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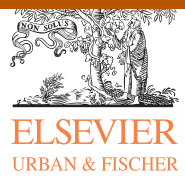

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Intellectual impairment and TCD evaluation in children with sickle cell disease and silent stroke

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KEYWORDS
Sickle cell disease;
Transcranial Doppler;
Silent strokes;
Cognitive impairment

Abstract
Background: Sickle cell disease (SCD) may impair intellectual activity; 25% of SCD patients have a significant cognitive deficit. Our aim was to verify in a cohort of children with HbSS if the presence of silent strokes or altered Time Averaged Mean velocities of Maximum blood flow (TAMM) detected by Transcranial Color Doppler (TCD) Sonography are indicators of impaired intellectual ability.
Methods: Thirty-five consecutive SCD patients (17 males; mean age: 8.6 ± 3.22) were subdivided into two groups according to neuro-psycological deficits. Cognitive function was assessed by WISC III (for the children aged 6—16 years) and WPPSI (for the children aged 4—6 years). All patients underwent a TCD scan of the main intracranial arteries, in order to detect any increase of TAMM velocities (normal <170 cm/s; altered >170 cm/s) and a cerebral MRI to reveal any silent stokes.
Results: According to the neuro-psycological evaluation, 29/35 (82.8%) patients (Group 1) had a ''normal'' Total Intelligence Quotient (TIQ $\geq$70), while 6/35 (17.2%) patients (Group 2) were defined intellectually impaired (TIQ <69).

TCD detected altered velocities in 8/35 (22.8%) patients. No significant differences were found in the percentage of altered TAMM velocities between the two groups (Fisher's exact test: $p = 0.42$).

MRI detected silent ischemic lesions in 14/35 patients (40.0%). No significant differences were found in silent stroke frequencies (Fisher's exact test: $p = 0.25$) between Group 1 and Group 2.
Conclusion: With the limitations of the study sample, according to our results, altered TAMM values and silent strokes do not seem to be indicators of impaired intellectual ability in SCD patients.

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Introduction

Sickle cell disease (SCD), a hematological disorder caused by an autosomic recessive inherited mutation in the hemoglobin genes (HbS), is considered the most frequent hemoglobinopathy in the world, with a peak incidence in the African population. SCD also represents the first cause of stroke in childhood, with a yearly first stroke risk of approximately 0.5%. [1]

Several studies [2—4] reported neuropsychological deficits in children with SCD; in fact, Schatz et al. observed that 25% of SCD patients had a significant cognitive deficit [5—7]. Are these deficits correlated to ischemic strokes? Adams and colleagues [8—13] demonstrated the importance of Transcranial Doppler (TCD) to prevent ischemic stroke in children with SCD. In the STOP study (Stroke Prevention Trial in Sickle Cell Anemia) they found that the stroke risk in these patients could be predicted by measuring Time Averaged Mean velocities of Maximum blood flow velocities (TAMM) of the major intracranial arteries. In particular, patients were categorized as ''normal'' if TAMM was <170 cm/s, ''conditional'' if TAMM was between 170 and 200 cm/s, ''abnormal'' if TAMM was $\geq$200 cm/s. Children with ''abnormal'' values are at the highest risk of stroke and are advised to undergo blood transfusion, in order to reduce their stroke risk and their cognitive impairment. However, Watkins et al. [14] and Schatz et al. [15,16] reported intellectual impairment in patients with SCD but without silent strokes compared to healthy controls. Consequently, these authors suggested that besides ischemic silent strokes (ISS), also a persistent low level of hemoglobin saturation could impair the intellectual function. In fact the reduced capacity of transporting O_2 is correlated with an insufficient cerebral perfusion that might cause regions of hypoperfusion and contiguous cerebral areas of compensatory hyperperfusion. TCD could identify this area by detecting increased flow velocity values.

The aim of our study was to verify in a cohort of children with SCD if the presence of silent strokes or altered TAMM detected by TCD are indicators of impaired intellectual ability.

Materials and methods

Thirty-five consecutive SCD patients (17 males, 18 females; mean age: 8.6 ± 3.22) were subdivided into two groups according to the detection of neuropsychological deficits by means of a neuropsychological evaluation: Wechsler Intelligence Scale for Children (WISC III) for the children aged 6—16 years and Wechsler Preschool and Primary Scale of Intelligence (WPPSI III) test for children aged 4—6 years. The subtests were organized into Verbal and Performance scales, and provided scores for Verbal Intelligence Quotients (VIQ) and Performance Intelligence Quotient (PIQ) in order to assess the Total Intelligence Quotient (TIQ). TIQ score $\geq$70 was defined ''normal''. Moreover we calculated the difference between Verbal and Performance Intelligence Quotient (VIQ-PIQ). A VIP-PIQ score $\geq$ than 8 represents an abnormal development of Verbal ability in comparison to Performance ability and a score $\leq$ than -8 represent an abnormal development of Performance ability in comparison to Verbal ability.

All patients underwent a TCD evaluation of the main intracranial arteries in order to detect any increase of TAMM velocities (normal <170 cm/s, altered $\geq$170 cm/s according to the STOP protocol); TCD was performed by an experienced neurosonographer, in a quiet atmosphere and without pharmacological sedation, using a 2 MHz probe (Viasys Healthcare Sonara).

All patients underwent brain magnetic resonance imaging (MRI) by means of a 1.5 T MR scanner (Achieva, Philips, Best, The Netherlands). The study protocol included axial Fluid Attenuated Inversion Recovery (FLAIR) sequence (repetition time 11,000 ms; echo time 140 ms; inversion time: 2800; echo train length 53; flip angle 90°; field of view 230 mm; matrix 256×256; slice thickness 5 mm; interslice gap 0.5 mm; number of averages 2) to disclose ischemic lesions.

Results

Regarding the neuropsychological evaluation, 29/35 (82.8%) patients (Group 1) had a normal ($\geq$70) TIQ, while 6/35 (17.2%) patients (Group 2) were defined intellectually impaired (TIQ <69).

TCD detected altered velocities in 8/35 (22.8%) patients: 6 in Group 1 and 2 in Group 2. No significant differences were found in the percentage of altered TAMM velocities between the two groups (Fisher's exact test: $p = 0.42$).

MRI detected silent ischemic lesions in 14/35 patients (40.0%): 12 in Group 1 and 2 in Group 2. No significant differences were found in silent stroke frequencies (Fisher's exact test: $p = 0.25$) between Group 1 and Group 2.

VIQ-PIQ was normal in 16/35 (45.7%) patients and altered in 19/35 (54.2%) patients. TCD detected altered TAMM in 5 patients with normal VIQ-PIQ and in 3 patients with altered VIQ-PIQ. No significant differences were found in the percentage of altered TAMM velocities between these two groups (Fisher's exact test: $p = 0.28$).

MRI detected silent ischemic lesions in 6 patients with normal VIQ-PIQ and in 8 patients with altered VIQ-PIQ. No significant differences were found in silent stroke frequencies (Fisher's exact test: $p = 0.52$) between these two groups.

Discussion

According to our results, altered TAMM values and silent strokes do not seem to predict cognitive impairment in SCD patients. Our results do not seem to confirm the data found in literature, particularly the association between cognitive impairment and silent strokes [5,6].

The relationship between brain tissue injury and cognitive impairment in SCD is not well understood. In fact the increase of TAMM velocities have been proven to be a strong predictor of ischemic stroke but it can also be considered as a compensatory reaction to chronic hypoxia consequent to the diffuse vasculopathy induced by the low level of hemoglobin saturation. ISS could be seen as a cumulative and additional lesion to a cerebrovascular system already impaired by chronic hypoxia. Moreover a recent study [17] pointed out that children with SCD have an impaired

cerebral blood flow autoregulation compared with age-matched healthy subjects, independently from their hemolysis rate. It suggests that children with SCD could have an impaired compensatory reaction to chronic hypoxia (that we consider a possible cause of cognitive impairment) without an increased intracranial blood flow velocities. So also a normal TAMM could be the expression of a pathological situation.

Furthermore we have to consider the particular anatomy of the vessels in these patients [18], with an increase of tortuous course not necessarily related to stroke development. This situation could cause an increase in TAMM velocities without a consequent cognitive impairment.

The higher brain plasticity of children compared to adult could explain why ISS detect by MRI do not correlate significantly with cognitive impairment. As altered TAMM are predictors of a high risk to develop ischemic stroke, it could express an initial damage that could induce a cognitive impairment after years. Only after a long-term follow-up of children with SCD and altered intracranial blood flow velocities a cognitive impairment could become clinically relevant.

This study has several intrinsic limits: the small sample size of the study population and the limits of TCD in children (large temporal acoustic windows with consequent errors in the measurements of intracranial blood flow velocities).

It is necessary to continue the study with a greater number of SCD children and to follow them up in order to assess the positive predictive value to develop cognitive impairment with a non invasive method (TCD) that already demonstrated a high potentiality in children with SCD.

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