Clinical types and possible etiologies of neonatal seizures: A hospital based study

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Summary:

Background: Seizures in the neonatal period are common. They can present as focal clonic, focal tonic, myoclonic, generalized tonic and subtle seizures. They can be caused by a variety of conditions, ranging from benign self-limited illnesses to severe life-threatening disorders.

Patients and methods: A prospective study included 75 neonates with seizures in the first 28 days of life were admitted to neonatal care unit in Children Welfare Teaching Hospital from January 15th 2009 to August 15th 2009. A Full history was obtained and patients were examined by a specialist in the neonatal care unit and the researcher. Laboratory investigations and neuroimaging studies were done for all patients.

Results: Out of 75 neonates, (55%) were males and (45%) were females with a male: female ratio of 1.2:1, (76%) of them was delivered at term. The onset of seizures was reported in the first 72 hours of life in (42.6%) of neonates. The most common type of seizure was tonic type (48%) followed by subtle type (24%), focal clonic 16% and multifocal clonic (12%). Hypoxic ischemic encephalopathy (HIE) was the commonest etiology (25.34%) then sepsis (24%), hypocalcaemia (14.67%), pyogenic meningitis (13.33%), hypoglycemia (9.33%), Kernicetrus (8%), IVH 4% and TORCH (1.33%).The consanguinity was detected in (26.7%) of patients. A response to Phenobarbitone alone was found in (42.1%) and to a combination of both phenobarbitone and phenytoin in (19.1%). The case fatality was (8%), (50%) of them were due to IVH.

Conclusions: Neonatal seizures occurred mainly in full term neonates with male sex preponderance with the majority reported in their first 72 hours of life and the tonic seizures were the commonest pattern. Hypoxic ischemic encephalopathy is the main etiologic factor of neonatal seizures followed by sepsis. Intraventricular hemorrhage occurs mainly in preterm infants and it was a major cause of death.

Keywords: Neonatal seizures, etiology, clinical types

Introduction:

A seizure or convulsion is a paroxysmal, time-limited change in motor activity and/or behavior that results from abnormal electrical activity in the brain. (1) Neonatal seizures (NS) are abnormal electrical discharges in the CNS of neonates usually manifesting as stereotyped muscular activity or autonomic changes. (2) NS by definition occurs within the first 4 weeks of life in a full term infant and up to 44 weeks from conception for premature infants. (3) NS can be divided into epileptic and non-epileptic seizures**:** NS of epileptic origin are generated by hyper-synchronous cortical neuronal discharges. There are age-dependent properties of the immature brain that enhance seizure initiation, maintenance of the seizure discharge and propagation of the seizure discharge. Non-epileptic seizures occur in the absence of electrical seizure activity. (4, 5)

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NS can be classified as focal clonic, focal tonic, myoclonic, generalized tonic and subtle seizures. (6) While EEG classification of NS as clinical seizures with a consistent EEG event, clinical seizures with inconsistent EEG events and electrical seizures with absent clinical seizures. (1)

NS can be caused by: Hypoxia-ischemia which is the most common cause of neonatal seizures , ischemic stroke which is more likely in neonates with polycythemia or with thrombophilia, infections such as meningitis and sepsis, hypoglycemia is common among infants of diabetic mothers, intracranial hemorrhage including subarachnoid, intracerebral, and intraventricular hemorrhage, hypernatremia or hyponatremia, hypocalcaemia (serum Ca level < 7.5 mg/dL [< 1.87 mmol/L]), hypomagnesaemia which may occur when the serum Mg level is < 1.4 mEq/L (< 0.7 mmol/L), and inborn errors of metabolism (e.g. amino or organic aciduria). (2, 7)

NS is evaluation by a detailed history and a physical examination. The history includes birth history(gestational age at birth, any complications during pregnancy, maternal diabetes, IUGR,

maternal drug use (heroin, cocaine), account of spells, age at onset(right from birth, few hours later, or after days) and family history of seizures.(8) The examination includes vital signs especially fever (suggesting CNS infection), Dysmorphisms as seen in Zellweger syndrome or Smith-Lemli-opitz syndrome, Cutaneous examination for vesicular rash of herpes simplex or incontinentia pigmenti, eye examination for chorioretinitis, scalp examination for needle marks suggesting inadvertent local anesthetic administration and then perform a neurologic examination. (9)

The evaluation also includes Electroencephalography (EEG) which plays a central role; it enables to confirm the epileptic nature of the ictal events, it allows to evaluate the prognosis and to guide the treatment decision, and sometimes may help in the etiological diagnosis.(4) Laboratory investigations: Glucose, calcium, sodium, urea, bilirubin, ammonia, blood gases and serum amino acids. Urine for amino acids, organic acids and 2-4 dinitrophenol (leads to precipitation if MSUD present).Consider lumbar puncture (LP) for cerebrospinal fluid (CSF) testing of glycine as well as to rule out CNS infection (especially bacterial meningitis).(8)Neuroimagings: Most infants should have a head CT which can detect intracranial bleeding and some brain malformations. Cranial ultrasonography may detect intraventricular bleeding but not subarachnoid bleeding; it may be preferred as a bedsides test for very sick infants who cannot be moved to radiology. (8,9) Prognosis of NS is generally bad and is essentially related to the underlying aetiology and probably to the duration of the active period of seizures.(4)

This study aimed to find out the clinical types, possible etiologic factors of NS in neonates admitted to children welfare teaching hospital, medical city complex, Baghdad.

Patients and methods:

A prospective study was completed for 75 neonates with NS who were admitted to neonatal care unit in children Welfare Teaching Hospital /Medical City /Baghdad, which is a tertiary center receiving cases referred from other governmental and private hospitals and private clinics for further management of suspected neonatal seizures. Cases were collected over 7 month period from January 15th 2009 to August 15th 2009.

The variables for analysis in this study includes; age, sex, mode of delivery, onset of seizure, mode of presentation (seizure pattern), feeding method, family history of seizure, consanguinity, maternal drug history, underlying causes of seizures, response to anticonvulsants and patient state on discharge from hospital. The information was taken from the mother. Gestational age of those patients were mentioned by term and preterm, because most of them arrived to hospital after their first day of life so precise gestational age could not estimated correctly. The diagnosis of HIE was made depending on the criteria by Sarnat and Sarnat in 1976.(10)

Blood cultures (blood agar and chocolate media) were done for all patients. Lumbar puncture(LP) was done for 56/75 of cases. The results of C.S.F. examinations were normal in 41 cases (73.21%) and match the following criteria. (10) For term neonates,WBC normal range of 0-32 cell / mm^3, protein 20-170 mg/dl, glucose 34-119 mg/dl, while for preterm neonates, WBC normal range of 0-29 cell / mm^3, protein 65-170 mg/dl, glucose 24-63 mg/dl. In the remaining 19 patients, LP was not done because their families refused it.

Neuroimages were done for all cases, brain ultrasound (42) and cranial CT-scan (34), some of them had both studies because when brain ultrasound was not informative, we sent them for cranial CT-scan. Metabolic studies were available only for the detection of serum levels of calcium and glucose, while serum magnesium and phosphorus were not evaluated because the facilities were not available in hospital's laboratory. Serum calcium was done for all patients and values <7mg/dl was considered as hypocalcaemia (Normal value of serum calcium during neonatal period is 7.0-12.0 mg/dl). (11)RBS was done for all patients (using bed side glucose test "glucometer") and values of <50mg/dl was considered as hypoglycemia (Normal value of serum glucose during neonatal period is 50-90mg/dl). (11) EEG done only for 10 cases at a private clinic (expensive) because it is not available in the hospital. TORCH screening was done only for 3 cases, one of them had positive result for toxoplasmosis, the remaining 72 patients were not sent for this investigation because it was not available in hospital laboratory.

Results:

Among 75 neonates, 41 (55%) were males, 34 (45%) were females with a male: female ratio of 1.2:1. This study showed that 57 neonates (76%) delivered at term and 18(24%) were preterm. This study found that 48 neonates (64%) were born vaginally, while 27(36%) were delivered by C/S.

The onset of NS in 1st 24 hours was observed in 13 neonates (17.3%) , 24hr-72 hours of life in 19 neonates(25.3%), 72 hr-1st week of life in 20 neonates (26.7%), and during 1st-4th week of life in 23 neonates (30.7%) , as shown in (tab 1).

Table 1: Distribution of patients with neonatal seizure according to the age of onset

Age of onset	***n***	**%**
1st- 24hr	13	17.3
>24hr - 72hr	19	25.3
>72hr - 1wk	20	26.7
>1 - 4wk	23	30.7
Total	75	100%

This study showed that 34 (45.33%) neonates were breast fed, 27 (36%) were bottle fed and 14 (18.67%) were mixed fed.

Among all affected neonates clonic, tonic seizures were observed in 36 (48%), focal in 12 (16%), multifocal clonic in 9 (12%) and subtle seizures in 18 (24%). Myoclonic seizure was not observed in this study, as shown in (Table 2).

Table2: Distribution of types of neonatal seizures.

Type of seizure	*n*	%
focal(clonic)	12	16
multifocal(clonic)	9	12
Tonic	36	48
Subtle	18	24
Myoclonic	-	-
Total	75	100

First degree consanguinity was found in 20 neonates (26.7%), while negative consanguinity was found in 55 neonates (73.3%).

Family history of seizures was present in 24 neonates (32%), [either neonatal seizures 5(20.83%), febrile convulsion 14(58.34%) or epilepsy of childhood 5(20.83%)], while it was negative in 51 neonates (68%).

Lumbar puncture was performed in 56 neonates (74.67%), 41(73.21%) showed normal results, 8(14.29%) were abnormal and 7(12.5%) were traumatic. L.P. was not done in 19 neonates (25.33%).

Blood cultures were done for all patients. The results were negative in 47 cases (62.67%) and positive in 28 cases (37.33%) The most common microorganisms detected were *enterobactor species, hemophilus influenzae, staphylococcus aureus* and *staphylococcus hemolyticus species.*

Neuroimaging studies were done for all patients with NS (either brain U.S. or cranial C.T. scan) , but some of them had both studies performed during hospitalization. So 42 cases (56%) underwent brain U.S., among them 41(97.62%) were normal and only 1 case (2.38%) was abnormal. Cranial C.T scan was done for 34 cases (45.33%) , 25 (73.53%) were normal and 9 cases (26.47%) were abnormal.

The study found that serum calcium levels were normal in 64 cases (85.33%) and low in 11 cases (14.67%). Blood glucose levels were normal in 66 cases (88%) and low in 9 cases (12%).

Among all neonates, the etiology of seizures was HIE(Sarnat and Sarnat in 1976) in 19 (25.34%), sepsis in 18 (24%), hypocalcaemia in 11(14.67%), meningitis in 10(13.33%), hypoglycemia in 7(9.33%), kernicterus in 6 (8%), IVH in 3(4%), and TORCH (toxoplasmosis) in one case (1.33%),as shown in (table3).

Table 3 : Etiology of neonatal seizures

Causes	*n*	%
HIE	19	25.34
Sepsis	18	24
Hypocalcaemia	11	14.67
Pyogenic meningitis	10	13.33
Hypoglycemia	7	9.33
Kernicterus	6	8
IVH	3	4
TORCH(Toxoplasmosis)	1	1.33
Total	75	100

In this study, the most common causes of NS after 72 hours were sepsis , hypocalcaemia, meningitis and kernicterus, while those in the first 72 hours were HIE, sepsis, hypocalcaemia and hypoglycemia as in table 4.

Anticonvulsants therapy started for 57 neonates (76%), phenobarbitone alone was used in 41 (71.93%), a combination of phenobarbitone and phenytoin was used in 15(26.32%). Thiopental infusion(G.A) was used only in one neonate (1.75%) who did not respond to the above mentioned anticonvulsants and died. Among neonates who received anticonvulsants, 35/57(61.4%) were responders(whose who responded to anticonvulsants during their stay in hospital), 24(42.1%) to Phenobarbital alone and 11(19.29%) to combination of both Phenobarbital and phenytoin. The non-responders were 22(38.6%) , 6 of them died and the others discharged on responsibility of their families before completion of therapy. Specific treatment was administered to 18 cases (24%), (I.V. infusion of calcium gluconate or 10% Glucose water for hypocalcaemia or hypoglycemia, respectively).(tab. 5)

Table 4: The causes of NS after 72 hours and in the first 72 hours.

>72 hours			1st 72 hours		
Causes of NS	No.	%	Causes of NS	No.	%
Sepsis	13	30.23	HIE	14	43.75
Hypocalcaemia	9	20.93	Sepsis	5	15.62
Meningitis	8	18.60	Hypocalcaemia	5	15.62
Kernicterus	6	13.95	Hypoglycemia	5	15.62
HIE	3	6.97	ICH	1	3.12
Hypoglycemia	2	4.65	TORCH	1	3.12
ICH	2	4.65	Kernicterus	1	3.12

Table 5: The types of anticonvulsant therapies in 75 neonates with NS

Type of therapy	*n*	%	Type of anticon-vulsant	*n*	%	Good response
No anticonv-ulsants use (but specific treatment	18	24				
Anticonv ulsants	57	76	Phenobar-bital	41	71.93	24 (42.1%)
			Phenytoin + Phenobarbital	15	26.32	11 (19.1%)
			G.A.	1	1.75	0

At time of discharge, 53 neonates (70.67%) improved and discharged well,10(13.33%) became spastic, 6 (8%) remained hypotonic, and 6 (8%) died, of them 3 (50%) died due to IVH. (tab.6)

Table 6: Outcome of patients with neonatal seizures at the time of discharge.

Outcome on discharge	*n*	%
Improved	53	70.67
Spastic	10	13.33
Hypotonic	6	8
Died	6	8
Total	75	100

Discussion:

In this study, there was an overall male sex preponderance (male: female ratio 1.20:1) which is consistent with Gupta study (2007). (12) In our culture, the male preponderance may be caused by social beliefs, so male babies are cared better by their parents and brought to the hospital even with minor complaints, but female babies are usually neglected and are managed at home even if they are very sick.

This study showed that 57(76%) of patients with NS were full term and this agree with Gupta (2007) (12) and Taksande (2005).(13)Also we found that 48 (64%) of these patients were delivered by normal vaginal delivery and this agreed with Taksande (2005)(13) and Sweta (2002).(14)

Regarding the type of NS, this study showed that tonic seizures were the commonest and account for 36(48%) of all cases followed by subtle seizures in18 (24%) of cases. This was inconsistent with Gupta (2007) (12) and Sweta (2002) (14) who found that subtle seizures were commonest type followed by tonic seizures. The difference in the results could be explained on the basis of etiology of NS which were variable in different studies and determined the type of seizures, in addition that not all seizures pattern were witnessed by ourselves and we depend on description obtained by the mothers or caregivers.

In this study, it was found that 32 neonates (42.6%) had first seizures before 72 hr. of age which was similar to Eriksson (1979) (15) and Gupta (2007). (12)This results can be explained by the etiology of NS in which the hypoxic ischemic encephalopathy (HIE) is the commonest cause of early onset NS followed by hypoglycemia.

Regarding etiology, this study showed that the commonest etiological factor for NS was HIE accounting for 19 (25.34%) of all cases, this agree with many studies done by Taksande (2005) (13), Watanabe (1980) (16) and Badran (2007) (17). HIE was followed by sepsis in (24%) of cases and this agreed with Gupta (2007) (12) , Taksande (13)and James (2004) (18).We found that pyogenic meningitis was an etiological factor in (13.33%) of cases and this was nearly similar to Taksande (2005) (13) and James (2004) (18) (11.1% and 14%) respectively.

Among metabolic causes, hypocalcaemia was observed in (14.67%) of patients with NS mainly in those who were breast fed, and hypoglycemia in (9.33%) due to delayed starting and improper breast feeding specially in infants of diabetic mothers and whom their mother underwent Caesarian section. These results were similar to Taksande (2005) (13) and Volpe JJ studies (1989) (19). Kernicetrus was reported in (8%) of cases as an etiological factor, While in Gupta study (12) (2007) the result was 2.94% of all patients. This can be explained by the late presentations of our patients due to delayed referral of neonates with severe jaundice and poor awareness of the families, and even health care providers about the serious sequel of severe neonatal jaundice. In this study, IVH was reported in only three cases (4%) who were preterm and this was higher than Gupta study (0.94%) (2007) (12), but less than that reported by Taksande(6.4%) (2005) (13) and James (17%) (2004). (18) The difference in the result may be due to less preterm infants reported in this study.

Regarding treatment, anticonvulsants were received by 57(76%) of patients with NS. A response to Phenobarbital was found in 24 (42.1%) patients and this was nearly similar to Painter (20) (1999) (43%) and for combination of Phenobarbital and phenytoin in 11 (19.1%) patients.

In this study, the consanguinity was detected in (26.7%) of all neonates with NS and this result was less than Badran study (2007) (17). This study showed that mortality rate among patients with NS was 6(8%), of them 3(50%) died due to IVH and this agree with Taksande (2005). (13) We concluded that neonatal seizures occur mainly in full term neonates with male sex preponderance in their 1st. 72hr. of life and the tonic seizures were the commonest pattern. The most common cause of neonatal seizures was HIE followed by sepsis, hypocalcaemia and hypoglycemia. Most of patients responded to anticonvulsant drugs. Intraventricular

hemorrhage occurs mainly in preterm infants and it was a major cause of death.

We recommend educations of pregnant women about the importance of antenatal care especially those with medical problems as diabetes mellitus and to avoid preterm deliveries, proper fetal monitoring during labor to avoid birth asphyxia and HIE as it is the major cause of neonatal seizures, early and proper management of neonatal sepsis and meningitis, early detection of neonatal seizures by close clinical observation with EEG study for suspicious seizures, especially during the first 72 hours of life, and early feeding with proper technique to avoid hypoglycemia especially in infants of diabetic mothers ,with monitoring of levels of calcium and sugar.

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