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SECONDARY LATE-ONSET LENNOX-GASTAUT SYNDROME: A CRITICAL VIEW

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Starting preferentially between 1 and 6 years of age, the epileptic siezures observed in the Lennox-Gastaut syndrome (LGS) may show characteristics due to the level of brain maturation in this age range. The observation of differences in the ictal behavior of patients whose syndrome had started after the 6th year of life (LOLGS) showed greater predominance of tonic-automatic and tonic-clonic seizures and of partial seizures with complex symptomatology[14]. These differences may be related to the level of brain maturation of the patients at the time of onset of the syndrome. Other notable characteristics of this group of patients with the syndrome initiating after the 6th year of life are the almost total absence of previous history of diffuse encephalic aggression and the moderate reduction of intellectual level. A review of the literature shows considerable incidence of cases starting after 6 years of age (22%) [1]. Thus the observation of the ictal, interictal and electroencephalographic behavior, as well as the detection of factors capable of triggering diffuse encephalic aggression in patients with LGS initiating after 6 years of age, compared to the same aspects in patients whose syndrome started before 6 years of age (EOLGS), becomes of great practical and theoretical importance. Characteristic patterns may indicate specific diagnostic treatment, evolutionary aspects and therapy for patients with LOLGS.

Clinical-electroencephalographic follow-up of a group of patients with LOLGS for an average period of 2.5 years permitted us to observe a behavior similar to that of patients with early-onset LGS, except for a few features [1-4]. The results are briefly presented here, followed by critical considerations.

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MATERIAL AND METHODS

In a group of 66 patients with Lennox-Gastaut syndrome, 15 were found to have had the first manifestations of the syndrome after the 6th year of life. Of these, 12 were followed for a period of time varying from 8 months to 6 years and 5 months (2 years and 8 months average). Eight patients were observed during hospitalization and all were followed on an outpatient basis, with visits scheduled every 2 months. The characteristics of the epileptic seizures, described by two or more relatives and/or observed by us, were recorded during each visit. Twelve patients were followed for more than 7 months, 11 for more than 1 year, 7 for more than 2 years, 3 for more than 3 years, and 2 for more than 5. At the end of the follow-up period all patients had reached puberty according to the criteria of Tanner [19]. The treatment used was in general agreement with the programs proposed by Speciali and Speciali & Lison [8]. Usually, a fixed drug treatment was maintained after the first year of follow-up. All patients were submitted to the INV [20] and WISC [21] tests during the last year of follow-up, except for patient ACM (case 2), who died in his sleep at 13 years and 5 months of age.

The characteristics of the seizures occurring during EEG examination were written on the recording paper in a time relationship with the respective graphic alterations. The epileptic phenomena were described according to the reviews of Lison [12], Gastaut & Broughton [8] and Bancaud [5]. Seizures with two types of epileptic phenomena in association are considered complex, and seizures with three or more phenomena are considered mixed, and have recently been the subject of a publication [4]. The EEG recordings made during the visits and during hospitalization were obtained with 8-channel GRASS apparatus, models 6 and 8 10B. We describe here the interictal electroencephalographic findings considered to be most relevant. Recordings were selected at variable time intervals of three months or more for counts of interictal generalized spike-slow wave complexes (frequency of 2.5 Hz. or less; usually from 2 to 2.5 Hz) (GSSWC). The counts were divided by the time, and the number of GSSWC per minute (GSSWC/min) was obtained. For the recordings of 4 patients (cases 3, 5, 7 and 11) it was possible to compare the frequency of GSSWC during rest and activation by hyperpnea. The EEGs of a patient (case 1) were not included in the counts because they did not satisfy these requirements. The EEG findings for complex and mixed seizures that were recorded by us and had not been previously reported in the literature have been published in a previous paper [4].

RESULTS

1. *Case Reports*

Case 5 — AGS (RGHCRP - 132.690). Age at the end of the follow-up period: 15 years and 2 months. Suffered his first seizure, probably an absence attack, at 9 years and 4 months while in the classroom. Seizures of the same type have been occuring at high frequency ever since, several of them witnessed by us, with or without EEG recording. We witnessed seizures characterized by sudden onset with loss of consciousness, continuous or intermittent neck flexion with conjugate deviation

of the eyes to the left. In some seizures, loss of consciousness appeared not to be complete, since during the episodes the patient seemed to try to find a better position in his chair, with movements that could not be characterized as automatic. However, he did not answer when called by his name for several seconds. Finally, he did answer when called, with his eyes still turned to the left. Occasionally he has abundant salivation. Variations of the manifestations described were observed clinically and the seizures recorded by EEG. The main ones were: palpebral myoclonus, conjugate deviation of the eyes and head to the left with palpebral myoclonus; previous findings associated with mastigatory automatisms. During follow-up, seizures with loss of tonus and falls with serious injuries occurred. Approximately three years after the onset of the epileptic picture, generalized tonic-clonic seizures started to occur, especially during sleep and coinciding with the introduction of ethosuccimide into the therapeutic program. A little before the beginning of the tonic-clonic episodes, oligoclonic tonic seizures occurred, but only when he was medicated with nitrazepan. At the beginning of the epileptic picture, the frequency was of 3 to 5 atypical absences per day, which were reduced after the onset of the tonic-clonic seizures. At the end of the period of observation he had tonic-clonic seizures, particularly during sleep, atypical absences and atonic seizures. The Weichbrodt reaction in the cerebrospinal fluid (CSF) was slightly opalescent. The patient was born by normal delivery and his neuropsychomotor development was normal until the onset of the syndrome. A paternal aunt has epilepsy. He has a history of teniasis. *Electroencephalographic features:* EEG obtained during wakefulness. Between 10 and 11 years of age, the background activity consisted of 10 Hz. alpha rhythm moderately irregular in the posterior projections and with good differentiation for the anterior ones. Theta waves were sporadically intermingled with the basal rhythm. Bursts of theta waves of high amplitude and up to 1.5 seconds duration occur in C_3-P_3. Diffuse, pseudorhythmic spike-wave bursts consisting of 1.5 to 5 Hz. spike-waves also occur. At times the spikes have a "slow" frequency. Activation by hyperpnea causes a slowing down of the background activity and frequent pseudorhythmic spike-wave bursts. Several atypical absences with palpebral myoclonus have been recorded. At times the pseudorhythmic burst are followed by delta waves. From 11 to 15 years of age the background activity slowed down progressively, reaching the theta band in the last recordings. Diffuse spike-slow wave bursts persist, always triggered at higher frequency by hyperpnea (which also causes diffuse slowing down of the recording). Intermittent photic stimulation did not modify the EEG.

Case 8 — OPP (RGHCRP — Miscellaneous). Age at the end of follow-up: 22 years and 2 months. Born by cesarean section after 8 months of gestation of twins, the 2nd to be extracted. She weighed 1,800 g and remained in an incubador for 4 days. The twin sister died 44 hours after delivery. No abnormality was noted in the patient despite prematurity. She only sat up at 9 months and walked at 2 years. Only at 4 years of age could she talk correctly. Impairment of the mental level did not permit education in school. At the age of 4 she became hyperkinetic and aggressive. She was rebellious and did not obey her parents until around 12 years of age, when rebukes began to have an effect. This improvement coincided with the beginning of irregular use of antiepileptic medication indicated even though the patient had no seizures. Menarche at 16. The patient suffered her first seizure at 17 years and

2 months, while watching television. The seizure was tonic and rapid. On the following day she suffered a fall in school, with transitory and brief loss of consciousness. From that time onward she started to have consciousness disorders of a paroxismal nature, with or without alterations in muscle tonus. Initially treated with phenobarbital and diphenyl-hidantoin + deoxyephedrine and later with several different therapeutic programs, she suffered tonic and tonic-clonic seizures and simple and complex atypical absences, atonic and hemitonic. Some generalized tonic-clonic seizures were preceded by massive bilateral myoclonus. The tonic seizures, which resisted treatment, predominated during somnolence. The results of neurological examination were normal except for the mental level. No familial history of epilepsy was reported. *Electroencephalographic features*: EEGs obtained during wakefulness. The background activity is irregular in shape and amplitude in all projections. Four to 6 Hz. theta rhythm, occasionally intermingled with beta waves, is encountered in all EEG recordings. No postero-anterior differentiation was observed. Amplitude is asymmetrical in several recordings with the presence of wider and lower-frequency waves on the left (L). Several bursts of spike-slow waves in the right (R) rolandic-parietooccipital or rolandic areas. Bifrontal spikes-slow waves of higher amplitude or symmetrical are observed on the L. Diffuse delta wave paroxisms predominating at times on the R and at times on the L, or unilaterally on the L, are recorded in some EEGs. Bilateral sharp wave paroxisms in a recording, and unilateral on the L in others. Diffuse delta wave bursts, or bursts limited in the projection to the L occurred in the penultimate recording obtained at 22 years of age. Diffuse SSWC are observed in all recordings except one. Diffuse SSWC were observed up to the end of follow-up. A predominance of bifrontal amplitude occurs in most bursts, to the R in some, and in P3-01 in others. Pseudorhythmic bursts of 3 Hz. and spike-slow waves are observed. Secondary bisynchronization is well characterized. SSWC paroxisms in T_6, $T_4 - T_6$ or $T_3 - T_5$ and $T_4 - T_6$ are followed by diffuse spike-slow wave discharges. Tonic, hemitonic seizures and complex atypical absences with palpebral myoclonus were observed during EEG recording.

Case 12 — JLZ (RG.HCRP.92.486). Age at the end of follow-up: 25 years and 9 months. Born by delayed delivery (30 hours of labor), he was cyanotic and hypotonic and remained unconscious (sic) for some time. He was slow in crying. Had apparently normal neuropsychomotor development, sitting up by 7 months and starting to walk at 1 year. Up to the onset of epileptic seizures, his performance in school was average. At 18 he completed high school and was unable to continue his studies because of the frequency and intensity of the seizures. He had his first epileptic seizure at 9 years of age, after a tiring day spent in an amusement park. The first seizure was characterized retrospectively as a generalized tonic-clonic attack. He also started to have absence attacks that could not be described specifically. He improved with antiepileptic medication, suffering only sporadic seizures, and remained under relative control up to 16 years of age. From this age on, frequent seizures and generalized tonic-clonic status epilepticus started to occur. It was possible to characterize retrospectively tonic seizures and possibly atypical absences. Several tonic seizures (most of the time in emprosthotonos, with EEG recordings coinciding with the «grand mal pattern» of Gibbs and Gibbs, were characterized and recorded with the EEG throughout the follow-up period, as well as typical and

atypical absences. We witnessed several tonic-clonic seizures during status epilepticus. The same epileptic manifestations identified at the beginning continued up to the end of the follow-up period, with daily tonic seizures. The intellectual level of this patient was the best in the group studied. A cousin died by drowning when he had a seizure while fishing in a river. A niece is epileptic. *Electroencephalographic features*: EEG recordings obtained during spontaneous somnolence. Background activity, observed during the times when the patient was awakened for activation by hyperpnea, consists of diffuse theta waves. Foci of delta waves projecting temporally-occipitally to the R (in a single recording) and of parasagittal spike-wave complexes of 3c/sec (also in a single recording) were identified. Bifrontal discharges of spike-slow wave complexes were identified in all EEG recordings. Three Hz. spike-wave complexes were observed in one EEG recording. Diffuse spike-slow wave discharges, 3 Hz. spike-wave and pseudorhythmic discharges (both complexes) were iidentified, although sporadically. Atypical attacks were observed during EEG, with palpebral myoclonus, tonic seizures and typical absences.

2. *History Related to Etiological Factors*

Four patients with LOLGS (cases 3, 7, 8 and 12) have a history of perinatal hypoxia. One patient (case 10) has a clinical and histological diagnosis of neurofibromatosis. A female patient (case 4) had early puberty. One patient (case 2) showed appendicular ataxia when examined neurologically. The patients with perinatal hypoxia had the following intervals between the first manifestations of the syndrome and the present ones: case 3, 10 years and 6 months; case 7, 10 years and 3 months; case 8, 7 years and 2 months, and case 12, more than 9 years. Four patients (cases 2, 4, 5 and 12) have relatives with epilepsy. Five patients had epileptic seizures (cases 2, 4, 6, 7 and 11) and nine showed psychomotor retardation (cases 1 through 4 and 6 through 10) before the onset of the syndrome. These findings demonstrate that prolonged intervals of time may elapse between diffuse encephalic agression and the onset of the syndrome, and that, with the exception of one patient (case 5) (with a relative suffering from epilepsy), the remaining 11 have some history of previous cerebral aggression.

3. *Intellectual Level and Neurological Examination*

The intelligent quotient (IQ) of 9 of our patients was less than 46 on the WISC scale. One patient reached 84 and another 76. Ten patients obtained less than 20% yield when submitted to the INV test, and one obtained 80%. In contrast to the elevated frequency of mental retardation, we noted the absence of neurological alterations in all patients except one who had appendicular ataxia 1.

4. *Epileptic Seizures*

The following kinds of seizures, in decreasing order of frequency, were identified during the first year of follow-up: tonic (10 patients), atypical absences (9), tonic-clonic (6), hemitonic (5), atonic (5), with secondary generalization (2), partial with auto-

matism (1), versive (1), and typical absences (1). After the first year, in addition to the previous ones, atonic seizures were identified in 2 patients, tonic-clonic seizures in 1, and tonic seizures in another. The most frequent associations occurred between tonic seizures, atypical absences, tonic-clonic seizures, and atonic and hemitonic seizures. In general, the frequency of epileptic manifestations during the first year of study was of one or more seizures a day or of one to 6 per week. Two patients had less than 9 seizures per year during the last 2 years of follow-up. The simple epileptic manifestations of our patients coincide with those of patients studied in our University Hospital whose syndrome started between 1 and 6 years of age, except for a higher incidence of generalized tonic-clonic attacks and for a lower frequency of seizures in LOLGS. Six of our patients showed complex and mixed epileptic manifestations that were or were not comparable to those observed in patients with EOLGS.

5. *Interictal EEG*

The paroxismal interictal EEG activity of our patients consisted of: generalized spike-slow wave complexes; generalized spike-fast wave complexes; pseudorhythmic bursts of generalized slow- and more than 3 Hz. spike-wave complexes; «grand mal pattern» of Gibbs, Gibbs and Lennox; focal discharges and secondary bysinchronization 3. Wide variability was observed in the incidence of spikes and slow waves throughout evolution. Hyperpnea may activate spike-slow wave complexes 3. Background activity was slowed down in all recordings. The EEG findings overlap with those encountered in EOLGS.

DISCUSSION

A critical reevaluation of the effects of antiepileptic drugs in the serious epileptic syndromes of childhood gave rise to surprising doubts on the efficacy of the treatment programs commonly used [10,11,16]. As a consequence, we recommend a perfectly controlled execution of drug trials keeping in mind the spontaneous fluctuations of the clinical signs and symptoms, of the EEG, and, above all, the search for criteria for determining the probabilities of satisfactory evolution. In cases with high risk factors in terms of the neuropsychological future of the child, correct evaluation of the medical history and of the age when the West and Lennox syndromes started was considered to be of the greatest importance, with a secondary role reserved for treatment. From this point of view, we emphasize the importance of determining guidelines considered to be critical in terms of the age range within which the syndrome arose. It is generally stated that, the earlier the onset of the syndrome, the worse the prognosis. In childhood myoclonic encephalopathy with hypsarrhythmia, the onset of spasms before 4 months of age is associated with higher mortality and lower incidence of recovery [10]. In the Lennox syndrome, deeply retarded patients suffer their first seizure, on the average, at 17.6 months, whereas those with good mental development had their first epileptic seizure around 4 years of age [7]. An important connection has been established between the precociousness of the first manifestation, the seriousness of the neurosycho-

logical sequelae and prior organic etiology. This represents the so-called secondary form of the syndrome, with the fixation of primitive types of epilepsy that generally resist treatment and are relatively unchanged throughout evolution [17].

On the basis of these considerations and of the findings by Oller Daurella [14], it may be possible to construct a theoretical model of late-onset Lennox-Gastaut syndrome. The patients involved are those most likely to show few organic antecedents (the older the age, the larger the number of "primary" cases) and better development up to the onset of the syndrome, who are subject to a high proportion of nonspecific epileptic attacks, either generalized (mainly tonic-clonic seizures and possibly atypical absences) or partial, with emphasis on seizures of complex symptomatology. The control of the epileptic and electroencephalographic manifestation is likely to be more common than in patients with the early form, and, as a rule, the devastating effects on intellectual function commonly observed during the evolution of the early form may not be observed.

Our findings, however, show that this model does not apply to our patients.

Investigation of the personal and hereditary history of intellectual level, of the semiology of the epileptic seizures and of the clinical and electroencephalographic evolution demonstrated a notable similarity between our patients and those whose syndrome started at the usual age. The most relevant difference is a longer "incubation period" of the epileptic syndrome which, in most cases, occurred in patients with a remote history of cerebral aggression (perinatal hypoxia and psychoneuromotor retardation). Thus, our group of patients is characterized by the predominance of "secondary" forms, which goes against the impression that, the later the onset of generalized epilepsy, the higher the frequency of primary forms.

The numerical importance of the secondary forms in the present group limits and fixes the clinical expression of the syndrome. As a consequence of the secondary nature of the affection, the evolutionary perspectives of neuropsychomotor development are reduced. This fact probably occurs with the epileptic seizures. The quantitative and qualitative similarity of the syndrome under study to EOLGS may not reflect the development of clinical expression at a time of higher or lower brain immaturity, as proposed by Osawa et al. [15]. LOLGS is characterized by the late onset of epileptic seizures in cases with a remote history of cerebral aggression which was certainly important, if not necessary, for the genesis of the syndrome. The clinical expression of the seizures results from a pathogenetic situation that arose, at least in part, during previous stages of brain maturation, and might take on characteristics typical of this period of brain development by interfering with the evolutionary capacity of the systems involved in the clinical and electroencephalographic expression of epilepsy. The primary forms must exhibit a different clinical and electroencephalographic symptomatology during and between the epileptic seizures which is compatible with the development

achieved up to the time of onset of the factors responsible for triggering the epileptic syndrome. It is probable that forms of transitions between "petit mal" and "petit mal variant" (the "intermediate petit mal" of Lugaresi [13]) and incomplete or atypical forms of Lennox syndrome are part of the primary forms.

The ictal and interictal differences in semiology are limited to the higher incidence of generalized tonic-clonic crises in patients with late onset of the syndrome, to the lower polymorphism of complex and mixed seizures and to the practical absense of neurological alterations in relation to the frequency of such alterations observed in patients with early onset Lennox Gastaut syndrome in our University Hospital.

SUMMARY

From a group of 66 patients with the Lennox-Gastaut syndrome, 12 whose manifestations had started after the 6th year of life were selected for study. These patients were observed clinically and electroencephalographically for an average period of 2.5 years. We concluded that the late-onset syndrome can: occur after a long interval between diffuse encephalopathy and the first clinical manifestations, with or without previous alterations in psychomotor development; be associated from the onset with serious mental retardation; exhibit simple, complex and mixed seizures similar to those observed in the early form. These patients can also: suffer complex and mixed epileptic seizures previously unreported; paroxismal interictal EEG abnormalities that overlap those of the early form; and spike-slow wave complexes in the EEG that can be actived by hyperpnea. Our results demonstrate that the incidence of LGS after 6 years of age does not necessarily imply a lower frequency of organic antecedents, or beter neuropsychomotor development up to the onset of the syndrome or the presence of a higher rate of nonspecific seizures (generalized or partial seizures, and mainly those with elaborate symptomatolgy). The critical and encephalographic expression of the syndrome, which is secondary and starts after the 6th year of age, may depend at least in part on the age when diffuse encephalopathy started.

RESUMO

Sindrome de Lennox-Gastaut secundaria com início após o 6º ano de vida: considerações críticas.

De um grupo de 66 pacientes com síndrome de Lennox-Gastaut (SLG), selecionaram-se e se observaram 12 com manifestações sindrômicas se iniciando após o 6º ano de vida. Esses pacientes foram observados clínica e eletrencefalograficamente durante um período médio de 2,5 anos. Concluiu-se que a síndrome com início tardio pode: ocorrer após um longo intervalo entre a agressão encefálica difusa e as primeiras manifestações clínicas com ou sem alteração prévia do desenvolvimento psicomotor; associar-se, desde o início, a retardo mental grave; apresentar semiologia crítica (simples, complexa ou

mista) semelhante à da forma precoce. Esses pacientes podem ainda apresentar: crises epilépticas complexas e mistas não referidas anteriormente na literatura; anormalidades EEG paroxísticas intercríticas que se sobrepõem às da forma precoce; no EEG complexos ponta-onda lenta que podem ser ativados pela hiperpnéia. Nossos resultados demonstram que a incidência da SLG após os 6 anos de idade, necessariamente não implica em menor freqüência de antecedentes orgânicos, em melhor desenvolvimento neuropsicomotor até o início da síndrome e na presença de maior proporção de crises não específicas (generalizadas ou parciais, principalmente as com sintomatologia elaborada). A expressão crítica e eletrencefalográfica da síndrome, secundária e se iniciando após o 6º ano de vida, poderia, pelo menos em parte, ser dependente da idade em que incidiu a agressão encefálica difusa.

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