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Benign Focal Seizures of Adolescence and Neuropsychological Findings in Patients from Community*

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ABSTRACT

Rationale: Benign focal seizures of adolescence (BFSA) described by Loiseau et al in 1972, is considered a rare entity, but maybe underdiagnosed. Although mild neuropsychological deficits have been reported in patients with benign epilepsies of childhood, these evaluations have not so far been described in BFSA. The aim of this study is to evaluate neuropsychological functions in BFSA with new onset seizures (<12 months). **Methods:** Eight patients with BFSA (according to Loiseau et al, 1972, focal or secondarily tonic clonic generalized seizures between the ages of 10-18 yrs., normal neurologic examination, normal EEG or with mild focal abnormalities) initiated in the last 12 months were studied between July 2008 to May 2009. They were referred from the Pediatric Emergency Section of the Hospital Universitário of the University of Sao Paulo, a secondary care regionalized facility located in a district of middle-low income in Sao Paulo city, Brazil. The study was approved by the Ethics Committee of the Institution. All patients performed neurological, EEG, brain CT and neuropsychological evaluation which consisted of Raven's Special Progressive Matrices – General and Special Scale (according to different ages), Wechsler Children Intelligence Scale-WISC III with ACID Profile, Trail Making Test A/B, Stroop Test, Bender Visuo-Motor Test, Rey Complex Figure, Rey Auditory Verbal Learning Test-RAVLT, Boston Naming Test, Fluency Verbal for phonological and also conceptual patterns – FAS/Animals and Hooper Visual Organization Test. For academic achievement, we used a Brazilian test for named "Teste do Desempenho Escolar", which evaluates abilities to read, write and calculate according to school grade. **Results:** There were 2 boys and 6 girls, with ages ranging from 10 yrs. 9 m to 14 yrs. 3 m. Most (7/8) of the patients presented one to two seizures and only three of them received antiepileptic drugs (AEDs). Six had mild EEG focal abnormalities and all had normal brain CT. All were literate, attended regular public schools and scored in a median range for IQ, and seven showed discrete higher scores for the verbal subtests. There were low scores for attention in different modalities in six patients, mainly in alternated attention as well as inhibitory subtests (Stroop test and Trail Making Test part B). Four of the latter cases who showed impairment both in alternated and inhibitory attention were not taking AEDs. Visual memory was impaired in five patients (Rey Complex Figure). Executive functions analysis showed deficits in working memory in five, mostly observed in Digits Indirect Order and Arithmetic tests (WISC III). Reading and writing skills were below the expected average for school grade in six patients according to the achievement scholar performance test utilized. One patient of this series who had the best scores in all tests was taking phenobarbital. **Conclusions:** Neuropsychological imbalance between normal IQ and mild dysfunctions such as in attention domain and in some executive abilities like working memory and planning, as well as difficulties in visual memory and in reading and writing, were described in this group of patients with BFSA from community. This may reflect mild higher level neurological dysfunctions in adolescence idiopathic focal seizures probably caused by an underlying dysmaturative epileptogenic process. Although academic problems often have multiple causes, a specific educational approach may be necessary in these adolescents, in order to improve their scholastic achievements, helping in this way, to decrease the stigma associated to epileptic seizures in the community.

Key words: Adolescence, focal seizures, epilepsy, benign, neuropsychology, community.

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RESUMO

Crises focais benignas do adolescente: disfunção neuropsicológica leve em pacientes da comunidade

Introdução: Crises focais benignas do adolescente (CFBA) descritas por Loiseau et al. em 1972, são consideradas raras, mas podem ser subdiagnosticadas. Déficits neuropsicológicos leves foram relatados em pacientes com epilepsias benignas da infância, mas até o momento tais avaliações não foram descritas na CFBA. O objetivo deste estudo é avaliar as funções neuropsicológicas na CFBA de início recente (<12 meses). **Métodos:** Oito pacientes com CFBA (segundo Loiseau et al. 1972, caracterizada por crises focais ou secundariamente tonico-clonico-generalizadas entre as idades de 10 a 18 anos), iniciadas nos últimos 12 meses, com exame neurológico normal, EEG normal ou com anormalidades focais, tomografia de crânio normal no período de Julho de 2008 a Maio de 2009. Os pacientes foram encaminhados do Setor de Emergência Pediátrica do Hospital Universitário da Universidade de São Paulo, que é hospital de atendimento secundário regionalizado localizado em um distrito de classe média da cidade de São Paulo, SP. O projeto foi aprovado pelo Comitê de Ética da Instituição. Todos pacientes realizaram exame neurológico, EEG e tomografia de crânio. A avaliação neuropsicológica consistiu dos seguintes testes: Matrizes Progressivas Especiais do Raven – Escala Geral e Especial (de acordo com as diferentes idades), Escala de Inteligência Wechsler para crianças – WISC III – com perfil ACID, Teste Trail Making A/B, Teste de Stroop, Teste Visuo-Motor de Bender, Figura Complexa de Rey, Teste de Aprendizado Auditivo Verbal de Rey – RAVLT, Teste de Nomeação de Boston, Teste de Fluência Verbal para padrões fonológicos e conceptuais-FAS/Animais e Teste de Organizacão Visual de Hooper. Para o desempenho escolar, foi usado o teste brasileiro chamado "Teste do Desempenho Escolar", que avalia as habilidades de leitura, escrita de acordo com o grau de escolaridade. **Resultados:** Foram estudados seis pacientes do sexo feminino e dois, do masculino, com idades variando de 10 anos e 9 meses a 14 anos e 3 meses. A maioria (7/8) dos pacientes apresentou uma a duas crises e somente três receberam drogas antiepilépticas (DAEs). Seis pacientes apresentaram anormalidades focais leves no EEG. Todos estavam alfabetizados, frequentavam escolas regulares do sistema público e apresentaram avaliação de Quociente Intelectual na faixa média para idade e sete mostravam discretos valores maiores nos subtestes verbais. Havia valores menores para atenção em diferentes modalidades em seis pacientes, especialmente na atenção alternada e no controle inibitório (Testes Stroop-like e Trail Making parte B). Quatro dos últimos casos que mostraram prejuízo tanto na atenção alternada como inibitória não estavam tomando DAEs. A memória visual estava prejudicada em cinco pacientes (Figura Complexa de Rey). As funções executivas mostraram déficits na memória operacional em cinco, especialmente observados nos subtestes de Aritmética e na Ordem Indireta de Dígitos (WISC III). A leitura e escrita estavam abaixo da média esperada para a série escolar segundo o teste de desempenho escolar utilizado, em seis pacientes. Um dos pacientes que apresentava os maiores valores do grupo em todos os testes estava recebendo fenobarbital. **Conclusões:** Uma desproporção entre QI normal e disfunções neuropsicológicas leves tais como na esfera atencional e em algumas funções executivas como memória operacional e planejamento de ação, assim como na memória visual e problemas acadêmicos na leitura e escrita, foram descritos neste grupo de pacientes com CBFA da comunidade. Isto pode refletir disfunções neuropsicológicas leves em pacientes com crises idiopáticas do adolescente provavelmente causadas por um processo epileptogênico dismaturativo sobrejacente. Embora problemas acadêmicos escolares frequentemente apresentem múltiplas causas, uma abordagem educacional específica pode ser necessária nestes adolescentes, a fim de melhorar seu desempenho, ajudando desta forma a minimizar o estigma associado às crises epilépticas na comunidade.

Unitermos: Adolescência, crises focais, epilepsia benigna, neuropsicologia.

INTRODUCTION

Benign focal seizures of adolescence (BFSA) described by Loiseau et al. in 1972, are considered to be rare, but maybe underdiagnosed. In 1978, after some series descriptions, BFSA was characterized by Loiseau & Orgogozo as a seizure susceptibility syndrome. Some other few reports have been made along the years (Table 1).

During the Marseilles' workshop held in 1983 the Commission on Classification and Terminology of the International League against Epilepsy there was a consensus to define BFSA. According to this, BFSA consisted of isolated simple or complex partial seizures, some of them evolving to generalized tonic-clonic (GTC) seizures, with normal neurological examination and EEG. The latter could present some mild focal abnormalities.

In a French observation study (CAROLE) 85 patients aged 12-19 yrs seen after a first unprovoked partial cryptogenic seizure were followed-up for two years without recurrence noted in 66 of them (Jallon et al., 1999).

Capovilla et al. in 2001 described 37 patients from five different centers in Italy recruited from the period of 1982 to 1997 with BFSA followed-up for 3 years and who had motor seizures with theta EEG changes over the centro-parietal regions or versive seizures associated with interictal spikes over the posterior regions. The waking and sleep EEG was normal in 46% of the patients. In this study the majority of the patients had either somatomotor or versive seizures; some of them reported a progression of symptoms, and in some cases the tongue was involved. Generalized tonic-clonic seizures were observed in 57% of the 37 cases. Although these patients were submited

to neuropsychological evaluation the results were not described in the publication.

Wolf, in 1997, has postulated the idea that isolated seizures can be defined as solitary seizure events that may occur once in a lifetime or very rarely and that they may not represent a separate syndrome. Loiseau et al., in 2002, agreed with the term "isolated partial seizures in adolescence" for this clinic-eletrographical presentation, once epilepsy by that time was defined as recurrent unprovoked seizures and in most of such cases only one seizure is present. Even in the new definition of epilepsy (Fisher et al., 2005) there should be an enduring predisposition to generate epileptic seizures.

The Marseille's group headed by Dr. Loiseau in 2002 has updated the initial series of patients and the following findings were observed in 108 cases of focal benign seizures in adolescents: male preponderance (71.3%), age of onset between 10 and 19 yrs., in 79.6% a single seizure, occurring mainly (87%) in wakefulness which consisted of simple partial manifestations in 14.5%, complex partial in 28.5% and secondarily GTC in 57%. All had normal EEG and did not received antiepileptic drugs (AEDs).

Mild neuropsychological deficits have been reported in patients with benign epilepsies of childhood, but not so far described in BFSA. The aim of this study is to evaluate neuropsychological functions in BFSA with new onset seizures (<12 months).

METHODS

Eight patients with BFSA (according to Loiseau et al, 1972, focal or secondarily tonic clonic generalized seizures between the ages of 10-18 yrs., normal neurologic examination, normal EEG or with focal abnormalities) initiated in the last 12 months were studied between July 2008 to May 2009. They were referred from the Pediatric Emergency Section of the Hospital Universitário of the University of Sao Paulo, a secondary care regionalized facility located in a district of middle-low income in Sao Paulo city, Brazil. The project was approved by the Ethics Committee of the Institution.

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Table 1. Summary of published cases about benign focal seizures of adolescence.

Authors	Year	n	Age Onset (yrs.)	Male %	Follow-up (yrs.)	Focal Sz %	SGTC %	Time	Sz n	Abnormal EEG Awake %	Abnormal EEG Sleep %	Therapy %
Loiseau et al.*	1972	14	13-18	64	4-12	SP (M 90, S 45, Aph 40, Vis 10, Aut 5)	70	W	1 (10/14); 2-3 (4/10)	64		–
Loiseau & Orgogozo**	1978	83	12-18 (84%)	72	5-17	SP (M 70, S 27) CP 3	80	–	1	36		96
Mauri et al. (abstract)	1996	10	12-19	70	≥ 3	SP 80 CP 20	50	–	–	10		–
Panayiotopoulos	1996	2	10-18	100	2-6	SP (M 50, Vis 50)	100	W	1	50		0
King et al.	1999	8	11-17	50	2-3.2	SP (M, S)	75	–	Several (50%)	25	50	37
Capovilla et al.	2001	37	11-16	60	3-13.6	SP (S 43, Versive 27, other 3) CP 27	57	W 62%	1 (30%) 2-3 (70%)	19	42	67
Fossas et al.	2001	1	16	100	5	SP (M) 100	100	–	Several	0		100
Loiseau et al.***	1985, 2002, 2005	108	10-19	71	5-20	SP 88 CP 12	57	W 87%	1 (80%)	0	–	–
Caraballo et. al.	2004	15	11-18	67	2-6	SP (M 67, Vis 20) CP 13	53	W 100%	1 (73%) 2-4 (27%)	0	0	0

Aph: aphasic; Aut: autonomic; CP: complex partial; n: number; M: motor; S: sensitive; SGTC: secondarily generalized-tonic-clonic; SP: simple partial; Sz: seizure; Vis: visual; W: wakefulness.
* This series of cases were updated by Loiseau et al. in 1978**, 1985, 2002 and 2005***.

RESULTS

There were 2 boys and 6 girls, with ages ranging from 10 yrs. 9 m to 14 yrs. 3 m. Most of the patients had a single seizure and only three of them received AEDs. The semiology of the seizures consisted of sensorio-motor manifestations in four patients, motor in two and sensorial in two; six patients presented secondary generalized seizures. Six patients had mild EEG focal abnormalities and all had normal brain CT, and one, a normal brain MRI (Table 2). The EEG discharges present in six patients consisted of spikes and sharply contoured waves over the central (2), centroparietal (1), parietal (1), temporal (1), and frontal (1) regions; in four of these patients the EEG abnormalities were observed only after sleep deprivation (Figures 1-3).

All were literate, attended regular public schools and scored in a median range for IQ, and seven showed discrete higher scores for the verbal subtests. (Table 3). There were low scores for attention in different modalities in six patients, mainly in alternated attention as well as inhibitory subtests (Stroop test and Trail Making Test part B). Four of the latter cases who showed impairment both in alternated and inhibitory attention were not taking antiepileptic drugs. Visual memory was impaired in five patients (Rey Complex Figure) (Figure 4). Executive functions analysis showed deficits in working memory in five, mostly observed in Digits Indirect Order and Arithmetic tests (WISC III). Reading and writing skills were below expected average for school grade in six patients according to the achievement scholar performance test utilized. One patient of this series who had the best scores in all tests was taking Phenobarbital (PB) and had discharges over the right central regions (patient 8). The most compromised patient was also taking PB and the discharges were observed in left frontal area (patient 1).

Table 2. Summary of clinical presentation and subsidiary exams.

Patient	Sex	Age of onset Yrs.	Focal seizures	STCG	Seizure n	Time	EEG Awake	EEG Sleep	Brain Imaging Study	Treatment	FUP in months
1	F	12 yrs.	Sensorial	Yes	1	W	Nl	LFC (SD)	Nl	No	15
2	F	12 yrs.	Sensorio-motor	No	2	W	RC	RC	Nl	PB	17
3	F	10 yrs. 6 m.	Motor	Yes	2	S/W	Nl	Nl (SD)	Nl	PB	18
4	F	13 yrs. 10 m.	Sensorio-motor	Yes	1	W	Nl	Nl (SD)	Nl	No	15
5	F	10 yrs. 4 m.	Sensorio-motor	No	Several	W	Nl	RP (SD)	Nl	No	17
6	M	12 yrs. 3 m.	Motor	Yes	1	W	RCP	RCP (SD)	Nl	No	14
7	M	13 yrs. 1 m.	Sensorial	Yes	1	W	Nl	RT(SD)	Nl	No	9
8	F	12 yrs. 9 m.	Sensorio-motor	Yes	2	W	Nl	RC (SD)	Nl	PB	18

FUP: follow-up; LFC: left fronto-central; RC: right central; RCP: right centro-parietal; RP: right parietal; RT: right temporal; S: sleep; W: wakefulness.

Table 3. Summary of neuropsychological findings.

Pt Sex	Age (Yrs/Months)	Full IQ	Verbal IQ	Performance IQ	Difference V/P	Attention			Memory		Executive Abilities		Reading Abilities	Writting Abilities
						SUS	AL	IN	VM	AM	PL	WM		
1 F	12y 05m	98 M	100 M	97 M	3 + V	M	INF	INF	INF	INF	IM	INF	INF	INF
2 F	13y 08m	87 IM	89 IM	87 IM	2 + V	IM	INF	IM	INF	INF	IM	INF	INF	INF
3 F	13y 10m	105 M	106 M	103 M	3 + V	M	INF	IM	INF	S	INF	INF	INF	INF
4 F	14y 03m	93 M	103 M	85 IM	18 +V	M	INF	INF	IM	SM	IM	INF	INF	INF
5 F	10y 09m	95 M	97 M	97 M	2 +V	M	INF	INF	INF	M	IM	INF	INF	INF
6 M	12y 08m	115 M	116 SM	113 SM	3 +V	M	M	SM	INF	M	M	M	S	S
7 M	13y 03m	95 M	95 M	99 M	4 +P	SM	INF	INF	SM	IM	M	M	INF	INF
8 F	13y 07m	104 M	107 M	100 M	7 +V	SM	M	M	IM	M	IM	M	S	S

AL: alternated; AM: auditory memory; B: borderline; IN: inhibitory; INF: inferior; IM: inferior medium; M: medium; PL: planning; S: superior; SM: superior medium; SUS: sustained; VM: visual memory; WM: working memory.

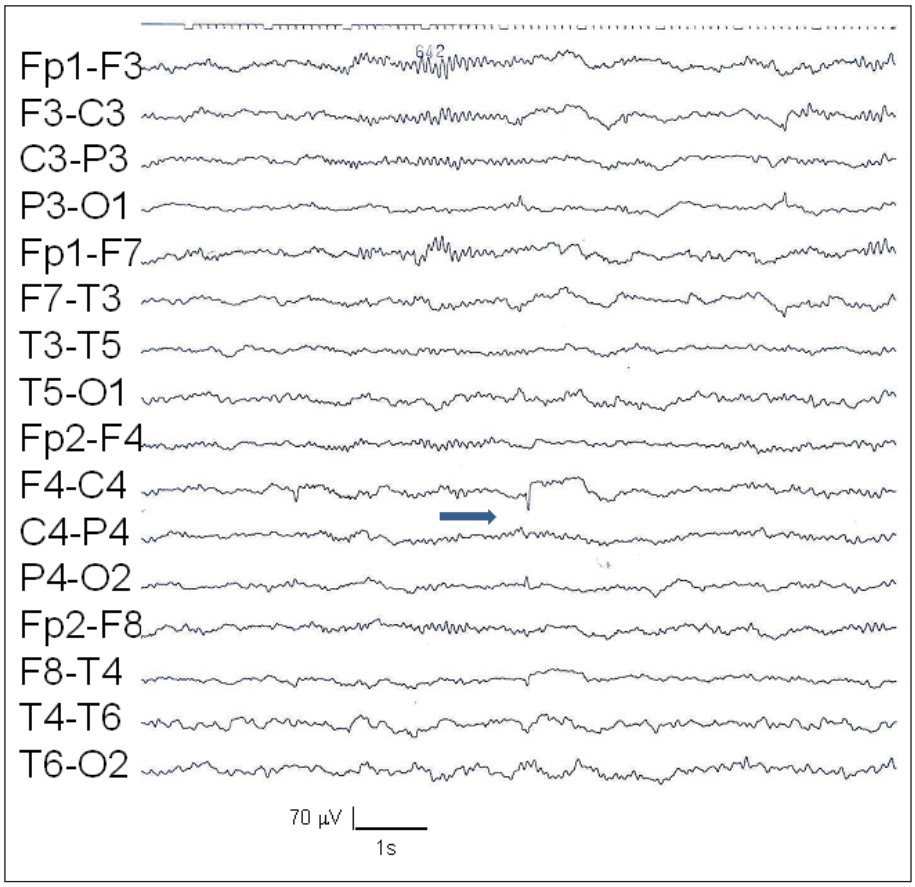


Figure 1. Sleep deprived EEG showing sharp waves over the right centroparietal area and less frequently on the homologous left region (patient 6).

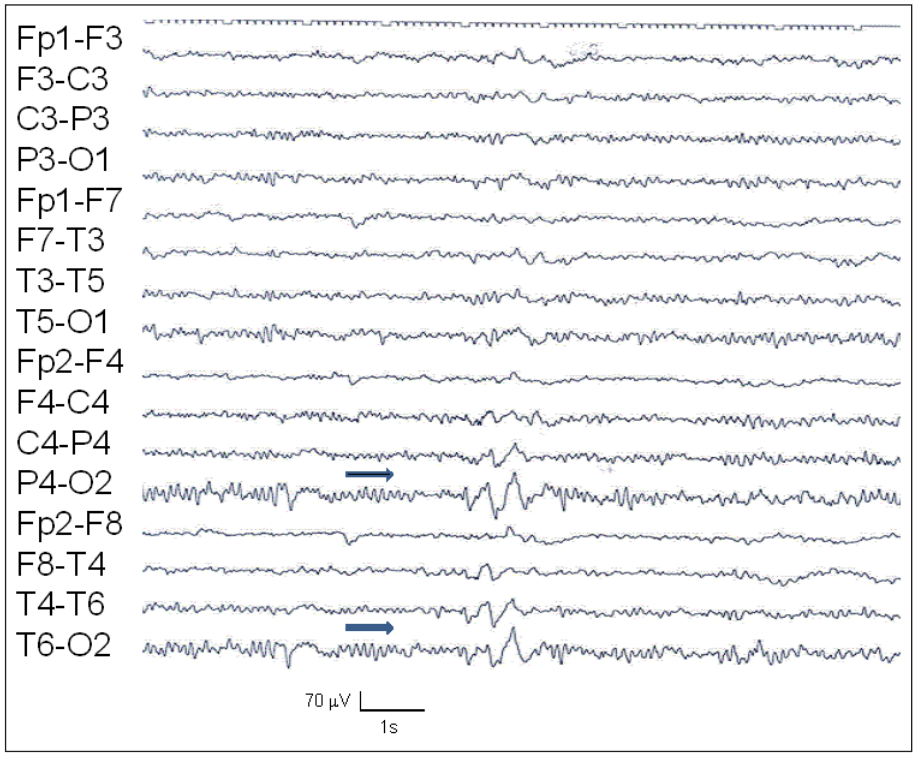


Figure 2. Sleep deprived EEG showing slow waves over the right posterior region (patient 5).

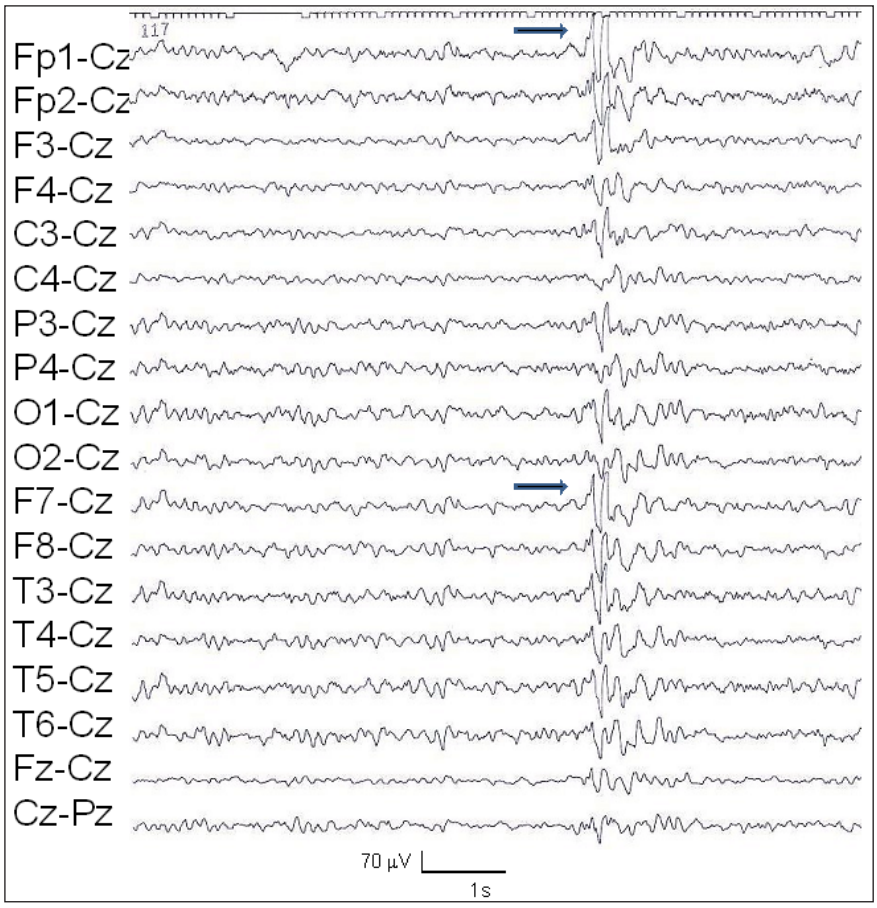
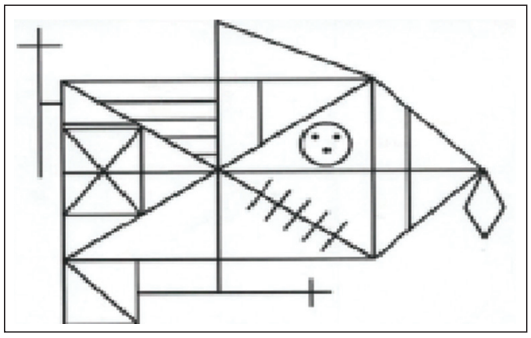
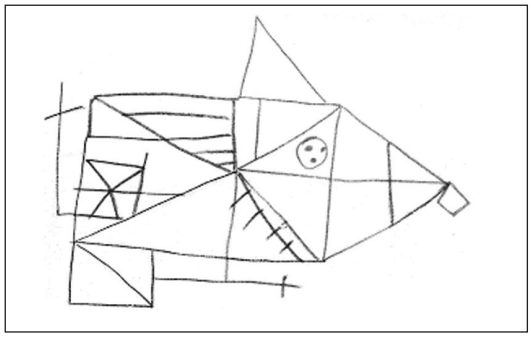


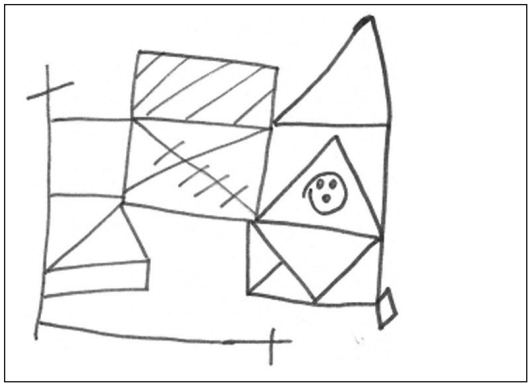
Figure 3. Sleep deprived EEG showing sharp waves over the left frontotemporal region with diffusion to contralateral area (patient 1).



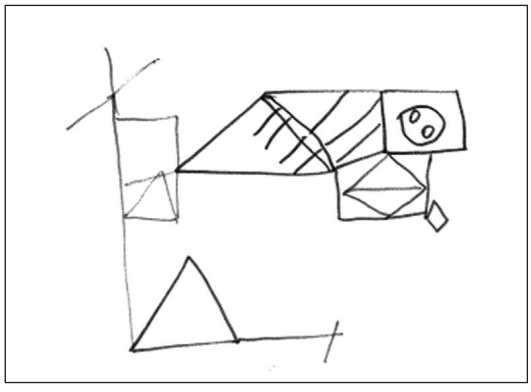
A – Complex Rey Figure



B – Copy



C – Immediate drawing from memory



D – Late drawing from memory

Figure 4. Rey Complex Figure test showing difficulties in immediate and late drawing from memory (patient 4).

DISCUSSION

Most of our patients were female (6/8) which is different from the previous reported series of BFSA, that mentioned the prevalence in males. By the other hand, the paucity of seizures as well EEG findings in our cases are similar to other studies (Table 1).

Neuropsychological findings were not previously reported in BFSA. Most of our patients presented mild neuropsychological dysfunction with normal IQs levels and academic problems. Although neuropsychological abnormalities are mostly described in children with symptomatic epilepsies and refractory seizures, there are some reports of cognitive impairment in new onset epilepsies in this age group. Recently in a prospective community-based study in the state of Indiana, USA, Fastenau et al. compared 282 children (aged 4-14 yrs. and with IQ ≥ 70) who had a first recognized seizure with 147 healthy siblings on a battery of standardized neuropsychological and academic tests. These authors noticed that although academic achievement was similar in the two groups, differences in cognition were observed between them, suggesting that may be a window of time since the beginning of the cognitive impairment until the appearance of scholastic problems in children with epilepsy.

Mild neuropsychological deficits have been described in children with benign focal epilepsies of childhood (Miziara, 2003). Croona et al. observed in 17 children with Benign Epilepsy with Centrotemporal Spikes (BECTS) apparent cognitive deficits, most prominently in memory and learning of auditory-verbal material together with executive functions. Pinton et al. have studied the neuropsychological aspects of 18 children with BECTS which presented normal verbal, memory functions and IQ but drawing and visuo-spatial skills, attention and visuo-spatial memory significantly weaker compared to the normal range for age; reading, numeracy and/or spelling ability were significantly delayed by one academic year or more in ten of these children.

Papavasiliou et al. studied in 32 children with BECTS written language skills including spelling, reading aloud and reading comprehension and they found that these children, as a group, performed significantly worse than controls.

In 2007 Fonseca et al. studied 42 Brazilian children with BECTS which presented inferior scores in the Brazilian School Performance Test compared to controls. In this study the time for the first seizure and the parents' scholastic level showed a positive correlation between neuropsychological results.

These reports refer deficits in brain posterior areas, such as auditory agnosia and written and visual-spatial deficits. It is widely discussed the implication of the frequent discharges in these patients, especially during sleep, when some of the most important neuropsychological functions like memory are consolidated.

Attention deficits have also been reported in children with BECTS. Attention deficits and specifically sensitivity to distractors in these children could also result from the occurrence of epilepsy during the development of attentional control. Deltour et al. observed longer reaction time during a computerized task in children with BECTS and with idiopathic generalized epilepsies when comparing to controls, and suggested the existence of a slowness of perceptual, motor or information processing in both groups of patients with epilepsy, but greater in BECTS. According to these authors children with BECTS seem to have an inability to inhibit distractors, which may contribute to less efficient attentional control.

Benign focal seizures of adolescence is characterized by discrete or none EEG abnormalities, so the discharges could be rarely implied as the sole cause of the neuropsychological dysfunction in these patients. Landau-Kleffner syndrome (LKS), or epileptic acquired aphasia in children, is one extreme example of the association of epileptiform discharges and neuropsychological dysfunctions. But even in this syndrome, the EEG may be normal in some phases of the disease process. The aphasia in LKS sometimes has a fluctuating pattern, which can be explained by an inconstant EEG abnormality. LKS is classified among the idiopathic epilepsies related to localization that in this syndrome corresponds to the speech area around the sylvian fissure, which could be damaged at a critical age to the development and maturation of this ability.

The epileptiform activity reflects a process of cellular dysfunction that can be or not manifested by clinical symptoms. In children this subject have been extensively discussed in the literature. Some authors speculate that the EEG abnormalities may be epiphenomena of the underlying structural process (Holmes 1981). Others imply the clinical symptoms to the electrical cortical dysfunction, once the brain maturation is dependent on several inputs, including the cortex and its surrounding networks (Deonna 1991, Deonna & Roulet 1991, Deonna et al. 1993).

Our patients presented mild attention and executive impairments and also neuropsychological dysfunction related to posterior brain areas, such as visual memory. Half of our patients with abnormal EEGs (3/6) showed epileptiform discharges in posterior areas and the remaining in anterior regions. As these associative areas are better maturated in adolescents, the neuropsychological dysfunction may be milder in these patients than in those in which epilepsy started in childhood, especially when speech synapses are best tuned between 4-6 yrs, classical time for the onset of aphasia in LKS.

Although reading and writing problems may be consequence of the low cultural environment and socio-

economic problems present in public schools in Brazil, impairment in visual memory skills may aggravate these difficulties. When comparing with the data of Fastenau et al (2009) their patients with new onset seizures and neuropsychological dysfunction did not present academic impairment at onset and most of our patients with idiopathic focal epileptic seizures present reading and writing problems. Although learning abilities are strongly related to socioeconomic factors, especially in developing countries, this fact points to the need of an early reeducation process in the Brazilian children with epilepsy, even in those who have few seizures, helping also in this way, to decrease the stigma associated to epileptic seizures in the community.

CONCLUSIONS

Mild neuropsychological deficits in attention domain and in some executive functions like working memory and planning, as well as in visual memory, which may aggravate academic problems related to reading and writing skills, were described in this group of patients with BFSA from community. This may reflect mild higher level neurological dysfunctions in benign focal seizures of adolescence probably caused by an underlying dysmaturative epileptogenic process. An educational approach may be necessary in some cases and a multidisciplinary team will be desired to work with these teenagers especially in developing countries, where education gaps are common.

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