THE RELATIONSHIP BETWEEN CLINICAL AND NEUROPSYCHOLOGICAL VARIABLES IN THE MENTAL HEALTH OF CHILDREN WITH SICKLE CELL DISEASE

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ABSTRACT
Objective: Compare psychological complaints of children with sickle cell disease (SCD) without clinical or radiological evidence of CVD, to a healthy group to find correlations between neuropsychological triages, clinical, and therapeutic variables. Method: A cross-sectional, descriptive, and analytical study was conducted. Sixty-five children with SCD and controls were subjected to neuropsychological avaliation while their caretakers responded to a survey on psychopathology. The results were compared between the groups and correlated with intelligence quotient (IQ), academic performance, clinical complications, and therapies. Results: The case group presented worse performance than the control group on the CBCL items referring to internalizing and externalizing problems. A direct, proportional relationship was identified between psychopathology, IQ, and academic performance. Conclusion: Children with SCD showed worse results in the psychopathological evaluation than healthy children, and psychopathological complaints were related to IQ and academic performance, which could suggest an indirect relationship between cognitive deterioration and psychopathology.

Keywords: Sickle Cell Disease; NeuropsychologyPsychopathology; Mental Health.

RELAÇÃO ENTRE VARIÁVEIS CLÍNICAS E DESEMPENHO NEUROPSICOLÓGICO NA SAÚDE MENTAL DE CRIANÇAS COM DOENÇA FALCIFOME

RESUMO
Objetivo: Comparar queixas psicopatológicas em crianças com doença falciforme sem evidências clínicas ou radiológicas de doença cerebrovascular em relação a um grupo saudável os resultados com avaliação neuropsicológica, variáveis clínicas e terapêuticas. Método: Estudo transversal, descritivo e analítico. Sessenta e cinco crianças com DF e controles foram submetidas à avaliação neuropsicológica e o cuidador respondeu questionário sobre psicopatologia. Os resultados foram comparados entre os grupos e correlacionados ao quoeficiente de inteligência (QI), desempenho acadêmico, complicações clínicas, e terapias (hidroxiuréia e hipertransfusão).Resultados: O grupo caso apresentou pior desempenho do que o grupo controles nos itens do CBCL em problemas internalizantes e externalizantes. Identificou-se relação diretamente proporcional entre psicopatologia e QI e desempenho escolar. Conclusão: Crianças com DF apresentaram piores resultados na avaliação psicopatológica do que crianças saudáveis, sendo que queixas psicopatológicas estão relacionadas ao quociente de inteligência e desempenho acadêmico, apontando para uma relação indireta entre deterioração cognitiva e psicopatologia.

Palavras-chave: Doença Falciforme; Neuropsicologia; Psicopatologia; Saúde Mental.

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INTRODUCTION

Sickle cell disease (SCD) is a genetic blood disorder with three better known and investigated subtypes: sickle cell anemia, sickle beta-thalassemia, and sickle cell hemoglobin C disease.[1] Approximately 7% of the world's population is affected by hemoglobinopathies.[2] In Brazil, the prevalence is from 0.1% to 0.3% among the black population.[3, 4] SCD is also present in other portions of the population due to the high index of miscegenation, affecting between 20–30,000 Brazilians.[5]

The highest risk of death from SCD comes from bacterial infections in infancy, splenic sequestration, aplastic crisis, acute chest syndrome, neurological complications, and vaso-occlusive episodes.[6, 7, 8] Since cerebrovascular accidents (CVA) are the primary risks in life for children with SCD, SCD carriers are at greater risk of acquiring cerebrovascular disease (CVD), which is 221 to 300 times more frequent in this population.[6, 9-10] An important neurological event within SCD is a silent stroke, defined as an ischemic change in the brain tissue visible on a magnetic resonance image (MRI); these are two times more frequent than a CVA [11]. The application of new technologies, such as MRIs and Transcranial Doppler, indicate that CVD develops progressively before clinical signs and symptoms appear, or before it can be seen in a conventional MRI, indicating the existence of cognitive deficits without the presence of any evident brain injury. It highlights, however, the importance of neuropsychological evaluations in patients without a history of CVAs, to investigate for possible cognitive deficits and learning difficulties.[6, 8, 12-14]

Studies show a positive relationship between mental disorders and chronic diseases because the illness includes experiences that can compromise the "normal" development of a child.[15] With respect to mental disorders in SCD, the disease can be a detriment to development and cause delays in sexual maturity, psychological disturbances, and difficulties relating to partners, placing this population at risk of psychological and emotional imbalance and impairment.[16] The most investigated psychopathologies in this population are anxiety disorders, characterized as internalizing problems, and rule-breaking and/or aggressive behavior, which are characterized as externalizing problems.[7, 16] Studies on the relationship between the brain and psychopathology in children with SCD are incipient and controversial since they present different methodologies and heterogeneous samples.[18–20] According to Schatz et al.[20], it is not clear which variables can compromise the central nervous system (CNS) of a patient with SCD, considering that many variables have the potential

to cause cognitive deficits, including successive micro-infarcts, chronic hypoxia, related to severe anemia, acute hypoxia, related to physical complications, and nutritional impairment. Beyond this, there are the indirect effects of social and environmental conditions. With respect to Brazilian studies, there is no literature on this type of correlation.

Kral et al.[6], defend the use of a neuropsychological evaluation as a possible "marker" for pathologies in the CNS in order to develop proper prevention and interventions for this group, despite inconsistencies found in the literature on the presence of cognitive deficits in children with SCD. This view is based on the understanding that the existence of an abnormal hemoglobin triggers countless processes that will compromise the CNS. Because of this, Schatz et al.[20] came to believe that this originally hematological disease, even though it has great neuro-cognitive repercussions, is like a neurodevelopmental disease. In the opinion of this author, neurodevelopmental diseases are characterized as a heterogeneous group of diseases, such as genetic diseases, acquired pre-natal diseases, or acquired perinatal brain injuries, which represent the presence of an abnormal condition at birth that affects the CNS, and are able to, as a consequence, have psychological or neuropsychological impacts.

This study aims to analyze the interrelationships between psychopathological complaints, neuropsychological results, and clinical variables in children without a diagnosed CVD, to infer the existence of a relationship between the SCD neurological pathophysiology and psychopathology.

METHODS

Subjects included patients with SCD, between[8–12] years of age, without alterations in an MRI or a history of CVD, regularly seen in the outpatient pediatrics ward at the Arthur Cavalcanti de Siqueira State Hematology Institute [Instituto Estadual de Hematologia Arthur Cavalcanti de Siqueira] (HEMORIO). The patients had to be in at least the 1st year of elementary school, registered, and attending school regularly.

The exclusion criteria included: a history of CVA/CVI, epilepsy, meningoencephalitis, use of anti-epileptic or psychotropic medications, or the presence of severe/chronic comorbidities or auditory complaints.

Socio-demographic and academic data were collected from the patients. The following data was collected from the caretakers: sex, age, degree of kinship, and

schooling. The clinical data were obtained by consulting the patient's chart.

Initially, 100 children were selected. After triage, 84 patients went through the neuropsychological evaluation and completed the CBCL. Sixty-five patients completed all of the steps in the study (22.6% loss). The CBCL was the instrument that showed the greatest loss due to it being self-completed. The controls were paired by sex and age; siblings, cousins, and neighbors were chosen with the aim of minimizing economic and educational differences.

With respect to the socio-demographic data, children from the case group had an average age of 9.5 ± 1.37 years. Thirty-six patients (55.4%) were female and 29 (44.6%) were male. The average schooling of the case group was 3.3 years ± 1.4, which denotes a one academic year lag compared to the average age. The schooling for the control group was 4.21 years ± 1.24, which was within what was expected with respect to age and the corresponding school year.

The caretaker who completed the CBCL for 55 patients (84.6%) was the mother, and the father was the caretaker for 6 patients (9.2%); others completed the CBCL for 4 patients (4.2%). The average schooling for the caretakers was 9.3 ± 2.8 years. The caretakers who completed the CBCL for the control group was the mother for 54 patients (83%), the father for 4 patients (6.2%), and others for 7 patients (10.8%). With respect to those responsible for the control group, the average schooling was 9.6 ± 3.46.

With respect to hemoglobinopathy, 47 presented SS hemoglobinopathy (72.3%) and 18 SC (27.7%). No caretaker presented with SCD. Five children showed visual deficits (7.7%), all of which used visual correction. There were no cases of priapism. Only one did a transfusion scheme, representing 1.5% of the sample. Twenty-one children (32.3%) used hydroxyurea and 17 (26.1%) showed at least one acute chest syndrome crisis in the last year.

The caretakers received explanations informing them of the content of the informed consent and the study was approved by the local ethics committee (No. 145/08).

INSTRUMENTS

The CBCL (Child Behavior Checklist) survey aims to collect information and evaluate social and academic competencies, adaptive functioning, and psychopathological problems in a simple and low-cost way for children and adolescents

in the[6–18] year age group. The survey should be completed by the parents/main caretakers or other people who live with the child. The respondent should evaluate and categorize the child's behavior with 112 items that refer to behavioral, emotional, and social aspects observed in the six months prior to filling in the CBCL. The data from the survey are entered into a properly computerized data bank that generates scores that can be presented as gross scores, T scores, or percentiles.[21]

The Weschler Intelligence Scale for Children (WISC-III)[22] was used to obtain the total IQ for neuropsychological triage along with the Academic Performance Test (APT), an academic performance test [23] designed to evaluate academic performance in reading, writing and math. The WISC-III is a clinical instrument for individual application that aims to evaluate the intellectual ability of children and adolescents from 6–16 years and 11 months of age, serving as a guide for possible cognitive dysfunctions and pointing to strong and weak points. The APT is an instrument that evaluates the fundamental abilities required for academic performance, specifically, in writing, math, and reading. It indicates, comprehensively, the areas of academic learning that are preserved or impaired in the person being tested. The age group covers the evaluation of students from the 1st to the 6th grade in elementary school.

STATISTICAL ASPECTS

The Statistical Package for Social Sciences Release (SPSS) 17.0 for Windows was used. Basic aspects of the data were presented using descriptive statistics. The qualitative variables (dichotomous and polytomous categories) were described in the form of simple frequencies, and quantitative ones were described using averages, limits, and standard deviations (SD).

Non-parametric tests including the Mann-Whitney, and Spearman's correlation coefficients were used, with a two-sided p value less than 0.05 as the level of significance.

The hypotheses of the study were as follows: 1) children with SCD will show worse performance on the CBCL than the control group and have a greater prevalence of internalizing problems; 2) there will be an inversely proportional relationship between IQ and academic performance with psychopathological variables; 3) there will be a positive relationship between psychopathology and the clinical variable of severity (STA), and 4) finally, a negative relationship exists between psychopathology and the clinical therapeutic variable, use of hydroxyurea.

RESULTS

CBCL Results

Table 1 shows the results from the CBCL when compared with the performance of the cases and controls. The control group showed worse performance with respect to the following themes: CBCL profile, CBCL competencies, disorders outlined in the DSM-IV, and other problems. There was no significant statistical difference in the items for academic competency, the DSM-IV items for ADHD, oppositional defiant disorder, conduct disorder, slow cognitive time, and externalizing problems.

Table 1 - Patients' and controls' performance on the CBCL

CBCL	Patients with SCD	Healthy Controls	*p**
CBCL Profile			
Internalizing	13.98 ± 6.68	9.01 ± 6.61	**0.000**
Externalizing	13.20 ± 7.58	10.50 ± 9.08	**0.027**
Total Problems	49.0 ± 20.66	36.13 ± 25.08	**0.002**
CBCL Competencies			
Activities	6.93 ± 3.30	5.37 ± 5.37	**0.013**
Social	7.41 ± 2.32	5.32 ± 5.32	**0.002**
DSM-IV Scale			
Affective	4.92 ± 2.89	2.84 ± 2.51	**0.000**
Anxiety	3.35 ± 2.33	2.32 ± 1.85	**0.012**
Somatic	2.87 ± 2.56	1.70 ± 1.94	**0.003**
Obsessive-Compulsive	3.67 ± 2.86	2.61 ± 2.30	**0.038**
Post-Traumatic Stress	9.53 ± 5.35	7.96 ± 7.32	**0.033**
Other Problems			
Social Problems	5.75 ± 3.22	3.59 ± 3.40	**0.001**
Thinking Problems	3.32 ± 2.33	2.32 ± 2.15	**0.010**
Attention Problems	4.89 ± 3.17	2.63 ± 2.69	**0.000**

p<0,005

5.2 Comparison between the neuropsychological and academic profile and the CBCL

There was a positive relationship between the IQ and psychopathology in the items shown in table 2. With respect to the comparison between academic performance and psychopathology, there was only a correlation between academic performance and attention deficit and hyperactive disorder (ADHD) (p = 0.05).

Table 2 - Comparison between IQ and CBCL

CBCL		**Total IQ** ***p****
CBCL Profile		
Externalizing		**0.031**
CBCL Competencies		
Activities		**0.043**
DSM-IV Scale		
Anxiety		**0.031**
Oppositional Defiant		**0.047**
Internalizing		
Anxious/Depressed		**0.041**
Other Problems		
Social Problems		**0.043**

p<0,005

5.3 CBCL x clinical and therapeutic variable comparison

There was no significant relationship between the psychopathological symptoms and the occurrence of STA or the use of hydroxyurea (tables 3 and 4)

Table 3 - CBCL and STA clinical variable comparison

CBCL	STA SS SSD	STA SC SSD	*p*
CBCL Profile			
Internalizing	14.20 ± 6.71	13.35 ± 6.76	0.441
Externalizing	13.60 ± 7.53	12.05 ± 7.84	0.338
Total Problems	50.20 ± 21.08	45.94 ± 19.69	0.416
CBCL Competencies			
Activities	7.29 ± 3.01	5.91 ± 3.93	0.183
Social	7.45 ± 2.43	7.29 ± 2.06	0.883
School	4.30 ± 0.94	3.94 ± 1.40	0.492
DSM-IV Scale			
Affective	4.91 ± 2.99	4.94 ± 2.65	0.946
Anxiety	3.53 ± 2.29	2.88 ± 2.44	0.275
Somatic	2.75 ± 2.38	3.23 ± 3.07	0.683
ADHD	6.45 ± 4.08	6.17 ± 3.87	0.764
Oppositional Defiant	3.31 ± 2.05	2.64 ± 1.86	0.263
Conduct Disorder	3.91 ± 3.43	3.41 ± 3.75	0.434
Slow Cognitive Time	6.52 ± 4.05	6.52 ± 4.62	0.822
Obsessive-Compulsive	3.68 ± 2.80	3.64 ± 3.10	0.857
Post-Traumatic Stress	9.93 ± 5.38	8.41 ± 5.25	0.243
Internalizing			
Anxious/Depressed	1.31 ± 1.30	1.35 ± 1.53	0.907
Isolated/Depressed	2.68 ± 1.76	2.05 ± 1.91	0.683
Somatic Complaints	7.35 ± 4.44	6.00 ± 3.98	0.205
Externalizing			
Rule-Breaker Behavior	5.27 ± 3.07	4.94 ± 2.58	0.713
Aggressive Behavior	2.20 ± 2.01	2.00 ± 2.17	0.564
Other Problems			
Social Problems	6.00 ± 3.33	5.05 ± 2.88	0.310
Thinking Problems	3.47 ± 2.36	2.88 ± 2.26	0.281
Attention Problems	4.70 ± 2.97	5.41 ± 3.74	0.718

$p<0,005$

Table 4 - CBCL compared with the use of hydroxyurea

CBCL	HA SS SCD	HA SC SCD	*p*
CBCL Profile			
Internalizing	13.93 ± 7.41	14.09 ± 4.97	0.678
Externalizing	13.02 ± 7.69	13.57 ± 7.52	0.618
Total Problems	48.72 ± 22.42	49.85 ± 16.86	0.758
CBCL Competencies			
Activities	6.97 ± 3.27	6.83 ± 3.43	0.730
Social	7.23 ± 2.41	7.78 ± 2.13	0.378
School	4.26 ± 1.05	4.09 ± 1.16	0.528
DSM-IV Scale			
Affective	4.68 ± 3.13	5.42 ± 2.29	0.187
Anxiety	3.63 ± 2.49	2.76 ± 1.86	0.243
Somatic	2.63 ± 2.71	3.38 ± 2.20	0.100
ADHD	6.27 ± 4.16	6.61 ± 2.74	0.607
Oppositional defiant	3.13 ± 2.10	3.14 ± 1.85	0.921
Conduct Disorder	3.70 ± 3.50	3.95 ± 3.55	0.703
Slow Cognitive Time	6.34 ± 4.20	6.90 ± 4.18	0.578
Obsessive-Compulsive	3.56 ± 2.73	3.90 ± 3.16	0.905
Post-Traumatic Stress	9.47 ± 5.59	9.66 ± 4.92	0.905
Internalizing			
Anxious/Depressed	1.31 ± 1.37	1.33 ± 1.35	0.913
Isolated/Depressed	2.72 ± 1.99	2.09 ± 1.30	0.278
Somatic Complaints	7.38 ± 4.90	6.19 ± 2.74	0.540
Externalizing			
Rule-Breaker Behavior	5.11 ± 2.93	5.33 ± 3.00	0.949
Aggressive Behavior	2.34 ± 2.23	1.76 ± 1.54	0.449
Other Problems			
Social Problems	5.97 ± 3.59	5.28 ± 2.28	0.810
Thinking Problems	3.31 ± 2.53	3.33 ± 1.93	0.671
Attention Problems	4.59 ± 3.26	5.52 ± 2.96	0.168

$p<0,005$

6 DISCUSSION

This study suggests that children with SCD present greater psychopathological indexes, highlighting internalizing and externalizing, affective, somatic, thinking, attention, , social, and total problems; anxiety; obsessive-compulsive disorder, and post-traumatic stress. In accordance with Thompson et al. [19], Benton et al. [7], and Yang et al. [16], children with SCD present a greater frequency of internalizing problems, similar to children who have other chronic diseases. However, in our study, there is a significant difference in the externalizing problems and the total problems as well. With respect to externalizing problems, Thompson et al.[19] and Alao et al.[21] highlight that externalizing types of behavior problems in children can occur due to two great mechanisms: injury to cerebral functioning or emotional or family dysfunction due to a chronic disease.

Children with SCD also show a greater frequency of complaints with respect to attention/hyperactivity, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder. With respect to the PTSD group in biographical reviews, we identified only one article about PTSD by Hofmann et al.[17]

The sample size was similar to other studies on psychopathology and SCD [12, 17]. The children that were evaluated were, on average, less than ten years old, and there was a balanced representation of the sexes. The average schooling was behind with respect to what was expected for the average age, which was also compatible with what was described in the literature regarding academic performance by children with SCD.[6, 14, 24]

In our sample, the children showed an IQ within what was expected for their age group and schooling; however, it was comparably less than the control group, which leads us to think that children with SCD in this sample did not show evidence of CVD. This is a characterization of a benign sample from a cerebrovascular point-of-view, although the transversal character of the study prevents us from commenting on what the tendency of this IQ would be over time. The environmental factors of chronic disease could also have been an influence. Studies on neuropsychology in SCD [12, 18, 20, 24] assessed children with a history of CVA or silent stroke by in comparison to a healthy control group. In our work, no children presented with any changes in the MRI, which was one of the exclusion criteria. Authors like Kral et al.[6], Steen et al. [12], and Bernaudin et al.[13] assert that CVD has a progressive course and the neuropsychological evaluation is a possible marker for cognitive deficits prior to detection in neurological

frameworks. In one perspective of the development of the disease, it is possible that our study could be inserted at a stage prior to the evident structural changes, in which the psychopathological and learning impacts have already been demonstrated.

Upon crossing the clinical variables and psychopathology, there was no statistically significant correlation between STA and CBCL variables. When comparing hydroxyurea and psychopathology, there is no statistically significant correlation, but there is a directly proportional relationship, a fact that was not expected. Hydroxyurea elevates the levels of fetal hemoglobin with little or no collateral effect.[25] According to Silva et al.,[3] this therapy has been extremely beneficial, reducing the frequency of hypertransfusion, preventing organ injury, and helping to reduce vaso-occlusive events. The protective potential of hydroxyurea leads us to reflect on the positive relationship with psychopathology and some variables that were not mapped in this study, such as the amount of time using hydroxyurea, hemoglobin level at the time of the study, and possible adverse reactions from hydroxyurea that could have directly influenced this result. It was not possible to compare variables that did not exist or were of a small positive number such as priaprism and hypertransfusion.

7 CONCLUSION

The results of this study show that children with SCD show greater behavioral problems mapped by the CBCL when compared to the control group. There is a directly proportional relationship between IQ and academic performance with respect to psychopathology, however, there was no significant correlation found between psychopathology and clinical variables.

This study is relevant because it attempts to relate psychopathology and cognitive functioning in children without evidence of CVD. Attempting to understand the cerebral functioning of children with SCD does not show a causal relationship and unidirectional consequence between IQ, academic performance, clinical variables, and psychopathology.

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Abbreviations

HEMORIO – Arthur Cavalcanti de Siqueira State Hematology Institute (Instituto Estadual de Hematologia Arthur Cavalcanti de Siqueira)

CBCL – Child Behavior Checklist

SCD – sickle cell disease

CVA – cerebrovascular accident

MRI – magnetic resonance imaging

CNS – central nervous system

WISC-III – Weschler Intelligence Scale for Children

APT– Academic performance test

SPSS – Statistical Package for Social Sciences

CSV – clinical variable of severity

ADHD -- attention deficit and hyperactive disorder

PTSD – post-traumatic stress disorder

OCD – obsessive compulsive disorder