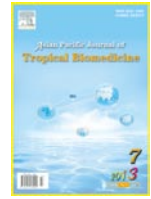




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Neurocognitive sequelae of cerebral malaria in adults: A pilot study in Benguela Central Hospital, Angola

Bruno Peixoto^{1*}, Isabel Kalei²¹Sciences Department of the Instituto Superior de Ciências da Saúde– Norte (CESPU), Research Unit on Psychology and Health, Gandra, Portugal²Central Hospital of Benguela, Benguela, Angola

PEER REVIEW

Peer reviewer

Corsina Velazco Henriques, MSc., PhD, Full Professor for Microbiology, Health Sciences University, Institut Cooperativa de Ensino Superior, Politécnico e Universitário, CESPU, CRL, Rua Central de Gandra, 1317, 4585–116 GANDRA PRD, Portugal.
Tel: +351–224 157 193
E-mail: corsina.henriques@iscsn.cespu.pt

Comments

The study of the neuropsychological assessment of malaria sequel carried out by the authors in adult patients would add and promote wider studies of this tragic disease, adding the already reduced number of jobs that can contribute to the prevention, control and treatment of malaria.
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ABSTRACT

Objective: To characterize the neurocognitive sequelae of cerebral malaria (CM) in an adult sample of the city of Benguela, Angola. **Methods:** A neuropsychological assessment was carried out in 22 subjects with prior history of CM ranging from 6 to 12 months after the infection. The obtained results were compared to a control group with no previous history of cerebral malaria. The study was conducted in Benguela Central Hospital, Angola in 2011. **Results:** CM group obtained lower results on the two last trials of a verbal learning task and on an abstract reasoning test. **Conclusions:** CM is associated to a slower verbal learning rate and to difficulties in the ability to discriminate and perceive relations between new elements.

KEYWORDS

Cognition, Neuropsychological assessment, Verbal learning, Abstract reasoning, *Plasmodium falciparum*, Angola

1. Introduction

Malaria caused by the *Plasmodium falciparum* (*P. falciparum*) affects 500 million people worldwide and causes 2.7 million deaths every year^[1]. In 2009, 3 million of Angolans were affected by the infection and almost 8 thousand died^[2].

Cerebral malaria (CM) is an encephalopathy resulting of the *P. falciparum* infection with frequency rates ranging from 0.001% to 37.200% in adult patients^[3–5]. According to the World Health Organization (WHO), CM is defined

as unrousable coma (non-purposeful response or no response to a painful stimulus) in a patient with evidence of peripheral parasitaemia and exclusion of other precipitating factors such as hypoglycemia, meningitis, encephalitis and post-ictal state^[1,6].

The most common clinical features of CM in adults are fever, headaches, anorexia, gradual disorientation, delirium and agitation, tonic-clonic seizures, jaundice^[3,7–9], symmetrical upper-motor-neuron signs, multisystem dysfunction and coma.

In some cases, after an episode of CM, several

*Corresponding author: Dr. Bruno Peixoto, Sciences Department of the Instituto Superior de Ciências da Saúde– Norte (CESPU), Rua Central de Gandra 1317, 4585–116 Gandra, Portugal.

Tel: +351 962501501

Fax: +351 224157102

E-mail: bruno.peixoto@iscsn.cespu.pt

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neurological abnormalities can persist up to 2 months after recovery, which is known as post-malaria neurological syndrome^[10]. This syndrome includes clinical features such as psychotic or acute confusional episodes, generalized convulsions and tremor, and it is directly related to the use of oral mefloquin^[10].

The characterization of long term neurocognitive sequelae of CM has been extensively studied in children. Impairments in a wide range of cognitive functions including memory, attention, language and executive functions have been reported^[11,12]. However, neurocognitive sequelae after CM in adults are not well documented^[13,14].

Therefore, the aim of the present study was to characterize the neurocognitive sequelae of CM in an adult sample of the city of Benguela, Angola.

2. Materials and methods

2.1. Study area

The city of Benguela lies on the central west region of the Republic of Angola and it is the capital of the province with the same name. The demographic density of the city is 223.5 inhabitants/km². The province landscape is marked by stepped plateaus cut by valleys and rivers; most of these rivers are dry and accumulate water on the raining seasons. The temperatures peak at 35 °C in summer (October to April) and fall to 10 °C in winter (May to August). The average relative humidity is 79% and there is an annual rain fall of 200 mm.

The city of Benguela presents serious weaknesses in terms of sanitation, drainage of rainwater and housing conditions.

2.2. Sample

The sample was divided into two groups: CM group composed by 22 subjects from the Central Hospital Benguela outpatient clinic diagnosed with CM according to the WHO's criteria, in the past 6–12 months prior to the neuropsychological assessment and Control group (CG) made of 19 adults without clinical history of CM. Characteristics of the two groups are shown in Table 1. The groups do not differ significantly regarding age ($P=0.095$), gender ($\chi^2=2.54$; $P=0.28$) and years of education ($P=0.057$).

Table 1

Characteristics of the sample.

Group	Gender		Age (years)	Years of education
	Male	Female		
Control group	9	10	23.63±8.85	9.19±3.23
Cerebral malaria group	15	7	28.92±10.01	7.08±1.74

The age and years of education are expressed as mean±SD.

Subjects with previous history of neurologic, psychiatric or systemic conditions or the presence of deficits in the neurological examination were excluded from the study.

2.3. Neuropsychological assessment

2.3.1. Wechsler's digit test

In this trial, we started with a series of three digits in the digit forward (DF) test and two digits in digits back (DB) test, up to the maximum series of 9 and 8 digits respectively. If the subject fails both trials in a given series, the test is terminated. The score was calculated on the basis of the results from the last series done. Through these tasks, we sought to evaluate the attentional efficiency and capacity to resist distraction^[15], as well as its influence on the capacity of immediate auditory and verbal memory recall^[16].

2.3.2. Verbal initiative

This task was retrieved from the Battery of Neuropsychological Assessment–Barcelona. In this task the subject must evoke in 1 minute words beginning with a given letter (e.g., "P"). This task was used in order to assess verbal fluency^[17].

2.3.3. Spanish verbal learning test–Complutense

From this test, we had selected a list of words. It consisted in reading to the subject a list of fifteen words, which must be immediately evoked. This procedure was repeated with the same word list over five trials. The score was the number of correct answers in each trial, and the perseverations are not considered to the final score. This test is for the assessment of the learning curve, retention of information in the short and long term, use of learning strategies and susceptibility to interference^[18].

2.3.4. Wechsler's matrices

In this task, a matrix with a missing element was presented to the subject and then he must select one of five alternatives to complete it. The final score was the number of correct selections. This task is a measure abstract reasoning^[19].

2.3.5. Wechsler's symbol search

In this task, the subject must decide by ticking the appropriate box, if one of the two symbols on right side of the sheet is present in a series of five symbols presented on the left side. The final score of this task corresponds to the difference between the correct and incorrect number of identified items in a period of 120 seconds. The performance on this task appealed to a good perceptive discriminatory capacity and visual attention^[19].

2.4. Procedure

This research protocol was approved by the hospital's ethics committee. The participants were recruited from the outpatient clinic at the Central Hospital of Benguela, according to analyses of the clinical charts. Patients with other health conditions, either neurologic or systemic, were excluded. The neuropsychological assessment was performed by the same researcher in a closed room. Identical procedures were taken for the assessment of the control group.

2.5. Statistical analysis

Statistical analysis was performed using the program SPSS for Windows version 18.0.

A comparison of the obtained results on the neuropsychological tasks by the two groups was made through the Mann–Withney’s U test. Significance was determined with $P \leq 0.05$.

3. Results

The results obtained by the two groups on the neuropsychological tasks are presented in Table 2.

Table 3 shows the comparisons of the neurocognitive performance of the two groups. The CM group obtained significantly lower results on trial 4 and 5 of list of words and matrices task.

Table 2

Descriptive statistics of the results obtained by the two groups.

Tests	Groups	<i>n</i>	<i>X</i>	SD
Digits forward	Malaria	22	5.810	2.073
	Control	19	5.840	1.068
Digits backward	Malaria	22	4.940	1.181
	Control	19	4.960	1.207
Verbal initiative	Malaria	22	12.250	3.568
	Control	19	12.040	2.776
List of words 1	Malaria	22	8.920	1.115
	Control	19	9.190	2.257
List of words 2	Malaria	22	10.040	1.020
	Control	19	10.560	2.159
List of words 3	Malaria	22	11.240	0.970
	Control	19	12.000	1.751
List of words 4	Malaria	22	12.040	0.790
	Control	19	13.130	1.821
List of words 5	Malaria	22	13.000	1.000
	Control	19	13.940	2.144
Matrices	Malaria	22	10.320	1.676
	Control	19	12.440	2.337
Symbol search	Malaria	22	39.160	7.526
	Control	19	41.560	12.516

Table 3

Comparison of the obtained results (Mean rank) through the Mann–Whitney’s U test.

Tests	Control group	Cerebral malaria group	<i>P</i>
Digits forward	22.03	20.34	0.651
Digits backward	21.34	20.78	0.879
Verbal initiative	21.16	20.90	0.946
List of words 1	23.66	19.30	0.240
List of words 2	23.91	19.14	0.200
List of words 3	24.34	18.86	0.141
List of words 4	26.53	17.46	0.015
List of words 5	25.53	18.10	0.046
Matrices	27.97	16.54	0.020
Symbol search	21.78	20.50	0.748

4. Discussion

The neurocognitive sequelae of CM is mainly a pediatric theme due to the fact that adults from endemic regions often become a symptomless carrier due to the strengthening of immunity. Despite the severity of the neurological impairments in adults is lesser than in children, there is a growing body of evidence suggesting that the falciparum infection may lead to neurocognitive impairments in this population.

The aim of this study was to determine the neurocognitive sequelae of CM adults from the province of Benguela, Angola. The obtained results pointed to impairments in verbal learning and in abstract reasoning in the CM group. In the verbal learning task, CM group showed a steady learning curve, but the number of evoked words was significantly inferior in trials 4 and 5. This performance, in the absence of an immediate memory deficit (normal results on digits forward and on the first learning trail), was highly suggestive of a slower learning rate in these subjects[16]. These data contrasted previous reports that suggested immediate memory deficits following cerebral malaria[14,20]. Abstract reasoning implied in the resolution of the matrices task refers to ability to discriminate and perceive relations between new elements. Functional magnetic resonance studies related the performance on this task to activations in cerebral areas associated to both verbal and spatial working memory[21]. The possible compromise of the two working memory systems as a result of cerebral malaria should be further investigated in the future. Verbal fluency, immediate auditory and verbal memory and perceptive discrimination, seem to be unaffected.

Taking together, these results are not easily compared to those in previous studies for three main reasons. Firstly, there are considerable differences between studies regarding the diagnostic criteria used for the sample selection, some used the definition of cerebral malaria, but with no reference to the diagnostic criteria[14,22], while others used the criteria for severe malaria[20]. Secondly, there is a considerable difference between the period of time running from the infection to the moment of the neuropsychological assessment, ranging from 6 months to over 20 years[14,20]; Thirdly, there is a great diversity concerning the neuropsychological tasks that have been used. In this context, we propose the formation of an international work party with the sole purpose of defining the directives for future research in this field.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

CM is observed in patients infected with *P. falciparum*, with the highest incidence in children. Several neurological abnormalities can persist in adults after an episode of CM, neurocognitive sequelae, which can harm the individual adult in their quality of life or schooling of children.

Research frontiers

This study uses neurological tests to assess neurocognitive sequelae of a group of 22 patients with CM after 6–12 months infection, compared with a control group of 19 people without CM. The CM group presented a slower verbal learning and difficulties to perceive relations between new elements.

Related reports

The methodology used for the neuropsychological assessment of the patients seems suitable according the recommendations of WHO.

Innovations and breakthroughs

Neurocognitive assessment studies in adult patients with sequelae of CM have been little studied. As noted by the authors, there is scarce research about these changes in adults. Longitudinal studies are especially aimed at children, perhaps because CM is fatal in this age group.

Applications

Malaria is one of the diseases that causes more serious neurological sequelae and/or death in children and adults in tropical countries, in particular, Africa, after infection with *P. falciparum*. The tests used in this study can be a useful tool to start sooner antipaludism treatments and perform an appropriate follow-up.

Peer review

The study carried out by the authors in adult patients would add and promote wider studies of malaria, adding the already reduced number of jobs that can contribute to the prevention, control and treatment of malaria.

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