EDITORIAL

The French connection: extracranial internal carotid artery and cerebral infarction in pediatric sickle cell patients

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In their article published in this issue of *Haematologica*, Bernaudin *et al.*[1] present extensive data on their single center prospective pediatric cohort of sickle cell disease (SCD) patients. These patients have been meticulously followed since 1998, with changing screening and treatment practices over the years, with a special focus on the extracranial part of the carotid internal artery (eICA) in the pathogenesis of stroke and silent cerebral infarction. In previous studies, high flow in the eICA or stenosis had been demonstrated to be an additional risk factor for stroke and silent cerebral infarction (SCI) in patients with normal transcranial Doppler (TCD) and magnetic resonance imaging (MRI) / magnetic resonance angiography (MRA) of the intracranial vasculature.[2] Therefore, in this cohort, chronic transfusion therapy was introduced in 2011 to prevent stroke in pediatric SCD patients with these findings.

The novelty of this report is the assessment of the impact of "conditional" increased blood flow (blood flow >160 cm/s and < 200 cm/s) in the eICA, which has been routinely analyzed in this center since 2011, a practice which has not been implemented in all centers around the world. Given the increased risk of developing an eICA stenosis with a "conditional" eICA flow, patients with this conditional flow and no stenosis of the eICA were given hydroxyurea (if not already prescribed) in order to prevent further deterioration. In this paper, the authors present their data by comparing the efficacy of this strategy introduced in 2011 in the "new cohort" (defined as pediatric SCD patients born after 2007) in comparison with their initial reported cohort (born before 2007), and the results are very interesting.

The first major finding is that chronic transfusion therapy in patients with either an increased eICA flow (>200 cm/s) or stenosis of the eICA successfully prevented stroke in this specific patient group, similar to what has been observed in SCD patients with abnormal TCD or stenosis of the intracranial vessel in severe pediatric SCD patients. The application of TCD, MRI/MRA of the intracranial vessels in combination with Doppler assessment of the extra-cranial carotid artery and MRI/MRA of neck was demonstrated to almost completely prevent stroke in children with severe SCD. This observation confirms that evaluation of the eICA flow and the presence of stenosis in the extracranial artery should be implemented in the routine Doppler and MRI check-ups in severe pediatric SCD patients.

Another major finding was that patients with "conditional" flow (160-200 cm/s) in the eICA treated with hydroxyurea did not develop extracranial carotid artery stenoses but appeared to experience continuous progression of silent cerebral infarct (SCI) lesions, resulting in an incidence of SCI at the age of 14 years of 25%.

These findings are not based on a randomized controlled trial and causality is, therefore, not proven in this prospective cohort study. However, these observations clearly suggest that the extracranial carotid arteries play an important role in the pathogenesis of stroke, which, in cases of high flow (>200 cm/s) or stenosis in the eICA, can be prevented by chronic transfusion, and SCI progression, which cannot be prevented by hydroxyurea. The question remains: what should be done to prevent progression of SCI in patients with conditional flow in the eICA? Transfusion therapy could be an option given the lack of SCI progression in patients transfused in whom therapy was initiated because of either an abnormal TCD or eICA Doppler, or stenosis of the intra- or extracranial carotid arteries, as seen in the cohort presented in Bernaudin *et al.*'s paper.[1] However, although the Silent Cerebral Infarct Transfusion (SIT) trial in pediatric patients at risk of SCI suggested that chronic transfusion therapy may reduce the progression of SCI, transfusion therapy reduced the risk of stroke (1 stroke in the transfused group *vs*. 7 strokes in

the non-transfused group) but not the progression of SCI (5 patients with SCI progression in the transfused group *vs*. 7 in the non-transfused group).[3]

As always, more questions remain than are solved but Bernaudin and colleagues certainly demonstrate that we have to widen our vision to the extracranial vasculature of the brain in pediatric patients with severe SCD.

Disclosures

No conflicts of interest to disclose.

References

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