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Clinical Study

Epileptic Encephalopathy in Children with Risk Factors for Brain Damage

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In the study of 887 new born infants with prenatal and perinatal risk factors for brain damage, 11 children with West syndrome that progressed into Lennox-Gastaut syndrome and another 4 children with Lennox-Gastaut syndrome that had not been preceded by West syndrome were found. In this study we present the main findings of these 15 subjects. In all infants multifactor antecedents were detected. The most frequent risk factors were prematurity and severe asphyxia; however placenta disorders, sepsis, and hyperbilirubinemia were also frequent. In all infants MRI direct or secondary features of periventricular leukomalacia were observed. Followup of all infants showed moderate to severe neurodevelopmental delay as well as cerebral palsy. It is concluded that prenatal and perinatal risk factors for brain damage are very important antecedents that should be taken into account to follow up those infants from an early age in order to detect and treat as early as possible an epileptic encephalopathy.

1. Introduction

The concept of epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time [1]. Although the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy, the West and the Lennox-Gastaut (LG) syndromes are clear examples of this concept. West syndrome is an intractable epileptic syndrome characterized by epileptic spasms and hypsarrhythmia that is frequently associated with developmental arrest. This syndrome may evolve to the LG syndrome. The LG syndrome is characterized by severe, intractable, mixed type of seizures, mental retardation, and a slow spike and wave pattern (1.5 to 2.5 Hz) on the EEG [2].

In this study we were interested to present the incidence of the LG syndrome from our cohort of children that were specifically involved because they present prenatal and perinatal antecedents of risk factors for brain damage and report the clinical, electroencephalographic, and magnetic resonance images (MRI) findings.

2. Material and Methods

The protocol was approved by the Research Ethics Committee of the Instituto de Neurobiología of the Universidad Nacional Autónoma de Mexico, and complies with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki.

2.1. Patients. In the period between 2003 and 2011 we have studied 887 infants. From our records we found 11 children with West syndrome that progressed to the LG Syndrome. Also another 4 children with LG Syndrome that had not been preceded by West Syndrome were found. The total sample was of 15 children, 8 were male. The mean gestational age

was of 35.46 + 4.17 weeks in a range between 28 to 40 weeks. All children came from different hospitals at the city of Querétaro referred to our Unit because they had risk factors for perinatal brain damage.

2.2. Clinical Examination by an Expert Pediatric Neurologist. Neurological assessment of the first study was done according to Amiel-Tison's neurological criteria [3, 4]. Children were followed every month during the first year, every 4 months during the second year, and later every 6 months.

2.3. Psychological Assessment

2.3.1. Bayley II Developmental Assessment. This test is for the developmental assessment for ages 1–42 months. It has 3 scores: mental, psychomotor, and behavioral scales. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months) [5, 6].

Other tests were used after 42 months: Wechsler Preschool and Primary Scale of Intelligence (WPPSI) that is adequate up to 7 years [7].

2.3.2. EEG Recordings. The study was performed in a dimly lit soundproof room. While recording each child remained on its mother's lap and wore a polyester cap with surface electrodes distributed according to the 10–20 International System (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz). Impedances were at or below 5000 ohms. EKG and EMG were recorded simultaneously. Referential EEG recordings were taken during spontaneous sleep for a 20 min interval using linked ear lobes as reference. A digital electroencephalograph (Medicid 4) was used with gain of 20,000, amplifier bandwidth was set between 0.5 to 100 Hz, and the sample rate was 200 Hz. Four EEG recordings were obtained in the first year of life, two at the second year and one at three, four, and five years old.

2.3.3. MRIs Studies. Scans were obtained using a 1.0-T Philips Intera in axial planes to obtain T1W, T2W, PDW, T2 FLAIR and T2-EPI sequences. T1W, T2W, and PDW data were also obtained in axial, coronal, and sagittal slices. A licensed pediatric radiologist reviewed all MRI scans and made the radiological diagnosis. Measurements of the volumes of the corpus callosum and the lateral ventricles were made. These values were compared against the normative values of our database. This normative data base was obtained from the MRI of 313 normal infants with an age range between 0 and 38 months (unpublished results).

3. Results

From the 887 infants with antecedents of risk factors for brain damage, 15 met criteria for West syndrome and later on 11 of these 15 presented the LG syndrome, therefore 15/887 (1.69%) was the prevalence of the West syndrome. Another group was composed of 4 children who had their debut with the LG syndrome without being preceded by the West syndrome. Thus, 15 children (15/887 = 1.69%) presented the LG syndrome.

Table 1: Number of children that present specific risk factors.

Factor	Number of children
Prenatal risk factors	
Abortion threat	1
Oligohydramnios	1
Vesicoureteral infections	1
Aged mother	1
Tobacco use	2
Addiction to solvents	1
Perinatal risk factors	
Prematurity	7
Severe asphyxia (3 with cardio respiratory arrest)	6
Underweight	4
Neonatal sepsis (1 with septic shock)	4
Neonatal seizures	4
Hyperbilirubinemia multifactorial	4
Respiratory distress	4
Acute fetal distress	2
Meconium aspiration	2
Congenital malformations	2
Anemia	2
Dystocic delivery	1
Placental abruption	1

3.1. Risk Factors. All children had prenatal and perinatal history of risk factors for brain damage. All children had more than one risk factor. Table 1 shows the number of children that present each factor. Prematurity and severe asphyxia (with 3 newborn infants that showed cardiorespiratory arrest) were the most frequent factors.

3.2. Clinical Features. Hypoxic ischemic encephalopathy was observed in 3 infants (20%), microcephaly in 4 (27%), and hydrocephaly in 4 (27%). Two infants presented bilirubin encephalopathy (13%) and one had pulmonary hypertension (7%). Cerebral palsy was observed later on in all children.

Types of Epileptic Seizures. Table 2 shows the number of subjects that had different types of seizures. In children with West syndrome many different types were observed, with epileptic spasms being the most frequent, while in the LG group myoclonic seizures were observed.

3.3. Psychological Evaluations. Ten children showed severe retarded psychomotor development and 5 showed moderate retarded psychomotor development.

3.4. EEG Findings. The average number of EEG recordings was 9 in both groups. Every child with West syndrome had

Table 2: Types of epileptic seizures found in children with West and Lennox-Gastaut syndromes.

	n	%
Epileptic spasms	8	53.3
Tonic seizures	3	20.0
Myoclonic seizures	2	13.3
Atonic seizures	2	13.3
Tonic-clonic seizures	1	6.7
Clonic seizures	5	33.3
Focal seizures with observable motor components	5	33.3
Dyscognitive seizures	2	13.3

hypsarrythmia and two of them had also abnormal focal slow waves. The hypsarrhythmia onset average age was 8.18 months (SD = 2.7, range of age = 4–12 months), while EEG features of the LG Syndrome began close to the 3 years old (Mean = 2.95 years, SD = 0.87, interval of age 2–5 years). Considering all the EEGs obtained in each child of both groups, it was observed that all showed single spikes, multiple spike complex, spike-wave complexes, slow spike-wave complexes, and polyspikes-wave complexes. The frequency of the spike-wave and sharp-wave complexes was between 1.0 and 2.5 Hz. Sharp waves were observed in 11 children. Three of the 15 children presented recruiting rhythm, and the discharges with burst suppression as well as initial focal discharges with secondary generalization were relatively frequent in both groups. Sleep organization of the slow phase was progressively deteriorated with age.

Figure 1 shows the EEGs recorded in one infant with West syndrome that evolved to LG syndrome on which it is possible to observe hypsarrhythmia at 6 months and later on, at 4 years, generalized discharges of slow spike-and sharp-wave complexes (around 1.0 Hz) and recruiting rhythm.

3.5. MRI. In all children MRI was abnormal. The most frequent abnormality was the presence of periventricular leukomalacia (PVL). Primary signs of PVL (presence of diffuse extensive intensities in the territory of the white matter and/or presence of macroscopic cysts [8, 9], were observed in 6 infants (3 cystic). Furthermore, the secondary radiological sequels of the PVL, irregularly dilated ventricles, and atrophy of the corpus callosum [8, 9] were found in 9 infants, thus all children showed MRI features compatible with PVL.

Other MRI observations were: 3 infants with intraventricular hemorrhages and 2 with periventricular hemorrhages, 3 with crossed cerebellar diaschisis, one with cerebellar hemorrhages, and one with a left parietal infarction. Cerebral atrophy was observed in 6 infants and hydrocephaly in 2 patients.

Volumes of the corpus callosum and the lateral ventricles were measured and compared with the normative values obtained in 313 normal infants with an age range between 0 and 38 months. These norms were computed in our institution allowing the comparison of the values of a particular subject with them. Deviations greater or lower than one standard deviation (SD) from the mean value according to age have a probability of belonging to the normal group equal or lower than 0.10, and deviations greater or lower than 2 SD of the mean have a probability of belonging to the normal group equal or lower than 0.05.

Values greater than 1 or 2 standard deviations (SD) from the mean value according to age of the lateral ventricles are considered moderate or severely abnormal. In the case of the Corpus Callosum, values lower than 1 or 2 SD are considered moderate or severely abnormal.

Table 3 shows the results of this analysis in all children made at one year of life and at 2 years old. First of all it is possible to observe that the volume of the Corpus Callosum was thin in 14 children at one year old and in all at 2 years old (only in one infant was moderately abnormal). The right lateral ventricle was severely enlarged in 12 children and in one moderately enlarged at one year old. However, at 2 years old, 14 children showed severely enlarged right ventricle. The left ventricle at one year old was severely abnormal in 12 children at one year old and in 13 at 2 years old. There was only one child with normal values of both lateral ventricles at one and 2 years old.

An example of the evolution of the different MRI features in a newborn with PVL is shown in Figure 2. This figure shows the MRI of a male infant born at 36 gestational weeks with PVL. He presented cardio-respiratory arrest, neonatal seizures, hypoxic-ischemic encephalopathy, and sepsis in the neonatal period. Later on he showed a severe retarded psychomotor development. At 2 months of corrected age it was possible to observe in the MRI the presence of diffuse leucomalacia in the occipital regions; the corpus callosum and the lateral ventricles had normal volumes. At 14 months of age the volume of the corpus callosum was very small (less than 2 SD) and the volumes of the lateral ventricles were greater than 2 SD from the norm, and at 32 months the corpus callosum maintains the small volume and the lateral ventricles maintain the great volumes.

4. Discussion

The aim of this study was to describe the incidence of the LG syndrome in a cohort of children that get into our research project in relation to the study of newborns with pre- and perinatal risk factors for brain damage, which was 1.69%. According to Gastaut et al. [10] the prevalence of the Lennox-Gastaut syndrome in a major epilepsy center (5.1% with 10.2% of patients below age 15 and 0.6% of patients above this age) is greater than the West syndrome, although Kurokawa et al. [11] observed the contrary in the Japanese population.

It has been described that in many infants with the West syndrome, mainly those with preexisting brain damage, a transition to Lennox Gastaut syndrome is common. This transition has been documented by Olmos-Garcia de Alba et al. [12].

In our population, 11 infants accomplished the criteria for West syndrome that evolved to the LG syndrome. Various authors have reported different percentages for this: 20% of the cases [13], 49% [14], 58.7% [15] and even 70% [16]. In our population of 887 infants, 15 children presented the West

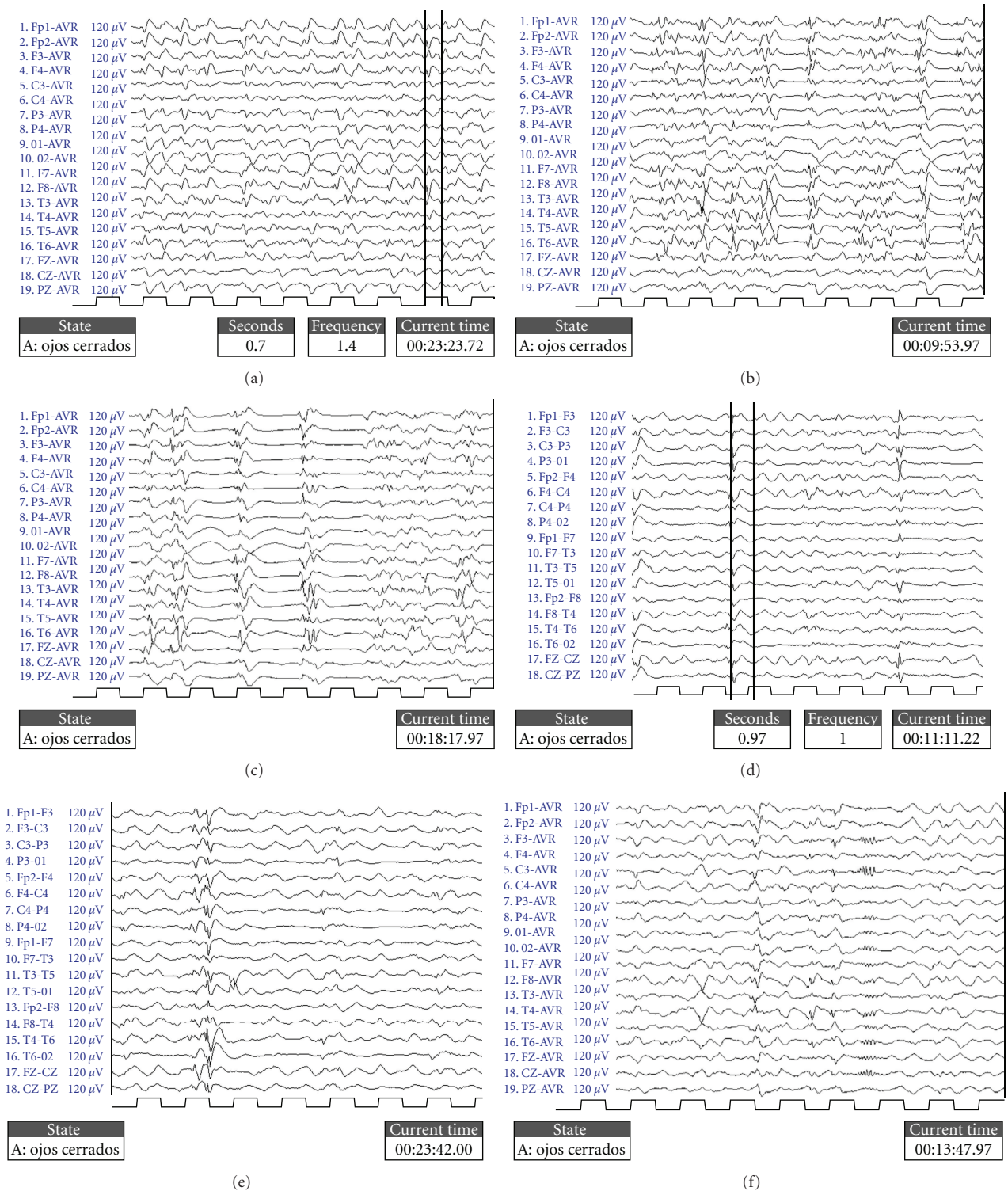

Figure 1: In the first and second rows of the figure appear three EEG segments from the recording obtained at 9 months (a, b, c). It can be noted the presence of hypsarrhythmia (a–c), slow spike and sharp-wave complexes (around 1.4 Hz), particularly in frontal regions (a), and also discharges of burst-suppression (b, c). In the second and third rows of the figure there are another three EEG segments (d, e, f) but now recorded at 4 years old. It can be observed (d, e) generalized discharges of slow spike and sharp-wave complexes (around 1.0 Hz) and recruiting rhythm (f).

Table 3: Individual volumes of the corpus callosum, right and left lateral ventricles obtained from MRI of the children at 1 and 2 years old[1].

Child	Corpus callosum volume (mL)		Right lateral ventricle volume (mL)		Left lateral ventricle volume (mL)	
	1 year	2 years	1 year	2 years	1 year	2 years
1	4.2	3.8**	9.9**	15.2**	6.2*	11.0**
2	0.7**	0.5**	8.6**	9.8**	12.2**	15.7**
3	0.5**	1.2**	71.6**	90.3**	242.0**	306.2**
4	0.3**	0.2**	147.2**	310.2**	220.8**	281.0**
5	0.3**	0.2**	36.3**	33.8**	235.6**	240.3**
6	2.3**	2.3**	3.7	7.3**	5.8*	8.7**
7	0.8**	0.7**	151.3**	172.8**	21.3**	27.9**
8	2.7**	3.47**	9.6**	9.7**	11.0**	11.2**
9	2.5**	1.9**	2.8	5.0	3.0	4.5
10	0.9**	2.0**	16.0**	19.0**	18.0**	21.0**
11	1.6**	1.8**	19.1**	18.5**	24.7**	23.5**
12	1.9**	2.0**	13.2**	19.8**	12.9**	18.9**
13	0.3**	1.6**	33.1**	98.9**	49.6**	143.4**
14	3.0*	4.8*	9.3**	8.7**	7.2**	6.9*
15	0.5**	0.7**	5.3*	8.0**	6.2*	10.3**

[1] Children numbers 12–15 belong to the group of Lennox-Gastaut syndrome that had not been preceded by West syndrome.
*One and **two standard deviations from the mean of the normative volumetric values corrected by age from normal children of 0–26 months (unpublished data from our research group).

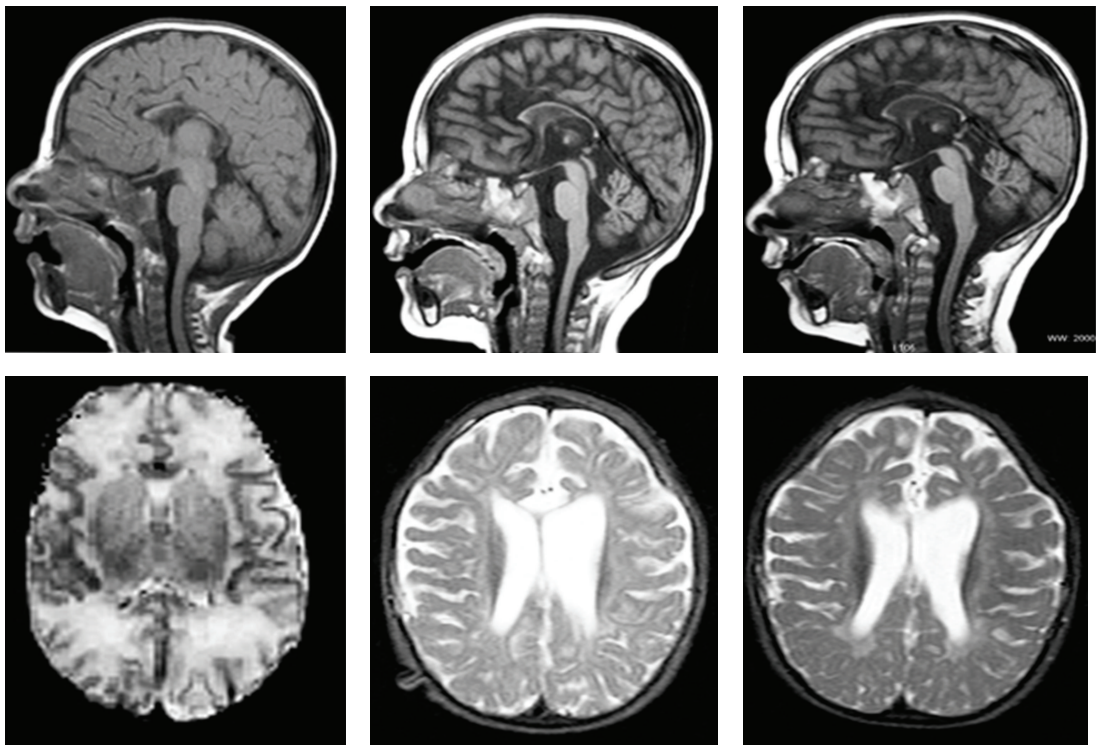

Figure 2: This figure shows the MRIs of a male infant born at 36 gestational weeks with PVL. At 2 months of corrected age it was possible to observe in the MRI the presence of diffuse leukomalacia in the occipital regions; the corpus callosum and the lateral ventricles had normal volumes. At 14 months of age the volume of the corpus callosum was very small (less than 2 SD) and the volumes of the lateral ventricles were greater than 2 SD from the norm, and at 32 months the corpus callosum maintains the small volume and the lateral ventricles maintain the great volumes.

syndrome, and from this, 11 (73%) showed this transition. Taking into consideration that all the children had severe brain lesions, the prevalence observed of this transition, although high, is not exceptional.

The most frequent risk factors were prematurity and severe asphyxia, which may explain the presence of PVL in all children. From the 887 infants studied in our institution, although 40% were lost in the followup, all of them had MRI scans and the primary diagnosis of PVL was made in 479 (54%), 9 of them present giant cysts almost without brain. The most frequent abnormality was the presence of diffuse excessive intensities in the territory of the white matter. Larger volumes of the lateral ventricles and delay myelination were very frequently observed as has been referred [17, 18]. The diagnosis of PVL in our study was confirmed by MRI in all subjects, 3 with abnormally increased signal intensity on T2-weighted images and 3 with macroscopic cysts in the white matter. In the remaining infants, sequels from PVL, as large volumes of the lateral ventricles and thin corpus callosum were observed. The statistical analysis of the volumes of the Corpus Callosum and the lateral ventricles also gave important information, since almost all the children showed values of their volumes that were out of the limits of the normal population according to our normative data. It is important to note that the values of the volumes were more abnormal at 2 years old than at one year old, indicating the structural severity that relates with more clinical and neuropsychological abnormal evaluations with age.

The West syndrome is a common complication (26%) of severe PVL [17]. Kuzmanic-Samija et al. [19] described 37 infants with West syndrome caused by PVL. However, in our population, from 479 infants with PVL only 15 developed the West or the LG syndrome (3.13%).

From the clinical point of view all children showed seizures of different types, severe to moderate retarded psychomotor development, cerebral palsy, and abnormal EEGs. Every child presenting the West syndrome had hypsarrythmia, and those with the LG syndrome show the characteristic slow spike and wave discharges. These clinical findings correspond to the concept of epileptic encephalopathy, according to the last ILAE classification [1].

5. Conclusions

Prenatal and perinatal risk factors for brain damage are very important antecedents that should be taken into account for the followup of the infant from an early age. Presence of PVL in premature newborns increases the risk for motor and cognitive sequelae and sequential, EEG recordings allow early detection of an epileptic encephalopathy to prescribe immediate treatment.

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