ARTICLE

Memory in children with symptomatic temporal lobe epilepsy

Memória em crianças com epilepsia de lobo temporal sintomática

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ABSTRACT

In children with temporal lobe epilepsy (TLE), memory deficit is not so well understood as it is in adults. The aim of this study was to identify and describe memory deficits in children with symptomatic TLE, and to verify the influence of epilepsy variables on memory. We evaluated 25 children with TLE diagnosed on clinical, EEG and MRI findings. Twenty-five normal children were compared with the patients. All children underwent a neuropsychological assessment to estimate intellectual level, attention, visual perception, handedness, and memory processes (verbal and visual: short-term memory, learning, and delayed recall). The results allowed us to conclude: besides memory deficits, other neuropsychological disturbances may be found in children with TLE such as attention, even in the absence of overall cognitive deficit; the earlier onset of epilepsy, the worse verbal stimuli storage; mesial lesions correlate with impairment in memory storage stage while neocortical temporal lesions correlate with retrieval deficits.

Keywords: neuropsychology, epilepsy, children, childhood, temporal lobe epilepsy, memory.

RESUMO

Em crianças com epilepsia de lobo temporal (ELT) os problemas de memória não são tão bem compreendidos como em adultos. O objetivo desse estudo foi identificar e descrever déficits de memória em crianças com ELT sintomática e verificar a influência de variáveis da epilepsia na memória. Avaliamos 25 crianças com ELT com diagnóstico baseado em aspectos clínicos, eletrencefalográficos e de neuroimagem. Vinte e cinco crianças normais foram comparadas com os pacientes. Todas as crianças foram submetidas à avaliação neuropsicológica para estimar nível intelectual, atenção, percepção visual, dominância manual, e processos de memória (verbal e visual: memória a curto prazo, aprendizado e recuperação tardia). Os resultados nos permitiram concluir que: além de déficit de memória, outros distúrbios neuropsicológicos podem ser encontrados em crianças com ELT, tais como déficit de atenção, mesmo na ausência de déficit cognitivo global; quanto mais precoce o início da epilepsia, pior o armazenamento verbal; lesões mesiais se correlacionam com prejuízo no armazenamento de memória enquanto lesões temporais neocorticais se correlacionam com prejuízos de evocação.

Palavras-chave: neuropsicologia, epilepsia, crianças, infância, epilepsia de lobo temporal, memória.

Memory may be defined as the ability to store all kinds of acquired knowledge by man in his relationship with the environment. It is the ability to learn new things, compare them with the stored information and build new ideas that can be remembered later on[1]. Temporal lobe epilepsy (TLE), particularly mesial, is frequently associated with memory deficits. In adults with TLE, hippocampal disorder of the language dominant temporal lobe is implicated in verbal memory decline, while disorder of the nondominant temporal lobe results in visual memory decline[2-6]. It seems that the relation between the laterality of the hippocampal pathology and memory deficit is more straightforward in patients with left TLE (verbal memory deficit) than in patients with right TLE[6]. However, memory deficits occur more often when the epileptogenic foci are found in both temporal lobes[7].

In childhood TLE, due to the great clinical, electrographic and etiologic diversity[8], the relationship between memory deficit and lateralization is still to be defined[9]. Some authors found that verbal memory deficit is correlated with left TLE and visual memory deficit is correlated with right TLE[10-11]. Nevertheless, other authors found correlation only between visual memory deficit and right TLE[11,12]. This is not in

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keeping with studies that showed a higher sensitivity of verbal memory tests in the assessment of left TLE in adults[3,6,13]. Finally, other authors found no correlation between laterality of the lesion and memory deficits in children with TLE[14-15].

The influence of the frequency of seizures, neuropathology, seizure onset, and duration of epilepsy on memory of children with TLE is not well understood[9,11,15]. Studies have shown that children with dual pathology perform more poorly in presurgical evaluation, including in memory tasks[15] and it seems that there is a negative influence of duration of epilepsy in mnemic functions in children[9,11].

Therefore, the aim of this study was to identify and describe memory deficits in children with TLE, and to verify the influence of etiology, laterality of lesion, seizure onset, frequency of seizures, duration of epilepsy, number of antiepileptic drugs (monotherapy or polytherapy), history of febrile seizures, and history of *status epilepticus* on memory.

METHOD

Participants

Patients

We evaluated 25 children with symptomatic TLE. Inclusion criteria were: diagnosis of TLE based on clinical, electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings; MRI showing hippocampal atrophy or temporal neocortical lesion (lesions restricted to the lateral temporal lobe); age from seven to 15 years and 11 months; normal neurological examination including brief visual and auditory ability; intelligent quotient (IQ) ≥70; and signature of informed consent. Exclusion criteria were: normal MRI; MRI showing extra-temporal lesion; signs or symptoms of antiepileptic intoxication; children who never attended regular school; and severe behavior disorder.

Control group

Twenty-five normal children were compared with the patients. Inclusion criteria were: similar age, gender, socioeconomic and educational level, and signature of informed consent. Exclusion criteria were: children who were relatives of the index patients; IQ lower than 70; use of medication which affects the central nervous system; children who never attended school; past history of neurological injury, such as, trauma, meningitis; abnormal neurological examination; and history of pervasive disorders. Therefore, the control group was composed of normal children from a similar socio-cultural level as our patients and whose parents agreed to participate in the study.

Considering that there is no normative data for the Brazilian population, the data from neuropsychological evaluation collected from the patients were compared with that collected from a control group. Both groups underwent an extensive neuropsychological assessment to estimate intellectual level, attention, visual perception, handedness, and particularly, memory processes (verbal and visual: short-term memory, learning, and delayed recall).

This study was approved by the ethical committees of both institutions (Universidade Estadual de Campinas and Universidade de São Paulo).

PROCEDURES

Neurological evaluation

The neurological evaluation included: medical history, neurological examination, serial EEGs, video EEG, and MRI. Symptomatic temporal lobe epilepsy was defined as a lesion restricted to the temporal lobe region (mesial or lateral) demonstrated with a 1.5T or 2T magnetic resonance image.

Neuropsychologial assessment

Subjects enrolled in this study underwent a neuropsychological battery made up of:

- Edinburgh handedness inventory[16] and dichotic listening tests[17] to determine hemispheric dominance for language;
- Wechsler intelligence scale for children - 3rd edition (WISC III)[1,18]: subtests of block design and vocabulary to estimate IQ;
- Perception of shapes and colors[17];
- Forward digit (subtest of WISC III)[18] to estimate attention span;
- Wide range assessment of memory and learning (WRAML)[19]. This is a battery that can be used from five to 17 years. It is made up of nine subtests to evaluate verbal and visual memory (short-term memory, delayed recall and learning): picture memory, design memory, verbal learning, story memory, finger windows, sound-symbol, visual learning, sentence memory, number/letter memory. We chose the following indices to evaluate children's memory performance: verbal memory, visual memory, learning (verbal and visual), delayed recall of verbal learning, delayed recall for stories, delayed recall for visual learning and story memory recognition, which allows verbal clues.

The raw data of both groups were compared. After that, each patient was classified according to each assessed item as adequate or inadequate, depending on whether the raw result was above or below the median and two standard deviations, based on the assessment of the control group. Then we compared the obtained data with epilepsy variables such as etiology, laterality of lesion, seizure onset, frequency of seizures, duration of epilepsy, number of antiepileptic

drugs (monotherapy or polytherapy), history of febrile seizures, and history of *status epilepticus*.

Statistical analysis

A general descriptive demographic analysis of the data was carried out. The Chi-square and Fisher's exact test were used to compare proportions and assess significance of associations among the variables, and the Mann-Whitney test was used to compare measures between the two groups. The significance level was set at 0.05.

RESULTS

The mean age at seizure onset of the patient group was 4.6 years (standard deviation (SD=2.9)) and the duration of epilepsy was 8.0 years (SD=4.0). The frequency of seizures was: six children (24%) had their seizures controlled for more than one year; 13 (52%) had five or less seizures per month; and six (24%) had more than five seizures per month. Fourteen children (56%) were on monotherapy and 11 (44%) on polytherapy. A history of febrile seizure was present in 14 children (56%) and *status epilepticus* in 16 (64%). The MRI findings were: 18 children (72%) had mesial lesions and seven (28%) had temporal lateral lesions. Fourteen children (56%) had right lesions and nine (36%) had left lesions; two patients (8%) had bilateral lesions.

Both groups were comparable in gender (p=0.77, Chi-square), age (p=0.86, Mann-Whitney), schooling (p=0.21, Mann-Whitney), handedness (p=1.00, Fisher) and dichotic listening (p=0.86, Fisher). None of the subjects in either group made mistakes in the color and form perception tests.

Table 1 shows the descriptive analysis (mean, standard deviation) of both groups in relation to the neuropsychological assessment and the comparison between them (p-value, Mann Whitney). We found differences in favor of the control group in the following items: IQ, digit forward (WISC III) and WRAML subtests verbal learning, visual learning, verbal memory, visual memory, delayed recall of verbal learning, delayed recall of stories (verbal) and story memory recognition.

The correlation between variables and neuropsychological assessment is provided in Table 2. Children with lateral lesions had better performance on story memory recognition than those with hippocampal atrophy. See Tables 2 and 3.

Epilepsy onset: The descriptive analysis and the comparison of epilepsy onset with each item appear in Table 4. Patients who presented with deficits in story memory recognition had lower age of epilepsy onset.

DISCUSSION

In this study we analyzed memory performance in two comparable groups of children according to gender, age, handedness, educational and socio-economic level. One group was composed of patients with symptomatic TLE and the other composed of normal children. Because both groups had strictly the same characteristics, we believe that our findings truly represent the differences in memory performance in children with TLE.

In spite of the exclusion of patients with mental retardation, the group of TLE children had significantly lower IQ than the control group. This reinforces the findings of other studies that children with symptomatic epilepsy have a lower IQ[12,20].

The difference between the groups in performance of the digit forward subtest (WISC III) suggests a possible focused attention impairment in the TLE group that may influence the memory process, as normal attention is required to perform any cognitive function, particularly for the encoding stages of memory function. Neuronal circuitry may be damaged in TLE children, as this type of attention depends on limbic and prefrontal cortices, which play important roles in voluntary attention[21].

Table 1. Performance on neuropsychological tests of patients with TLE (n=25) and controls (n=25).

	Patients Mean [SD]	Controls Mean [SD]	p-value (Mann-Whitney)
IQ (WISC-III)	96.4 [13.3]	109.7 [11.7]	**0.0013**
Forward digits (WISC-III)	6.8 [1.9]	7.9 [1.9]	**0.0386**
Verbal learning (WRAML)	37.1 [7.9]	42.4 [6.0]	**0.0053**
Visual learning (WRAML)	24.3 [10.0]	31.4 [9.9]	**0.0254**
Verbal memory (WRAML)	46.8 [16.2]	69.7 [11.7]	<**0.0001**
Visual memory (WRAML)	70.6 [13.6]	87.0 [9.8]	<**0.0001**
Delayed recall of verbal learning (WRAML)*	1.8 [1.7]	0.6 [1.0]	**0.0033**
Delayed recall of stories (WRAML)*	4.6 [3.1]	2.8 [3.2]	**0.0060**
Delayed recall of visual learning (WRAML)*	0.2 [1.6]	0.3 [1.1]	0.9840
Story memory recognition (WRAML)	9.2 [3.2]	12.6 [1.4]	<**0.0001**

WISC-III: Wechsler intelligence scale for children – 3rd edition (Wechsler, 1991/2002);
WRAML: Wide range assessment of memory and learning (Sheslow and Adams, 1990).
*Higher numbers correlate with worse performance; TLE: temporal lobe epilepsy; IQ: intelligent quotient; SD: standard deviation.

Table 2. The correlation between variables of epilepsy and neuropsychological assessment.

	Frequency of seizures (≤5/month or <5/month)	Use of AED (mono or polytherapy)	History of febrile seizure	History of *status epilepticus*	Site of lesion (cortical or mesial)	Laterality of the lesion	Duration of epilepsy (Mann-Whitney)
IQ	p=0.5067*	p=0.6043*	p=0.6043*	p=0.2589*	p=0.5485*	p=0.2601*	p=0.7359
Forward digit	p=0.2381*	p=1.0000*	p=1.0000*	p=0.1501*	p=0.6372*	p=0.3401*	p=0.1173
WRAML verbal learning	p=0.1159*	p=0.6968*	p=0.2406*	p=0.6785*	p=1.0000*	p=1.0000*	p=0.1491
WRAML visual learning	p=1.0000*	p=0.1160*	p=0.4347*	p=0.2060*	p=0.4065*	p=0.0894*	p=0.0519
WRAML verbal memory	p=0.2338*	p=0.2337*	p=1.0000*	p=1.0000*	p=0.6396*	p=0.6570*	p=0.4146
WRAML visual memory	p=1.0000*	p=0.4347*	p=1.0000*	p=0.4028*	p=0.4065*	p=0.2138*	p=0.5839
WRAML delayed recall of verbal learning	p=0.1231*	p=0.0660*	p=0.0660	p=0.4003*	p=0.2016*	p=0.1968*	p=0.8918
WRAML delayed recall of stories	p=0.7780*	p=0.6043*	p=0.2878*	p=0.5331*	p=0.5485*	p=1.0000*	p=0.6314
WRAML delayed recall of visual learning	p=0.2190*	p=1.0000*	p=0.3406*	p=1.0000*	p=1.0000*	p=0.6106*	p=0.4563
WRAML story memory recognition (storage)	p=0.3438*	p=0.1804*	p=0.1804*	p=0.3509*	p=**0.0324*** **See table 3.**	p=1.0000	p=0.5450

*Fisher exact test; Chi-square test; IQ: intelligent quotient; WRAML: Wide range assessment of memory and learning.

Our study showed that memory is significantly impaired in children with TLE. In fact, their performances were lower in all evaluated subtests, except delayed recall of visual learning. Other authors have also found memory deficits in children with TLE[9,10,11,14,15].

Correlation between the assessment of memory and epilepsy variables showed that patients who presented with deficits in story memory recognition had lower age of seizure onset, suggesting that when epilepsy starts early in life, the verbal storage process may be damaged. Within the TLE group, the frequency of seizures, treatment with antiepileptic drugs in monotherapy or polytherapy, history of febrile seizures and *status epilepticus* did not show significant differences, and this is in agreement with other studies[9,15]. The laterality of the lesion did not influence the performance on the tests either, as was also found in other studies[9,14,15].

Our data do not agree with other studies that found a negative influence of duration of epilepsy on mnemic functions of children with TLE[9,11,12].

Table 3. Wide range assessment of memory and learning story memory recognition (storage) and site of lesion (cortical versus medial).

Lesion	With deficit	Without deficit	Total
Cortical			
Frequency	3	4	7
Percentage	12.00	16.00	28.00
Medial			
Frequency	16	2	18
Percentage	64.00	8.00	72.00
Total			
Frequency	19	6	25
Percentage	76.00	24.00	100.00

Etiologically, our patients had either hippocampal atrophy or temporal lateral lesions. Children with lateral lesions had better performance on story memory recognition than those with hippocampal atrophy. This difference suggests that children with mesial TLE have difficulty in storing information, while those with lateral lesions seem to have more difficulty in retrieving information, once their performance improved substantially when verbal clues were offered (story memory recognition).

Performance in other memory subtests was similar in both groups, independent of the site of the lesion. This indicates that TLE is frequently associated with memory disturbance[2,22] as, when the MRI shows hippocampal atrophy, the anatomical damage usually extends beyond the hippocampus and affects amygdala, entorhinal cortex and parahippocampal gyrus[23,24]. Mesial temporal structures are related to declarative long-term memory processes during childhood development. This means that an early lesion in temporal structures may not be compensated for by activation of alternative regions and the mnestic deficit is correlated with the age in which the lesion was acquired[22]. However, not only mesial structures but also lateral adjacent regions play a role in memory process[25].

One study[26] found that memory is more frequently impaired in children with mesial as opposed to lateral TLE. The lateral lesion group showed intact memory function relative to normative standards. These results do not agree with our data and those of Nolan et al.[12] Furthermore, the authors did not find evidence for differences in memory function between children with left and right TLE. The memory deficits were not lateralized.

Table 4. Descriptive analysis and comparison of epilepsy onset with each item of neuropsychological assessment.

	n	Mean	SD	p-value*
IQ (WISC-III)				0.5540
Inferior	21	4.50	2.98	
Mean	4	5.13	3.12	
Direct digits (WISC-III)				0.8643
With deficit	6	4.62	3.59	
Without deficit	19	4.60	2.83	
Verbal learning (WRAML)				0.7595
With deficit	10	4.52	2.93	
Without deficit	15	4.66	3.06	
Visual learning (WRAML)				1.0000
With deficit	11	4.90	3.11	
Without deficit	14	4.37	2.90	
Verbal memory (WRAML)				0.5989
With deficit	17	4.55	3.04	
Without deficit	8	4.71	2.92	
Visual memory (WRAML)				0.7006
With deficit	14	4.56	3.39	
Without deficit	11	4.66	2.42	
Delayed recall of verbal learning (WRAML)				0.8272
With deficit	13	4.33	2.40	
Without deficit	12	4.90	3.53	
Delayed recall of stories (WRAML)				0.7086
With deficit	4	5.00	2.16	
Without deficit	21	4.53	3.11	
Delayed recall of visual learning (WRAML)				0.3773
With deficit	5	5.45	1.82	
Without deficit	20	4.39	3.17	
Story memory recognition (WRAML)				**0.0161**
With deficit	19	2.05	2.57	
Without deficit	6	5.41	2.62	

WISC-III: Wechsler intelligence scale for children – 3rd edition (Wechsler, 1991/2002);
WRAML: Wide range assessment of memory and learning (Sheslow and Adams, 1990).
*Mann-Whitney test. IQ: intelligent quotient; SD: standard deviation.

We cannot rule out the fact that other aspects may be important in determining neuropsychological deficits in children with TLE. Quantitative MRI studies have shown that the deficits may be due not only to the lesion but also to the dysfunction of other temporal regions[27]. Yet, besides temporal regions, extra-temporal areas, such as the frontal lobes, may be altered in symptomatic TLE[28].

To conclude, our results showed that besides memory deficits, other neuropsychological disturbances may be found in children with TLE such as attention, even in the absence of overall cognitive deficit; the earlier onset of epilepsy, the worse verbal storage; mesial lesions correlate with impairment in memory storage while neocortical temporal lesions correlate with retrieval deficits.

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