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STROKE IN PATIENTS WITH SICKLE CELL DISEASE

Clinical and neurological aspects

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Abstract – The aim of this study was to characterize a group of patients (n=8) with sickle cell disease (SCD) and ischemic stroke concerning the clinical, neurological, imaging and progressive aspects. Data were collected from records and completed with an interview of patients and their parents. In this study there were 8 patients with ages ranging from 10 to 23 years old; SCD diagnosis was given between one and two years of age with clinical features of fatigue and anemia. The stroke was ischemic in all individuals and the first cerebrovascular event occurred before 6 years of age; 3 patients had recurrence of stroke despite prophylactic blood transfusion therapy and both cerebral hemispheres were affected in 4 patients. Clinical and neurological current features observed were: acute pain crises, sialorrhea, mouth breathing, motor, and neuropsychological impairments resulting from cortical-subcortical structure lesions.

KEY WORDS: stroke, sickle cell anemia, neurological manifestations.

Acidente cerebrovascular em pacientes com anemia falciforme: aspectos clínicos e neurológicos

Resumo – O objetivo deste estudo foi caracterizar um grupo de sujeitos (n=8) com antecedentes de anemia falciforme (AF) e acidente vascular cerebral (AVC) isquêmico, dos pontos de vista clínico, neurológico, radiológico e evolutivo, reavaliados através de exame neurológico e neuropsicológico. A partir de prontuários dos sujeitos com diagnóstico comprovado de AF e AVC, coletamos dados, complementados por entrevista com pacientes e responsáveis. Foram avaliados 8 pacientes; atualmente com idades entre 10 e 23 anos; diagnóstico da AF entre um e dois anos; quadro clínico de fraqueza e anemia. Em todos, o AVC foi isquêmico e o primeiro evento na maioria ocorreu antes dos 6 anos de idade; houve recorrência do AVC em 3, apesar da profilaxia com transfusão sanguínea; ambos os hemisférios afetados em 4; no quadro clínico e neurológico atual constatamos crises dolorosas, sialorréia, respiração oral e importante comprometimento motor e neuropsicológico, resultantes de lesões estruturais cortico-subcorticais.

PALAVRAS-CHAVE: acidente cerebrovascular, anemia falciforme, manifestações neurológicas.

Stroke is 221 to 300 times more frequent in patients with sickle cell disease (SCD) when compared to healthy children[1,2], occurring in approximately 11% of homozygote individuals (SS) under the age of 20[3], with a prevailing incidence between four and 15 years of age[2,4]. The cerebrovascular event may be devastating in 7% of the children with SCD, with a possibility of new episodes (0,7% per year) during the first twenty years of life. The episodes appear isolated or associated with infection, dehydration, acute pain crisis, aplastic crises, priapism, among others[3,5]. A research involving 42 children with asymptomatic SCD and normal neurological clinical exam revealed that, among all hematimetric parameters and clinical indicators, the mean corpuscular volume was significantly risk predictive, and the magnetic resonance image (MRI) was an important resource of image, detecting cerebrovascular abnormalities in asymptomatic patients caused by ischemia in territory of the middle cerebral artery and perforating branches[6].

A study with 146 patients found that in older ages it is usual the involvement of large vessels by stenosis or occlusion with consequent encephalomalacia. In younger ages, small vessels impairment predominates, with cystic fibrosis probably of embolic cause. In decrescent order, effects were more evident in the white matter, caudate, putamen, and thalamus particularly involving the region of lenticulostriate arteries[7]. In a retrospective study, researchers compared a group of 14 children with SCD and stroke to another group of SCD children without any

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cerebrovascular event. In order to highlight the physical and cognitive effects of the vascular events, the individuals were evaluated with *Motor Assessment Scale, Barthel Index, WISC, California Test of Personality and Test of Language Development*. Patients of the experimental group were physically independent, with a slight or no motor deficit of postural acquisitions; however, they presented moderate to severe dysfunction in hand motor function (42%); intellectual deficits; severely impaired speech; disorders in psychosocial adjustment[8].

The aim of this study was to characterize a group of patients (n=8) with SCD and ischemic stroke, concerning the clinical, neurological, imaging and progressive (neurological and neuropsychological) aspects. This study is part of a larger project involving a prospective evaluation of SCD patients with and without cerebrovascular events.

METHOD

After the project approval by the Ethical Committee on Research of FCM/UNICAMP, 22 patients with SCD and age ranging from 5 to 25, who receive specific clinical and hematological attendance at Ambulatories of HC/UNICAMP, were pre-selected. After analysis of the records, 8 patients with SCD and clinical stroke validated by hematological tests and neurological imaging were selected. These patients attended the Ambulatory for Research of Cerebrovascular Disease of the Faculdade de Ciências Médicas (FCM/UNICAMP).

Patients and their parents were informed about the research objectives and procedures and agreed to participate by signing a Free Consent Agreement Form. A protocol was organized including identification data, neurological clinical exam, neuropsychological assessment, laboratorial and neurological imaging screening; data were collected from records and completed with an interview of patients and their parents.

RESULTS

Table 1 presents the identification data (gender, color, age when SCD was diagnosed, SCD initial clinical signs and age at present study).

Five patients were female; six patients had brown skin color and two were black; the SCD diagnosis was screened before the first year of age in two patients, between one and two years in five patients and at five years in one. The initial clinical signs were fatigue, pallor and the first stroke in three patients; jaundice, dehydration and acute pain crisis in two; syncope in one patient. The age of the patients during the present study ranged from 10 to 23 years old.

Table 2 presents data related to cerebrovascular event (age at stroke; type; number of events; impaired brain hemisphere; arterial territory; and neurological imaging exam).

It was observed that the first stroke occurred before two years of age in three children, patient 4 presented a second stroke during the evolution; between two and six years of age, stroke occurred in two; between seven and 10 years of age it occurred in two patients, with recurrence for case 3; and above 10 years of age, in one. The cerebrovascular events were ischemic in all patients; two patients presented clinical evidences of transient ischemic attacks (TIA) with radiological and therapeutical procedures. Both brain hemispheres were affected in six patients; the left hemisphere in one, and the right hemisphere in another. The arterial territory affected was that of the middle cerebral artery (MCA) and perforating branches, anterior cerebral artery (ACA), posterior cerebral artery (PCA), and superior cerebral artery (SCA).

Table 3 depicts data relating to the treatment of the patients; to their general clinical signs at present study; the neurological exam of the acute stroke period (I) and the neurological exam at the present study (II) conducted between 2 and 13 years after the last cerebrovascular event.

Seven patients maintain a chronic transfusion therapy for secondary prophylaxy and use of desferrioxamine. The clinical features observed at present study were: hemosiderosis in eight patients; snores and pain crises in three; sialorrhea in two; jaundice in one and cardiac murmur in another patient. Mouth breathing was found in seven patients (except on case 6). During the acute period after stroke the neurological exam revealed hemiparesis

Table 1. Identification data of and related to SCD diagnosis.

Patients	Gender	Color	Age*	Clinical signs**	Current age
1	F	Brw	3 m	jaundice	10 y
2	F	Brw	1 y 6 m	dehydration pain crisis stroke	15 y
3	F	Brw	1 y 8 m	dehydration	23 y
4	F	Brw	1 y	pain crisis stroke	12 y
5	F	B	1 y 2 m	fatigue pallor syncope	19 y
6	M	Brw	8 m	fatigue pallor jaundice	16 y
7	M	Brw	1 y	fatigue pallor	17 y
8	M	B	5 y	stroke	12 y

SCD, sickle cell disease; *age at SCD diagnosis; **clinical signs of SCD diagnosis; F, female; M, male; Brw, brown; B, black; y, years; m, months.

Table 2. SCD and stroke, general data and neurological imaging.

Patient	Age *	Type	N	Hemisphere	Arterial region	Neuro-imaging (ed)
1	9m	I stroke	1	L R	SCA PCA bilat	CT (11/95) CT (7/97)
2	1y 6m	I stroke	1	L	MCA L	CT (2/91)
3	8y 12y 13y	I stroke	4	L R	MCA ACA bilat PCA R	CT (89) CT (9/94) CT (95)
4	1y 8y 10y	I stroke (TIA) **	2 (1)	L R	ACA MCA bilat PB R	CT (4/00) SPECT (1/01)
5	11y	I stroke	1	L R	MCA PCA L ACA R	CT (7/97)
6	4y	I stroke	1	R	MCA L	CT (5/93)
7	7y 8y	I stroke (TIA) **	1 (1)	L R	MCA ACA L PB bilat	CT (8/94) CT (2/00)
8	5y	I stroke	1	L R	MCA ACA PCA BN L ACA R	CT (12/98)

SCD, sickle cell disease; *at stroke; **clinical evidence; I stroke, ischemic cerebrovascular event; TIA, transient ischemic attack; L, left; R, right; SCA, superior cerebellar artery; PCA, posterior cerebral artery; bilat., bilateral; MCA, middle cerebral artery; ACA, anterior cerebral artery; PB, perforating branches; BN, basal nucleus; ed, exam date; CT, cranial tomography; SPECT, single photon emission computed tomography.

Table 3. SCD and stroke, clinical sign and neurological exams I and II.

Patients	Treatment	Clinical Sign	Neurol Exam I	Neurol Exam II
1	Blood transf desferrioxamine	HMS	NPMR Hp R VD	global hypot VD MD
2	___	HMS pain crisis jaundice	NPMR Hp R VD	Hp R hypert R > L VD
3	Blood transf desferrioxamine	HMS sialorrhea	Hp L S aphasia	Hp L aphasia MD
4	Blood transf desferrioxamine	HMS snore	Hp L	Hp L MD
5	Blood transf desferrioxamine	HMS pain crisis snore heart murmur	Hp R	Hp R
6	Blood transf desferrioxamine	HMS	pain paresth L hand rhyme deviation	Hp R hypert R > L
7	Blood transf desferrioxamine	HMS pain crisis snore	Hp R dysphagia	hypot L
8	Blood transf desferrioxamine	HMS sialorrhea	Hp R S	Hp R aphasia MD

SCD, sickle cell disease; Neurol Ex I, at hospital discharge; Neurol Ex II, at present study; Blood transf, regular blood transfusion; HMS, hemosiderosis; NPMR, neuropsychomotor retardation; Hp, hemiparesis; R, right; L, left; hypot, hypotonia; hypert, hypertonia; VD, visual deficiency; S, seizure; MD, mental deficiency; paresth, paresthesia; ___, without information.

in seven patients; neuropsychomotor delay, visual deficit and seizure in two; each of the following symptoms was found in one patient: paresthesia; rhyme deviation; aphasia and dysphagia. In the present neurological exam it was assessed spastic hemiparesis in six patients (two with bilateral assimetric hypertonia), mental deficiency in four and visual deficit in two. Mental deficiency was detected by previously applied neuropsychologic test (WISC) and present clinical neurologic exam.

All patients received therapeutic orientation except for patient 2; hemosiderosis was found in eight patients in addition to other events such as acute pain crises, snore and sialorrhea, among others. Neurological exam I demonstrated hemiparesis in seven patients and neuropsychomotor delay in two patients. The neurological exam of the present research indicates that the uni or bilateral structure lesions in frontal, parietal, occipital, and cerebellum areas persist, according to the analysis of Tables 2 and 3.

DISCUSSION

In a study with 3647 patients with SCD it was found a predominance of ischemic cerebral events in individu-

als under 20 and above 29 years old and of hemorrhagic events in the group between 20 and 29 years of age, which determined a larger number of deaths (26%) in the latter[2].

In the present study, it was observed a predominance of brown skin female and SCD diagnosis under two years of age. Despite the low number of individuals evaluated, findings are in accordance with data of references, evidencing patients with SCD and stroke in early age, all with ischemic event. There was bilateral hemisphere involvement by stroke in six patients, with recurrence in two and a single event in four patients.

Neuropsychomotor development in SCD children was considered normal until three years of age with progressive performance decay in neuropsychological and motor function tests due to ischemic cerebral insults and/or silent infarct[9]. Similar findings was observed in this present study. The psychomotor function was intact and an early decay of cognitive functions was detected in SCD children between 12 and 24 months of age[10]. Children with SCD and ischemic stroke usually present motor deficits, aphasia, learning difficulties and cognitive impairment, and it seems that silent infarcts are the main cause of cerebral insults causing learning disorders, low intelligence quotient and other neurocognitive deficits[6,11].

Most of our patients presented vascular event after four years of age and had apparently adequate neuropsychomotor development until the stroke. The present neurological exam evidenced important neurological sequelae: motor deficit in eight patients; mental deficiency in four; aphasia and visual deficit in two patients. Throughout the assessment, we observed lack of initiative, difficulty to understand the clinical neurologic assessment and slowness in motor and speech responses.

Chronic transfusion therapy has been indicated as prophylaxis for the cerebrovascular event recurrence since 1976 by Lusher et al.[12]. Unfortunately, stroke risk returns once the transfusion scheme is interrupted. Recent studies revealed that such practice may decrease but does not eliminate totally the risk[13]. In a retrospective study, 44 patients were evaluated in blood transfusion therapy after ischemic stroke. A high index of recurrence (41%) was observed and detected the presence of collaterals Moyamoya like (43%)[14].

In this study, patients 3 and 4 presented stroke recurrence, even under prophylactic blood transfusion therapy. Both presented important motor and cognitive impairments; patient 4 also presented TIA. Even though not being an objective of the study, mental deficiency was detected in quantitative tests in patients 1, 4 and 8, and qualitative mental deficiency was observed in patient 3. Among these cases, 3 and 8 presented higher impairment in the current neurological exam, suggesting a possibility of silent infarcts determining motor sequelae, mental deficiency and aphasia.

In summary, from the eight patients, seven received prophylactic blood transfusion therapy for stroke recurrence during at least five years. Three of them had no benefit, progressing with stroke recurrence and neurological signs aggravation. The cases also revealed cerebrovascular event in younger ages and higher neurological impairment compared to literature data. Although not quantitatively analyzed, we observed important social-economic difficulties, as well as family members low level of understanding about SCD, its management and possible co-morbities. Such condition may have favored a lower adherence to treatment, thus increasing the probability of cerebrovascular events and highly impairing sequelae.

In conclusion, the present study detected the SCD diagnostic in early age with ischemic stroke identified as the initial sign in three patients; high occurrence of ischemic cerebral event in children above four years of age; stroke and TIA recurrence in spite of secondary prophylactic blood transfusion therapy; neuropsychological impairment in our patients, identified by specific tests; and it was possible to find motor impairments resulting from cortical-subcortical structure lesions involving one brain hemisphere or both.

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