

Are we ready for new strategies to prevent stroke in children with sickle cell disease?

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In this issue of *Haematologica* De Ligt *et al.*¹ report on the use of magnetic resonance angiography (MRA) to further tailor the identification of children with sickle cell disease (SCD) who are at risk of developing overt stroke. During a 22-year period the authors withheld red blood cell transfusion in children aged 2-18 years with abnormal transcranial doppler (TCD) and normal MRA; regular transfusion was started only when intracranial stenosis was demonstrated by MRA. Their local TCD screening protocol was more intensive and expanded than the Stroke Prevention Trial in Sickle Cell Anemia one (STOP)² because they performed TCD biannually between the age of 2-10 years and annually between 10-18 years, with bilateral insonation not only of the middle cerebral arteries (MCA) and the internal carotid arteries (ICA) but also of the anterior carotid arteries (ACA). Classification of abnormal and borderline velocities (i.e., conditional) in their protocol reflected the STOP one for non-imaging TCD thresholds (abnormal >200 cm/sec; borderline/conditional between 170-199 cm/sec) but used reduced thresholds for TCD imaging (abnormal >180 cm/sec; borderline/conditional between 155-179 cm/sec).³ Children with abnormal TCD or TCD imaging on two different occasions performed 1 month apart, underwent MRA within 6 weeks, with sedation if below 7 years of age. MRA was performed according to a standardized procedure and the authors report the use of a grading system to determine the severity of the stenosis (mild 25-49%, moderate 50-74%, severe 75-99%, occlusion >99%). If MRA-defined vasculopathy was identified, children performed chronic transfusion therapy; otherwise, they continued with ongoing treatment. In case of persistent abnormal or borderline TCD, MRA was performed every 2 years.

In their cohort 30 of 209 patients had abnormal TCD (14.4%). MRA was normal in 14 of 30 (47%), 12 of which did not start transfusion therapy. However, nine of them began hydroxyurea (HU) for other reasons, even though the time of HU beginning and the dose are not reported.

None of the patients in this group developed a cerebrovascular accident (CVA) with a follow-up of 120.7 patient-years. Sixteen of 30 (53%) patients with abnormal TCD had stenosis on MRA, although neither vascular site of stenosis and grading were reported at diagnosis or follow-up, nor did grading apparently impact therapeutic choices. Among the 16 patients with MRA-defined vasculopathy, 15 started chronic transfusion therapy. Two of them developed CVA. Due to the fact that none of the patients with abnormal TCD/TCD imaging and normal MRA developed a CVA, the authors cautiously conclude that their retrospective analysis suggests that MRA improves the accurate identification of patients with an increased risk of developing a CVA and thereby reduces the proportion of patients requiring chronic transfusion therapy, which would therefore reduce iron overload and alloimmunization with consequent positive repercussion on patient's daily life and health system resources. They appropriately underline, however, that only a prospectively randomized trial could determine whether withholding transfusion therapy in children with abnormal TCD/TCD imaging and normal MRA is non-inferior compared to the current standard of care.

SCD is a monogenic disorder with significant phenotypic variability.³ In spite of the outstanding improvement in the comprehensive care of children with SCD in the past decades, possibility for precision medicine has been slow to develop and stroke and CVA continue to cause significant mortality and morbidity in high-income countries: stroke is still one of the main causes of mortality in children under 5 years of age in children diagnosed and taken in care since birth⁴ and still causes major impact in terms of general and intellectual disabilities.⁵ The results of De Ligt *et al.* are in line with the most recent clinical achievements, that look for a refined precision therapy in SCD, trying to calibrate interventions and treatments, tailoring them to the individual clinical situation or to well defined subgroups of

patients.⁶ New strategies for risk stratification of cerebral vasculopathy are, therefore, deeply warranted and studies in this field are welcomed.

However, several aspects of neuroimaging methodology should be taken into consideration to adequately assess stroke risk and therapeutic strategies. First of all, Doppler technique and velocities thresholds. The authors neither report how many patients performed TCD-imaging instead of TCD, nor in which vessels the abnormal velocities were recorded (MCA, ICA, ACA). The use of different thresholds for TCD-imaging has been shown to overestimate the classification of abnormal results,⁷ hence it is possible that some patients who were classified as abnormal using TCD-imaging in this study might have been, in fact, normal and cannot be counted as impacting the low percentage of CVA in the MRA-defined vasculopathy group. Careful comparison between TCD and TCD-imaging values needs to be performed in future studies in order to adequately identify high-risk patients. Secondly, the vascular site and the grade of stenosis at MRA were not indicated, therefore no specific correspondence between the TCD identification of abnormal velocities in a certain vessel and the corresponding MRA stenosis (and grading) in the same vascular area could be identified. Several studies have compared TCD and MRA sensitivity and specificity but different classifications have been used so far,^{8,9} therefore in future studies the MRA protocol should detail

which findings are considered significant (tortuosity? mild stenosis? or only moderate and severe?). This is crucial to avoid MRA interpretation to be even more operator-driven than TCD, which relies on numeric thresholds.

Another important factor to be considered, is the concomitant use of HU or other disease-modifying therapies. The authors withheld transfusion, but in this cohort HU therapy was initiated for other reasons in most patients with abnormal TCD and normal MRA. We know the positive effect of HU on lowering TCD velocities, thus being an alternative to transfusion¹⁰ in the prevention of cerebral vasculopathy: withholding transfusion does not mean leaving the children without other treatment.

In conclusion, the results of the study by De Ligt *et al.* are very encouraging toward implementing precision medicine in SCD, with more accurate clinical phenotype definition and risk stratification and prospective trials specifically designed to clarify this topic.

Disclosures

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Contributions

RC and GR drafted and revised the editorial.

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