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Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler

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Abstract Cerebral arteriopathy can be detected in children with sickle cell disease (SCD) by transcranial Doppler (TCD). Abnormally high velocities are predictive of high stroke risk, which can be reduced by transfusion therapy. We report the results of the screening of 291 SCD children followed in our center, including the clinical and imaging follow-up of 35 children with abnormal TCDs who were placed on transfusion therapy. We postulated that patients with normal MRA findings and abnormal TCD velocities that normalized on a transfusion program could be safely treated with hydroxyurea (HU). We report their outcome (median follow-up of 4.4 years). Of 13 patients with normalized velocities on transfusion, 10 had normal MRAs, and transfusion therapy was stopped and HU begun. Four of these ten patients redeveloped high velocities off transfusion, so currently only six remain transfusion-free. Six other transplanted patients remain transfusion-free. Abnormal TCD velocities detect a high-risk group, justifying the research for suitable transplant donors. Multicenter studies comparing HU therapy to long-term transfusion might help identify which patients can avoid transfusion and its complications while avoiding vasculopathy.

Keywords Sickle cell disease · Transcranial Doppler · Cerebrovascular disease

Introduction

Large-vessel cerebrovasculopathy can be detected in children with sickle cell disease (SCD) by transcranial Doppler (TCD) [1–5]. Abnormal high velocities are predictive of high stroke risk; that risk can be significantly reduced by transfusion therapy [6, 7].

High velocities are related to stenosis as well as severe anemia and tissue hypoxia. Since the STOP trial, it has been recommended that children aged 2–16 years with SCD be screened by TCD to identify those at high risk for stroke [7]. These high-risk children are then offered transfusion regimens for stroke prevention. Although stroke risk decreases with this therapy, side effects include alloimmunization and iron overload. In addition, 60% of this subgroup of patients might never develop stroke even without transfusion therapy. Thus, two questions remain unresolved: how long should transfusion therapy be continued, and how can children with high velocities but small stroke risk be identified in order to avoid the side effects of chronic transfusions.

In 2001, we reported our experience concerning the 1-year treatment with hydroxyurea (HU) of 43 children, 14 with severe anemia (Hb ≤ 7 g/dl) [8]. In addition to a significant increase of hemoglobin and hematocrit levels, a significant decrease in time-averaged mean of the maximum velocity (TAMMX) ($P = 0.02$) of prior normal or conditional MCA velocities was noted after HU therapy. We postulated that patients with normal or questionable MRA findings and TCD velocities that

normalized on a transfusion program could be safely treated by HU.

Materials and methods

Patients

Two hundred and ninety-one pediatric SCD patients (237 SS, 40 SC, 3 Sβ0, 11 Sβ+) were followed in our center between 1992 and January 2004. In our series, 58.7% had no α-thalassemia, 32.8% had one gene deleted, and 8.5% had a deletion of two α-genes. Concerning the β-genotype, the majority of patients had a Bantou homozygosity (44.4%), whereas 23.7% had a Benin homozygosity and 9.6% a Senegal homozygosity. Others (22.2%) had mixed or atypic genotypes.

Two populations of patients have been studied: (1) the Créteil newborn-screened population ($n=150$) (median age 7.4 years, range 0.2–18 years) who had the initial TCD examinations between 12 months and 18 months of age; and (2) a population of children with SCD referred to our center ($n=141$) at various ages (mean age 8.8 years, range 0.7–18 years).

Methods

Transcranial color Doppler imaging (TCDI) was performed using several imaging systems (Acuson, GE Medical Systems, Hitachi). Using the temporal and suboccipital approach, TAMMX was obtained in the distal internal carotid artery, the middle cerebral artery from the MCA/ACA bifurcation to the periphery, the proximal anterior cerebral artery, the posterior cerebral artery, and the basilar artery. No angle correction was used. The envelope of the waveform was traced manually or electronically, depending on the quality of the waveform (Fig. 1). As per the STOP study, velocities were considered abnormal when the TAMMX was greater than or equal to 200 cm/s in MCA, bifurcation or ICA. TCD was performed once a year or once a trimester when abnormal or conditional.

MRI/MRA was usually performed only on children 5 years of age or older. MRIs or MRAs were obtained within 3 months of detection of an abnormal high TAMMX. Because of the high rate of false-positive MRAs in anemic patients (which is related to artifact generated by the dephasing of proton spins in blood-mimicking stenosis), we chose only to perform MRAs after two or three transfusions were completed. Conventional arteriography was performed in 11 patients between 1993 and 2001 to prove the existence of stenosis before initiating long-term transfusion or transplantation. With improved MRA techniques, including the use of shorter TE and higher matrixes, arteriography is no longer performed.

Results

Abnormally high velocities defined as a TAMMX of ≥200 cm/s were found in 35 sickle cell patients. All were SS (35/237 SS patients).

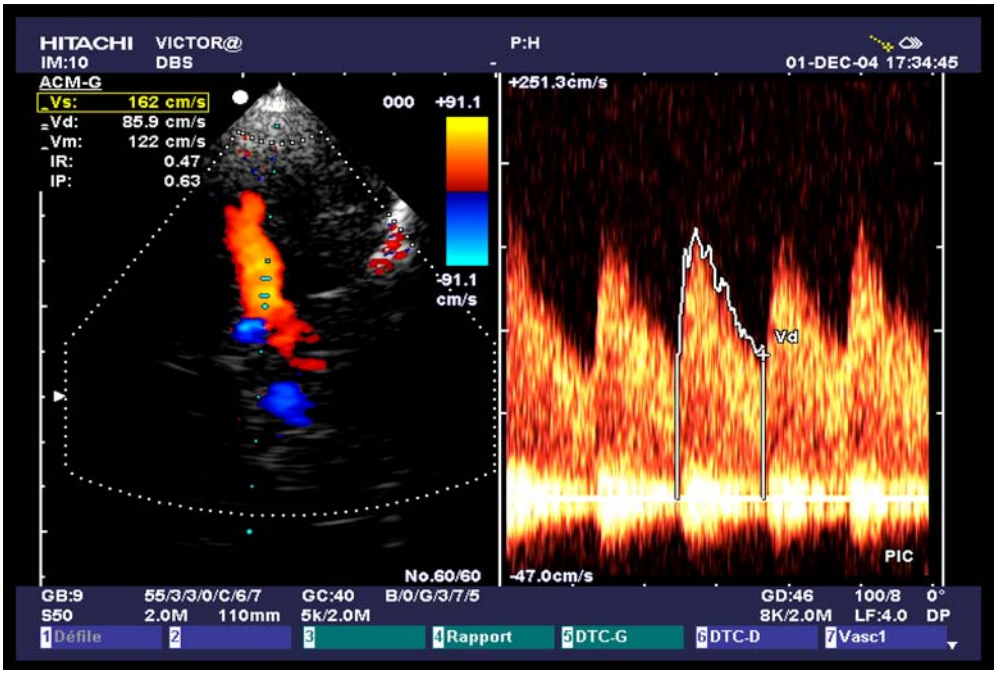

Fig. 1 Normal TCDI. Electronic measurement of the left MCA waveform calculates a TAMMX (Vm) of 122 cm/s

Patients with a stroke history and abnormal TCD ($n = 11$)

Ten children (six girls, four boys) were referred to our center because a stroke had occurred at the mean age of 6.5 years (range 2.3–10.5 years). One additional girl who had been followed since birth in our center had abnormally high velocities at the initial TCD study at 1.5 years of age and developed a stroke 1 month later prior to repeat TCD examination and the initiation of transfusion. All 11 of these patients had abnormal MRI and MRA examinations. Three had bilateral abnormal high velocities, 4 had normal (< 170 cm/s) velocities on one side and abnormal velocities on the other side, and 4 had absence of flow related to thrombosis on one side and abnormal high velocities on the contralateral side, as shown in the example in Fig. 2.

Seven of the 11 patients were maintained on a long-term transfusion program (median follow-up of 4.2 years). Two patients, following a 1-year transfusion program, were then being treated with HU therapy when they were lost to follow-up because they returned to Africa. Two patients were successfully transplanted.

Transcranial Doppler could no longer be performed on follow-up in four patients because of decreasing window size—this included the two transplanted patients and two receiving transfusions. In the remaining seven patients, follow-up TCD demonstrated persistent thrombosis in the four patients with unilateral thrombosis, while those with abnormal high velocities remained abnormal (≥200 cm/s) or conditional (> 170 cm/s and < 200 cm/s).

Patients with no stroke history and abnormal TCD ($n = 24$)

Among the 226 SS patients without stroke history, 24 had abnormally high velocities (≥200 cm/s). The observed incidence was 11%. Considering the hemoglobin and hematocrit levels and MCV at baseline, the frequency of low hemoglobin level (Hb < 7 g/dl) was

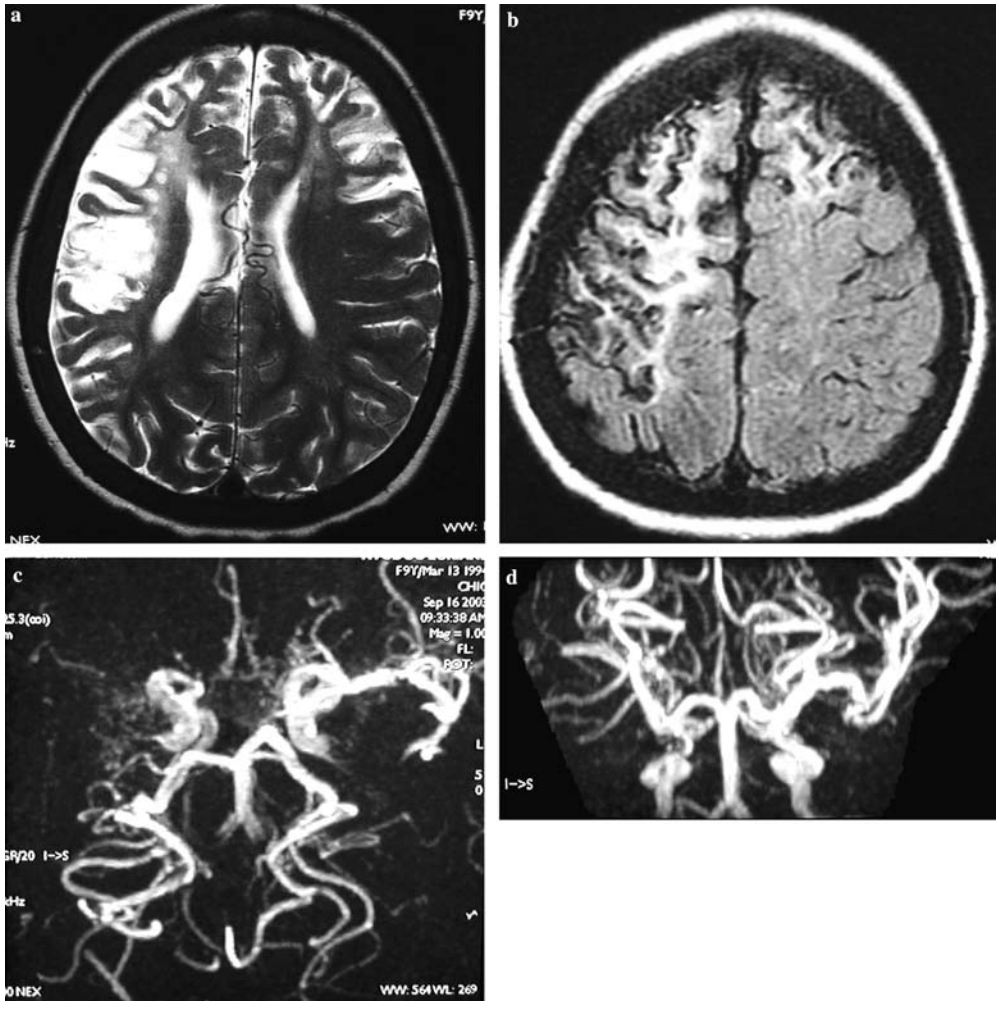

Fig. 2 MRI in a 9-year-old girl with an acute onset of left hemiplegia at the age of 5 years with recurrence the following year. **a** Axial T2-weighted and **b** axial FLAIR images demonstrate old right MCA infarction and left anterior junctional infarction with focal atrophy. **c** Axial and **d** coronal 3-D-reconstructed time-of-flight MRA shows absence of flow to the right MCA and the right and left ACA, narrowing of both supraclinoid internal carotid arteries, and irregularities of the left MCA. The posterior circulation is prominent

significantly increased in the SCD population with abnormal high velocities (50% vs 23%). High velocities were found in the left MCA ($n=11$), right MCA ($n=8$), left and right MCA ($n=3$), or right ICA ($n=2$). Velocities in these patients were 230 ± 40 cm/s. Figure 3 demonstrates an example of cerebral vasculopathy detected by TCD in a stroke-free girl.

Among the patients regularly evaluated with TCD since the age of 12–18 months, 12 SS patients developed abnormal high velocities at a median age of 5.7 years (range 1.5–12.5 years). The preceding TCD performed 1 year prior was normal in 6 of the 12 patients (mean age 6.3 years) and conditional in the remaining 6 (mean age 6 years).

In the patients not followed from birth, abnormal velocities were found in 12 patients at the initial examination at the median age of 8.2 years (range 3.1–14.5 years).

Ten of the 24 high-velocity patients had a normal MRI and MRA, 7 of 24 had abnormal MRIs and MRAs, and the other 7 had either an abnormal MRI or MRA. Velocities were significantly higher ($P=0.002$) in patients with abnormal MRI and MRA (Table 1). Data were significantly different (Table 1) in patients regularly evaluated with TCD since birth in our center compared to those who were secondarily referred. The incidence of ischemic lesions and stenosis was significantly higher ($P=0.02$) in patients recently referred (7/12 abnormal MRI and 7/12 stenosis) compared to those regularly evaluated since birth (1/11 abnormal MRI and 2/11 stenosis). Velocities were significantly higher ($P=0.02$) in patients with abnormal MRA ($n=9$) (243 ± 40 cm/s) than in those with normal MRA ($n=12$) (211 ± 16 cm/s).

Conventional arteriography was performed in 11 patients between 1993 and 2001 to prove the existence of stenosis before initiating long-term transfusion or transplantation. Results were concordant with MRA in eight cases. Stenosis was found in one case with normal

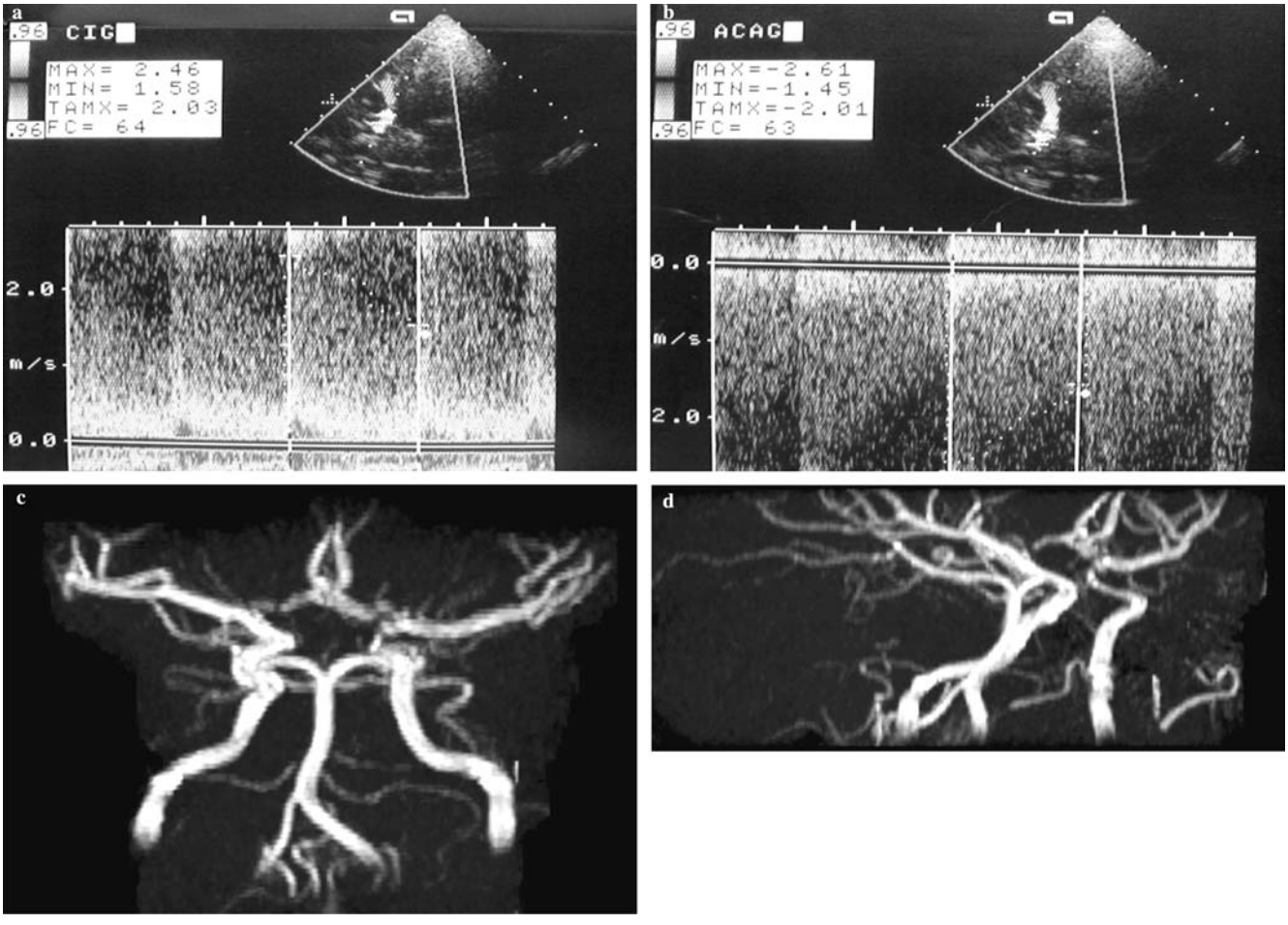

Fig. 3 TCDI in a girl followed since birth without history of stroke. Abnormal velocities were identified in the left MCA (**a**) and ACA **(b)**. Coronal (**c**) and oblique coronal (**d**) 3-D-reconstructed time-of-flight MRA images show stenosis of the left supraclinoid internal carotid artery and both proximal anterior cerebral arteries

Table 1 Velocities and MRI/MRA results in newborn screening cohort versus secondary referrals (*n* normal, *abn* abnormal, ? questionable abnormality, *ND* not determined)

Age (years)	Velocities (cm/s)	MRI 1	MRA 1
Secondary referrals			
3.1	200	n	n
14.5	260	abn	abn
9.1	233	n	abn
14	250	abn	abn
7.8	227	abn	abn
8.7	238	n	?
7.7	306	abn	abn
13.8	300	abn	abn
7.5	235	abn	n
4.2	202	n	n
10.2	204	abn	abn
6	180	n	n
Newborn screening			
6.5	200	n	abn
6	212	n	n
2.8	239	n	n
4	237	ND	ND
6.25	200	n	n
10.5	217	n	n
4	216	abn	n
3	200	n	n
9.5	204	n	abn
5.7	224	n	n
3	201	n	n
12.5	219	n	?

The incidence of ischemic lesions and stenosis was significantly higher ($P = 0.02$) in patients recently referred (7/12 abnormal MRI and 7/12 stenosis) as compared to those evaluated since birth (1/11 abnormal MRI, 2/11 stenosis)

MRA. In the two cases with questionable MRA findings, one had stenosis and the other had a normal arteriogram.

Protocol applied to the 35 patients with abnormally high velocities

In our series, patients have been systematically evaluated with TCD since 1992. Early in our series, those with stenosis detected by TCD and MRA and confirmed by conventional arteriography were transfused. Since the STOP study was published in 1998 [7], children with abnormal velocities and normal MRA have been transfused. However, in those patients with normal MRA and normalized velocities on transfusion, a switch to HU therapy was attempted according to the following protocol (Fig. 4).

Figure 4 shows the protocol that has been used in our center since 1998. As soon as abnormal velocities are identified, a transfusion program is administered for 3 months. TCD is repeated and MRI/MRA then performed. If the MRA demonstrates a stenosis, the patient is maintained on transfusions and a genoidentical donor is sought within the family, and stem cell transplant (SCT) is performed when possible. If MRA is normal, TCD is repeated quarterly. If velocities remain abnormal, the transfusion/exchange program is continued and a SCT eventually proposed. If TCD normalizes (< 170 cm/s) during transfusions, HU is initiated with an overlap of 2 months with transfusion therapy. TCD is then repeated quarterly, and if velocities return to abnormal values on HU, a transfusion program is again begun.

Except for the young girl who had a stroke at 1.6 years just before initiation of the transfusion program, no stroke or recurrence of stroke was observed during the study, with a median follow-up of 4.4 years (ranging from 6 months to 11.4 years). In two patients with a stroke history and moyamoya disease, transient ischemic attacks were observed during the transfusion program.

Eight of the 11 patients with a stroke history were followed with TCD (3 had no window at follow-up). All eight maintained abnormal (≥200 cm/s) ($n = 6$) or conditional ($n = 2$) velocities despite transfusion.

Among the 24 stroke-free patients on transfusion, 11 patients had persistently elevated velocities (> 170 cm/s) and were maintained on long-term transfusion. Seven of these 11 patients had abnormal initial MRAs. Among the four patients with normal initial MRA studies, MRA became abnormal in two cases. Thus, two cases with persistently abnormal TCD on transfusion and normal initial MRA progressed to abnormal MRAs. On the other hand, we observed a normalization of

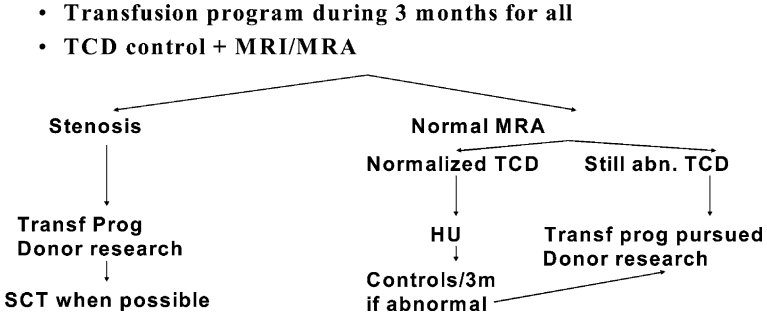

Fig. 4 Scheme proposed in patients with TCD > 200 cm/s

velocities (< 170 cm/s) in 13 patients (median time course 0.75 years [range 0.25–2.3 years]. Initial velocities were significantly lower ($P = 0.03$) in the patients who normalized on transfusion (215 ± 15 cm/s) as compared to those patients who did not (241 ± 38 cm/s). Age, Hb and Hct levels, and MCV at baseline were not predictive of normalization. A normal initial MRA was significantly ($P = 0.006$) related to a higher rate of velocity normalization with transfusion. MRA and/or arteriography had been initially performed in 12 of the 13 patients who normalized on transfusion. In 4 of those 12 patients, MRA was initially abnormal and became normal in 2 of the 4 cases on transfusion for 1.2 years and 2.4 years, respectively.

In patients with normalized velocities and normal or normalized MRA, transfusion was stopped ($n = 10$). A switch to HU therapy was proposed for seven of these ten patients; one patient with low oxygen saturation received nocturnal oxygenation and two patients, who had been transfused for 3 years, had no additional treatment. High velocities redeveloped in four patients (three of the seven patients treated with HU and the patient receiving nocturnal oxygenotherapy). These four patients were again placed on a transfusion program.

Genoidentical stem-cell transplantation was performed in six patients, two of whom had a stroke history. No stroke recurrence was observed in the two children with previous strokes, although TCD could not be performed at follow-up because of the lack of an available temporal window. Four patients without stroke history and persistently abnormal velocities despite transfusion were transplanted. After transplant, TAMMX velocities dramatically decreased in two patients who had abnormal velocities throughout transfusion therapy, and two patients maintained abnormal velocities on one side. So far, all six patients have been stroke free since transplant. Transfusions were stopped with a mean follow-up of 6.5 years (range 2–10.9 years).

Discussion

It has been demonstrated that TCD is a reliable screening test for stroke risk in SCD [1–6]. Transfusing patients at risk can significantly decrease this stroke risk [7]. However, transfusions expose patients to multiple other risks, including alloimmunization, viral contamination, and iron overload. Up to 60% of patients with abnormal velocities do not develop a stroke. With these issues at stake, it appears that selected patients might do better avoiding a long-term transfusion program.

Velocities are correlated with the degree of anemia [1, 3], and the efficacy of HU in increasing the hemoglobin level has been demonstrated in SCD patients [8–11]. We observed a significant decrease in cerebral velocities in patients treated with HU [8]. However, using HU in patients with cerebral vasculopathy can be dangerous [12]: a 19% stroke recurrence has been observed in patients with stroke history treated with HU [13]. Because of this risk, we decided only to use HU in patients who had normal MRAs and whose velocities normalized on a transfusion program.

Abnormal velocities were identified in 11% of the SS patients in this series and were more frequently observed in the most anemic patients. Abnormal velocities were related to MRA-imaged stenosis and contralateral thrombosis, but were also found in 9 of the 24 stroke-free patients. Abnormal TCDs preceded abnormal MRAs in two cases. Abnormal TCDs were frequently associated with ischemic MRI lesions, particularly in patients not followed closely since birth. Transfusion initiation associated with TCD follow-up and maintenance transfusion therapy in cases of persistent abnormal velocities has worked to avoid stroke occurrence in all our protocol patients. Early TCD screening (12–18 months) might be particularly useful in preventing early strokes and silent strokes.

The aim of this monocenter study was to determine whether it was possible to avoid a long-term transfusion program safely in selected patients with normal MRA studies whose velocities were normalized on transfusion. Of 13 patients with normalized velocities on transfusion, 10 had normal MRAs, and transfusion therapy was stopped and HU begun. Four out of ten patients developed high velocities off transfusion, so only six remain transfusion-free.

In conclusion, this TCD protocol demonstrates effective stroke prevention in 35 patients with a history of abnormal high TAMMX velocities. Long-term transfusion therapy was safely stopped in the six transplanted patients and in six others, four of whom are still on HU therapy. Abnormal TCD velocities detect a high-risk group, justifying the research for suitable donors for stem cells transplantation [14–16]. Multicenter studies comparing HU therapy to long-term transfusion should be initiated to identify further which patients can safely avoid transfusion and its complications, while avoiding the occurrence of ischemic lesions and vasculopathy.

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