Clinical and electroencephalographic study of infants with risk factors for neurological damage

Estudio clínico y electroencefalográfico en lactantes con factores de riesgo de daño neurológico

Abstract

Introduction: It’s estimated that between 3-5% of living newborns have neurology risk. The damage that occurs in perinatal period cause 55-75% of neurology deficit. Timely detection, follow-up and intervention permits prevent and/or minimize those aftermarts.

Objectives: To characterizer clinic and electroencephalographic of a group of children with neurology damage risk factors.

Methods: An early clinic-neuropsychiologic evaluation of 87 infants in ages from one month to one year (M 67.53, SD 48.67 days, respectively) was carried out because they showed some neurology damage risk factor. They were undergoing to digital electroencephalography studies. The statistical analysis of data was performed with the Mann-Whitney U test, IC 95% in hypothesis test (p < 0.05).

Results: Birth risk factors had the highest frequency predominantly perinatal asphyxia and respiratory distress. The concurrence of 3 or more risk factors was discovered in 66.66% (58/87) of them. A percentage of 59.09 of EEG performed showed moderate disorders. There was a significant statitical association between clinical course of children and presence of seizures, as well as between gestational age, seizures and 3 or more risk factors.

Conclusions: The early clinical-electroencephalographic evaluation could be used to guide, modify or suggest therapeutic strategies and follow-up in infants with neurology damage risk factors.
Resumen

Introducción: Entre 3-5 % de los recién nacidos vivos tienen riesgo de daño neurológico. Los daños que ocurren en el periodo perinatal causan entre 55-75 % de los déficits neurológicos. La detección, seguimiento e intervención oportuna permite prevenir o minimizar estas secuelas.

Objetivos: Caracterizar clínica y electroencefalográficamente un grupo de niños desde 1 mes hasta el año de edad, con factores de riesgo de daño neurológico.

Métodos: Se realizó evaluación clínica y electroencefalográfica de 87 niños (media edad 67.53 días, desviación estándar 48.67) con algún factor de riesgo de daño neurológico, realizándoseles estudio electroencefalográfico digital. Para el análisis estadístico se utilizó el test no paramétrico U Mann-Whitney con un 95 % de confianza en las pruebas de hipótesis (p<.05)

Resultados: Los factores de riesgo natales fueron los más frecuentes predominando la asfixia perinatal y el distrés respiratorio. El 66.66 % (58/87) de los niños presentaron 3 o más factores de riesgo. De los EEG realizados, el 59.09 % mostraron alteraciones moderadas. Existió una asociación estadísticamente significativa entre la evolución clínica y la presencia de convulsiones, así como entre la edad gestacional y la presencia de convulsiones y 3 o más factores de riesgo.

Conclusiones: La evaluación clínica y electroencefalográfica temprana podría ser de utilidad para orientar, modificar o sugerir conductas terapéuticas y de seguimiento en recién nacidos con factores de riesgo de daño neurológico.

Palabras clave
Electroencefalograma, lactantes, factores de riesgo, daño neurológico.

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Introduction

Infant brain damage is estimated at 2-5% of live births,\(^1\) with a series of prenatal, perinatal, postnatal, and social risk factors that increase the risk of developing neurodevelopmental deviations in children.

The damages that occur in the perinatal period cause 55-75% of the neurological deficits. Preterm newborns constitute a vulnerable population with a high risk of suffering medical problems and neurobehavioral disabilities\(^2,3\) including poor cognitive performance, greater learning difficulties, and an elevated risk of presenting behavioral disorders. Up to 47% of the total number of premature children present cerebral palsy, 27% show important cognitive disorders, and 23-37% sensory disorders.\(^4,5\)

Undetected neurodevelopmental deviations (NDD) that don’t receive early intervention can cause children to face serious difficulties achieving an adequate level of education as well as full integration and social inclusion. Detection, follow-up, and timely intervention allow preventing and/or minimizing these negative consequences.

The electroencephalogram (EEG) has been one of the most widely used tools in the evaluation of premature babies, newborns with low birth weight, with asphyxia at birth, and neonatal seizures, among other risk factors for future development of NDDs.\(^6,7\)

The EEG is a non-invasive technique of great value that can be used during the neonatal period to quantify the rapidly changing aspects of the bioelectric activity of the cerebral cortex or detect brain damage and dysfunctions.\(^8\)

Compared with magnetic resonance imaging, the EEG has a higher temporal resolution and is relatively easy to obtain in young children at a lower cost. During childhood, the causative agents of most of the alterations of the central nervous system are related to disorders in the normal process of cerebral maturation. Most of the studies make references to the alterations found in the EEG associated with a specific risk factor; however, they do not perform a comprehensive assessment of the effect that the coexistence of several risk factors would have on brain maturation and, especially, on electrical activity for the development of Childhood Neurodevelopment Delay (CND).

The objective of this work is to characterize clinically and electroencephalographically a group of children between one month and one year of age, with different risk factors for neurological damage.

Methods

This is a descriptive study of 87 patients from one month of birth to one year of age (mean 67.53 days, SD 48.67) referred to the Neurodevelopment clinic due to the presence of some neurological risk factor. A neurological risk factor is classified in children who, due to their pre-, peri-, or postnatal antecedents, are more likely to develop cognitive, motor, sensory, or behavioral problems in the first years of life, which may be transient or definitive.\(^9\) The data was obtained from the clinical records. Seventy-seven children received an EEG evaluation, and ten children were excluded because their parents did not give informed consent.

The EEG was performed in a room with dim light and in spontaneous sleep. The digital electroencephalograph MEDICID 5 (Neuronic SA) was used with an amplifier gain of 10,000, sampling frequency of 200 Hz, and filters with a bandwidth of 0.5-30 Hz. We used 19 surface electrodes placed according to the international system 10-20. Short-circuited electrodes located in both earlobes were used as reference. The visual inspection of the EEG was carried out offline by three experts independently.
The EEG studies were classified as:
a) Normal, if the EEG activity was in accordance with their conceptional age at the time of the study;
b) With minimal alterations (immaturity of the base rhythms, interhemispheric asynchrony, voltage drop);
c) With moderate alterations (persistent focal or generalized acute spikes and waves);
d) With critical tracing (with focal patterns during crises, focal or multifocal monorhythmic discharges during crises);
e) With serious alterations (presence of isoelectric tracing or with a salvage suppression pattern).10

The conceptional age is calculated as the sum of the baby’s gestational age in weeks at the time of birth, added to the chronological age of the baby in weeks at the time of the study.

In order to determine significant differences between the means of two populations, a statistical analysis was performed based on a non-parametric U Mann-Whitney test with a 95% confidence in the hypothesis tests (p<.05). The populations were formed considering the different risk factors in the sample studied. The results of the EEG and the clinical evolution of the 77 patients who underwent EEG were compared.

Ethical Considerations
An informed consent from the parents was requested to admit children to this study. Individual data were not disclosed and the established ethical norms were complied with. The research was approved by the Research Ethics Committee of the Juan Manuel Márquez Pediatric Hospital and the Faculty of Medicine of the Autonomous University of Querétaro, complying with the ethical standards of the Declaration of Helsinki of 2000.

Results
A total of 87 subjects were studied clinically. Neurological alterations predominated in the male sex (56.32% male and 43.68% female), of which 54 were full-term newborns and 33 pre-terms with an average gestational age of 36.84 weeks (SD 3.59, confidence interval: 25-42 weeks). The average birth weight was 2771 g (DE 915.58, confidence interval: 772-4506). In only 10 cases (30.30%) the weight was less than 1500 g.

When analyzing the behavior of the risk factors, Table 1 shows that the perinatal risk factors are the most frequent, with asphyxia and respiratory distress predominating. However, 66.66% (58/87) of the children showed the concurrence of three or more risk factors, 16.09% (14/87) presented two risk factors, and 17.24% (15/87) only one risk factor.

Neonatal seizures occurred in isolation (as the only risk factor) in 27.2%, associated with another risk factor in 18.1%, and with more than two risk factors in 53.7%.

Table 2 shows the results of the statistical analysis to determine significant differences between the populations with different risk factors in the sample studied.

The results of the clinical evaluation at one year of age showed that 70.02% presented a good clinical evolution (Table 3).

EEG Results
Of the total sample, 77 children received EEGs, the results of which are shown in Table 4. Note that 55.26% of the EEGs performed showed moderate alterations due to the presence of generalized or focal spikes and waves, persistent during tracing. The evaluation of the clinical manifestations and the EEG findings are shown in Table 5, showing no significant association between them.

In the study, 22 patients presented with neonatal seizures of which 81.82% (18/22) were full-term
newborns. Of the total number of patients with neonatal seizures, the EEG tracing was normal in 13.63% (3/22), 9.09% (2/22) presented minimal alterations, 59.09% (13/22) moderate alterations, and 18.18% (4/22) serious alterations.

**Tabla 2.** Results of the statistical analysis of the associated conditions.

<table>
<thead>
<tr>
<th>Associated conditions</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age - Seizures</td>
<td>0.02</td>
</tr>
<tr>
<td>Gestational age - Presence of 3 or more risk factors</td>
<td>0.00</td>
</tr>
<tr>
<td>Gestational age - Low birth weight</td>
<td>0.00</td>
</tr>
<tr>
<td>Gestational age - Perinatal asphyxia</td>
<td>0.00</td>
</tr>
<tr>
<td>Gestational Age - Respiratory distress</td>
<td>0.00</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Low birth weight</td>
<td>0.02</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Respiratory distress</td>
<td>0.01</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Asphyxia at birth</td>
<td>0.00</td>
</tr>
<tr>
<td>Low weight - Respiratory distress</td>
<td>0.01</td>
</tr>
<tr>
<td>Low weight - Perinatal asphyxia</td>
<td>0.02</td>
</tr>
<tr>
<td>Low weight - Presence of 3 or more risk factors</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical evolution - Seizures</td>
<td>0.00</td>
</tr>
<tr>
<td>Perinatal asphyxia - Respiratory distress</td>
<td>0.00</td>
</tr>
</tbody>
</table>

95% confidence (p < .05)
Table 3. Clinical evolution at one year of age of the subjects in the sample.

<table>
<thead>
<tr>
<th>Clinical evolution</th>
<th>% / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good evolution</td>
<td>70.2 % (61/87)</td>
</tr>
<tr>
<td>PDR</td>
<td>9.3 % (8/87)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12.6 % (11/87)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2.3 % (2/87)</td>
</tr>
<tr>
<td>PDR and epilepsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Hydrocephalus and epilepsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Cerebral palsy and epilepsy</td>
<td>2.3 % (2/87)</td>
</tr>
<tr>
<td>Total</td>
<td>100 %</td>
</tr>
</tbody>
</table>

PDR: Psychomotor Development Retardation.

Table 4. Electroencephalographic alterations of the sample.

<table>
<thead>
<tr>
<th>EEG alterations</th>
<th>% / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal EEG</td>
<td>18.42 % (14/77)</td>
</tr>
<tr>
<td>Minimal alterations</td>
<td>18.42 % (14/77)</td>
</tr>
<tr>
<td>Moderate alterations</td>
<td>55.26 % (43/77)</td>
</tr>
<tr>
<td>Critical tracings</td>
<td>0 %</td>
</tr>
<tr>
<td>Serious alterations</td>
<td>7.89 % (6/77)</td>
</tr>
</tbody>
</table>

Table 5. Association between clinical variables and the EEG.

<table>
<thead>
<tr>
<th>Associations</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG - Gestational age</td>
<td>0.68</td>
</tr>
<tr>
<td>EEG - Seizures</td>
<td>0.56</td>
</tr>
<tr>
<td>EEG - Low birth weight</td>
<td>0.92</td>
</tr>
<tr>
<td>EEG - Respiratory distress</td>
<td>0.60</td>
</tr>
<tr>
<td>EEG - Asphyxia</td>
<td>0.60</td>
</tr>
</tbody>
</table>

95% confidence (p <.05)

Discussion

The care provided to newborns in the neonatal intensive care unit (NICU) has led to their increased survival, but at the same time, an increasing number of high-risk newborns are discharged.11-12 These advances in neonatal critical care have improved survival rates, but have not managed to fully monitor the appearance of a series of neurodevelopmental sequelae in a significantly elevated portion of survivors. Sequelae include cerebral palsy, mental retardation, epilepsy, auditory and visual deficits, attention deficits, hyperactivity, and emotional lability, with later learning failures. The rate of severe neurological alterations in preterm infants weighting less than 1500 grams has remained between 10% and 30%, with less favorable results for those infants who are severely asphyxiated.11-14 Perinatal asphyxia was the most representative risk factor in this study, coinciding with reports in the literature.15 Perinatal asphyxia is a serious incident in neonates due to hypoxia and generalized ischemia that causes biochemical and functional changes...
of a systemic nature, particularly in the central nervous system. Nagdyman et al. affirm that approximately a third of newborns with asphyxia present hypoxic-ischemic encephalopathy. The diagnosis of a perinatal asphyxia event implies the early onset of a neonatal neurological syndrome. Several studies have proven the neurological sequelae of perinatal hypoxia, which can range from mild to severe.

Neonates with perinatal asphyxia who are more at risk of dying or have subsequent neurological disability are those who have persistent low Apgar scores, other neurological signs, and seizures in the first 48 hours of life. The score of the Apgar at five minutes of life is the one that presents greater concordance with the metabolic acidosis and better correlation with the risk of neurological sequelae, although the presence of a normal Apgar score does not exclude the possibility of future neurological sequelae. A study by González de Dios reports that 47.1% of newborns with tachypnea in their sample presented extraneurological manifestations, the most frequent being respiratory pathology, mainly respiratory tachypnea of the newborn, and meconial fluid aspiration syndrome. This research corroborated a strong statistical association between respiratory distress and perinatal asphyxia.

Seizures in the neonatal period are the main clinical expression of CNS dysfunction. Unlike in other pediatric ages, in this period they are idiopathic only exceptionally (1-2%). It is considered that 0.15 to 1.4% of newborns present seizures in this stage, reaching up to 6% in newborns under 36 weeks. The incidence increases until reaching 25% if the population of neonates of NICU is analyzed. Most of the patients who presented seizures were full-term (81.82%) compared to 18.18% preterm newborns. This behavior has been related to the underlying etiology: intraventricular hemorrhage in extremely premature infants and hypoxic-ischemic encephalopathy in full-term infants. Hypoxic-Ischemic Encephalopathy (HIE) is a neurological syndrome caused by failure in the supply of oxygen and cerebral perfusion and occurs in one to three of every 1000 live full-term infants. Neonates with moderate encephalopathy have a relatively low mortality (5%) and neurological sequelae present in 20-40% of survivors. Those who have a severe HIE have a 75% chance of dying (75%), while 60-100% of survivors have severe neurological sequelae.

The EEG alterations described in the group of patients who presented neonatal seizures in this investigation are similar to those found by Campistol et al. highlighting that most of the patients presented moderate and severe alterations. Alcover-Blocha et al. report that the recording of a pathological EEG (critical or with serious alterations) is associated with an unfavorable evolution in most cases. A more accurate prognosis in these patients can be made from the etiology of neonatal seizures and EEG patterns. The persistence of pathological records beyond 72 hours of birth is invariably associated with death or serious neurological sequelae, while early recovery, before 12 or at least 36 hours, is associated with normal results or with minor neurological alterations. In general, existing research studies on electroencephalography in infants at high risk of neurological damage are
scarce, with small samples, addressing different views of the problem, and without strict monitoring during the neonatal period.

In the study by Jiménez et al.\textsuperscript{34} the appearance of clinical neurological alterations during the first week of life, such as the presence of seizures and a pathological EEG, are described as the main prognostic factors in perinatal asphyxia. Similar conclusions were obtained by Andre et al.\textsuperscript{35} who stated that those asphyctic newborns who continued to present clinical and EEG alterations on the seventh day of birth, later showed sequelae in up to 75\% of the cases.

Conventional electroencephalography has a series of limitations in the study of these patients, among which are: difficulties in prolonged monitoring, excessive number of electrodes, electrical interference by environmental equipment, difficulties in the interpretation of the study (when staff with training in clinical neurophysiology is necessary), and the realization of such brief registers (45-60 minutes) that, even with periodic evaluations, information is lost on the evolution of the alterations of the base activity, sleep states, and sporadic convulsions. The incorporation of EEG integrated by amplitude (EEGa), also known as brain function monitor, is a simple method of continuous recording of cortical electrical activity which allows predicting the final neurological evolution in as short a time as the first six hours of life.\textsuperscript{8,33,36}

Neurological lesions in newborns may have an onset in the prenatal stage and can be explained by the activation of inflammatory cascades that seem to predominate more in male neonates, as in our sample. This coincides with the results of other authors, so it is assumed the possible existence of neuroprotective factors for the female gender.\textsuperscript{10,37,38}

Three-quarters of our sample had an overlap of risk factors. A study conducted by Salinas-Álvarez et al.\textsuperscript{38} in patients with a high neurological risk described that on a scale of 1 to 10 risk factors, their sample had an average of 4.1 factors. It has been reported that these cases are more likely to develop some disability and that the accumulation of risks is not equivalent to a sum but rather that its effect is enhanced.\textsuperscript{9} Some risk factors carry a higher risk of causing an impairment of psycho-neuro-sensorial development, among which weight at birth stands out.\textsuperscript{28}

On the other hand, the prediction of morbid damage has made necessary the search of biochemical, neurophysiological, and neuroimaging indicators by morphological and functional alterations to identify early lesions that threaten the satisfactory evolution of children.

Bearing in mind that the interval between the initial neurological injury and the development of permanent damage offers a window of opportunity to start therapeutic interventions to stop the damage or promote neurological evolution, it is crucial to identify high-risk newborns who may benefit from neuroprotective management.
Conclusions

Early clinical and electroencephalographic evaluation could be useful in guiding, modifying, or suggesting therapeutic and follow-up options for newborns with risk factors of neurological damage. It would be crucial to create programs that allow early evaluation and follow-up of newborns identified with risk factors.

Conflicto de intereses
The authors declare that in this study there are no relevant conflicts of interest.

Fuentes de financiamiento
There was no particular source of funding for this scientific report because the patients come from the free public health service.
References
