and tocilizumab in severe cases was similar for both groups (*P* > 0.05). Convalescent plasma was administered to a healthcare professionals whose clinical condition was critical (Table 6).

Considering the course of COVID-19 infection, SCD cases required more hospitalization than healthcare personnels (26 vs 7%; *P* = 0.002). Patients with Hgb S β + thalassemia needed less hospitalization than those with homozygous Hgb SS disease (7 or 30%; *P* = 0.33). Hgb SE genotype negatively affected the course of the disease with multiple hospital admissions and pneumonia requiring long-term oxygen support. Compared with

Table 1 Baseline characteristics of the two patient cohorts

	SCD Patients <i>N</i> = 39	Healthcare professionals <i>N</i> = 121	<i>P</i> -value
Age, y, mean (range)	35 (18–64)	35 (21–53)	0.468
Sex, n (%)			
Male	17(43)	50 (42)	0.802
Female	22 (56)	71 (59)	
Smoking > 5 p/year, n (%)	3 (8)	19 (16)	0.175
Diabetes, n (%)	0	3 (2)	N/A
Hypertension, n (%)	0	3 (2)	N/A
COPD, n (%)	2 (2)	5 (4)	0.653
Sickle cell related, n (%)			
Hemoglobin genotype			
SS/Sβ ⁶	23 (59)	N/A	
Sβ ⁺	15 (39)	N/A	
SE	1 (2)	N/A	
Hydroxyurea treatment	25 (64)	N/A	
ACE treatment at admission	13 (33)	N/A	
ASA treatment at admission	18 (46)	N/A	
Transfusion in last 3 months	8 (20)	N/A	
Pulmonary hypertension	4 (10)	N/A	
Neurological attack	15 (38)	N/A	
Acute chest syndrome history	5 (13)	N/A	

SCD, sickle cell disease; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ASA, acetyl salicytic acid

Table 2 COVID-19 associated symptoms

	SCD patient <i>N</i> = 39	Healthcare profession- als <i>N</i> = 121	<i>P</i> -value
Acute chest syndrome, n (%)	0	0	NA
Painful crisis, n (%)	10 (25)	0	NA
Cough, n (%)	21 (54)	43 (35)	0.042
Myalgia, n (%)	20 (51)	77 (66)	0.169
Loss of taste and smell, n (%)	12 (31)	6 (5)	<0.00001
Headache, n (%)	10 (26)	38 (31)	0.494
Fever, n (%)	21 (54)	24 (20)	0.0004
Respiratory distress, n (%)	6 (15)	10 (8)	0.197
Abdominal pain/ diarrhea, n (%)	2 (5)	7 (6)	0.950
Throat ache, n (%)	8 (20)	26 (22)	0.915

Table 3 Clinical and radiological pulmonary findings at presentation

	SCD patient <i>N</i> = 39	Healthcare profession- als <i>N</i> = 121	<i>P</i> -value
Mild to moderate pneumonia, n (%)	17 (43)	15 (12)	<0.002
Severe pneumonia, n (%)	3 (8)	3 (2)	0.136
ARDS, n (%)	0	2 (2)	N/A
Positive chest X-ray, n (%)	8 (20)	10 (8)	0.035
Positive HRCT, n (%)	19 (49)	18 (15)	0.003

ARDS, adult respiratory distress syndrome; HRCT, high resolution computerized tomography

Table 4 Laboratory findings of the two patient cohorts

	SCD patient <i>N</i> =39	Healthcare professionals <i>N</i> =121	<i>P</i> -value
Lym ($\times 10^9/L$), mean \pm SD	3.3 (\pm 1.4)	1.6 (\pm 0.7)	0.024
d-dimer (ng/mL)	2453 (\pm 2642)	398 (\pm 404)	<0.00001
Ferritin (mcg/L)	847 (\pm 908)	98 (\pm 118)	<0.00001
Troponin (ng/L)	2.8 (\pm 2.7)	1.1 (\pm 2.1)	0.015
LDH (IU/L)	481 (\pm 269)	195 (\pm 70)	0.013
Fibrinogen	3.4 (\pm 1.1)	3.28 (\pm 0.5)	0.188

SCD, sickle cell disease

Table 5 Comparison of steady-state d-dimer and ferritin levels with those during COVID-19 infection in SCD patients

	Steady state level <i>N</i> =39	During COVID-19 <i>N</i> =39	<i>P</i> -value
Ferritin (ng/mL)	416 (\pm 405)	847 (\pm 908)	0.006
d-dimer (ng/mL)	1304 (\pm 1106)	2453 (\pm 2642)	0.121

Table 6 Treatment drugs used in two patient cohorts

Groups parameters	SCD patient <i>N</i> =39	Healthcare professionals <i>N</i> =121	<i>P</i> -value
Antiviral treatment, n (%)	30 (76)	106 (88)	0.10
Antibacterial treatment, n (%),	13 (33)	15 (12)	0.003
Prophylactic LMWH, n (%),	16 (41)	11 (9)	<0.0001
Salicylate, n (%),	11 (28)	1 (1)	<0.0001
Corticosteroid, n (%),	4 (10)	6 (5)	0.15
Tocilizumab, n (%),	2 (5)	2 (2)	0.22
Convalescent plasma, n (%)	0	1(0.8)	N/A

LMWH, low molecular weight heparin

Table 7 Patient outcome

Groups parameters	SCD Patient (<i>n</i> =39)	Healthcare profes- sionals (<i>n</i> =121)	<i>P</i> value
Hospitalization, n (%)	10 (26)	9 (7)	0.002
Intubation, n (%)	4 (10)	1 (1)	0.003
Exitus, n (%)	2 (5)	0	N/A

healthcare professionals, SCD patients needed more intubation procedures (10 or 1%; $P=0.003$). While 2 patients died in the SCD patient group (mortality rate 5%), no patients were lost in the healthcare professionals group (Table 7). Even though a SCD patient is alive, he continuously needs respiratory support. Except for this case, no apparent late complications were noted in the groups.

Discussion

Sickle cell patients are known to have structural defects in defense against infections [11, 12, 14]. The susceptibility of the patients to infections appears to be associated with immune system dysfunction and reduced organ reserves [12, 13]. The cause of sinopulmonary and recurrent urinary infections in patients is phagocytic function defect due to asplenia [11]. However, it is not clear whether there is a significant predisposition to viral infections. On the contrary, there is an increase in the cytotoxic function of NK cells and the activation of naive cytotoxic T lymphocytes that secrete interferon- γ (IFN- γ) [20]. On the other hand, tissue and organ damage deteriorate the natural barrier against infectious agents. Vasoocclusive crises, endothelial activation, and inflammatory state that occur throughout the life cause varying degrees of tissue and organ damage among patients [21]. The reason for this difference is not clear.

It is understood that SCD patients, more than anyone else, compiled the protective issues determined by the

World Health Organization (WHO) and used by the public after the COVID-19 pandemic had occurred. The frequency of referral of patients, the monitoring system that is a part of the Baskent Sickle Cell Care Program (BASCARE) and the social media account used among patients support this observation [19]. However, it was detected that the frequency of COVID-19 infections registered in the BASCARE system is higher than that of in the general population. It can be suggested that the reason for the high frequency of COVID-19 infection among patients may be the familial factors other than susceptibility to infection. Almost all of the SCD patients living in the Eastern Mediterranean Region have the life style of Eti-Turks with extended families. Infection of family members of patients may be a factor [2, 3].

For COVID-19 treatment, a similar approach is used in SCD patients with the normal population. As a national policy, it has been adopted to initiate anti-viral treatment (favipiravir) as early as possible in all COVID-19 infections. Sickle cell patients with COVID-19 infection are contacted via telephone within the framework of the BASCARE program and are informed about treatment. Almost all patients use prophylactic LMWH or antiaggregant therapy. Pulmonary embolism was suspected in the patient with SCD who died. However, confirmed thrombosis did not develop in either group. On the days when anti-viral therapy is administered, hydroxyurea is discontinued to prevent hepatic toxicity. Corticosteroid is initiated in cases with hypoxia in accordance with the COVID-19 guideline (<https://covid19.saglik.gov.tr/TR-66299/covid-19-tedavi.html>). Although corticosteroid therapy seems to trigger painful crises in SCD patients, this observation needs to be supported by further studies [22]. It was determined that, many times, the patients used antibiotics more than necessary because of high steady-state inflammation markers.

When compared with healthcare professionals infected with COVID-19 in the same age group, it is seen that patients have more comorbid conditions and develop more pneumonia as expected [23–25]. It was noteworthy that in addition to the comorbid state, one-third of the patients used ACE inhibitors for proteinuria or cardiac reasons. It has been speculated that COVID-19 infection may be severe in patients using ACE inhibitors, but it has not been fully proven [26].

In this study, it was revealed that the mortality rate in patients was higher than in healthcare professionals. In our study, it is seen that treatment non-compliance and the tissue/organ damage are predisposing factors for mortality. The first of the two cases that developed mortality did not accept COVID-19 treatment despite a previous neurological attack, and the other case had chronic liver disease. Causes of mortality were acute coronary event for the first case and respiratory failure in another.

Our study has some limitations. The actual infection rate may be higher in SCD patients due to being unaware of their infection or being unable to admit to the hospital while healthcare professionals are more likely to be identified at a subclinical stage. Therefore, the infection rate may be underestimated and corresponding mortality rate may be overestimated in SCD patients. These limitations could be minimized as follows. The majority of SCD patients were registered in the BASCARE program, and followed up regularly. Within the scope of this program, COVID-19 issues were discussed in cooperation with Adana Thalassemia and Sickle Cell Anemia Patients Protection and Solidarity Association (email: www.atoder.org.tr). The patients who were symptomatic or had contact history were regularly interviewed with the responsible physicians through the telemedicine method. These conversations were recorded.

In conclusion, it can be stated that family members need serious training on the isolation of SCD patients for protection from COVID-19 infection. Transmission of the disease may be easier than other patients. Sickle cell disease-related factors make the diagnosis of the disease difficult. The course of the disease can be more severe. For all these reasons, the importance of establishing a collaboration with the centers becomes evident.

Data availability All data are available upon request.

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