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THE FREQUENCY-AMPLITUDE GRADIENT IN THE SLEEP EEG OF CHILDREN AND ITS DIAGNOSTIC SIGNIFICANCE

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ABSTRACT - *Objective:* 1014 EEGs of children in the 3-months to 12-years age group were obtained during sleep with the purpose of assessing the frequency and amplitude gradient (FAG) its absence thought to be an indicator of neurological disorder. *Method:* FAG findings were divided into present/absent. The neurdogical findings were classified according to the presence (abnormal neurological finding-ANF) or absence (normal neurological finding-NNF) of neurological disorder. The association and significance between FAG and neurological findings was determined by prevalence ration (PR) and chi-square test (χ^2). *Results:* FAG showed a characteristic distributions of voltage output during non-REM sleep, stage II, in the 3-months to 5-years age group with NNF. The PR and the χ^2 test demonstrated a strong association between FAG absent and ANF. *Conclusion:* FAG is an age-dependent EEG sleep parameter and absence of FAG in the 3-months to 5-years age group is highly suggestive of neurological disorder.

KEY WORDS: pediatric sleep EEG, frequency-amplitude gradient, posterior slow waves, neurological disorder.

O gradiente de freqüência-amplitude do EEG em sono de crianças e seu significado diagnóstico

RESUMO - *Objetivo:* Estudaram-se 1014 EEG de crianças na faixa etária de 3 meses a 12 anos de idade obtidos em sono com o objetivo de avaliar o gradiente de freqüência-amplitude (GFA) ausente como possível indicador de comprometimento neurológico. *Método:* O GFA foi caracterizado: 1 - presente; 2 - ausente. O padrão neurológico foi classificado segundo a presença ou ausência de comprometimento neurológico em padrão neurológico anormal (PNA) e normal (PNN), respectivamente. *Resultados:* O GFA mostrou-se um parâmetro EEG próprio da criança em sono na faixa etária dos 3 meses aos 5 anos de idade e com PNN. O teste do qui quadrado e a razão de prevalência mostraram relação altamente significativa para o GFA ausente, e o PNA. *Conclusão:* O GFA é um parâmetro EEG do sono idade-dependente e sua ausência na faixa etária dos 3 meses aos cinco anos é altamente sugestivo de comprometimento neurológico.

PALAVRAS-CHAVE: EEG pediátrico em sono, gradiente de freqüência-amplitude, ondas lentas posteriores, comprometimento neurológico.

Adequate knowledge of the electroencephalogram (EEG) maturation process in children - awake and asleep - is the prerequisite for a competent interp retation of EEG patterns in children[1,2]. The graphoelements proper to the child's sleep patterns and their development have been reported in the literature by several authors, notably by Petersén and Eeg Olofsson[3]; Eeg Olofsson[4,5] and Eeg-Olofsson et al.[6].

In addition to this bulk of knowledge Slater and Torres[7] described for the first time the frequency-amplitude gradient (FAG) as an important electro e ncephalographic (EEG) sleep parameter in children. It is characterized by a pro g ressive voltage reduction f rom occipital to frontal areas, associated with a frequency decrease in the antero-posterior direction. FAG is intermittent during stage-2 sleep and becomes continuous in deep NREM sleep, generally not appearing before the age of 4 months. Slater and Torres[7] further pointed out that FAG was absent in acute and chronic pathologies of the child central nervous system (CNS). In the daily clinical practice of interpreting EEG of sleep in children, FAG has drawn our attention to chronic neurological disorders[8].

Thus, the purpose of this study was to assess the

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Table 1. Number and percentage of clinical diagnosis of the 1014 children refer for EEG, by age group.

Clinical diagnosis	Age / group					
	3 mos • 3 y		3 y • 6y		6 y • 12 y	
	Number	Percentage	Number	Percentage	Number	Percentage
No epileptic paroxismal disorder	86	8.5%	96	9.5%	31	3.0%
Epilepsy	143	14.1%	85	8.4%	84	8.2%
Cerebral palsy	75	7.4%	62	6.1%	47	4.6%
Headache	22	2.2%	38	3.7%	77	7.5%
Attention-deficit/hiperactivity disorder (ADHD)	4	0.4%	26	2.5%	68	6.7%
Brain injury	25	2.5%	4	0.4%	4	0.3%
Arachnoid cysts	13	1.3%	1	0.1%	1	0.2%
Hydrocephalus	8	0.8%	0	0	0	0
Neurocysticercosis	4	0.4%	1	0.1%	1	0.2%
Kawasaki syndrome	4	0.3%	4	0.4%	0	0
Total	384	38%	317	31.2%	313	30.8%

absence of FAG as a possible indicator of neurological disorder in the child.

METHOD

EEG recording – The sample consisted of 1014 EEGs of children in the 3 months to 12-year age group referred to the Clinical Neurophysiology Laboratory, Hospital Universitário de Brasilia, from January 1997 to March, 2003, with the following indicators for performing EEG (Table 1).

Procedures – The study was transversal and analytical, based on a population of children who underwent EEG during sleep. The selection criteria for EEG examinations were: *inclusion* (1) spontaneous or chloral-hydrate-induced sleep of more than 20 minutes of duration, (2) good technical conditions for visual analysis, (3) non-REM in phase-II sleep, and *exclusion* (1) EEG obtained in acute phase of neurological or pediatric disorder; (2) EEG only in phase-III and IV non-REM sleep and (3) unsatisfactory technical conditions. After EEG selection, only cases with the following were included: (1) medical report with all the information required by the study protocol; (2) ambulatory follow-up of at least 3 clinical visits; (3) clinical EEG referral, distinctly noted on the medical report and (4) complete neurological examination of the child.

The EEGs were performed with 3 machines of analogue-type: (1) Berger, 8-channel, model 345 AGF, of Brazilian manufacture, (2) Nihon Kohden - Neurofax - 18 channels and (3) Neurotec - Neurofax - 22 channels. The calibration used was: time constant of 0.3 seconds, high-frequency filter 70 Hz, sensitivity of 5 microvolts per millimeter and paper velocity of 30 millimeters per second. The total duration of the recording was from 30 to 60 minutes. The induced sleep was obtained by chloral hydrate, 10%, in 40 to 100 mg/kg/dose. The electrodes were placed according to the 10-20 international system[9]. The stimulation test used was intermittent photic stimulation (IPS) - 5 to 20 flashes/second -, which was performed in all of the cases.

Data analysis – The variables studied for FAG were: (1) visual analysis in the referential montage (longitudinal or AP direction) and bipolar montage (scalp to scalp in the transverse and coronal direction); (2) EEG profile description as to morphology, duration, voltage, frequency and location; (3) characterization of FAG as present or absent according to electroencephalographic pattern. The neurological findings were obtained from the medical reports, analyzing the following variables for FAG association: (1) motor pattern; (2) cranial perimeter; (3) mental retardation ; (4) other neurological signs. Subsequently, neurological pattern analysis was characterized according to the presence or absence of neurological disorder, as normal neurological finding (NNF) and abnormal neurological finding (ANF), respectively.

EEG interpretation – EEG visual analysis was performed individually and independently by two electroencephalographers without prior knowledge of the EEG study or neurological findings. The tracings which were not in accordance were discussed afterwards by both readers. The agreement index was 86% with Kappa 0.83. After EEG selection by visual analysis, the investigators analyzed the medical reports in order to define and correlate neurological findings with FAG.

The EEGs were interpreted according to maturation sleep pattern described by Niedermeyer[1] and FAG criteria according to Slater and Torres[7]. The electroencephalographic findings were reported using the EEG terminology proposed by Chatrian et al.[10].

Statistical analysis – The purpose of the statistical analysis used in this study was to verify the degree of association between FAG and ANF. Thus, the following were calculated: (1) prevalence of FAG absent in ANF children; (2) prevalence of FAG present in NNF children; (3) prevalence ratio (PR) of items 1 and 2. The association between FAG absent and ANF was considered high as to PR>1; (4) determination of confidence interval (CI) for 95% of PR; (5) determination of the statistical significance of the results by chi-square test, with correction by Yate's technique, for an error

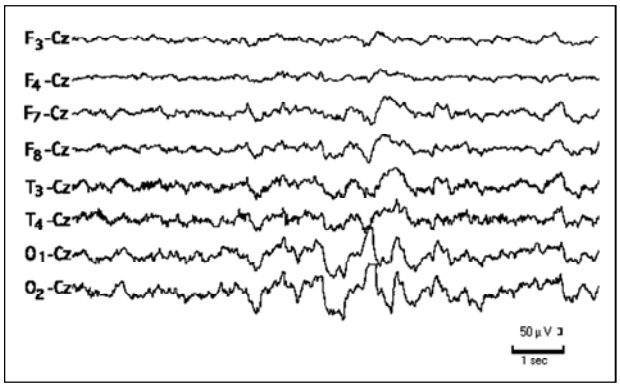

Fig 1. Good frequency-amplitude gradient in 9-month-old child with nonepileptic paroxysmal disorder and normal neurological finding; referential recording; induced sleep by chloral hydrate. The posterior slowing is slightly discontinuous and of a somewhat burst-like character.

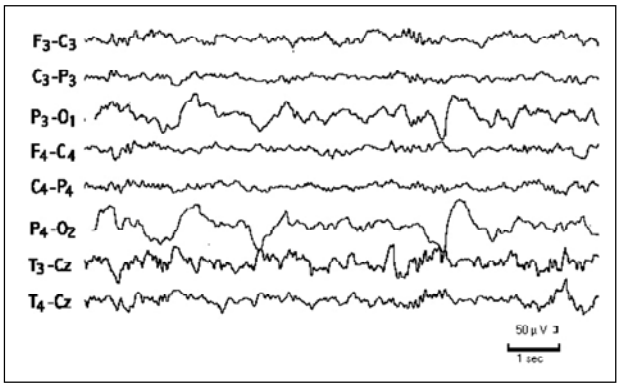

Fig 2. Large posterior slow waves in pediatric sleep (PSWPS) in 26-month-old child, with epilepsy and normal neurological finding, taking phenobarbital, induced sleep by chloral hydrate.

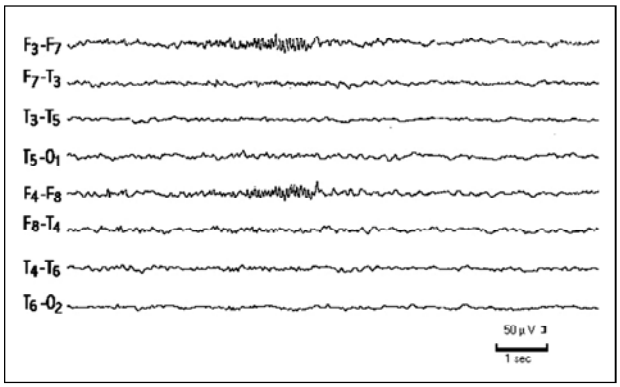

Fig 3. Absent posterior slow waves in pediatric sleep (PSWPS) in 3-year-old child with chronic encephalopathy and epilepsy, abnormal neurologic finding, taking valproate, spontaneous sleep.

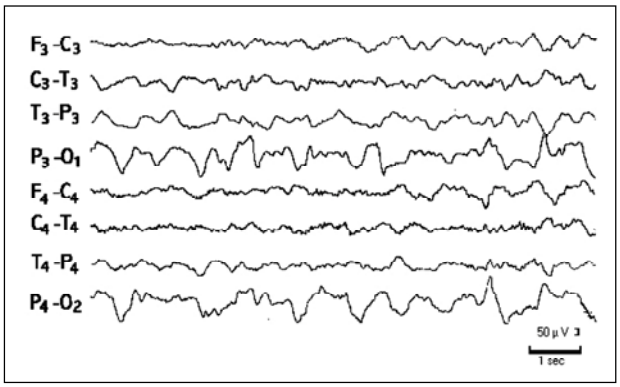

Fig 4. Continuous posterior slow waves in pediatric sleep (PSWPS) in 3-year-old child with chronic encephalopathy and abnormal neurologic finding, no medication, spontaneous sleep.

x of 5%, that is, for a confidence level of 95% ($p<0.05$). The data were electronically processed in the EPI-INFO program, version 6.0.

This study was approved by the Institutional Review Board.

RESULTS

In FAG analysis of 1014 EEGs it was possible to characterize three parameters based on the referential montages (longitudinal or AP direction) and bipolar (scalp-to-scalp in the transverse and coronal direction) in stage-II non-REM sleep. In referential montages, FAG consists of slow waves slightly discontinuous or burst-like, showing a sharp decline in voltage from occipital to frontal areas, middle-posterior amplitude of 150-300 microvolts and middle-anterior of 35-60 microvolts, associated with a frequency reduction in the antero-posterior direction, intermittent and with average duration of 250-300 milliseconds (Fig 1). In other children, the FAG is much better demonstrable in bipolar montages. These posterior slow waves of pediatric sleep (PSWPS) occur at 3-to-6-second intervals, and are either synchronous or asynchronous (Fig 2). One has to keep in mind that vertex reference has drawbacks, especially in sleep, when spindles over Cz appear to be diffuse naturally. A_1 and A_2 references also have their disadvantage. In some patients, FAG was not recorded, neither in bipolar nor in referencial montages (Fig 3). In the bipolar montage were recorded as a continuous pattern (Fig 4). Table 2 demonstrates the main neurological pattern alterations and their relation to FAG absent and present. Mental retardation, motor disorders and cranial alterations were the principal neurological findings encountered in children with ANF.

Tables 3 and 4 show FAG divided into age groups in 1014 EEGs of NNF and ANF patients (658 and 356 children, respectively). Listed according to age FAG

Table 2. Number and percentage of the main neurologic pattern alterations (NPA) by presence or absence of frequency-amplitude gradient (FAG) in the 358 children.

NPA	FAG			
	Presence		Absence	
	Number	Percentage	Number	Percentage
Upper motor neuron disorder[a]	25	7.0%	183	51.4%
Mental retardation[a]	2	0.5%	297	83.4%
Developmental language disorder[a]	27	7.5%	48	13.4%
Microcephaly[a]	27	7.5%	144	40.4%
Macrocephaly[a]	4	1.1%	19	5.3%
Choreoathetosis[a]	18	5.0%	27	7.5%
Ataxia[a]	22	6.1%	29	8.1%

[a], not mutually exclusive

Table 3. Distributions of frequency-amplitude gradient (FAG) present or absent in 658 EEG of children with normal neurological finding (NNF), by age group.

Age group	FAG			
	Present		Absent	
	Number	Percentage	Number	Percentage
3 mos • 1 y	73	11.0%*	12	1.8%
1y • 2 y	87	13.2%*	4	0.6%
2 y • 3 y	85	12.9%*	3	0.4%
3 y • 4 y	85	12.9%*	4	0.6%
4 y • 5 y	77	11.1%*	4	0.6%
5 y • 6 y	56	8.5%	6	1.0%
6 y • 7 y	42	6.3%	7	1.1%
7 y • 8 y	40	0.6%	11	1.7%
8 y • 9 y	16	2.4%	13	1.9%
9 y • 10 y	8	1.2%	14	2.1%
10 y • 11 y	0	0	5	0.7%
11 y • 12 y	0	0	6	1.0%
Total	569	86.4%	89	13.6%

*Age group with predominant good frequency-amplitude gradient.

is most evident in the 3 months to 5 years age group with NNF. In Table 5, prevalence ratio, confidence interval for 95% and chi-squared corrected by Yates technique are discriminated for all age groups and those of 3 months to 5 years, for FAG and PSWPS. The analysis shows that there is a strong association of FAG absent in ANF patients, in all the 1014 EEG age groups, since the prevalence ratio was 5.9. The association becomes stronger when the 3-months to 5-years age group is considered, PR=12.61. Chi-square test, corrected by Yates technique, showed a highly significant relation for FAG absent in both samples (p= 0.00000001). For posterior slow waves, a strong association was also observed in the absence of or with continuous PSWPS pattern in ANF patients. The prevalence ratio for all the age groups was 6.04, and 12.32 for the ages of 3 months to 5 years. Chi-square test, corrected by Yates was also highly significant for both samples (p=0.00000001). The 95% confidence interval was extensive in all four samples submitted to this evaluation.

DISCUSSION

The maturation of cerebral bioelectric activity is an important milestone in the childhood development and for this reason the EEG can yield crucial clinical information in part confirming the relation between progressive changes in myelinization and cerebral morphogenesis during this period[11]. Thus, the interpretation of electroencephalographic findings in children becomes more difficult due to the large numbers of models and patterns which normally occur at different ages. FAG is yet another age-dependent parameter which, unfortunately, has an

Table 4. Distribution of frequency-amplitude gradient (FAG) present or absent in 356 EEG of children with abnormal neurological pattern (ANF) by age group.

Age group	FAG			
	Present		Absent	
	Number	Percentage	Number	Percentage
3 mos • 1 y	9	2.5%	30	8.4%
1y • 2 y	10	3.0%	38	10.7%
2 y • 3 y	5	1.4%	24	6.7%
3 y • 4 y	8	2.2%	27	7.6%
4 y • 5 y	7	1.7%	23	6.5%
5 y • 6 y	6	2.0%	15	4.2%
6 y • 7 y	7	1.9%	36	10.1%
7 y • 8 y	8	2.2%	28	7.8%
8 y • 9 y	6	1.7%	24	6.7%
9 y • 10 y	6	1.7%	36	10.1%
10 y • 11 y	0	0	0	0
11 y • 12 y	0	0	3	0.8%
Total	72	20.4%	284	79.6%

Table 5. Prevalence ratio, confidence interval for 95% and the chi-square test to verify the degree of asso - ciation between FAG absent and abnormal neurological pattern (ANF) in 1014 sleep EEG of children, Hospital Universitário de Brasília - Section of Electroencephalography, Brazil.

ANF				
Statistical analysis	FAG 1014 EEG	FAG 3 mos – 5 y	PBWPS 1014 EEG	PBWPS 3 mos – 5 y
Prevalence ratio	5.9	12.61	6.04	12.32
95% Confidence interval	4.83 – 7.20	8.68 – 18.31	4.95 – 7.38	8.61 – 17.62
chi-square test	433.18	330.80	455.88	351.66
p=0.00000001	SS	SS	SS	SS

FAG, frequency-amplitude gradient; PSWPS, posterior slow waves in pediatric sleep; SS, statistically significant (p<0.05).

undervalued role in childhood electroencephalography. A review of the literature reveals only one study which objectively underlines the value of FAG as an EEG pattern for pediatric sleep and its relation with central nervous system disorders[7].

From the EEG point of view, FAG shows some dependence on the montages being used. In referential montage, the findings are totally in accordance with Slater and Torres[7]. In more complex is the evaluation of bipolar montages especially with regard to the occipital EEG activity. The term "posterior slow waves of pediatric sleep" (PSWPS) should underline the spatial accentuation of this EEG sleep pattern. Whether isolated or in series, isolated or concomitantly in series, this pattern may lead to erroneous interpretations of an apparent epileptogenic paroxysm. In 1952, Kellaway[12] described slow posterior waves in pediatric sleep and drew attention to the fact that they were more significant in deep sleep without emphasizing it as FAG in phase-2 of non-REM sleep.

FAG in referential and bipolar montages were present and well-formed in children with NNF. In ANF patients, FAG was mostly absent or with continuous PSWPS. Slater and Torres[7] have already verified that several acute or sequelar CNS neurological injuries were associated to the absence of FAG. Among the 100 patients evaluated in his study, 33 had severe neurological injury and in this subgroup, there was no FAG formation in 100% of the cases. Of 32 patients with moderate neurological injury, 14 were FAG absent and 15 had regular FAG formation. Of 35 patients with mild neurological injury, 27 had well-formed FAG.

The results of our study not only confirm the previous observations by Slater and Torres[7], but also demonstrate the relationship between non-progressive chronic neurological disorder and absence of

FAG. This portion of our observations, based up on the sequelae or intercritical phases of inactive CNS disorders, have not yet been reported in the literature. The high statistical significance serves as further support for our findings. There were no significant statistical differences between referential and bipolar montages for FAG. However, the unique PSW-PS EEG configuration led us to study it in greater detail. This drew our attention to the fact that this parameter, when present, reflects CNS normality. However, when absent or present with continuous PSWPS, it expresses neurological disorder in the 3-months to 5-years age group. The importance of this parameter gradually declines as age advances and may be related to CNS maturation. It is reasonable to assume that FAG tends to disappear with the end of myelination as an important pass of maturation until it becomes totally absent from the age of 10 years. Thus, the information derived from the FAG in childhood with NNF is time-limited and shrinks after age 5 years. In ANF patients, however, FAG absence tends to persist through childhood.

Since this is a transversal study, FAG analysis in longitudinal or evolutive cohort, in relation to age group, would better show the development and disappearance of FAG as a consequence of maturation and myelinization of the CNS. In our study we observed its significance in normal children from the age of 3 months, a younger age than that observed by Slater and Torres[7].

Thus, FAG absent in referential or bipolar montages can be found in two distinct situations: (1) EEGs of NNF children in a more advanced age group (>10 years), representing a normality sustained by cerebral maturation; and (2) EEGs in ANF children with neurological alterations, in the 3-months to 5-years age group, reflecting basic neurological disorder.

Analyzing PR of FAG in 1014 EEGs of the study population, we verified that the probability of FAG absence in patients with altered neurological pattern is 5.9 times greater than in NNF patients. If we restrict FAG analysis to the 3-months to 5-years age group, we observe that the probability of FAG absence in children with ANF is 12.61 times greater than FAG absence in NNF children. The higher PR is a result of the increase in FAG- absent proportion in the 9 to 12 years age group, due to maturation, which acts as a false-positive result. Since the 3-months to 5-years age group has not yet presented FAG absent due to maturation, the number of false- positives is reduced, with a resultant increase in PR declines with advancing age.

From the analysis of our results we conclude: (1) FAG is an excellent indicator of neurological disorder in children; (2) the prevalence of well-formed FAG is found in the 3 months to 5 years age group in children with NNF; (3) there are variations according to the montage used (referential or bipolar); and (4) the probability of FAG absence in EEGs of children with ANF is significantly greater than that of NNF patients, particularly in the 3 months to 5 year age group.

This study shows that a well trained electroencephalographer without digital EEG technology or computerized database[13] can make solid prognostic statements for the benefit of pediatricians and distressed parents of children with neurological problems and that clinical electrophysiology retains its essential role[14].

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