Chapter

Detection and Management of Cerebral Vasculopathy

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Abstract

Cerebral vasculopathy in children with sickle cell anemia is responsible for strokes and silent cerebral infarcts and is the most debilitating complication providing motor sequelae and cognitive deficiency. However, the most important advance in pediatric management is the detection of children at a risk of stroke using transcranial Doppler with chronic transfusion applied in children detected at risk, which reduces the stroke risk from 11% to less than 2%. In this chapter, we will describe the place of Doppler, magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) with neck assessment and the place of different treatments, i.e., chronic transfusion, hydroxyurea, new drugs, and stem cell transplantation.

Keywords: sickle cell disease, sickle cell anemia, stroke, silent cerebral infarcts, transcranial Doppler, color Doppler ultrasound, cerebral magnetic resonance imaging (MRI), cerebral magnetic resonance angiography (MRA), neck MRA, hydroxycarbamide, chronic transfusion, hematopoietic stem cell transplantation

1. Introduction

Sickle cell disease is a group of inherited hemoglobinopathies. The most severe types are hemoglobin SS and hemoglobin Sβ0 thalassemia, which are referred to as sickle cell anemia (SCA). It is a systemic disease characterized by a chronic hemolytic anemia, vaso-occlusive events, and susceptibility to bacterial infections with a great variability of the clinical presentation. The cerebral complications are particularly severe as they are a common cause of disability, often at a young age. Imaging plays a central role in the screening, diagnosis, and treatment optimization of patients with SCA.

2. Physiopathology

Deoxygenated hemoglobin S forms polymers with other hemoglobin molecules producing rigid filaments that deform the red blood cell into a sickle shape. The properties of the red blood cells are modified, making them fragile with a shortened life span, explaining the chronic hemolytic anemia, but also making them rigid, poorly deformable, and adherent to vascular endothelium. This causes intravascular sludging in terminal arterioles and capillaries and damage to the wall of large and medium

arteries due to a cascade of endothelium activation, overexpression of adhesion molecules (endothelin 1 and BCAM), nitric oxide depletion, hypercoagulability, splitting of the internal elastic lamina, intimal hyperplasia, and smooth muscle proliferation that reduce the lumen diameter [1, 2]. The genesis of arterial lesions also involves arterial remodeling in response to high blood flow and velocities, disturbed wall shear stress associated with severe chronic anemia, and abnormalities of oxygen transport.

3. Cerebral manifestations

3.1 Overt ischemic stroke

3.1.1 Clinical symptoms and outcome

Ischemic stroke is a major cause of cognitive impairment, disability, and death. Strokes are suggested by hemiparesis, aphasia, dysphasia, or seizures and are frequently associated with vaso-occlusive crises and fever, although not always. Early on, survival is observed in 98% of children, with 62.5% of them exhibiting total motor recovery [3]. However, there are high risks of cognitive impairment and recurrence, which can reach 67% in the absence of transfusion, especially if there is an underlying arteriopathy [4]. SCA confers a higher risk of stroke in children than any other pediatric disease. Without prevention strategies, 11% of patients with SCA will suffer an overt stroke by the age of 20 years and 24% by the age of 45 years [3]. The risk of a first stroke is highest in the first decade of life, with a peak between the ages of 2 and 5 years.

3.1.2 Imaging

Acute infarction usually involves the parenchyma supplied by the carotid circulation, either in the territory of the middle cerebral artery (MCA) and/or anterior cerebral artery (ACA) or in the superficial and deep border zones between the anterior and MCA territories. It is related either to an arterial occlusion or to an acute drop of blood supply to the brain distal to an arterial stenosis.

Magnetic resonance imaging (MRI) is the preferred imaging modality because it shows the cytotoxic edema characteristic of ischemic stroke within the first hour of symptomatology, in contrast to brain computed tomography (CT), which is often normal during the first 24 hours. Within approximately 7 days of the onset of ischemia, the infarct will show high signal on diffusion weighted imaging (DWI) and low values on the apparent diffusion coefficient (ADC) map. The absence of high signal on fluid-attenuated inversion recovery (FLAIR) images indicates an infarct onset of less than 4–6 hours.

Time-of-flight magnetic resonance angiography (TOF MRA) of the Willis circle and of the cervical arteries shows an intra- and/or extracranial steno-occlusive arteriopathy in about three quarters of cases, most often of the anterior cerebral circulation.

3.1.3 Risk factors for ischemic stroke

The risk factors reported for overt ischemic strokes are a low baseline hemoglobin level, the rate of acute chest syndrome (ACS), a recent episode of ACS, and elevated

systolic blood pressure [3]. Strokes can be promoted by hyperviscosity induced by transfusion of large volumes or by serere anemia during exchange in patients with stenosis. Cerebral desaturation is common in SCA patients, is correlated with the severity of anemia, and is a risk factor for stroke. Cerebral tissue hemoglobin saturation is positively correlated with hemoglobin, whereas cerebral blood flow (CBF) is negatively correlated with hemoglobin. Thus, in patients with severe anemia, there is a compensatory cerebral hyperperfusion in response to SCA-associated reduction in O_2-binding capacity. Cerebrovascular reserve capacities are already close to the maximum in SCA; thus, any decrease in CBF as observed during infection, fever, or ACS carries a risk of imbalance between brain oxygen demand and supply.

3.1.4 Prevention of recurrence

After a stroke, chronic transfusion to maintain the HbS level lower than 30% and hemoglobin between 9 and 11 g/dL has allowed reduction of the risk of recurrence from 67% to 10–20% [5, 6]. However, if chronic transfusion is stopped, the risk of recurrence is still about 50% [7]. Hydroxyurea has been used in patients with stroke history, but 19% recurrence was observed within 4 months [8]. Thereafter, a randomized trial comparing stroke recurrence on chronic transfusion + oral chelation to hydroxyurea + phlebotomies was prematurely stopped because of a significant higher incidence of recurrence in the hydroxyurea arm (7/67 versus 0/66 on chronic transfusion) [9]. Thus, chronic transfusion with oral chelation remains the reference treatment for secondary stroke prevention. In a review of a worldwide experience including 73 patients with a stroke history who have received a matched sibling donor stem cell transplantation (MSD-SCT), the occurrence of four hemorrhagic strokes (5.5%) has been reported, but no ischemic stroke recurrence [10, 11]. Thus, MSD-SCT offers the best prevention for secondary stroke. Different procedures of direct or indirect cerebral revascularization surgery in addition to regular blood transfusion have been proposed for patients with SCD, moyamoya syndrome, and a history of stroke or transient ischemic attack (TIA). However, the risk/benefit ratio of surgery in addition to other therapies, such as HSCT, is unclear, and prospective studies are needed.

3.2 Other acute neurovascular complications: Aneurysms, intracranial bleeding, fat embolism, posterior reversible encephalopathy syndrome (PRES), and reversible cerebral vasoconstriction syndrome (RCVS)

Aneurysm rupture is rarely responsible of intracranial hemorrhage in SCD pediatric patients, unlike in adults. However, saccular aneurysms are found on routine imaging in approximately 4% of children [12]. Compared to the general population, SCD patients are more likely to have multiple aneurysms. The internal carotid artery (ICA) is the most commonly involved artery followed by the posterior cerebral artery (PCA). Sustained endothelial injury causing vessel wall weakening is the presumed reason for the increased prevalence of aneurysms in patients with SCD.

Subarachnoid and intracerebral hemorrhage also occurs as a result of rupture of fragile moyamoya vessels or of venous sinus thrombosis, often in association with vaso-occlusive crisis, transfusion, or acute respiratory illness.

Fat embolism syndrome due to extensive bone marrow necrosis is a rare and devastating complication in sickle cell disease. Paradoxically, it affects exclusively patients with mild forms of SCD, predominantly HbSC and HbSβ^+. A significant number of cases occur in the context of human parvovirus B19 infection. The

diagnosis is made by cerebral MRI showing innumerable bilateral punctate foci of restricted diffusion on diffusion-weighted imaging in a starfield pattern throughout the brain and associated petechial hemorrhage on susceptibility-weighted imaging. Early recognition and intervention with red cell exchange transfusion can be life-saving [13].

Posterior reversible encephalopathy syndrome (PRES) has been reported in the context of hypertension and cyclosporine use for nephrotic syndrome, as well as after ACS.

Reversible cerebral vasoconstriction syndrome (RCVS) has been reported in children with SCD. Arterial constriction affects not only large but also distal arteries of both anterior and posterior circulations and is rapidly reversible. RCVS can be complicated by cerebral infarction, bleeding, or PRES.

4. Transcranial and neck Doppler ultrasound (Doppler-US), an essential tool in the management of sickle cell anemia

4.1 Rationale

Transcranial and neck Doppler ultrasound (Doppler-US) is a noninvasive technique, which measures flow velocities in the large cerebral arteries and can determine the risk of stroke in children with SCA [14]. A risk of stroke of 10% per year was found in SCA children with a mean velocity in the terminal ICA or MCA ≥200 cm/s versus 2% if velocities were normal [15]. In the Stroke Prevention in Sickle Cell Anemia (STOP) trial [16], the risk of stroke among children with high transcranial Doppler (TCD) velocities was reduced by 90% by maintaining HbS concentrations at <30% through chronic transfusion therapy. Doppler-US is also used to diagnose and monitor cerebral arteriopathy in an acute or steady state. Several cohort studies have shown the remarkable effectiveness of chronic transfusion, including the French study that found a reduction in the risk of stroke at age 18 to 1.9%, compared with the historical risk of 11% [17].

4.2 Anatomy review of the cerebral arteries

The internal carotid artery is a terminal branch of the common carotid artery. It arises around the level of the fourth cervical vertebra. Terminologia Anatomica in 1998 subdivided the artery into four segments: "cervical," "petrous," "cavernous," and "supraclinoid" (**Figure 1**).

The cervical segment runs vertically upward in the carotid sheath anteriorly and medially to the internal jugular vein in front of the transverse processes of the upper three cervical vertebrae and then enters the carotid canal of the temporal bone in the base of the skull. It does not give any branch.

The petrous segment runs from carotid canal to foramen lacerum within the petrous temporal bone. It first has a vertical course and then a horizontal course along the middle ear.

The cavernous segment passes from the petrous apex to the dural ring of the anterior clinoid process surrounded by cavernous sinus where its course describes a hairpin bend, called the siphon.

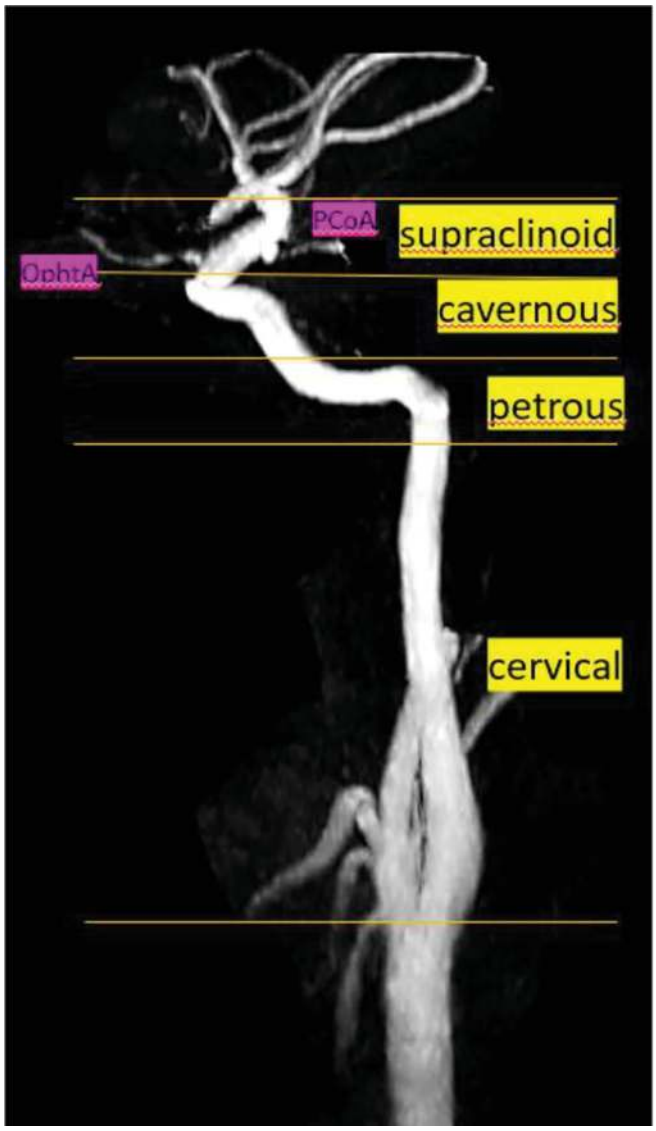

Figure 1.
The four segments of the internal carotid artery. Lateral view.

Then, *the supraclinoid segment*, also called cerebral segment, runs above the clinoid process through the dura into the subarachnoid space. Several important branches arise from the supraclinoid carotid, such as ophthalmic, posterior communicating, and anterior choroidal arteries. It gives two terminal branches: the MCA and ACA.

The circle of Willis is an anastomotic arterial ring located at the base of the brain that communicates blood flow between the two hemispheres and between the anterior and posterior arterial circulations. It is formed by the initial segment of the ACAs, the anterior communicating artery, the two posterior communicating arteries, the two ICAs, and the initial segment of the two posterior cerebral arteries (**Figure 2**). These shunts are involved in the case of occlusion or severe stenosis of a segment. Variations are possible in the A1, P1, and posterior communicating segments, but they are rare in pediatric age.

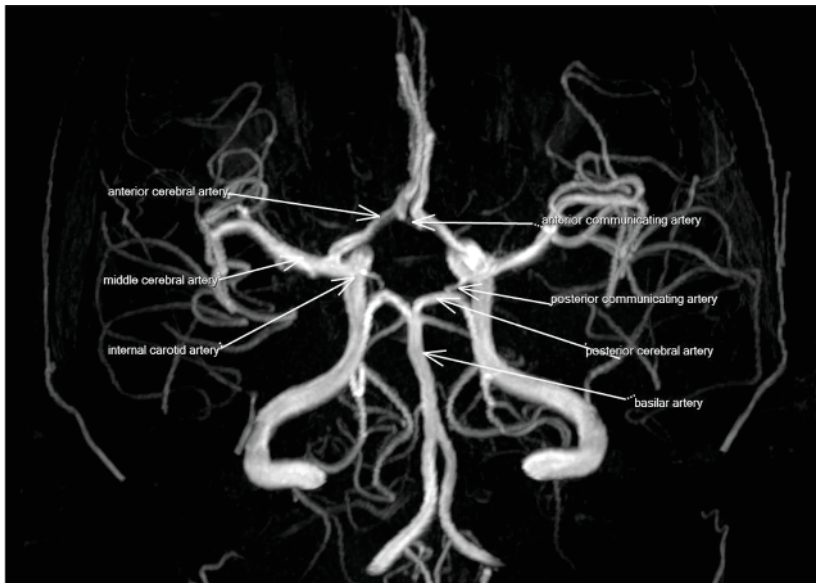

Figure 2.
3D TOF MRA. Axial view of the circle of Willis.

The most important branch of the ICA in diameter and length is the *MCA*, which supplies most of the lateral aspect of the hemisphere and provides 60–80% of the hemisphere's blood flow. After its origin, the MCA runs laterally and horizontally toward the Sylvian fissure. Its terminal branches anastomose with the terminal branches of the anterior and posterior cerebral arteries at the surface of the brain.

The *ACA* is the other terminal branch of the ICA. It has a horizontal course anteriorly and medially in its precommunicating A1 segment. At the entrance to the interhemispheric fissure, it anastomoses with the contralateral ACA via the anterior communicating artery, which participates in the circle of Willis. Downstream of the communicating artery, the ACA curves upward and runs parallel to the contralateral artery in the hemispheric fissure.

The *basilar artery* has a vertical ascending course on the anterior surface of the pons in the basilar sulcus. At the level of the peduncles, it gives the two posterior cerebral arteries.

4.3 Transcranial and neck Doppler ultrasound methodology

4.3.1 Equipment and acoustic window

Historically, validation data used a nonimaging dedicated TCD technique by probing the temporal acoustic windows to determine flow velocities in the terminal ICA and proximal MCA. Arteries are identified by the depth of the sample volume, the direction of blood flow relative to the probe, and the position and angulation of the probe relative to the patient' head. In contrast, the TCD imaging technique combines pulsed-wave Doppler ultrasound with a color-coded cross-sectional view of the intonation area to visualize the arteries. Today, all centers in France and more than half in the United States and Great Britain use a color Doppler ultrasound device, which is routinely used in imaging and vascular medicine units.

Familiarity with the technique and ease of use, combined with a quicker achievement of competencies, favor this technique, and this is the one we describe here. The probe is either a sector or phased array cardiac or dedicated probe with a small imaging footprint and a Doppler frequency of 1.8 or 2 MHz to adequately penetrate through the skull. Transcranial and cervical Doppler ultrasound allows a real-time assessment of cerebral arterial hemodynamic. The objective is to assess the circulatory velocities of the large intracranial arteries and the cervical segment of the ICAs to detect abnormal velocities. The probe is positioned on specific sites, called acoustic windows, which are two temporal windows on the right and left temporal bones, the suboccipital and two submandibular windows under the mandible. The scan bilaterally records the MCA, ACA, PCA and the supraclinoid and cavernous segments of the ICA and to finish the complete course of the cervical extracranial segment of the ICA (eICA). The basilar artery is assessed by the suboccipital approach, placing the probe at the tip of the neck, just below the hairline, and angling it superiorly. It looks like a Y encoded in blue as the blood flow is going away from the transducer.

4.3.2 Settings

The settings must be adapted to the age and pathology of the patients, who have chronic anemia. The field of exploration will be of 8–10 cm, the velocity scale of the color Doppler from −100 to +100 cm/s, as well as that of the pulsed Doppler, which has to be increased in case of spectral aliasing. The pulsed Doppler gate should be wide enough (4–5 mm) to capture all the velocities within the vessel lumen, the fastest flows having a lower intensity. The size of the spectrum display and the gain should be adapted to allow an optimal tracing of the velocity spectrum.

4.3.3 Procedure of the examination

The examination is performed with the patient in the supine position and the examiner siting bedside on the patient's right, as for an abdominal scan, with the forearm resting on the patient's shoulder or chest to assure good stability and a little restraint of the child (**Figure 3**).

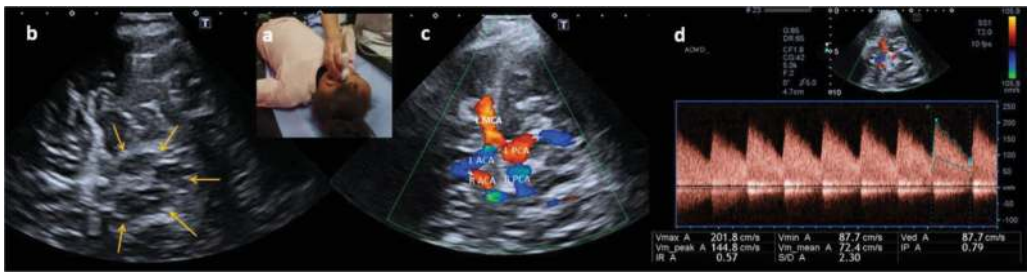

Figure 3.
Temporal window. (a) Positioning of the probe on the patient's temple. (b) Identification of the hypoechoic butterfly-shaped mesencephalic brainstem in a gray-scale axial view of the brain base. (c) In the color mode, the circle of Willis projects forward. (d) Spectral display of MCA velocities. Normal time average mean of maximal velocity (TAMV) 144 cm/s.

4.3.3.1 Temporal window

The probe is placed in front of the upper part of the tragus of the ear and above the zygoma, and an axial gray-scale view of the base of the brain is obtained depicting the hypoechoic, butterfly-shaped mesencephalic brainstem, surrounded by hyperechoic subarachnoid cisterns, which is the reference landmark. In the color mode, the circle of Willis projects anteriorly. The MCA, which is the main artery receiving 75–80% of the ICA flow, courses laterally toward the probe from the ICA bifurcation and is encoded in red. After switching to the spectral Doppler mode, the Doppler sample gate is placed on the ICA bifurcation and moved toward the periphery along the MCA. Since the objective of the examination is to detect focal acceleration of blood flow, it is important to carefully explore the entire course of the artery by sweeping the sample gate along the MCA and the ICA during spectral recording and by optimizing the recording at each depth by tilting and sliding the transducer slightly in order to get the highest velocity. Expert operators rely on the sound signal: the higher the pitch, the higher the velocity. Blood flow spectrum is above baseline. Two to three velocity recordings are captured from ICA bifurcation toward the periphery, and the highest velocity is collected. By moving the Doppler gate deeper, the proximal segment of the ACA is then examined, which is coded blue as the blood flow moves toward the midline away from the probe. After angling the probe inferiorly, the ICA is visualized as two round structures, because it is seen in transverse section as ICA has a vertical course. The red structure is the supraclinoid segment, and the blue structure, which is slightly inferior and anterior, is the cavernous hairpin segment. To obtain a good view, the transducer often needs to be slid posteriorly. Next, the PCA is scanned and coded red in the proximal segment and blue as it travels around the cerebral peduncle. After completing the study on one side, it is repeated on the other side after asking the child to turn his head to the other side.

4.3.3.2 Suboccipital window

Terminal segments of the vertebral arteries and basilar artery can be visualized via the suboccipital window with the patient in the lateral decubitus. The probe is placed in the middle position at the top of the neck right below the hairline and angled superiorly. The Y-shaped, blue-encoded confluence of the vertebral and basilar arteries is depicted in an oblique frontal view.

4.3.3.3 Submandibular window

The probe is placed under the angle of the mandible, directed upward, parallel to the midline. The extracranial cervical segment of the ICA (eICA) is visualized in a frontal view, encoded in blue, medial to the internal jugular vein encoded in red. The course of the artery is studied, which can be straight or sinuous, and possible blood flow acceleration zones are detected by the presence of aliasing. The spectral display of velocities is acquired along the entire course of the artery, from origin to entry into the carotid canal, by moving the Doppler gate along the artery in search of focal acceleration of blood flow (**Figure 4**). It is important not to compress the artery with the probe, in order not to induce false positive.

4.3.3.4 Tips and tricks

No angle correction should be made because arteries are short and sinuous. Moreover, stroke risk has been stratified using dedicated TCD without angle

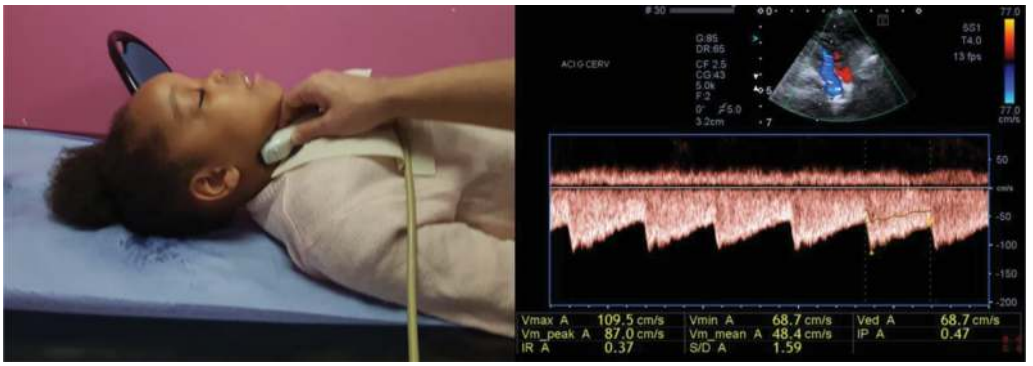

Figure 4.
Submandibular window. (a) Position of the probe. (b) Color mapping of the ICA and internal jugular vein and spectral display of velocities.

correction. Introducing an inappropriate angle correction would result in overestimation of flow velocities, potentially leading to overtreatment. It should be noted that an incorrect 60° angle correction will double the value of the measured velocity value and result in a very high risk of false diagnosis. The tracing is assumed to be obtained at an optimal angle of 0°.

4.3.3.5 Indication of the exam

Doppler-US screening is recommended for children with SCA from the second year of life. Children should then be rescanned annually if normal, quarterly if conditional, and chronic transfusion should be initiated in case of abnormal velocity. Doppler-US cannot be replaced by MRA, as it is a more sensitive technique and detects arterial disease at an earlier stage than MRA. However, children with abnormal velocity and stenosis on MRA are at higher risk for stroke than those with an abnormal Doppler alone. MRA is recommended in children with abnormal Doppler-US as well as in children with inadequate exam when there is no patent acoustic window.

The utility of using Doppler-US to monitor children with established stroke and cerebral vasculopathy is unclear. A multidisciplinary approach to decision is required.

4.3.4 Factors influencing velocities

4.3.4.1 Aging

Velocities increase during the first years of life, reaching a maximum value between the fourth and the sixth year of life, and decrease thereafter to about 70% of the maximal velocities by the age of 18 years.

Figure 5 shows the mean velocity [95% confidence interval (CI)] at annual check-up during aging in SCA children of the Créteil newborn cohort in right and left MCAs, ACAs, ICAs, and eICAs.

Velocities in the vertebrobasilar circulation are lower than in the carotid circulation.

4.3.4.2 Hematocrit

There is an inverse linear relationship between hematocrit and velocity. Velocities increase in anemia due to increased cardiac output, decreased blood viscosity, and

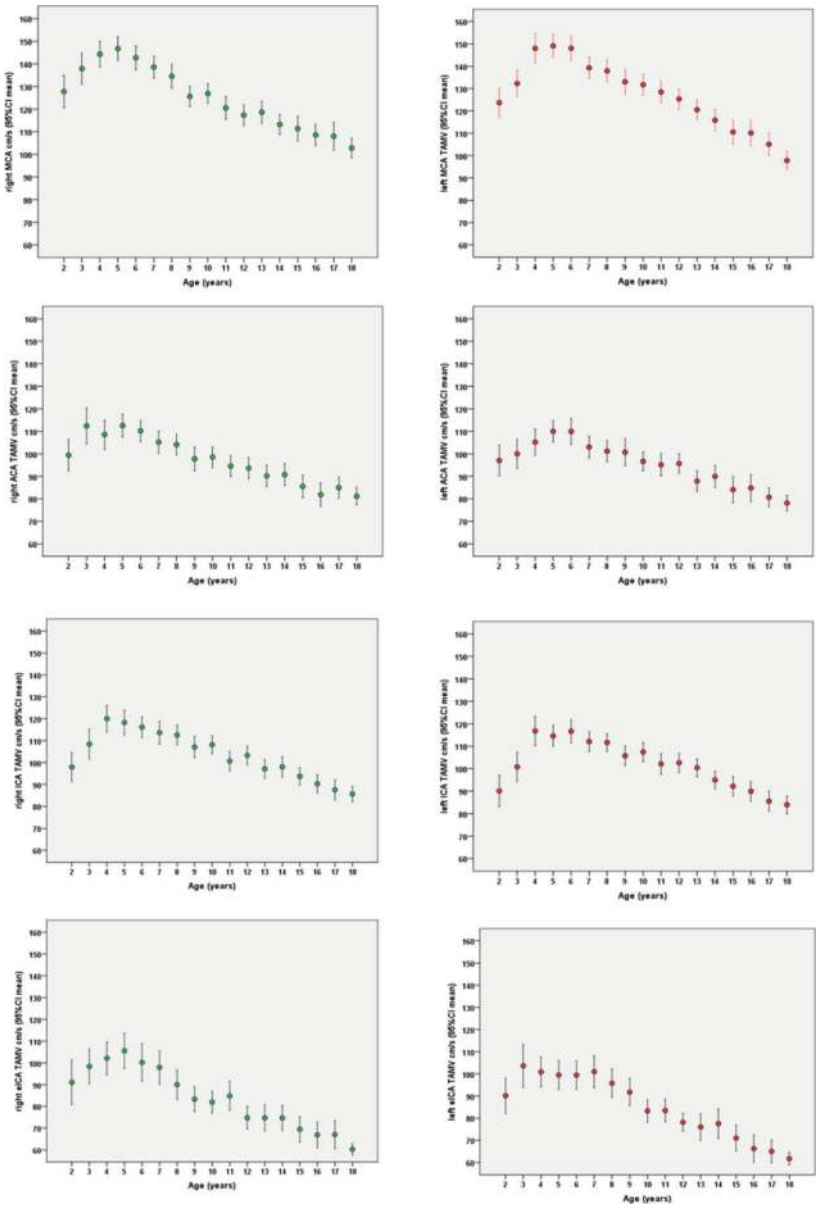

Figure 5.
Outcome of cerebral velocities during aging in SCA children.

decreased intracranial resistance, allowing a sustained normal oxygenation of the brain. This explains why children with SCA have high velocities, even in the absence of a stenosis. Consequently, thresholds for normal/abnormal velocities are different in SCA children, compared to non-SCA children.

4.3.4.3 Carbon dioxide (CO2)

Carbon dioxide (CO2) is a powerful modulator of CBF and intracranial velocities, as is the partial pressure of oxygen (PaO2). Hypercapnia induces vasodilatation, a dramatic increase in velocities, and a decrease in pulsatility index (PI) and resistance index (RI). In turn, hyperventilation, via a reduction of PaCO2 and hypocapnic alkalosis, induces

the constriction of distal intracranial arterioles, a significant decrease in intracranial velocities, and an increase in PI and RI. These mechanisms called cerebral vasoreactivity are mediated via changes in extracellular pH. Sleep may increase velocities slightly due to hypercapnia. Crying may decrease velocities due to hypocapnia. Fever increases blood flow by about 10%. As a consequence, examination should be performed in a healthy condition, and children must remain awake during the exam. Sedation of young children is not recommended. The usual preparation and diversion techniques in pediatrics will be used (watching video, soft words from the attendant, etc.).

4.4 Detection of abnormally high cerebral velocities

4.4.1 Time average mean of maximal velocity (TAMV)

Three key parameters can be obtained from the Doppler spectrum display: flow direction, velocities, and indices for arterial resistances. Flow direction can be assessed by the color code. By convention, blood flow toward the transducer is encoded in red and is above baseline, and blood flow away from the transducer is encoded in blue and is under the baseline. The velocity parameter that is used in children with SCA is the time average mean of maximum velocity (TAMV), also called mean velocity, which can be measured by the manual or automated outlining of the envelope of the spectral display over one or a few cardiac cycles. Pay attention that TAMV is different from maximum systolic velocity. Doppler-US looks for abnormal blood flow acceleration signaling hemodynamic stenosis of the artery indicative of an increased risk of arteriopathy and stroke. Remember that as long as blood flow is maintained downstream of the stenosis, a reduction in luminal caliber is coupled with an acceleration of flow.

TAMV is used to classify the scan. Intracranial velocity thresholds for risk stratification are adapted from the STOP study [15]. If velocities in at least one intracranial artery are equal to or higher than 200 cm/s, the scan is abnormal indicating a 40% stroke risk within 36 months; between 170 and 199 cm/s, it is conditional with a 7% stroke risk; and it is normal if velocity in any artery is lower than 170 cm/s with a stroke risk of only 2%. For the cervical ICA, the abnormally high velocity threshold is 160 cm/s [18].

The absence of the visibility of MCA in a patient with a patent temporal window and a TAMV below 50 cm/s in the MCA are also abnormal findings and are associated with an increased risk of stroke. Note that low velocity is significant only in an MCA, whereas low velocity in the proximal segment of the ACA probably corresponds to the constitutional hypoplasia of the artery with low blood flow. Low MCA velocities are due to measurements within poststenotic main artery or within collaterals moya-like in the presence of an MCA occlusion or to re-entry flow in the MCA from a communicating artery in the presence of an occlusion of the homolateral ICA or in the presence of a large infarcted area with little metabolic demand and marked reduction of flow, all these suggesting the possibility of severe vasculopathy and the need for an MRI/MRA. Usually, MCA spectral display is demodulated with a resistance index IR < 0.45 and a pulsatility index IP < 0.60.

4.4.2 Incidence of abnormal cerebral arterial velocities

4.4.2.1 Abnormally high intracranial velocity (intracranial TAMV ≥200 cm/s)

In STOP-I, the classification at initial TCD examinations was: 67% normal, 17.6% conditional, 9.3% abnormal, and 6% inadequate. The follow-up of the Créteil SCD

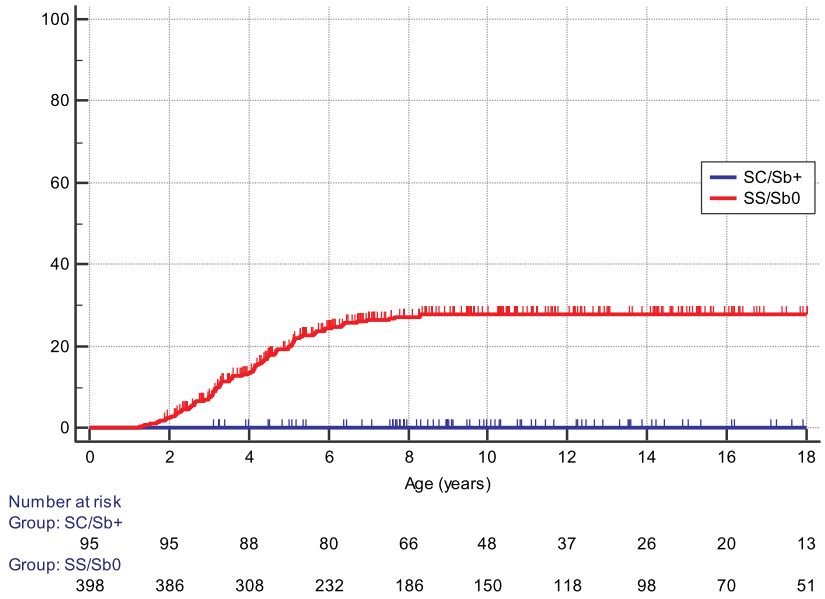

Figure 6.
Cumulative incidence of intracranial TAMV ≥200 cm/s in the Créteil newborn SCD cohort: 27.6% (95%CI: 22.8–32.4%) in SCA versus 0% in SC/Sb + children by 10 years of age (p < 0.001).

newborn cohort, assessed since 1992 by TCD as soon as 18 months of age, showed that abnormally high velocity occurred at median (range) age of 3.6 years (1.3–8.3 years) in SCA patients and was not observed in SC/Sb + patients, whereas the cumulative incidence of abnormally high velocity in the SS/Sb0 patients reached a plateau of about 30% by 9 years of age (**Figure 6**) [19].

4.4.2.2 Conditional velocity (intracranial TAMV 170–199 cm/s)

In the Créteil cohort, the rate of conversion from conditional to abnormal TCD was 34.5%. The median age of conditional TCD was 2.5 years (range, 1.2–5.5) and the median delay 1.1 years (range, 0.03–7). Age below 4 years old was a significant risk factor for conversion (odds ratio (OR) = 6.7; 95%CI: 1.7–27; p = 0.007) [17]. In the STOP study, the conversion risk was 97% in very young children with two consecutive conditional TCD examinations, and 13% in teenagers seen for the first time at the age of 14 years. This demonstrated the need for repeat screening of children with SCA throughout their childhood and argued for the closer monitoring of those with conditional TCD.

4.4.2.3 Abnormally high extracranial velocity (eICA TAMV ≥160 cm/s)

A cross-sectional study performed in two centers in France (Debré and Créteil) reported that eICA TAMV ≥160 cm/s was present in 9.2% of SCA patients without concomitant abnormal intracranial velocities and were strongly associated with eICA MRA-defined stenosis. Thus, this threshold was used to define abnormally high eICA velocities [18]. This study also showed that low hemoglobin level and tortuosities were associated risk factors.

The follow-up of the newborn Créteil cohort showed that abnormal high eICA TAMVs were detected at median (range) of 5.0 (1.3–10.0) years. The cumulative incidence of eICA TAMV ≥160 cm/s in SCA children was 17.4% by 10 years of age. The probability of developing high TAMV eICA ≥160 cm/s began in the second year of life, at the same age as intracranial velocities, and reached a plateau at age 10 years. Most often, eICA TAMV ≥160 cm/s was isolated (without intracranial TAMV ≥200 cm/s) and the probability of isolated eICA TAMV ≥160 cm/s was 13.8% by age 10 (**Figures 7** and **8**) [19].

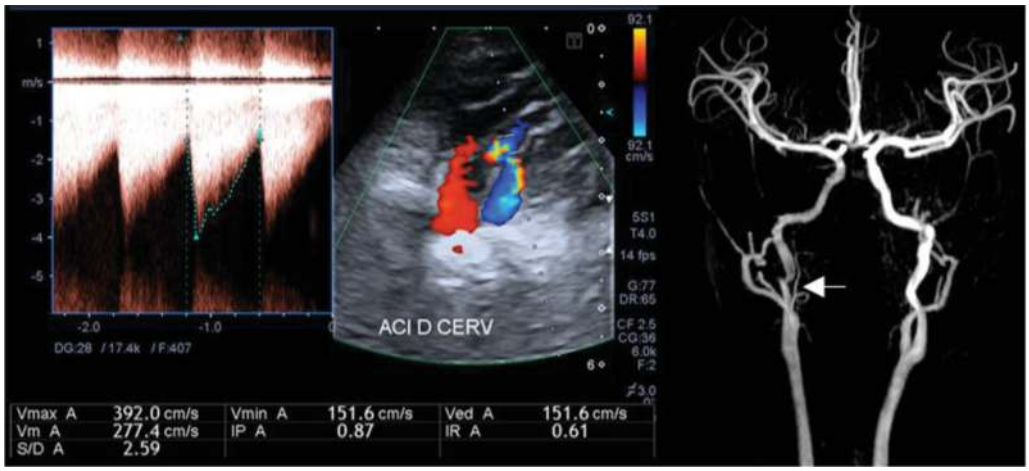

Figure 7.
Six-year-old boy without history of stroke. Routine Doppler ultrasound detected focal acceleration in the middle part of the right cervical ICA with TAMV 277 cm/s. 3D TOF MRA shows focal marked narrowing of the artery associated with a kink. Notice the hypointensity of the right ICA due to poor flow.

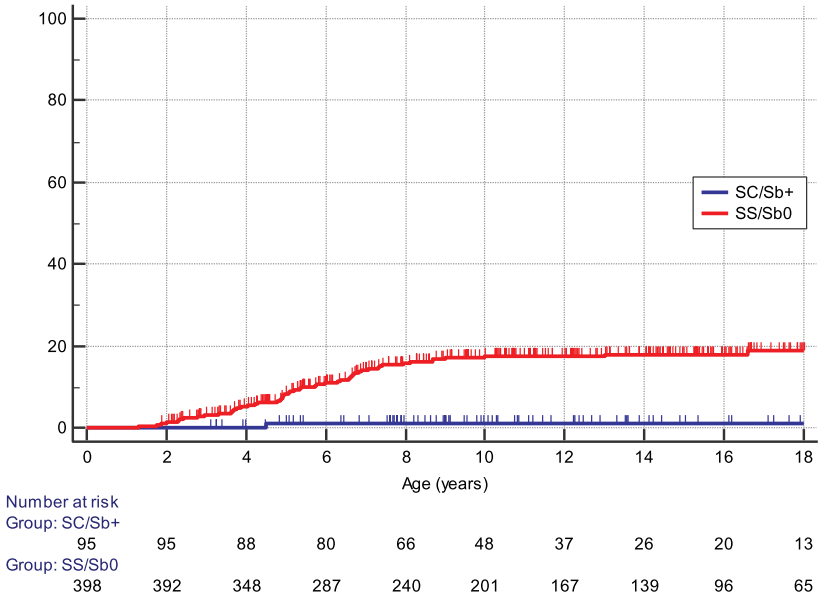

Figure 8.
Cumulative incidence of eICA TAMV ≥160 cm/s in the Créteil newborn SCD cohort: 17.4% (95%CI: 13.2–21.6%) in SCA versus 1.1% (95%CI: 0–3.4%), in SC/Sb + children ($p < 0.001$) by 10 years of age.

4.4.3 Predictors for abnormal velocities

Among genetic markers, G6PD deficiency and the absence of alpha-thalassemia have been described to be predictive risk factors for abnormal intracranial velocities [20]. Among biological parameters recorded during the second year of life away from vaso-occlusive crisis or transfusion and always before any intensive therapy, severe anemia, hyperleukocytosis, and hyperreticulocytosis were predictive risk factors for intracranial velocities.

For eICA velocities, the presence of tortuosities and severe anemia were risk factors for abnormal high eICA velocities [18].

4.5 Prevention of abnormally high cerebral velocities

4.5.1 Intracranial velocities

Hydroxyurea treatment in SCA children by inducing an increase of HbF% reduces the polymerization of HbS and hemolysis and decreases white blood cell (WBC) and reticulocyte counts [21]. The safety of its use in young children has been proven [22] (Baby-Hug) in high- and low-income countries such as in Africa [23, 24]. All these effects allow the reduction of cerebral velocities [25, 26], and several studies have shown the reduction of the incidence of abnormally high intracranial velocities, of conversion from conditional to abnormal velocities, and of strokes [27–33]. Similarly, in the Créteil newborn cohort, among the 53 children for whom HU was introduced before year 3, only 2/53 (3.8%) developed abnormal intracranial velocities, while the incidence after later HU initiation was 99/345 (28.7%), $p < 0.001$. Thus, we confirm that hydroxyurea significantly reduces the risk to develop abnormal intracranial velocities and could be systematically and early given as recommended by US guidelines [34].

4.5.2 Extracranial velocities

As we have shown that high eICA velocities were associated with severe anemia and presence of tortuosities themselves favored by anemia, drugs such hydroxyurea or voxelotor [35] could be good candidates to decrease eICA velocities.

4.6 Management of abnormally high cerebral velocities

4.6.1 Chronic transfusion

The STOP-1 trial randomizing chronic transfusion versus simple observation for 3 years in children with TAMV ≥200 cm/s in MCA or ICA demonstrated that stroke risk was highly significantly reduced by 92% with chronic transfusion ($p < 0.001$) [16]. Thereafter, the randomized STOP-2 trial posed the question of the required duration of chronic transfusion and compared pursuing to stopping chronic transfusion in patients who had been on chronic transfusion for at least 30 months, had normalized velocities on chronic transfusion, and had no severe stenosis. A high rate of stroke and abnormal TCD recurrence was observed after the discontinuation of chronic transfusion [36]. TCD screening and chronic transfusion applied in children detected at risk by TCD was the most significant progress in the managing of children with SCA reducing the risk of stroke by age 18 years from 11% [3] to less than 2% in the Créteil newborn cohort [17]. However, considering the risks related to long-term chronic

transfusion, such as those of alloimmunization and iron overload and the benefits obtained with hydroxyurea by reducing hemolysis, hyperleukocytosis, and anemia severity, it seemed interesting to switch from chronic transfusion to HU patients who had normalized velocities on chronic transfusion and had no stenosis [37].

4.6.2 Switch to hydroxyurea

In the United States and Canada, a randomized, noninferiority trial comparing continued chronic transfusion versus hydroxyurea after at least 12 months of chronic transfusion has been conducted between 2011 and 2013 in patients with no severe vasculopathy [38]. Noninferiority was met, but the follow-up was short, with only 50% enrolled having reached the 2-year follow-up, the mean 4.5 years' duration of chronic transfusion prior to enrolment was long, and the mean age at enrolment was 9.7; therefore, most of patients might have not have been at risk at the time of enrolment [10].

In Créteil, France, all the SCA children with TAMV ≥200 cm/s patients were placed on long-term chronic transfusion, but those with normalized velocities on chronic transfusion and no stenosis were switched to hydroxyurea since 1998, with a quarterly control of TCD and immediate reinitiation of chronic transfusion in case of reversion to abnormal velocities [10]. No stroke was observed, but reversions occurred in about one-third of the patients, requiring chronic transfusion reinitiation [10]. Thus, longer follow-up periods are required to ensure that such early switch to hydroxyurea is safe.

4.6.3 Stem cell transplantation

The French multicenter prospective DREPAGREFFE trial compared outcomes after matched sibling donor stem cell hematopoietic transplantation (MSD-HSCT) versus chronic transfusion for at least 1 year in children with SCA and a history of abnormal cerebral velocities. This trial showed that transplantation compared to standard care was associated at 1 and 3 years with a significant reduction in cerebral velocities of 40 cm/s [39]. This large difference favoring the transplantation group confirms previous findings in a retrospective cohort study. The result is likely due in part to the correction of anemia, as well as to the exclusive presence of normal red cells after transplantation in contrast to the simultaneous presence of normal and sickle red cells in the circulation after transfusion.

4.6.4 Recommendations for the follow-up of cerebral velocities and management of abnormally high velocities

Recommendations in patients with SCA with abnormally high cerebral velocities have been recently updated in UK [40], United States [41], and Brazil [42]. We present here the protocol proposed in France for the follow-up and management in patients with abnormally high intracranial or cervical arterial velocities.

It is recommended to assess SCA children with intracranial and cervical Doppler ultrasound as soon as the second year of life, annually if intracranial TAMV <170 cm/s and eICA <140 cm/s, quarterly if conditional TCD (intracranial TAMV 170–199 cm</s or eICA 140–160 cm/s.

For children younger than 6 years with high conditional TCD (185–199 cm/s), we recommend to control TCD within a month.

For all children with intracranial or cervical TAMV ≥ 200 cm/s, it is important to analyze on the same day the blood parameters.

If Hb is <6 g/dL or < 20% baseline Hb level, as observed, for example, with acute splenic sequestration or parvoB19-related erythroblastopenia, we recommend to transfuse once time and to check TCD at 1 and 3 months post-transfusion.

If Hb is in the range of baseline Hb, we recommended to initiate monthly chronic transfusion with the goal to maintain Hb between 9 and 11 g/dL and HbS% lower than 30%. Exchange transfusions are more efficient to decrease HbS level and to avoid hyperviscosity and iron overload; however, they are more difficult to initiate in very young children (<1–4 years) and simple transfusions (10–15 mL/kg according to Hb level) are most often sufficient to maintain HbS lower than 30% after two transfusions. Cerebral MRI/MRA with neck MRA is performed after two or three transfusions. Images are better after the correction of severe anemia in order to discriminate anemia-related turbulences from true stenosis. Moreover, sedation required in very young children will be safer in transfused children.

Thereafter, the duration of chronic transfusion will depend on the presence or absence of stenosis on MRA and neck MRA, on the evolution of velocities, and on the age of the child.

For patients with MRA-depicted stenosis, we recommend to maintain chronic transfusion until stenosis disappearance or stem cell transplantation. At date, we do not know if there is a benefit to associate HU to chronic transfusion in these patients.

For patients without MRA-depicted stenosis, we recommend to initiate hydroxyurea treatment if not already given and to maintain chronic transfusion at least until the maximal tolerated dose of hydroxyurea is reached. US recommendations are to transfuse for at least 1 year. However, the suitable duration of chronic transfusion has not been clearly defined. We consider that the duration of chronic transfusion should be adapted to the age of the child and to velocities.

- For children with normalized TAMV (< 170 cm/s), chronic transfusion is stopped. For children younger than 6 years, it is safe to control TCD every 3 months until age 6. For those older than 6 years, annual TCD control is recommended.

- For children with conditional TAMV (170–199 cm/s), we recommend to maintain chronic transfusion until age 6. Thereafter, on hydroxyurea, high conditional TCD should be controlled every 3 months.

- Any reversion to abnormal TAMV (≥200 cm/s) requires to reinitiate chronic transfusion.

For all children with SCA, we recommend to perform cerebral MRI/MRA with neck MRA every 2 years for children older than 5 years or earlier in those already on chronic transfusion for abnormally high velocities.

Familial human leukocyte antigen (HLA) typing should be recommended in children with a history of abnormally high velocities. For children with an HLA-identical sibling donor, HSCT is recommended in all children having cerebral arterial stenosis and/or ischemic cerebral lesions or persistent abnormally high velocities or cognitive deficiency.

For eICA TAMV 160–199 cm/s, we recommend to perform MRI/MRA with neck MRA and to initiate chronic transfusion in presence of eICA-stenosis. In absence of eICA-stenosis, we recommend to initiate hydroxyurea if not already given.

5. Cerebral arterial stenoses

5.1 MRA-defined large vessel arteriopathy

TOF MRA has a good sensitivity and specificity for detecting steno-occlusive lesions in cerebral arteries (**Figure 9**) [43].

SCA arteriopathy is a progressive stenotic arteriopathy of the large cerebral arteries affecting the proximal MCAs, proximal ACAs, and ICAs in their intracranial but also cervical portions. They may be associated with the development of bypassing collateral vessels in the basal ganglia, known as moyamoya, from the Japanese expression describing the angiogram appearing like a "puff of smoke." Posterior pial collateral vessel circulation is not rare (**Figure 10**).

We showed in the Créteil newborn cohort that cervical ICA arteriopathy develops as soon as the second year of life, reaching a plateau at about 10 years of age, similarly to intracranial arteriopathy [19]. Extra and intracranial arteriopathies are most often not linked, and eICA assessment identifies 13.5% additional patients at a risk of stroke (eICA-TAMMV ≥200 cm/s or eICA stenosis) who have no intracranial arteriopathy. Cervical stenoses are frequently associated with severe tortuosities

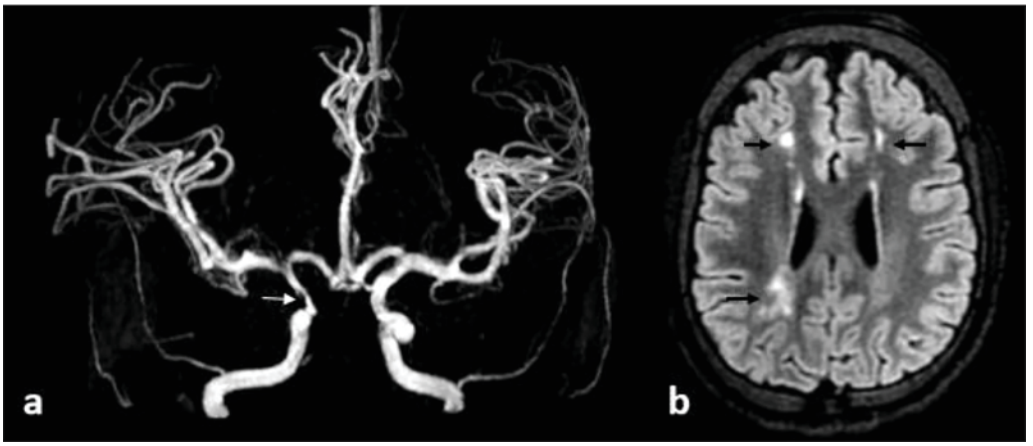

Figure 9.
3D TOF MRA. (a) Frontal view of the anterior circulation after segmentation. Marked narrowing of the supraclinoid segment of the right ICA, proximal right ACM, and right ACA. (b) Axial FLAIR image showing bilateral hyperintensities in the deep borderzones.

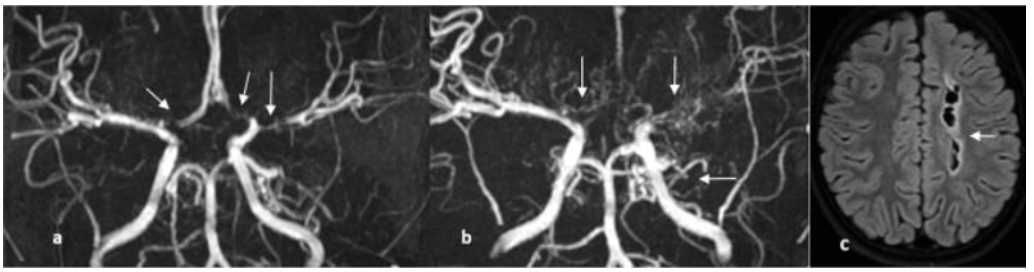

Figure 10.
SCA patient who suffered a stroke at the age of 3 years. A 3-year severe narrowing of proximal right and left ACAs and left MCA. (b) At seven years of age, occlusion of left MCA and both ACAs and extensive bilateral lenticulostriate perforator collaterals and left cerebellar collaterals (arrows) suggestive of a Moya network. (c) At seven years of age, FLAIR axial view. Sequelae of the left internal borderzone infarct.

called kinkings that are more prevalent than in the general population and evolve over time as a function of the degree of anemia and eICA-TAMVs [44]. This favors a remodeling mechanism as a consequence of high blood flow associated with severe chronic anemia. Extracranial ICA arteriopathy can affect the entire course of the ICAs with a more severe evolution of proximal web-like lesions (**Figure 11**) [44].

5.2 Incidence of stenoses during aging

In the Créteil cohort, cerebral MRI/MRA has been systematically performed since 1992, every 2 years since age 5 or earlier in children placed on chronic transfusion for abnormally high cerebral velocities and was available in 375 SCD children. Neck MRA was added in 2011 [19].

5.2.1 Incidence of intracranial stenosis

No SC/Sb + child developed intracranial stenosis during infancy, while intracranial stenosis was detected in 37/332 (11.1%) MRA-assessed SCA children, in which 31 had a history of intracranial abnormal velocities. Among the six children without abnormal intracranial velocities, five had history of conditional velocities and one had no available temporal window.

The presence of intracranial stenosis was highly significantly associated with a history of abnormal high intracranial velocities: OR = 13.7 (95%CI: 5.8–32.3), $p < 0.001$ (**Figure 12**).

5.2.2 Incidence of eICA stenosis

No SC/Sb + child developed eICA stenosis, while it was detected in 32/306 (10.5%) SCA children assessed with neck MRA whose 27 had a history of eICA ≥160 cm/s and 30 had eICA kinking. The presence of eICA stenosis was highly significantly and independently associated with a history of eICA TAMV ≥160 cm/s: OR = 15.2 (95%CI: 3.2–71.4), $p < 0.001$ and with the presence of eICA kinking: OR = 15.2 (95%CI: 3.2–71.4), $p = 0.001$. eICA kinking was also significantly associated with the number of SEN-beta-haplotypes: OR = 1.5 (95%CI: 1.04–2.08), $p = 0.028$ (**Figure 13**).

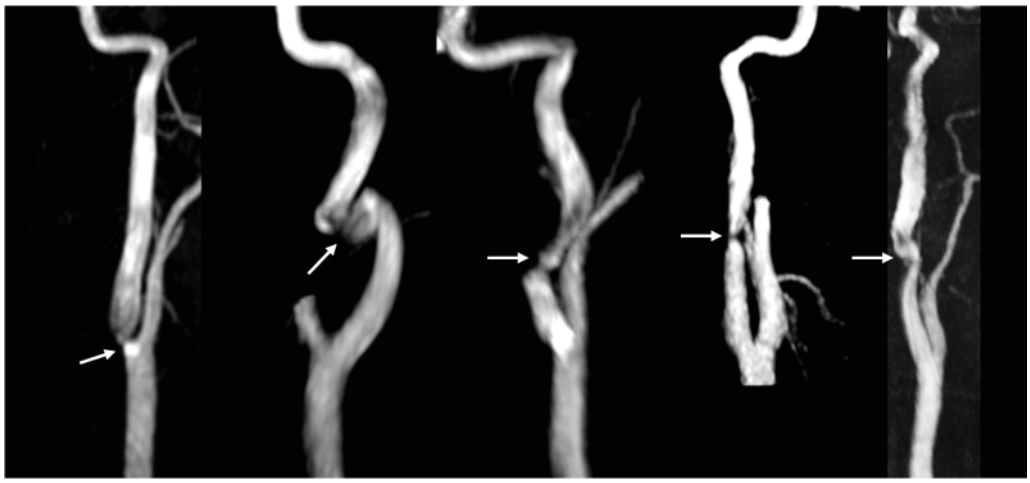

Figure 11.
3D TOF MRA of the cervical ICA after segmentation. Cervical ICA stenosis in five different patients.

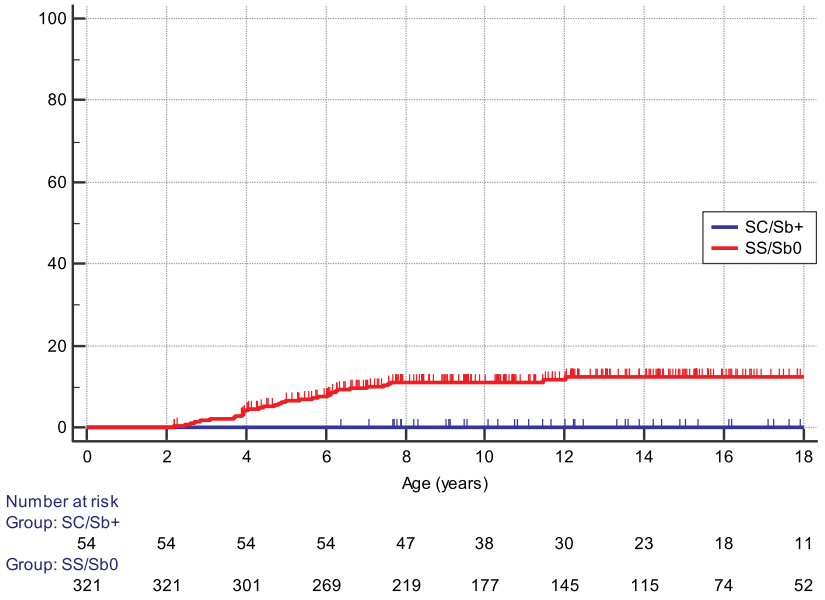

Figure 12.
Cumulative incidence of intracranial stenosis in Créteil SCD cohort: at 10 years of age: 11.1% (95%CI: 7.5–14.7%) in SCA versus 0% in SC/Sb + children (p = 0.001).

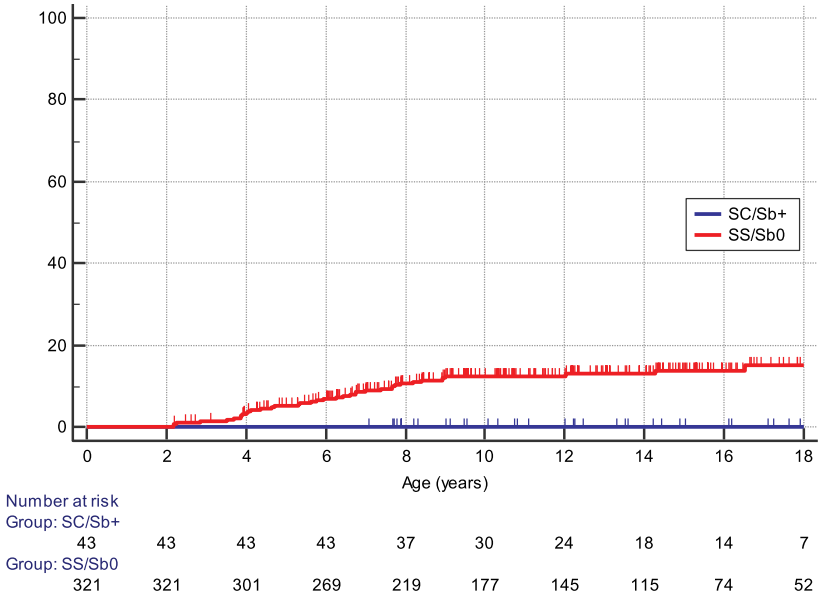

Figure 13.
Cumulative incidence of eICA stenosis in the Créteil SCD cohort: at 10 years of age: 12.3% (95%CI: 8.3–16.3%) in SCA versus 0% in SC/Sb + children (p = 0.015).

5.3 Management of cerebral arterial stenoses

In France, the recommendation for intracranial stenoses is to initiate and maintain chronic transfusion unless there is a possibility of transplantation. In the DREPAGREFFE trial, comparing chronic transfusion to transplantation, among the 67 patients with a history of cerebral TAMV ≥200 cm/s, 60 were stroke-free and 28 of them had stenosis at enrollment: 14 of them were transplanted, while the other 14

children were maintained on chronic transfusion. The outcome of stenosis score was significantly better in the transplanted group than in the transfused group [45].

By contrast, there is no recommendation concerning eICA arteriopathy and the impact of hydroxyurea treatment is unknown. In Debré center, it has been recently shown [44] that eICA stenosis score was more reduced on chronic transfusion than on hydroxyurea or on simple observation.

6. Silent cerebral ischemia (SCI)

6.1 MRI detection of silent cerebral ischemia

Silent cerebral ischemia (SCI) refers to ischemic damage identified on imaging that does not have a clinical correlate. SCI is detected in MRI that is recommended to do systematically from the age of 5 years in SS/Sb0 children when it does not require sedation. It is defined as a hyperintensity focus of at least 3 mm in diameter, visible in two planes on FLAIR MRI [46]. SCI occurs in infants as young as 1 year of age and continue throughout childhood [47].

SCIs reflect the severity of the disease, as they are associated with cognitive impairment, reduced academic achievement [48, 49], and a 14-fold increased risk of overt ischemic stroke [50]. Lesions are mostly confined to the white matter within the frontal and parietal border zone areas. The predilection for these areas is explained by the lower blood supply from end arterioles between the deep and the superficial territory of the MCA and between vascular territories.

6.2 Incidence of SCI

Despite early TCD screening and systematic assessment by cerebral MRI/MRA since age 5, the cumulative incidence of SCIs in the SCA Créteil newborn cohort was 37% by age 14 and did not reach a plateau [17]. This finding was confirmed in an adult series showing a prevalence of 53.3% by age 30 [51]. Contrary to large vessel arteriopathy, only observed in SCA children, SCIs were also observed in SC/Sb + children.

6.3 Risk factors for SCI

Risk factors for SCI are low baseline hemoglobin [17, 52, 53], intracranial and extracranial stenoses [17, 53, 54], relative hypertension, male sex [52], and acute and chronic anemia [53]. As a matter of fact, SCIs are more frequent in the presence of extra and intracranial stenoses [53, 55], but are also seen in the absence of large vessel arteriopathy, suggesting a contribution to tissue-level hypoperfusion and hypoxia, such as during episodes of acute anemia due to splenic sequestration or erythroblastopenia or during episodes of hypoxia during thoracic syndromes.

6.4 Management of SCI

The SIT trial compared in SCA children with SCI the 3-year outcome on chronic transfusion versus simple observation. The recurrence rate was significantly lower on chronic transfusion ($p = 0.04$) than on simple observation, but the difference between both groups was not enough sufficient to convince practitioners to initiate long-term chronic transfusion with the risks of alloimmunization, blood availability,

and iron overload risk. No randomized trial comparing hydroxyurea to simple observation or to chronic transfusion is available. However, SCI being significantly associated with lower cognitive performances and anemia justify to introduce hydroxyurea if not already given. However, several studies have reported SCI occurrence despite ongoing hydroxyurea treatment [56, 57]. Moreover, SCI presence being a marker of SCA-related severity encourages to consider chronic transfusion and to search for an available donor for transplantation [58].

7. Conclusion

Early assessment of children with SCA by transcranial and cervical Doppler ultrasound should be recommended not only to prevent overt but also SCI associated with poor cognitive performance. In addition, brain MRI and neck MRA are recommended to look for ischemic lesions and arterial stenosis and to choose the most appropriate treatment.

Hydroxyurea, by improving anemia and hemolysis, reduces the risk of abnormally high velocity and stroke, but chronic transfusion is still recommended for children identified as being at risk of stroke due to abnormally high brain velocities. A switch from chronic transfusion to hydroxyurea is recommended in children with normalized velocities and no arterial stenosis. However, in the presence of arterial stenosis, chronic transfusion and especially stem cell transplantation are more effective and should be recommended. These recommendations need to be reconsidered in low-income countries, where cost, availability, and safety of blood products are a major limit.

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