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Neuropsychological assessment of refractory epilepsy in children – a case series in neuropediatric outpatient clinic

Abstract

Epilepsy is reported as a brain disorder where it has a persistent predisposition to epileptic seizures, which may give rise to neurobiological, cognitive, psychological and social sequels. The aim of this study was to characterize the cognitive performance of children with refractory epilepsy in a specialized outpatient clinic, in order to observe the neuropsychological development of these patients.

Method This investigation followed a quantitative method of case series study. Nine children from a hospital's neuropediatric outpatient clinic with an average age of 8.6 years-old (md=11; sd=2,10) were evaluated, with seven boys and two girls. The cognitive functions assessed were language, arithmetical and motors skills, intelligence, memory and executive functions.

Results Of the nine patients assessed, there were five different types of epilepsy, being very difficult to standardize the group. There was no statistical significance related to patients' IQ when compared to the mean standardized value of 90. However, it may be observed that the patients who had the earlier onset of the crises presented the lower IQ. There were important deficits in the attention and in the activities related to the verbal fluency of the evaluated patients.

Conclusion It is known that epilepsy is a syndrome, which can often be disabling, present in a significant portion of the population. Studies on the condition must be performed in order to increase the understanding and the interest of the professionals for a better treatment of these patients.

Keywords: refractory epilepsy, intractable epilepsies, medication resistant epilepsies, neuropsychological assessment, children

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Tatiane Trivilin,[1] Prof. Dr. Francisco Scornavacca,[2] Prof. Dr. Gabriela P. Wagner[3]

[1]PhD student in the Psychology program, Federal University of Rio Grande do Sul (UFRGS), Brazil
[2]Department of Pediatrics, Federal University of Health Sciences of Porto Alegre (UFCSPA), Brazil
[3]Department of Psychology and Postgraduate Program in Psychology and Health (PPG PSICO), Federal University of Health Sciences of Porto Alegre (UFCSPA), Brazil

Correspondence: Tatiane Trivilin, PhD student in the Psychology program, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil, Tel +55 51982413565, Email tatianetr.psi@gmail.com

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Introduction

E.of epilepsy. There is still much to advance in this field, especially with the improvement of technology, especially in genetics and neuroimaging. In general, epilepsy is reported as a brain disorder that has a persistent predisposition to epileptic seizures, which may give rise to neurobiological, cognitive, psychological and social sequels.[2]

Classification also informs the risks of comorbidities including learning difficulties, intellectual disability, psychiatric features such as autism spectrum disorder, and mortality. The classification often guides the selection of antiepileptic therapies.[3]

Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepilepctic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[4] Between 7 and 10% of individuals in general had some type of epileptic seizure at some time in their lives, and the lifetime risk of epilepsy is 3%.[5]

According to the World Health Organization (WHO), the worldwide prevalence of active epilepsy is around 0,5% to 1% of the general population (all age groups) and around 30% of these cases present some kind of refractory epilepsy.

In order to discuss the standardization of the refractory epilepsy's diagnosis, the ILAE conducted a large study with several health professionals, where it was determined the definition of three categories that may facilitate the diagnosis:

"Seizure free": this term refers to any variety of seizures , including auras; there is a consensus that, in order to be considered free of seizures, the patient should be at least three times longer without seizures than the normal seizure intervals and this period cannot be less than twelve months;

"Undefined": if the patient is free from seizures three times the interval determined to be considered "free of seizures", but in less than e months has a seizure, the seizure control should be categorized as indefinite or indeterminate ; and,"Treatment Failure": if the patient has more than one seizure before the age of twelve months, treatment should be categorized as "failed".[4]

It is important to emphasize that the diagnosis of refractory epilepsy does not imply a withdrawal from the patient's treatment. In some cases, patients with refractory epilepsy can be free of convulsions with some antiepileptic drug.[4,6] A patient may be classified in at least one of the three above-mentioned options to be considered refractory to treatment.

The manifestations of refractory epilepsy are much more heterogeneous in children than in adults. In addition, more severe forms of epilepsy begin in childhood. The etiological factors and

syndromes presented by children are much more diverse than those presented by adults.[7]

It is also emphasized that epilepsy is one of the most prevalent and potentially disabling chronic disorders throughout life.[7] Usually, epilepsy is accompanied by neuropsychiatric and systemic comorbidities.[7] Some of childhood-initiated epilepsies are typically associated with intellectual development disorders.[8] Like any other neurological disease, epilepsy may be associated with cognitive deficits and behavioral and emotional changes that may be as symptoms of the condition as a result of cerebral maturation that allow greater awareness of the deficits.[7] However, it is important to emphasize that not all people with refractory epilepsy will present cognitive, behavioral or emotional symptoms.[8]

The aim of neuropsychological evaluation is to identify the cognitive difficulties related to epilepsy and its etiological attribution to lesions, epilepsy activity, drug treatments and the way in which the neuropsychological development of the patient of any age group occurs.[9] Only after occurs significant changes in the child's cognitive or adaptive functioning, neuropsychological services been provided (Hardy, Olson, Cox, Kennedy & Walsh, 2017).[10] Despite this, neuropsychology has become one of the essential components of periodic children health consultations, requiring the use of appropriate instruments for this purpose, such as neuropsychological tests and scales for the evaluation of the child development.[11,12] A typical neuropsychological assessment should present different components: history of development; academic achievements; behavioral, emotional and social assessment.[7] These components should be investigated beyond of the cognitive processes.

The pattern of deficits observed in patients after evaluation usually reflects the functions controlled with the participation of the area that produces the epileptic focus.[13] Child neuropsychological assessment should investigate both general and specific cognitive abilities, motor, visual and auditory perception, verbal and non-verbal skills, memory systems, executive functions and academic abilities.[7]

There are no studies reporting neuropsychological assessment protocols in children with epilepsy who are not undergoing surgery. Currently, there is still little work involving refractory epilepsy in childhood, and those available in the literature sometimes have discordant information.[14] There are different types of protocols and neuropsychological tests used to evaluate epilepsy in the preoperative situation, and it is very difficult to follow a standard protocol for different clinics and countries. It is agreed among the surgical centers of epilepsy that memory, language, attention and executive functions should be evaluated. The research and clinical centers also agree that the materials used for the assessment should be validated and standardized for the reality of each country.[9] This is a special problem in the country where this research project was conducted due to lack of well-known international instruments standardized for the Brazilian population. Examples include Wechsler Memory Scale[15] and Wide Range Assesment of Memory and Learning,[16] for memory systems, and the Stroop Colors and Words Test [17] and Trail Making Test,[18] both for executive functions. None of them has a formal standardization for Brazil.

Voygt et al.,[9] report that there is a consensus among centers and teams specialized in epilepsy on the protocol of evaluation of refractory frames used at the pre- surgical time. Among the issues evaluated are: location of epilepsy (seizures), epileptic dysfunctions, contraindications of drug effects, and continued monitoring. The cognitive, behavioral and psychosocial domains that should be evaluated are: memory, attention, executive functions, language, visuospatial skills, intelligence, depression, anxiety and quality of life.[7] Thus, the literature points out to some shortcomings:

1. Proportionally there are few studies with neuropsychological evaluation in children with refractory epilepsy;
2. When they exist, the studies with children with refractory epilepsy focus on pre-surgical evaluation;[4]
3. Generally the studies favor general intellectual abilities (IQ), not emphasizing evaluation of neuropsychological functions.[7] In view of these aspects, the aim of this study was to characterize the cognitive performance of children with refractory epilepsy in a specialized outpatient clinic, in order to observe the neuropsychological development of these patients.

Method

This investigation followed a quantitative method of case series study. Data collection took place in the city of Porto Alegre (Brazil) from January 2018 to December 2018, in the Neuropediatric outpatient clinic of a specialized hospital that is a reference in pediatric care of high complexity. The hospital, despite having an outpatient clinic specialized in epilepsy, does not offer surgery to treat the syndrome. Despite of being a hospital that is not entirely public and also serves alto to the private health system (SUS), the population often is usually of low-income.

Participants

The participants were screened through the hospital's records. All the electronic registers from January 2018 to December 2018 was evaluated for the study, resulted in fifty children (n=50) aged between nine and twelve years-old were in agreement with the inclusion criteria of the study. The researchers tried to contact all the 50 patients diagnosed with refractory epilepsy according to the criteria established by ILAE,[4] previously reported in this study. All of them were contacted through phone calls. Three attempts were made to contact each family of the patients in order to schedule the neuropsychological assessment. Of these families, three refused to participate in the study, twelve agreed to participate but did not attend to the scheduled meetings, and six had incorrect registration data, making it impossible to contact them for the neuropsychological assessment. So, from the 50 patients who initially fulfilled the criteria, 21 were lost.

From the remaining 29 patients, 20 of them were unable to assess due to severe intellectual disability[19] and / or cerebral palsy and other comorbidities. Three other patients did not participate because they had visual and/or verbal impairments. As a final sample, nine children with an average age of 8.6 years-old were evaluated (md=11; sd=2,10), with seven boys and two girls. Participants were patients who had previously been diagnosed with refractory epilepsy[4] by the physicians and were treated at the hospital's neuropediatric outpatient clinic.

Instruments

A battery of instruments was used to evaluate several socio-demographic characteristics and cognitive abilities:

Sociodemographic data sheet, which was specially constructed for this research to collect data about patients' clinical history. This interview was answered by the person responsible for the child and had questions related to gestation, childbirth, neuropsychomotor development, data

on the diagnosis and treatment of epilepsy and family history. There were cases of children who live in shelters; in these cases, social workers were the responsible for giving information about the infants.

Wechsler abbreviated scale of intelligence - WASI: The instrument provides the Verbal IQ, Performance IQ, and Total IQ scores through four subtests: Vocabulary, Cubes, Similarities, and Matrix Reasoning. The scale has a wide age range for application, and can define IQs of individuals from 06 to 89 years-old of age;[15]

Benton visual retention test - BVRT: this is an instrument that evaluates visual memory, visual perception and visuoconstructive praxis. The test consists of two administration formats (Copy and Memory, respectively Forms A and C), with 10 slides each. There are application patterns, punctuation based on the number of correct productions and the frequency of the specific types of errors made by the examinees, as well as performance norms for age and schooling;[20]

Brief Neuropsychological Assessment Instrument for Children - Neupsilin-Inf: is a brief neuropsychological instrument that evaluates components of eight neuropsychological functions, through 26 subtests: orientation, attention, visual perception, memory systems (working memory, episodic, semantic), arithmetic skills, oral and written language, visuoconstructive skills and executive functions. The Neupsilin-Inf standards correspond to children aged between 6 and 12 years-old and 11 months;[21]

FDT - Five Digits Test: it is a neuropsychological test that evaluates the cognitive (executive) functions, especially the sustained attention. The goal of the instrument is to measure the speed of cognitive processing, the ability to focus and reorient attention and deal with interferences - subcomponents inhibitory control and cognitive flexibility of executive functions.[22]

Data collection procedures

The first contact with the parents and/or caregiver of the children for the invitation to participate in the study was made through the telephone, obtained through the patient's electronic records. The purpose of the survey was briefly explained and, for those who accepted, an appointment was set for an interview for data collection. For each participant, the assessment consisted of two meetings lasting roughly one hour each. Three marking attempts were performed for each patient who met the criteria for taking part in the study.

Initially the objectives and procedures of the study were explained. After the responsible person agreed to the participation of the child and authorized it, an Informed Consent (IC) was signed. In the first meeting, the first stage of the evaluation was carried out (data collection with socio-demographic data, with parents or caregivers of the participants) and the second stage (application of the tests with the participants) was started. First the objectives and procedures of the study were explained and after the child accepted to take part, he/she signed a Term of Assent (TA), according to the Ethics Procedures in Brazil. After signing this document, each child was assessed with the WASI and the BVRT Collection were started. On the second assessment day, Neupsilin-Inf and FDT were applied, and the evaluation was closed.

Data analysis procedures

Data from the clinical interview of the patients (according to caregivers) were used to present and discuss the cases. For the analysis of the results obtained from the patients participating in the study, the data was standardized according to the manuals of each instrument used.

The data of Brief Neuropsychological Assessment Instrument for Children (Neupsilin- Inf)[21] were presented in standardized z scores, mean and standard deviation, and tables were organized corresponding to the age group and type of educational institution to which the patient was linked (public or private). The cut-off point of the scores equal to or below -1.5 standard deviations was considered to be indicative of neuropsychological deficits (considering + 1.5DP for the analysis of the execution time of the task of attention for cancellation of figures).

For the Benton Visual Retention Test (BVRT),[21] the quantitative analysis was used for the standard score and the qualitative and quantitative analysis for the error score, both for the application form C and for D. The results (raw scores) were converted to z score, in the same way as the results found in Neupsilin-inf.

For the Wechsler Abbreviated Scale of Intelligence (WASI)[15] the T scores were considered to link to the raw score of each participant. The Table of Standards and Conversion of Brazilian Sample Scores corresponding to each age group were used. The classification of Full IQ, Performance IQ and Verbal IQ was also considered according to the manual.

The FDT Five Digits Test[22] was used to convert the Direct Scores to percentiles. The table corresponding to the age group of the participants was used. Percentiles between 25 and 75 were considered average, perceived 5 were considered below average and 95 percentiles were considered superior.

The results were presented through mean, median, standard deviation, frequency and percentage. In order to test the sample for reference/normal values, t tests were used (in comparison to normative standards). Comparisons of the mean scores according to the type were performed through ANOVA and correlations of the instruments with age and age at the beginning of the seizures by Spearman correlation coefficient, respectively. The statistical significance was 5% and the analyses were performed using SPSS software version 25.

Ethical procedures

The project was submitted through the Plataforma Brasil and evaluated and approved by the Ethics Committee of the Hospital where the evaluations were carried out. The procedures adopted in the study obeyed to the Criteria of Research Ethics according to Resolution number 466/12 of the Conselho Nacional de Saúde (Brazil).

An Informed Consent (IC) was sent to parents or caregivers, explaining the purpose of the study, as well as their rights. A Term of Assent (TA) was also given to the child participating in the study, which clearly stated the procedures that would be performed.

Results

Of the nine participants who took part in the study, seven were male (77% of the sample). Only six were literate (67% of the sample), which limited the assessment of language and arithmetic skills with the Neupsilin-Inf Test, and the evaluation of executive functions through the Five Digits Test. These data can be seen on Table 1.

The age of onset of the seizures and the type of epilepsy varied considerably, with participants having their first epileptic seizures soon after birth and another presenting the first observed symptoms at the age of seven years-old. The time between the appearance of the first symptoms and the diagnosis of refractory epilepsy also varied widely, ranging from one month to more than ten years (Table 1).

For a better presentation of the data collected in the study, it was decided to divide the results into two categories: quantitative statistical analysis and qualitative analysis of the scores.

Quantitative statistical analysis

The performance of the indexes related to the participants' full IQ (FIQ), verbal IQ (VIQ) and performance IQ (PIQ) are considered below average when surveyed using the WASI scale manual, when performing the t-test according to the standards of the manual of the test, the results for VIQ and FIQ show statistical significance (both with p<0,05). That is, the mean of the participants' scores is statistically lower than the mean value standardized by the WASI scale with respect to the VIQ and PIQ indices. This also occurs in the FIQ, where there was a statistical difference when the related results are observed (p<0,05).

The lowest IQ scores were found in patients 8, 7, 5, 4, respectively. Among these four participants, three of them were not literate (4, 7 and 8) and all of them had the first epileptic seizures as infants, up to one year-old of age (Table 1). The neuropsychological performance on different cognitive domains can also be seen on Table 1.

Table 1 Characterization of the sample and test results used

	Patient data								
	1 ♂	2 ♂	3 ♂	4 ♂	5 ♂	6 ♂	7 ♂	8 ♀	9 ♀
Age	12	7	11	12	12	8	9	12	7
Literate	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
Age of onset of seizures	2y	5y	1y4m	1a	8m	7y	NB[1]	NB[1]	4y
Tipe of epilepsy	Tonic- Clonic Generalized	Focal	Focal	Typical absence generalized	Atonic generalized	Tonic-clonic generalized	Focal secondarily gerneralized	Tonic-clonic generalized	Focal secondarily gerneralized
Diagnostic/ treatment time	2 years	2 years	4 years	11 years	10 years	1 month	9 years	4 months	1year
IQ WASI (Raw Score)	145	165	134	106	93	111	89	83	140
IQ WASI	73	83	69	56	47	58	45	42	71
(Scaled score)[2]									
Verbal IQ (Raw Score)	75	91	62	40	46	58	49	40	59
Verbal IQ (Scaled Score)	79	93	68	45	52	64	55	45	65
Performance IQ (Raw score)	70	74	72	66	47	53	40	43	81
Performance IQ (Scaled Score)	75	79	77	71	53	59	45	49	85
FDT reading time[3]	<5	<5	<5	D.A.[4]	<5	25-May	<5	D.A.[4]	50
Counting time[3]	25	<5	<5	D.A.[4]	<5	50	<5	D.A.[4]	50/75
Choosing time[3]	25	<5	<5	D.A.[4]	<5	75	<5	D.A.[4]	25
Shifting time[3]	25	<5	<5	D.A.[4]	<5	<5	<5	D.A.[4]	5
Reading errors[3]	5	95	95	D.A.[4]	95	<5	95	D.A.[4]	95
Counting errors[3]	25-May	5	<5	D.A.[4]	25-May	95	25-May	D.A.[4]	95
Choosing errors[3]	50	25-May	<5	D.A.[4]	5	50/75	25	D.A.[4]	50
Shifting errors[3]	50/75	50	<5	D.A.[4]	5	25-May	<5	D.A.[4]	25
Inhibition[3]	<5	25	<5	D.A.[4]	<5	95	<5	D.A.[4]	25/50
Flexibility[3]	5	25	5	D.A.[4]	25-May	<5	<5	D.A.[4]	25/50
Benton correct memory[5]	-2,72	-2,94	0,05	-3,27	-3,83	-1,76	-2,94	-3,83	0,58
Errors memory	3,29	4,46	0	4,54	5,79	1,34	7	9,12	-1,15
Correct copy5	-10,87	-2,94	0,71	-10,87	-7,12	-2,55	-3,66	-12,12	-0,33
Errors copy	13,37	1,79	-0,7	13,37	8,37	2	4,27	32,12	4,8
Neupsilin-Inf[5] orientation	0,36	-1,28	-2,79	-6,45	-4,18	-0,10	-2,34	-8,72	0,82
Attention	-0,94	-2,76	-2,34	-5,94	-2,89	-1,53	-6,7	-14,28	-0,58
Perception	0,44	0,40	0,34	0,44	0,44	0,25	0,46	-4,91	0,4
Memory	-0,1	-3,10	-5,64	-6,69	-5,20	-4,01	-5,2	-7,75	-1,26
Language	*-2,88*	*-1,02*	*-8,41*	*-19,24*	*-16,06*	*-3,29*	*N.A.*	*N.A.*	*-0,74*
Visuoconstructive skills	*0,67*	*-4,40*	*-4,33*	*-7,43*	*-8,7*	*-3,67*	*-15,18*	*-7,43*	*-2,9*
Arithmetic skills	0,66	0,52	-10,4	-19,67	-19,67	-2,19	-6,09	-20,52	-0,45
Verbal fluency	-1,43	-2,29	-2,84	-2,44	-2,44	-3,91	-2,3	-3,73	-1,64

[1] newborn; [2] t score; [3] percentile; [4] didn't answer; [5] z score

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The results of the correlation analysis between IQ values and the age of onset of seizures can be seen on Table 3. For the sample evaluated in this study, it was noticed that there was a significant correlation between the variables – the earlier the seizures started, the lower the IQ of the participants (p>0,05).

The analyzed data from this sample show that the lower the IQ, the greater the impairment in the short-term visual memory, evaluated through the application of BVRT's Form C (r=0,733; p<0,05). It is also possible to correlate significantly with the evaluation of attention (r=0,833; p<0,05) and visuoconstructive skills (r=0,812; p<0,05) evaluated through Neupsilin-Inf (Table 2).

Table 2 Correlation of participants' assessment results raised through the test manuals and characteristics related to age and onset of crises

The Performance IQ also showed statistical significance when correlated with Visuoconstrutive Skills (r=0,711; p<0,05) and with attention (r=0,667; p<0,05) evaluated in Neupsilin-Inf. In the case of short-term visual memory, BVRT Form C, there was a significant correlation between the performance in the test and the age of onset of seizures (r=0,778; p<0,05). There were no significant correlations between the performances of children related to BVRT's Form A with other tests used (Table 2).

In the evaluation of Memory Systems, which encompasses working memory, semantic memory, verbal semantic episodic memory, and visuoverbal semantic episodic memory, seven of the nine patients had z scores lower than -1.5 standard deviations and none of these seven had z scores greater than -3 standard deviations in Neupsilin's tasks. These findings can indicate significant losses in the memory of these children. Of all memory systems evaluated and reported previously, only visuoverbal semantic episodic memory did not present significantly lower scores than the mean (r=0,080; p<0,05) (Table 3).

Table 3 Skills assessed in Neupsilin-Inf compared to average according to the test manual

Skill	Mean	Standard deviation	p-value
Orientation – full score	-2,74	3,22	0,034
Attention – full score	-4,55	4,30	0,013
Auditory attention - digit sequence repeat	-3,27	2,09	0,002
Memory – full score	-4,33	2,49	0,001
Working memory	-4,16	2,31	0,001
Working memory - phonological and central executive components	-3,40	1,85	0,001
Visuospatial working memory (reverse order)	-3,77	2,50	0,002
Verbal semantic episodic memory	-1,59	1,83	0,031
Verbal semantic episodic memory – Immediate evocation	-1,26	2,16	0,119
Verbal semantic episodic memory - late evocation	-1,46	1,36	0,012
Semantic memory	-3,53	4,38	0,042
Visuoverbal semantic episodic memory	-1,01	1,52	0,080
Language	-7,38	7,51	0,041
Oral Language	-5,57	4,57	0,006
Phonological awareness - Rhyme	-3,87	4,07	0,022
Phonological awareness - phonemic subtraction	-7,80	7,13	0,011
Oral comprehension - Inferential processing	-1,99	1,31	0,002
Writing words and pseudowords	-7,04	6,86	0,035
Spontaneous Writing	-1,84	1,91	0,043
Visuoconstrutive Skills	-5,93	4,48	0,004
Arithmetic skills	-8,65	9,17	0,022
Mathematical calculations	-8,62	9,15	0,022
Verbal fluency	-2,56	0,83	0,000

Legenda: Average of participants and z = 1

Although two sample participants were unable to perform written language tasks, not generating a score for language abilities as a whole, statistical significance can be found between the results of verbal IQ and the Neupsilin-Inf Language tasks – both oral and written components (r=0,714; p<0,05). This result may have occurred due to the extremely low score in the language tasks of Patient 4 (z=-19,24), who, according to the legal responsible for the patient, was not literate but managed to perform some written language tasks.

No correlation tests were performed with FDT results because the test presents a percentile interpretation, which makes it difficult to analyze correlations in small groups. The presentation of these results will be carried out next, in the qualitative analyzes of the statistical data.

Qualitative analysis of the scores

Six participants were far below the expected mean for age and type of school standardized patterns in the Neupsilin-Inf[21] Orientation assessment. In Brazil, the difference in the quality of education between public and private schools is noticeable, and for this reason, standardized and validated tests for the Brazilian population generally have different means and scores, depending on the type of school the participating children use.

This task presents questions related to personal orientation (name and age, for example), temporal orientation (day of the week and day of the month, for example) and spatial orientation where it is currently, for example).

In language tasks (Neupsilin Inf), which include evaluation of both oral and written domains, two participants did not score on the test because they were not literate. Of the seven remaining participants, five had a z-score below expectations, and of the five, there was a very large variation: the highest score was from Patient 1 ($z = 2.88$) and the lowest score was from Patient 4 ($z = -19.24$). In oral language, eight patients were below average for their age and type of school.

In the evaluation of attention (Neupsilin Inf), it is important to report that Patient 8 had a much lower z score than the other participants (z= -14,28), with a difference of more than 7 z score points of the second worst result. The same pattern can be observed at the Semantic Memory task from Neupsilin Inf (difference of 4 points of z score). Also, the same happened in the evaluation of oral language. This same question occurred with the z score of Patient 4 (z= -22,72) in the written language task. This is important because it differs a lot from the other participants, lowering the group average. All of these data can be seen on Table 3.

In the FDT,[22] it was noticed that the participants had difficulties to understand the instructions of the task. Two patients could not perform the test because they did not know the numbers. Of the seven remaining participants, five had low scores at reading time, and four at the counting time, which is the beginning of the activity and is expected to be performed more easily. These difficulties perpetuated in times of choosing and shifting.

There have also been many errors in counting and alternating. Overall, the participants presented difficulties related to the executive functions evaluated, four of them had below- average scores regarding inhibition of behaviors and five presented impairments in cognitive flexibility. FDT data can be seen on Table 1.

Discussion

The aim of this study was to evaluate and characterize the neuropsychological aspects of children with refractory epilepsy diagnosis at an outpatient clinic from a specialized hospital. There are important considerations that need to be made regarding the number of patients who took part in the study:

(1) The public attending the neuropediatrics clinic was one hundred percent linked to the Brazil's *Sistema Único de Saúde (SUS)* (the public health system), usually used by families with low income (they often cannot afford to go the hospital);[23]

(2) There were some questions related to the outdated information in the medical records, which impaired the contact trials with some patients;

(3) Some patients attended by the neuropediatrics outpatient live in the countryside - hours away from the city and from the hospital; it was difficult for them to have access to the outpatient clinic at the hospital.

The participants of the study were diagnosed with uncontrolled refractory epilepsy and the frequency of seizures was relatively high. The electrical disturbance caused by epileptic seizures influenced the decline of cognitive functions. However, Thompson e Duncan[24] reported in a study that the remission periods of the seizures were associated with an improvement in the cognitive performance of the evaluated patients, worsening the epileptic seizures with cognitive decline. Thus, it can be understood that cognitive decline can be mitigated by decreasing the frequency of the seizures.

Of the nine patients evaluated, there were five different types of epilepsy, being very difficult to standardize the group. This difficulty is found in other environments and brought in the literature as one of the obstacles to understanding the cognitive impairment of epileptic syndrome.[25] Despite these data, there is considerable evidence that children with refractory epilepsy have greater cognitive impairment than children with controlled epileptic seizures.[25,26] The different types of classification of epilepsy have different symptoms, which cannot always be compared with each other, and this classification help to inform the risks of comorbidities including learning difficulties, intellectual disability, psychiatric features such as autism spectrum disorder, and mortality risk such as sudden unexpected death in epilepsy.[3]

It was possible to observe significance related to patients' IQ when compared to the mean of 90 from normative population according to the manual. Besag[27] says that cognitive impairment is more evident in cases of refractory epilepsy. It is important to consider that one of the exclusion criteria of the study was the presence of comorbidities with other neurological diseases, such as cerebral palsy, which are often related to refractory epilepsy.[28]

For the sample of this study, it may be observed that the patients who had the onset of seizures earlier in life presented lower IQ. Cognitive deficits and learning difficulties are often associated with epilepsy, factors such as age at onset of seizures, cause of seizures epilepsy, and type of epilepsy are some of the characteristics that may influence these results.[25,29] Cormarck et al.,[30,31] studied children with refractory epilepsy and concluded that among all factors, the greatest predictor of intellectual disability is the age at which seizures start. Yoong et al.,[32] reported that low cognitive performance with cognitive scores at least two standard deviations below population means can be observed in 40% of patients who had their first epileptic seizure before the age of five.

All the participants of this study were attending to school, but three were not yet literate and needed special attention in the classroom. There were still others who had adapted curriculum at school because of the difficulties encountered in learning. Smith, Eliott e Lach[29] conducted a study comparing intelligence, memory, attention, and academic skills of children with refractory epilepsy who had not undergone surgery and children with epilepsy who had undergone surgery (mean age of 13 years). The authors found that there was little statistical difference related to the abilities evaluated in the groups when compared to each other.[29] However, all the participants attended to school and most of them presented important difficulties, requiring adaptation that varied between special class placement, one-to-one help within the classroom from an educational assistant, and curriculum modifications.

Children with epilepsy tend to score lower on executive functions when compared to their peers.[33] In this study, there were important deficits in the attention and in the activities related to the verbal fluency of the evaluated participants, suggesting impairments in the executive functions, which are essential for learning. Bailey and Im-Bolter[34] through a meta-analysis found that studies report significant language deficits in children with epilepsy when compared to children who do not have the diagnosis. In addition, it was found that the deficits are more expressive when evaluated semantic language and verbal fluency are. In the participants evaluated in this study, these same difficulties that are reported in the literature could be observed, highlighting the patients who, even attending regular school, were not literate.

Patients with refractory epilepsy generally perform worse in skills such as concept formation, problem solving, mental flexibility, set-shifting, attention, and concentration. These difficulties are found in

several patients with refractory epilepsy, but, in patients with frontal lobe dysfunction, these deficits are more cautiously observed.[35] It is important to report that working memory was one of the evaluated skills that presented a lower average among the participants of the study, and among patients with refractory epilepsy.[27]

Conclusion

When considering the prognosis of a patient with refractory epilepsy, a great deal of emphasis is placed on the reduction or stopping of epileptic seizures and very little attention is paid to cognitive and social factors, even though they are aware of the enormous importance that these factors have in the life of these patients.[27] There are few published studies on childhood refractory epilepsy in a systematic review of the past five years, only six articles were found.[36] It is suggested that further studies could be conducted with these patients.

Epilepsy is a syndrome, which can often be disabling, present in a significant portion of the population. Studies on the condition must be performed to increase the understanding and interest of the professionals for a better treatment of these patients. There is absolutely no reason to re-stigmatize epilepsy, but there is every reason to make sure physicians, patients, families, as well as educators and others are adequately prepared to recognize any such difficulties and appropriately as they arise.[37]

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Conflicts of interest

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