Clinco-Biochemical Profile Of Neonatal Seizures

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الخلاصة

تعد الاختلاجات العصبية الولادية من أكثر الصور البارزة للاختلال الوظيفي العصبي. تحدث الاختلاجات العصبية الولادية خلال الأسابيع الأربعة الأولى من عمر الرضيع المكتمل و لغاية الأسبوع الرابع والأربعين من بدء الحمل للمبتسرين وتقدر نسبة حدوثها ب 1.8 إلى 3.5 في كل 1000 طفل حي مولود .

لدراسة الأنواع السر يريه ،في أي وقت بدأت،و لتحديد المسببات البايو كيميائية للاختلاجات العصبية الولادية.تمت دراسة (88) مريضاً من الأطفال حديثي الولادة المكتملين والمبتسرين ممن لديهم اختلاجات عصبية ولادية و الراقدين في مستشفى بابل التعليمي للنسائية والأطفال(الردهات العامة وردهات حديثي الولادة) مستقبلياً بالنسبة إلى اللمحة السريريه البايو كيميائية للاختلاجات العصبية الولادية وذلك للفترة من الأول من حزيران عام 2009 ولبداية الأول من كانون الأول 2009 .كانت نسبة الأطفال مكتملي الحمل 95.4% أما المبتسرين فكانت نسبتهم 4.6% .إن من أكثر أسباب الاختلاجات عند حديثي الولادة هي الاضطرابات البايو كيميائيه ونسبتها 47.7% يتبعها الاختناق الولادي 15.4% و التهاب السحايا 6.6% والتشوهات التركيبية 4.4% .أما الاختلاجات غير معروفة السبب فكانت نسبتها 27.2%.إن نسبة 80% من حالات انخفاض السكر حدثت عند الذكور .إن الاختلاجات التوترية كانت تمثل 100% من الأنواع عند الأطفال المبتسرين .إن الاختلاجات المخفية كانت من بين أكثر الأنواع وتمثل 31.8% ثم الاختلاجات التوترية 24.3%ثم الاختلاجات الارتجافية المحددة 16.2% ثم العامة 11.3% والارتجافية المتعددة 10.3%.إن من بين أكثر أسباب الاختلاجات الولادية كانت الاضطرابات البايو كيميائية.الاختلاجات المخفية كانت أكثر الأنواع شيوعا عند الأطفال مكتملي الحمل والاختلاجات التوترية أكثر أنواع شيوعا عند الأطفال المبتسرين .يجب استبعاد الاضطرابات البايوكيميائية عند كل مرضى الاختلاجات الكيميائية. تحسين الخدمات المخبرية و توفير غير الموجود منها. المتابعة المثلى الجنين خلال فترة الولادة لتجنب الاختناق الولادي.

Abstract

Background: Neonatal seizures are the most prominent feature of neurological dysfunction during neonatal period.

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Neonatal seizures occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infant.
Neonatal seizures are occurring in approximately 1.8 – 3.5 / 1000 live birth.
Objectives: To study clinical types, time of onset and to determine the etiology of neonatal seizures.
Methods: Out of eighty eight full term and preterm neonates with seizure at neonatal care unit and general wards of Babylon Gynecology and Pediatrics teaching hospital were studied prospectively in regard to clinco-biochemical profile of neonatal seizures from period 1st of May 2009 to 1st of December 2009.
Results: Eighty eight full term and preterm neonates, (95.4%) of them were term and (4.6%) were preterm. The most common cause of neonatal convulsion was metabolic disturbances collectively constitute (47.7%).The other causes were asphyxia (15.4%),meningitis (6.6%),structural abnormalities (4.4%) and unknown cause (27.2%). Tonic type occurred in (100%) of preterm patients while in term patients, (31.8%) of them were subtle type ,followed by tonic type (24.3%) , focal clonic (16.2%),generalized tonic clonic (11.3%) and multi focal clonic type(11.3%).
80% of hypoglycemia occurred in male patients.
Conclusions: The commonest cause of seizure was metabolic abnormalities. Subtle seizures were the commonest type of seizure observed in term babies and tonic seizures were the most commonest type in preterm babies in this study
Recommendations: Metabolic abnormalities should be excluded in every case of neonatal seizure. Improving of the laboratory services and the availability of other investigations must be available. Proper fetal monitoring during labor is recommended to avoid birth asphyxia .

Introduction

Neonatal seizures are abnormal electrical discharge in the central nervous system of neonates, usually manifesting as stereotyped muscular activity or automatic changes [1]. Neonatal seizures by definition occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infants[2] and are most frequent during the first 10 days of life. [3] Seizures occur when a large group of neurons undergo excessive, synchronized depolarization, which can result from excessive excitatory amino acid release or deficient inhibitory neurotransmitter . Another potential cause is disruption of ATP-dependent resting membrane potentials, which causes a flow of sodium into the neuron and potassium out of the neuron. Hypoxic-ischemic encephalopathy disrupts the ATP-dependent sodium-potassium pump and appears to cause excessive depolarization. It is an important cause of neonatal seizures. The biochemical effects of neonatal seizures include derangements of energy metabolism. [4,5] Seizures during neonatal period is common occurring in approximately 1.8 – 3.5 / 1000 live birth. In the neonatal intensive care unites the incidence goes as high as 10 -25%, out of which about 15% will die and 35 – 40% will have major neurological Squeal. [2] Seizures in the neonatal period are one of the emergencies when prompt diagnostic and therapeutic plan are necessary, a delay in therapy often result in poor neurological outcome.[6] No racial preponderance is known and the sex-based frequency differences have not been described. [7] The major causes of neonatal seizures are perinatal asphyxia, metabolic abnormalities (hypoglycemia, hypocalcaemia, hypomagnesaemia, pyridoxine dependency and deficiency, hyponatremia and hypernatremia, amino aciduria, and Kernicterus), infection (sepsis, meningitis and encephalitis), bleeding (subarachnoid, subdural, thrombosis and Intraventricular hemorrhage), developmental anomalies (cerebral dysgenesis and incontinentia pigmenti), and other

causes (drug withdrawal , hyperthermia, benign familial neonatal seizures, benign idiopathic neonatal seizures and benign sleep myoclonus). [2,4,7] Seizures resulting from hypoxic ischemic encephalopathy may be seen in both term and premature infants. They frequently present within the first 72 hours of life. Seizures may include subtle, clonic, or generalized seizures. [8,9] Although disturbances of glucose, calcium, magnesium, electrolytes, amino acids, organic acids, blood ammonia, and certain intoxications, especially local anesthetics, pyridoxine dependency or deficiency, and hyperbilirubinemia, all are associated with convulsive phenomena in newborn infants , the aberrations of glucose and the divalent cataions are the most frequent. [1,10] Intracranial bacterial & non bacterial infections are not uncommon causes of neonatal seizures, accounting for 15% of the cases . Onset of seizures in these instance is most commonly in the latter part of the first week and subsequent to that period. [11] Intracranial hemorrhage is a common cause of neonatal seizure in preterm infant; occur between 1 – 3 days of age. [11] Five major clinical types of neonatal seizure are identified: subtle, generalized, tonic, multifocal cIonic, focal cIonic and myoclonic [10]. Neonatal seizures may be difficult to be recognized clinically from normal neonatal behaviors which are not substantiated by E.E.G, so studies using polygraphic E.E.G recording with video monitoring, have greatly enhanced the characterization of neonatal seizures and their medical management.[12]

Aims of study

1- To study the clinical manifestations of neonatal seizures (clinical types).

2- To determine the biochemical etiology of neonatal seizures.

3- To find the onset of neonatal seizures.

Patients and method

Eighty eight full term and preterm neonates with seizure at neonatal care unit and general wards of Babylon Gynecology and Pediatrics teaching hospital were enrolled in this study from period 1st of May 2009 to 1st of December 2009. Data were collected by the researcher through direct interview with caregivers and the type of seizure was observed by the care provider. The interview encompass the gender and gestational age of neonate, age of seizure onset , its duration , frequency , recurrence and the family history of neonatal seizure . A complete examination of neonates were done. The neonate weight was measured in kilogram by an accurate electronic scale(SECA ,Germany made ,maximal weight 16 kilogram). The type of seizure was classified according to clinical type by doctors observation .The following investigations for detection the etiology of seizure were done:

1. Blood sugar levels :it was regarded significant if it was less than 35 mg/dl (1.9mmol/L)between 1 – 3 hrs of life, less than 40 mg/dl(2.2mmol/L) between 3 – 24 hrs of life and less than 45 mg/dl(2.5mmol/L)after 24 hrs of life. Glucose was estimated by enzymatic method using kit provided by Plasmatic ,(United Kingdom).
and measured specterophotometrically at 505nm.

2- Total serum calcium < 7mg /dl (1.75 mmol/L)was considered as hypocalcaemia .The calcium was estimated by chemical method using a kit provided by Biolabo,(France).and measured specterophotometrically at 570nm.

3- Serum magnesium < 1.5 mg/dl or 0.62 mmol/dl was considered as hypomagnesaemia .Magnesium was estimated by calmigate photometric using a kitprovided by Biomeghreb (Tunisian) and measured by spectrophotometer at520 nm.

4- Serum sodium <135mEq/L(135mmol/L)/L was considered as hyponatremia and if it was > 150 mEq/L(150mmol/L)/ was considered as hypernatremia.

Sodium was determined by photometric method using a kit supplied by Human ,(Germany) and measured specterophotometrically at 360-410 nm.

5-Blood culture and sensitivity if indicated.

6-Cerebrospinal fluid examination was done when indicated.

7-Ultrasonagraphy or CT-scan of the head was done for all patients.

Statistic analysis: By using SPSS software package version 17. Frequencies, cross tabulation and Chi square tests were used for analyzing data .P value <0.05 was considered as significant.

Results

Eighty eight full term and preterm neonates, who develop seizure from the first day – 28 days of life, 84 cases of them were term(95.4%) and 4 cases of them were preterm(4.6%). The gestational age was ranging from 28-40 weeks. Mean ±SD was (38.6±1.76) weeks. Forty eight patients (54.5%) of newborns were males and 40 (45.5%) were females. The ratio of male to female was 1.20:1. Eighty two patients (93.1%) were weighting > 2500 g, 2 patients (2.3%) were very low birth weight <1500 g .and the remaining 4 patients (2.3%) were low birth weight (1500-2500). The mean ± SD of weight was (2.99±0.55) kg . Weight ranges from 1200 g to 4500 g. Regarding seizure type ,out of the total 88 patients, 28 patients (31.8%) had subtle type,22 patients(25%) had tonic type,12patients (13.6%) had multifocal clonic type,10 patients(11.3%) had generalized tonic clonic type , 6patient(7%)had focal clonic and10 patients(11.3%) had unclassified seizure.

The etiology of neonatal seizures had been identified depending on the clinical criteria, laboratory work up and imaging studies (table-1). Metabolic disturbances collectively constitute 42 patients(47.7%), 16 patients of them(18.1%) were due to hypomagnesaemia , 8 patients (9%) were due to hypocalcaemia, 6 patients (6.8%) were due to hypoglycemia , 6 patients (6.8%) were due to hyponatraemia .

Hypocalcaemia and hypomagnesaemia was reported in 6 patients (6.8%). Asphyxia was demonstrated in 14 patient (15.4%). Four of them(4.4%) were an isolated asphyxia and the remaining 10 patients had association with other abnormalities like hypoglycemia and hypocalcaemia in 4 patients (4.4%),2 patients (2.2%) with hypocalcaemia and hypomagnesaemia ,2 patients (2.2%) with hypoglycemia and another 2 patients (2.2%) with meningitis , hypoglycemia and hyponatraemia . Meningitis accounting for 6 patients (6.6%) . All of them were associated with metabolic abnormalities, 2 patients(2.2%) with hypoglycemia and hypomagnesaemia, 2 patients (2.2%) with hypoglycemia and structural abnormalities and another 2 patients(2.2%) with hypoglycemia and hyponatraemia .Structural abnormalities was recognized in 4 patients (4.4%), 2 patients (2.2%) with meningomylocele, that associated with meningitis and hypoglycemia and the other 2 patients (2.2%) had anencephaly with Hyponatraemia and hypocalcaemia. Twenty four patient(27.2%) had unknown etiology.

Table 1: Etiological distribution of neonatal seizures

Etiology	NO.	%
Hypomagnesaemia	10	10.1
Hypocalcaemia	8	9
Hypoglycemia	6	6.8
Hyponatraemia	6	6.8
Hypocalcaemia- Hypomagnesaemia	6	6.8
Asphyxia+ Hypoglycemia+ Hypocalcaemia	4	4.5
Hypoglycemia+ Hypomagnesaemia+ Meningitis	2	2.2
Hypoglycemia+ Hypomagnesaemia- Hyponatraemia	2	2.2
Asphyxia Hypocalcaemia+ Hypomagnesaemia	2	2.2
Asphyxia+ Hypoglycemia	2	2.2
Asphyxia	4	4.5
Anencephaly Hyponatraemia+ Hypocalcaemia	2	2.2
Meningitis -Meningomylocele -hypoglycemia	2	2.2
Meningitis Hypoglycemia Hyponatraemia Asphyxia	2	2.2
Unknown cause	24	27.2

We classified the neonatal seizures by the age of onset into three groups, <3 days, 3-7 days and > 7th day of age. Twenty six patients (29.5%) had seizure during the first 2 days, in 38 patients (43.2%) it occurred between 3-7 days and 16 patients (18.2%) had seizure after the seventh day of life. Eight patients(9.1%) had unknown time as shown in table- 2.

Table 2: Distribution of neonatal seizure according to the age of onset.

Age of onset (Days)	NO.	%
0-2	26	29.5
3-7	38	43.2
> 7th	16	18,2
Un known time	8	9.1

Regarding maturity ,we found that tonic type occurred in all the 4 preterm patients while in term patients, 28 of them(33.3%) had subtle type ,18 patients (21.4%) had tonic type ,12 patients (14.2%) had multifocal clonic ,10 patients (11.9%) had generalized tonic clonic and 6 patients (7.1%) had focal clonic type as shown in table- 3 , P value was (0.02). The seizure type ,onset and etiology had no significant relationship with maturity.

Table- 3 :Relation of maturity to type of seizure.

Maturity	Type of seizure					
	Subtle	Tonic	Multifocal clonic	Generalized tonic clonic	Focal clonic	Un known
Preterm	0	4 100%	0	0	0	0
Term	28 33.3%	18 21.4%	12 14.2%	10 11.9%	6 7.1%	10 11.9%

Regarding gender ,we found that 16 cases (80%) of hypoglycemia occurred in male while only 4 case (20%) of hypoglycemia occurred in female. The P- value was (0.001).

There is significant relationship between onset of seizure and hypocalcaemia, P- value(0.02),where (54.5%)of cases occurred <3days , (36.4%) between (3-7)days and (9.1%) after the 7th day as shown in (table- 4).

There is significant relationship between onset of seizure and hypoglycemia, P- value(0.02),where in 60% of patients, it occurred <3days , (20%) during period (3-7)days and (20%) more than 7th day as shown in Table- 5. The weight ,type of seizure and etiology had no significant relationship with onset of seizure.

Table 4:Relation of onset to hypocalcaemia.

Onset (day)	Hypocalcaemia	
	No.	%
0-2	12	54.5
3-7	8	36.4
>7th	2	9.1

Table-5: Relation of onset to hypoglycemia.

Onset (Days)	Hypoglycemia	
	No.	%
0-2	12	60
3-7	4	20
>7th	4	20

There is no significant relationship between hypocalcaemia and hypomagnesaemia
, P- value was (0.742)

Discussion

The current study had shown that majority of patients who developed seizures were full term 84/88 (95.4%) with mean ±SD gestational age equal to (38.6±1.76) weeks .This result was nearly similar to a studies done by Yaser [13] and Alcover BE[14] who found that 93.1% and 90% were full term with mean gestational age of 36.9 weeks and 36 weeks respectively.

Weight in the majority of our patients were > 2500 g 82/88 (93.1%), this is similar to Sweta LM[15] . There is male preponderance which goes with Yaser study[13] (53.4%), and 63.6% in Alcover BE study. [14] About one third 28/88(31.8%) of seizure activity in term neonate in the current study was the subtle type which is due to incomplete urbanization of myelin sheets[16]; this result was similar to Scher *et a1* study [17] who mentions that subtle type as the commonest type of seizures. Volpe JJ [10] ,Sweta LM [15] , Yaser y[13]and Ross [18] studies had shown nearby similar results (50%), (45%), (46.5%) and (40.6 %) respectively. Tonic seizures were the second most common type in our study accounting for one quarter of patient 22/88 ; this result was consistent to what was reported by Sweta LM [15]. The clonic type(focal and multifocal) was the third common type constitute 18/88(20.6%);this was inconsistent with Ross Al et[18] and Yaser studies [13] who found that clonic type was the second most common cause(35.95%)and (30%) respectively. The myoclonic type was not recognized in the current study . Amar M.[19]study mentioned that myoclonic seizure was the least type(2.5%). In the preterm baby ,we found that tonic type occurred in 4/4(100%);this was consistent with Amar M[19] who mentions that the commonest type of seizures observed was tonic (41.6%) seizures followed by subtle seizures (33.3%) in preterm. In our study most seizures had been seen during the period between 3rd -7th day of life accounting for 43.2% of patients; this was followed by seizures that happened in the first two days of life (29.5% of patients), and finally those happened after the 7th day of life accounting for 18.2% of patients and unknown time was observed (9.1%), while in Coen RW [11] and Amar.M.[19] studies most of seizure onset occurred in those less than 3 days of age (81 %) and (63 %) respectively. This difference could be explained by that most of their patients in those studies were preterm and the most common etiology for seizure was asphyxia. The most common cause of neonatal seizures in the current study was

metabolic abnormalities 42/88 patients(47,7%). Birth asphyxia represent the second most common cause in the study 14 patient (15.9%) . The third common cause was meningitis 6 patients (6.8%) .The least cause was structural abnormalities 4 patients (4.5%) .These results were inconsistent with other studies like Shah GS[20] who found asphyxia was the most common cause (44%) ,metabolic abnormalities secondly as(22%) .Amar M.[19]also found asphyxia was the most common cause (42.7%) ,metabolic abnormalities (20%) secondly. This difference may be explained by that most of their patients were preterm and also because of that Shah GS[20]and Amar M.[19] did not mention the combined etiology for seizure . In the current study, the unknown etiology was recognized in 24 patients (27.2%) which could be related to that there is no facility to diagnose most of inborn errors of metabolism and pyridoxine dependent seizure, neonatal drug withdrawal was not recruited in this study. Idiopathic seizures were found in 10% of patients in two studies done by Tom L [21] and William WH *et al* [22], which were diagnosed by exclusion and we could not exclude all other causes of neonatal seizures. In relationship of onset to hypocalcaemia, we found that 12 patients (54.5%) occurred during the first two days of life, 8 patients (36.4%) during the period (3-7)days and 2 patients (9.1%) more than 7days.This results was consistent with Amar M [19]study who shown that (46.2%) of patients during first two days,(38.4%) during period 3-7 days and (15.4%)in the period >7days . Shah GS[20] also found that 80% of hypocalcaemia occurred in the first two days,(10%) during period 3-7 days and (10%) in the period >7days . Regarding sex ,we found that 16 case(80%) of hypoglycemia occurred in male while 4case (20%) of hypoglycemia occurred in female. this result goes with that found by Cornblath M, Schwartz R.[23]

Conclusions

1- The commonest cause of neonatal seizure was metabolic abnormalities .
2- Subtle seizure represents the commonest type observed in full term.
3- Tonic seizure represents the commonest type observed in preterm babies.

Recommendations

1- Metabolic abnormalities should be excluded in every case of neonatal seizure in spite of presence of other causes as meningitis or asphyxia and structural abnormalities .
2- Proper fetal monitoring during labor is recommended to avoid birth asphyxia .
3- Improvement of the laboratory services and the availability of other investigations like , serum ammonia, blood gases analysis (Astrup) and other advanced procedures, to detect and diagnose an inborn error of metabolism , because most of them are missed .
4- Increasing and improving the radiological departments in the hospitals, and offering a good trained staff for early and proper diagnosis of neonatal seizures .

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