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Stroke and presence of patent foramen ovale in sickle cell disease

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Abstract
Sickle cell disease (SCD) is an inherited monogenic hemoglobinopathy characterized by formation of sickle erythrocytes under conditions of deoxygenation. Sickle erythrocytes can lead to thrombus formation and vaso-occlusive episodes that may result in hemolytic anemia, pain crisis and multiple organ damage. Moreover, SCD is characterized by endothelial damage, increased inflammatory response, platelet activation and aggravation, and activation of both the intrinsic and the extrinsic coagulation pathways. Cerebrovascular events constitute an important clinical complication of SCD. Children with SCD have a 300-fold higher risk of acute stroke and by the age of 45 about 25% of patients have suffered an overt stoke. Management and prevention of stroke in patients with SCD is not well defined. Moreover, the presence of patent foramen ovale (PFO) increases the risk of the occurrence of an embolic cerebrovascular event. The role of PFO closure and antiplatelet or anticoagulation therapy has not been well investigated. Moreover, during COVID-19 pandemic and taking into account the increased rates of thrombotic events and the difficulties in blood transfusion, management of SCD patients is even more challenging and difficult, since data are scarce regarding stroke occurrence and management in this specific population in the COVID-19 era. This review focuses on pathophysiology of stroke in patients with SCD and possible treatment strategies in the presence of PFO.

Keywords Patent foramen ovale · Sickle cell disease · Stroke · Cerebrovascular event · COVID-19 · Antiplatelet therapy · Endothelial dysfunction

Highlights

- Patients with sickle cell disease (SCD) suffer from cerebrovascular events even from the early childhood. This has significant socioeconomic consequences, since it regards mainly young patients.
- Therapeutic management of SCD patients with cerebrovascular events is not well defined, even in most recent ASH guidelines, due to multifactorial pathophysiological mechanisms of stroke occurrence in this population.
- Presence of patent foramen ovale increases the risk of the occurrence of an embolic stroke. However, the role of PFO closure and antiplatelet/anticoagulation therapy has not been well investigated for these patients.
- Moreover, during the COVID-19 pandemic and taking into account the increased rates of thrombotic events and the difficulties in blood transfusion, management of SCD patients with stroke is even more difficult.
- This review focuses on pathophysiology and treatment strategies of stroke in patients with SCD and PFO.

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Introduction

Sickle cell disease (SCD) is an inherited haemoglobinopathy caused by a single amino acid substitution at the sixth residue of the beta (β)-globin subunit (p. Glu6Val), which results in the formation of the characteristic haemoglobin

S (HbS) [1]. In conditions of deoxygenation (when haemoglobin is not bound to oxygen), haemoglobin tetramers, which include two-mutant sickle β-globin subunits (HbS), can polymerize causing the erythrocyte to take a crescent or sickle cell shape [2]. These sickle cells are rigid and unstable, and also play a crucial role in acute and chronic SCD clinical manifestations. The increased adhesion of the sickle cells induces microvascular obstructions in capillaries resulting in blockage of blood flow with ischaemic/reperfusion injury [3]. SCD is a multi-system disorder that causes multiple organ damage [3, 4]. Vaso-occlusion, haemolytic anaemia, and vasculopathy are the hallmark of SCD while organ damage is also associated with hypercoagulability and inflammation [5].

Sickle cell disease is characterized by endothelial damage, increased inflammatory response, platelet activation or aggravation and activation of both the intrinsic and the extrinsic coagulation pathways [3–6]. Cerebrovascular events constitute an important clinical complication of SCD. Children with SCD have a 300-fold higher risk of acute stroke and by the age of 45 about 25% of patients have already suffered an overt stoke. Subclinical cerebrovascular disorder, confirmed by magnetic resonance imaging (MRI) scans, appears in another 10–20% of SCD patients [7, 8].

Prevention, recognition and management of stroke in SCD patients are of incremental interest because of the young patients' age as well as the detrimental effect of stroke to quality of life, morbidity and mortality [9]. For this reason the 2020 American Society of Hematology (ASH) guidelines have suggested several recommendations for prevention and recognition of stroke in SCD patients as well as for treatment and rehabilitation [10]. However, as the guidelines pinpoint and according to a recently published systematic review, currently proposed management options have failed to prove significant benefits in the aforementioned goals when compared to improved standard care [10, 11].

The presence of a patent foramen ovale (PFO) is common in the general population and can be found in up to 25% of asymptomatic adults [12]. Paradoxical embolism through a PFO has been recognized as a cause of cryptogenic stroke in the general population and is present in a about 50% of those patients [13]. Thus in young patients with a cryptogenic stroke, thorough cardiovascular investigation aims to recognize PFO related stroke events and subsequently direct appropriate therapeutic interventions [14, 15]. PFO closure is superior to pharmacologic treatment when several clinical, echocardiographic and central nervous system imaging criteria are fulfilled [16, 17]. However, more data are needed before the implementation of such guidelines in specific populations such as in SCD patients [18].

Till now, it is not well understood how the presence of PFO affects the prognosis of SCD patients and thus investigation for the presence of PFO and modification in the management approach is not yet recommended. The scope of this review is to present the pathophysiology of stroke in patients with SCD and in patients with PFO with the view to recommend possible diagnostic and treatment strategies for SCD patients with presence of PFO.

Cerebrovascular events in SCD patients

Epidemiology

The occurrence of cerebrovascular events in patients with SCD is very high with severe socioeconomic consequences and constitutes the most important cause of neurocognitive deficits, reduced quality of life and increased morbidity among young SCD patients [10]. It is estimated that children with SCD sustain stroke 300—times more frequently than other children, in the form of silent cerebral infarctions, transient ischemic attacks, overt ischemic or hemorrhagic strokes [4, 8].

Clinically silent strokes are detectable accidentally in MRI by the age of 6 years in about 25% of children with SCD and this rate increases at 35% in young adults [19]. Moreover, about 25% of SCD patients by the age 25 will have had suffered at least one overt stroke [20]. Intracranial hemorrhage accounts for 3% and 10% of SCD patients in childhood and adulthood respectively [20].

For this special population, risk factors for ischemic stroke except for traditional risk factors, such as systemic arterial hypertension, renal disease, atrial fibrillation, hyperlipidemia and diabetes mellitus, include anemia, reduced O_2 mean pressure (especially nocturnal hypoxia), reticulocytosis, and elevated lactate dehydrogenase or homocysteine levels [21].

Pathophysiology

Endothelial dysfunction and coagulation abnormalities are the main pathogenic mechanisms for a cerebrovascular event in patients with SCD. Hemolysis of sickle erythrocytes results in intravascular release of hemoglobin and haem, both of which promote oxidative stress, reactive oxygen species (ROS) production and severe reduction of nitric oxide (NO) production [22]. Moreover, intravascular hemolysis releases the enzyme arginase I and the asymmetric dimethylarginine (ADMA), both of which promote the uncoupling of NO synthase from NO production. As a result, there is a decreased NO production and increased ROS production and synthesis of polyamines, which facilitate cell proliferation and vascular remodeling [4, 22]. The subsequent impaired vasodilatory microvascular response to NO could induce the expression of adhesion molecules from endothelial and blood cells and production of endothelin 1. The increased

expression of endothelial adhesion molecules (such as vascular cell adhesion protein 1, intercellular adhesion molecule 1, P-selectin, E-selectin, leukocyte surface antigen CD47 and αVβ3 integrin) result in leukocyte, erythrocyte and platelet adhesion, aggregation and activation and thrombus formation [23, 24]. In addition, activated endothelial cells produce inflammatory mediators, such as interleukin-1b, interleukin-6 and tumor necrosis factor leading to chronic inflammatory response [4, 23].

Endothelial dysfunction leads to vascular stenosis and obstruction, which, given the high cardiac output state in anemic SCD patients, leads to increased blood flow velocity in cerebral arteries as can be measured by transcranial Doppler (TCD) (Table 1) [25]. When total perfusion increases more than intrinsic mechanisms of the central nervous system can compensate, there is impairment of vasodilatory capacity and cerebral artery steal phenomenon is observed in areas supplied by stenosed arteries [26]. This in turn, leads to a reduction of oxygen supply in areas with cerebral stenosis, increasing vessel dysfunction, sickling of red blood cells and blood hyperviscosity, and thus promotes thrombosis of the cerebral arteries [27–29]. Recurrent episodes of thrombosis and subsequent thrombolysis exacerbate even further the endothelial dysfunction leading to accelerated cerebral artery dysfunction [23].

Microparticles derived from sickle cells hemolysis and endothelial dysfunction induce and maintain a hypercoagulable state in SCD patients through activation of both intrinsic and extrinsic coagulation pathway with the activation of tissue factor and factors VII, X, XI, XII [30]. It has been reported that SCD patients have increased plasma levels of prothrombin fragments, thrombin anti-thrombin complexes, D-dimers, fibrinogen and von Willebrand factor, while factors V, IX, XII and proteins C and S are decreased [30–32].

SCD patients have cerebral arteries stenosis and occlusion due to intima media proliferation, involving mostly internal carotid artery [3]. Subsequently, angiogenesis pathways are activated and collateral vessels are created around Circle of Willis to form a non-inflammatory vasculopathy named Moyamoya disease with a typical angiographic pattern [33, 34]. This situation predisposes to recurrent ischemic strokes due to hypoperfusion and hemorrhagic stroke. Atherosclerosis or aneurysm of cerebral arteries is another cause of cerebrovascular events similarly to the general population. Finally, another common cause of stroke is paradoxical embolization. Patients with SCD have predisposition to venous thrombosis due to hypercoagulable state. In addition, during a vaso-occlusive crisis, due to bone marrow necrosis, the formation of fat emboli is common. In the presence of right- to- left shunt, embolization of thrombus or fat can result in ischemic stroke [21, 35].

Diagnosis

Diagnosis of stroke in SCD patients is similar to general population [36]. However, clinical signs and symptoms may be subtle and especially in pediatric population diagnosis can easily be missed. For that reason high clinical suspicion is at most importance.

Symptoms may include focal neurologic deficits, vision or language abnormalities, dizziness, vertigo, seizures, headache or migraines [37, 38]. Importantly, SCD patients often suffer from headache or migraine and it seems to be an association between severe headache and elevated mean cerebral flow velocities in TCD. In addition, severe headache may be the clinical symptom for cerebral sinus venous thrombosis, which may lead to stoke if diagnosis and anticoagulation therapy is delayed.

Computed tomography is the first imaging modality that can diagnose the presence of a hemorrhagic stroke in the acute phase. However, MRI with diffusion-weighted imaging is the preferred modality for assessment of ischemic stroke, even in the early phase [39]. Magnetic resonance angiography or venogram plays a crucial role in differential diagnosis of the cause of stroke (artery stenosis, venous thrombosis, embolic stroke or arterial aneurysm).

Last but not least, complete blood count, basic metabolic and electrolyte profile, blood glucose level, coagulation blood test and thrombophilic profile should be obtained for every patient with SCD presenting with signs and symptoms suggestive of a cerebrovascular event.

Table 1 Transcranial doppler

A. Parameters measured during Transcranial Doppler
Peak velocity (PV)
End-diastolic velocity (EDV)
Mean velocity (MV): MV = [PV + (2xEDV)]/2
Pulsatility index (PI): PI = (PV − EDV)/MV
B. Grade of right to left shunt based on microembolic signals (MES) grading
No shunt: 0 MES
Low grade shunt: 1–10 MES
Moderate grade shunt: 11–25 MES
High grade shunt: ≥ 25 MES (shower effect) or uncountable (curtain effect)

Prevention and management

Little evidence exists regarding the management of cerebrovascular events in patients with SCD for both primary and secondary prevention.

Primary prevention

The only approved strategy for primary prevention of stroke in patients with SCD is chronic blood transfusion and treatment of traditional risk factors, such as smoking cessation, hypertension, dyslipidemia or diabetes mellitus. Stroke Prevention in Sickle Cell Anemia ("STOP") Study, a multicenter randomized clinical trial which enrolled more than 2000 children with SCD, highlighted the role of TCD and the therapeutic value of blood transfusion in primary prevention of stroke for patients with SDC [40]. The role of TCD in identifying high risk patients for a cerebrovascular event has been established in recent ASH 2020 guidelines for SCD [10]. Annual TCD screening is recommended for children with HbSS or HbSβ^0 thalassemia (ages 2–16 years) and is suggested for children who have compound heterozygous SCD other than HbSC and have evidence of hemolysis in the same range as those with HbSS [10].

Recent ASH guidelines recommend regular blood transfusion for at least a year with the goal of keeping maximum HbS levels < 30% and maintaining hemoglobin levels > 9.0 g/dL to reduce the risk of stroke for children with HbSS or HbSβ^0 thalassemia (ages 2–16 years) who have abnormal TCD velocities and live in a high-income setting (where regular blood transfusion therapy, typically every 3–4 weeks, is feasible to maintain the maximum HbS level < 30% and maintain the hemoglobin level > 9.0 g/dL) [10]. This is recommended also for children who have compound heterozygous SCD other than HbSC, who have evidence of hemolysis in the same range as those with HbSS, an abnormal TCD velocity, and live in a high-income setting [10].

The role of hydroxyurea in primary prevention of cerebrovascular stroke event has been investigated in the TCD With Transfusions Changing to Hydroxyurea (TWiTCH) Trial [41]. It is suggested that hydroxyurea treatment at the maximum tolerated dose can be considered to substitute for regular blood transfusions for children with SCD (ages 2–16 years), abnormal TCD results and without MRA-defined vasculopathy or silent cerebral infarct, who have been receiving transfusion therapy for at least 1 year, and are interested in stopping transfusion [10].

It is not known whether screening these patients for the presence of PFO with high risk features would be beneficial for primary embolic stroke prevention. Due to increased bleeding risk, the role of antiplatelet and anticoagulation therapy for primary prevention has not been investigated [6].

Secondary prevention

Exchange blood transfusion and hydroxyurea have been proven to be effective for secondary prevention of ischemic stroke in SCD patients [10, 41]. For children with HbSS or HbSβ^0 thalassemia and a history of prior ischemic stroke, ASH guidelines recommend blood transfusion for secondary stroke prevention aiming at increasing the hemoglobin > 9 g/dL at all times and maintaining the HbS level at < 30% of total hemoglobin until the time of the next transfusion [10].

Despite the presence of endothelial dysfunction, platelet activation and aggregation, increased inflammation and hypercoagulable state, concerning the role of antiplatelet and anticoagulation therapy in patients with SCD regarding primary and secondary prevention of stroke, scarce studies have been published supporting that there is increased risk for bleeding complications [6]. Until nowadays, aspirin is recommended for secondary prevention of stroke and the administration of heparin or warfarin is limited only for patients with paradoxical emboli and proven deep venous thrombosis, both based on recommendations for the general population [42]. However, ongoing trials are investigating the role of antiplatelets (eptifibatide and prasugrel) and anticoagulants (dalteparin and warfarin) as well as statins or new molecular anti-inflammatory or anti-oxidant agents in secondary prevention of stroke [6]. Crizanlizumab is a first-in-class, recombinant, humanized monoclonal antibody that blocks interactions between P-selectin and may play a crucial role in the prevention of sickle cell stroke [43].

Patent foramen ovale and stroke in the general population

Epidemiological data and pathophysiology

Patent foramen ovale is a communication between the right and the left atrium at the intra-atrial septum due to uncomplete fusion of the primum and secundum septum after birth. It is estimated that 25% of the general population has PFO, almost diagnosing accidentally with subtle clinical impact [44]. Nevertheless, the presence of PFO has been associated with paradoxical emboli. Subsequently, patients with a history of embolic stroke of unknown source should be evaluated by a cardiologist with transthoracic (TTE) or transoesophageal echocardiography (TEE) for possible embolic sources, such as the presence of right- to- left shunt through a PFO, aortic atheromatosis, cardiac masses (thrombus, myxoma or fibroelastosis) or atrial fibrillation.

The presence of PFO per se does not definitely set the diagnosis for paradoxical embolic stroke in a patient having suffered an ischaemic stroke. The patient history, clinical information and the cardiovascular and brain imaging data

should be taken into account during consultation of a cardiologist, neurologist and radiologist. Certain clinical features, anatomical characteristics of the atrial septum and imaging features of brain MRI constitute the high risk patient for embolic stroke (Table 2). [44, 45].

Diagnosis and management

The combination of contrast TTE and contrast TCD could be the initial diagnostic approach for the evaluation mainly of young patients with ischemic stroke (Fig. 1) [46, 47]. Contrast TEE with intravenous administration of agitated saline and with simultaneous performance of Valsalva, with or without abdominal compression or cough maneuvers remains the most accurate method for diagnosing the presence of PFO [45, 47]. In addition, the anatomical characteristics and the size of foramen ovalis can be accurately defined by 2D and 3D TEE, as well as the aforementioned coexisting high risk anatomical characteristics that increase the likelihood of paradoxical emboli. The etiological relationship of embolic stroke with the presence of PFO should be carefully evaluated (Table 2) [44, 45].

Percutaneus PFO closure is the treatment of choice, but surgical closure is preferred when the anatomy of PFO is inappropriate for percutaneus closure. According to current recommendations for the general population, PFO closure is recommended for patients aged < 60 years old, with recent ischemic stroke and presence of PFO with high risk criteria, as mentioned in Table 2, that is felt to be the most likely cause for stroke after etiological evaluation by a stroke expert (Fig. 2) [45, 48]. For patients not fulfilling the above-mentioned criteria, clinical features suggesting paradoxical emboli, should be taken into consideration in addition to high risk characteristics of the patient, the PFO anatomy and the stroke imaging characteristics (Table 2) [45, 46].

Patent foramen ovale in SCD patients with stroke

Patients with SCD and stroke have been reported to have higher prevalence of PFO than the general population with stroke, although there are no prospective clinical trials that have studied the prevalence of PFO in individuals with SCD independently of stroke occurrence [49, 50]. Moreover, SCD patients with PFO and right- to- left shunt may have increased risk for paradoxical embolism, since the pain they feel during a pain crisis may lead to increased endothroracic pressures, like when performing Valsalva maneuvers [44, 45]. In addition to the hypercoagulable state and the high prevalence of arterial pulmonary hypertension in these patients, it seems that they are at high risk for stroke occurrence and recurrence [35, 50]. Finally, they are young patients and stroke prevention must be a priority due to

Table 2 High risk features suggesting paradoxical embolism as the cause of stroke

Clinical features
Young age
Presence of deep venous thrombosis
Hypercoagulable states (carcinomatosis, antiphospholipid syndrome, sickle cell disease, homocysteinaemia, thrombophilia etc.)
Immobilization
Recent major surgery
Extended car or airplane journey
Valsalva manoeuvres at the time of stroke, such as heavy lifting or straining at stool (conditions characterized by increased intrathoracic pressure)
Obstructive sleep apnoea with stroke on waking
Pulmonary arterial hypertension (permanent high right atrial and ventricular pressure)
PFO related features
Size ≥ 2 mm (maximum separation of the septum primum from the septum secundum)
Significant shunt: detection of > 10 microbubbles into the left atrium in the first 3–5 cardiac cycles following right atrial opacification or "curtain effect"
Presence of significant shunt at rest
Presence of an atrial septal aneurysm (defined as an excursion > 10 mm of the dilated segment of the septum beyond the level surface of the atrial septum)
Tunneled PFO
Coexisting right atrial septal pouch
Presence of prominent Eustachian valve/Chiari network
Presence of prominent Eustachian ridge
Presence of an hybrid defect
Imaging related features
Non-lacunar ischemic lesions with cortical involvement on brain imaging suggesting embolic infracts

PFO: patent foramen ovale

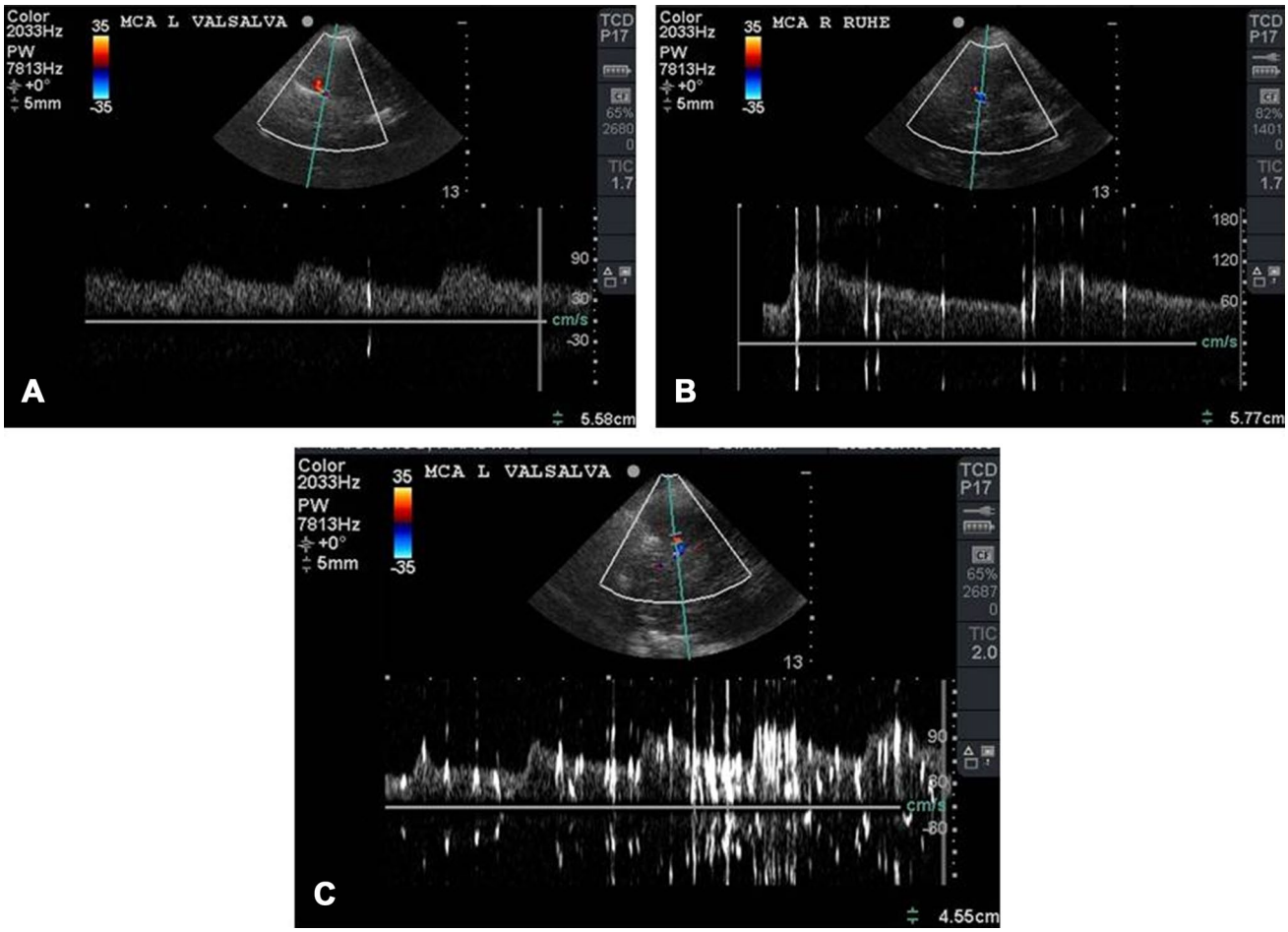

Fig. 1 Grade of right to left shunt based on microembolic signals (MES) grading. Transcranial Doppler of patients with **a** low grade shunt: 1–10 MES, **b** moderate grade shunt: 11–25 MES and **c** high grade shunt: ≥ 25 MES or "shower" effect

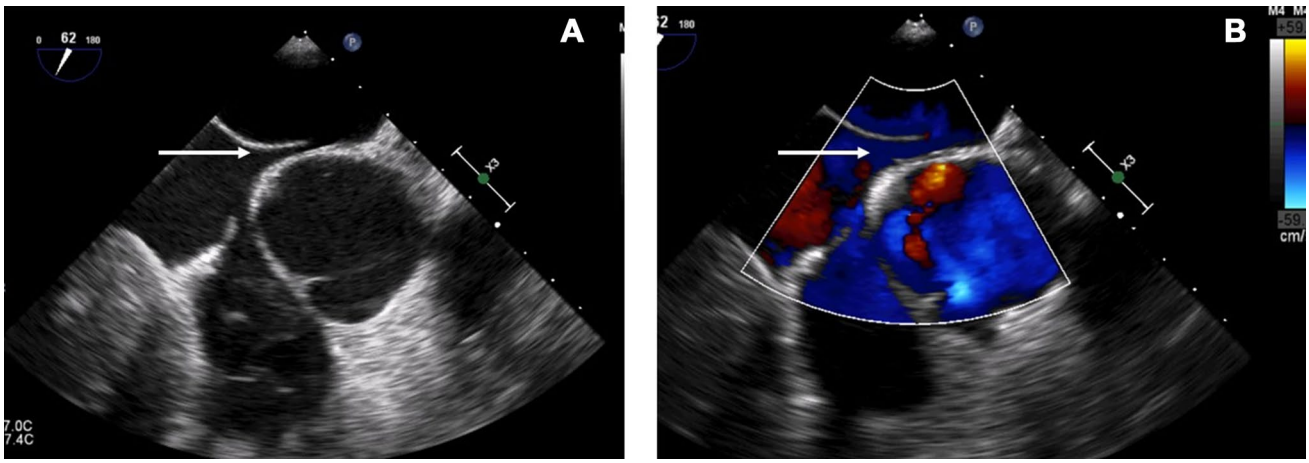

Fig. 2 **a** 2-D echocardiography reveals the presence of a tunneled patent foramen ovalis with high risk features (white arrows). **b** Color Doppler reveals significant shunt at rest

severe physical (immobility, neurocognitive dysfunction), psychological and socioecomnomical consequences. Subsequently, the decision of PFO closure for these patients should be made taking into account all these parameters.

Future perspectives

The role of transcatheter closure of a PFO in patients with SCD has not been well investigated. However it may be effective in a portion of SCD patients having suffered an embolic stroke. The Risk of Paradoxical Embolism Score (RoPE score) has not been validated for SCD patients and its value has not been clearly defined in clinical practice. Recent European position for the management of patients with PFO suggests that in the presence of hypercoagulable state, deep vein thrombosis or pulmonary embolism, PFO closure may be considered when there is the need for only temporary anticoagulation therapy or when there is high risk for recurrence of stroke despite on anticoagulation therapy [45]. As mentioned before, patients with SCD are characterized by hypercoagulable state and are at increased risk for thrombosis. On the other hand the lifelong anticoagulation therapy increases the cerebral bleeding risk. Subsequently, PFO closure for patients with SCD having suffered an embolic stroke might be beneficial for secondary prevention and reduce the bleeding complications of anticoagulation therapy. Until recently, no study exists regarding the role of PFO closure in preventing a cerebrovascular event in patients with SCD, only case reports have highlighted the gap in literature for these patients [4].

In the lack of recommendations, management of SCD patients having suffered an ischemic cerebrovascular event should be individualized. Cerebral MRI and magnetic angiography are very helpful with high diagnostic accuracy in differential diagnosis of an embolic stoke from an ischemic stroke due to underlying vasculopathy, like Moyamoya disease (Fig. 3). In the presence of a cerebral cardioembolic event, c-TEE should be performed (with Valsalva, abdominal compression or cough maneuver) in order to define the precise anatomy of fossa ovalis as well as the presence of right to left shunt. Transcranial Doppler should also be taken into account in order to proceed to the diagnostic and therapeutic approach (Fig. 1 and Table 1). Consultation of a neurologist, a hematologist, a radiologist and a cardiologist is very important in decision making for PFO closure and further treatment strategy for these patients.

It's uncertain whether the PFO closure should offer more or less confidence and safety in this patient population. However, taking into account the pathophysiology of cerebrovascular events in SCD, the increased endothoracic pressures during crisis, the increased bleeding risk while on anticoagulation therapy and the young age of these patients, it seems that PFO closure might be beneficial and interventional approach should be preferred over conservative management.[51] Moreover, scarce evidence exists regarding optimal antiplatelet therapy after PFO closure for SCD patient and suggestion should be based on recommendations for the general population. In general, dual antiplatelet therapy with aspirin and clopidogrel is recommended for 3 to 6 months after successful PFO closure followed by single antiplatelet, preferred with clopidogrel 75 mg/day, indefinitely. [51] Strong data should be reported on that issue.

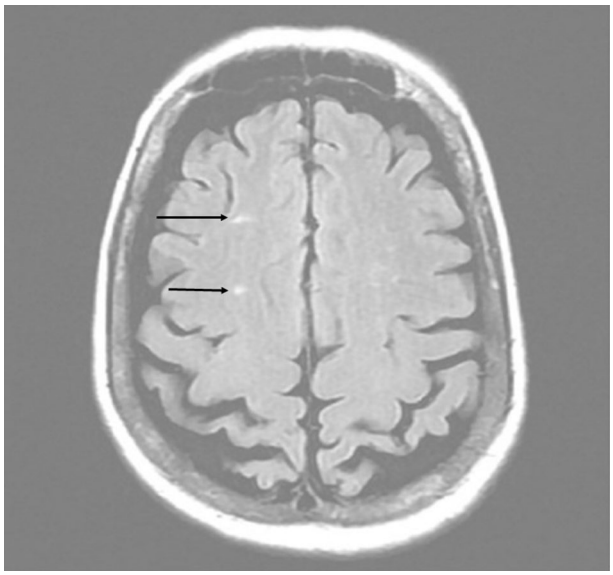

Fig. 3 Two high-intensity foci of ischemic origin located at the upper section of the right parietal lobe (black arrows) indicative of embolic stroke

In the COVID-19 era, strong evidence exists regarding the increased rates and higher mortality of thrombotic events and strokes [52]. Moreover, the lack of blood offer consists an important problem for patients at need for regular transfusion therapies, such as SCD patients. Data are scarce regarding stroke occurrence and management for SCD patients during the pandemic. However, this highlights the need for more evidence regarding anticoagulation and antiplatelet therapy beyond or in addition to blood transfusion and hydroxyurea for these patients.

Conclusions

Patients with SCD are at increased risk of stroke. The presence of a PFO increases the risk of stroke occurrence and recurrence in these patients. Decision for PFO closure in these patients should be made after multidisciplinary consultation of a cardiologist, a neurologist, a hematologist and a radiologist and taking into account the high risk features of the PFO, the stroke characteristics in brain imaging and

the patients' ischemic and bleeding risk. More prospective clinical trials are needed for stroke prevention and treatment strategies in SCD patients.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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