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Importance of EEG, USG skull and CT/ MRI brain in neonatal seizures

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Abstract

Aim and Objectives: The present study was undertaken to evaluate the importance of EEG, USG skull and CT/MRI brain in the diagnosis and management of neonatal seizures.

Methods: Total 75 neonates with clinically identified seizure episodes were enrolled in the study.EEG was done for 73 neonates and USG skull was done for all, whereas CT/MRI brain study was undertaken only if indicated by history, examination or other basic investigations. The findings of these investigations were correlated with various demographic parameters like gestational age, gender and birth weight and clinical parameters like age of onset and type of seizure, etiology of seizure, presence of status epilepticus, need for anticonvulsants and mortality.

Results: A greater percentage of neonates with 1st seizure occurring before 72 hours of life were found to have an abnormal EEG (14.70%), USG (14.28%) and CT/MRI (50%) as compared to later age of onset (5.12% and 5.00% and 34.6% respectively). Multifocal clonic and multiple types of seizures have a greater association with EEG abnormalities as compared to other types. There was a statistically significant association between clonic neonatal seizures and USG as well as CT/ MRI abnormalities.EEG, USG and CT/MRI studies revealed a higher incidence of abnormalities in patients with status epilepticus and found a statistically significant correlation between presence of status epilepticus and CT/MRI abnormalities. Most cases of metabolic convulsions do not require anticonvulsants.

Conclusion: Interictal EEG provides a useful non-invasive test to diagnose neonatal seizures due to diffuse brain lesions. USG is a rapid, inexpensive and sufficiently accurate modality in evaluation of neonatal brain pathology and in the diagnosis of various lesions that occur in the first weeks of life. CT/MRI further added to our knowledge in understanding the nature and extent of the underlying intracranial pathology by revealing findings which were not easily picked up on USG skull.

Keywords: Electroencephalogram, Ultrasonography, Magnetic resonance imaging, Neonates, Seizures, Status epilepticus, Anticonvulsants.

1. Introduction

Seizures are common and frequent representations of neurological abnormalities in neonates [1]. They carry a major risk of death and long-term morbidity including mental retardation in neonates [2,3]. Experimental evidence suggests that seizure activity in the immediate postnatal period, a time of both active myelination and continuing

cell division, may result in reduction in DNA content and brain cell number. It is therefore important to diagnose and treat neonatal seizures and their underlying causes with great precision [4].

Clinical diagnosis of seizures is challenging in newborns due to the subtle semiology. Concomitant video EEG recording is ideal for revealing unsuspected and subtle seizures as well as confirming non-epileptiform abnormal movements. However, when video EEG is unavailable, interictal EEG has been shown to be superior in several ways to clinical examination and other tests in the early detection and prognostication of brain dysfunction, particularly diffuse brain lesions, in newborns.

Neonatal brain USG introduced an entirely new area of diagnostic imaging into neonatal medicine. The anterior fontanelle is an acoustic window that allows visualization of the neonatal brain in great detail. The portable real time sector scanner results in extensive use of this modality in evaluation of neonates whose transport is difficult. Its use in the workup of neonatal seizures also stems from the fact that it detects most of the common lesions responsible for seizures in neonates. Moreover it is rapid and inexpensive [5].

CT and MRI brain enable detailed visualization of the cross-sectional and pathologic anatomy of the neurocranium, such as abnormal calcifications, brain edema, hydrocephalus, many types of tumors and cysts, hemorrhages, large aneurysms and vascular malformations. MRI, as compared to CT, is a safe method by which aspects of function and chemical tissue composition can be determined, thus giving added dimensions to an anatomic analysis. However, in both these methods correlation with a careful history and a thorough physical examination is important for interpretation [6].

Hence, considering the potential problems in the clinical diagnosis and evaluation of neonatal seizures and the need for further laboratory evaluation in these cases, we decided to conduct a study to evaluate the importance of EEG, USG skull and CT/ MRI brain in neonatal seizures.

2. Material and Methods

After obtaining institutional ethical committee approval and parent's written informed consent, this prospective analytical study was undertaken in the Neonatal Intensive Care Unit (NICU) of a teaching institute and tertiary care centre in Mumbai, for a period of 18 months. The inclusion criteria were: 1. Detailed and unequivocal description of neonatal seizures by the mother or qualified medical staff, 2. Seizures unresponsive to restraining maneuvers and unprovoked on stimulation, 3. Occurrence of first convulsion up to 28 days of life. Both preterm and term neonates as well as both inborn (i.e. those born in the obstetric unit of the same hospital) and outborn (i.e. those referred from other hospitals) neonates were included in the study. The exclusion criteria were: 1. Uncertain clinical manifestations, 2. Consent refused by parents.

Total 75 neonates admitted to the NICU with clinically identified seizures or who developed seizures during the NICU stay and fulfilling the definition of neonatal seizure and the inclusion and exclusion criteria were enrolled in the study. In all these neonates, a prospective evaluation was done by collecting and recording the baseline characteristics (sex, gestational age and birth weight), maternal history, birth history, neurological examination, seizure details. The age of onset of first seizure was classified as < 24 hours, 24 – 72 hours, 3 – 7 days and ≥ 7 days as the common etiologies in each of these groups would be different. For types of seizure the classification proposed by Volpe was used which includes four essential types: subtle, clonic, myoclonic and tonic. We additionally included all neonates with multiple types of convulsions into a separate group. Relevant laboratory investigations in mother and in all subjects were done in the biochemistry/ pathology laboratory of the same institute.

EEG was done in 73 neonates as soon as the clinical condition of the neonate was stable enough for transport. The remaining 2 babies succumbed before an EEG could be done. USG skull was done in all patients at the earliest, preferably within 48 hours of onset of seizures. It was done using a portable USG machine in the NICU itself. Some of the neonates were further subjected to a CT/ MRI brain study as indicated by clinical history, examination and baseline investigations. CT scan and MRI were done in the radiology department of the institute itself.

Additional investigations were done as guided by the history, examination and the essential investigations. They included blood culture, CSF study, renal function tests, and metabolic profile for inborn errors of metabolism. Any recurrence of seizures, neurological profile, and general hemodynamic status were monitored throughout the NICU stay and any medical or surgical interventions especially anticonvulsants required were noted. All babies were treated using standard treatment protocol.

2.1 Statistical Analysis

The statistical analysis was performed using Graph Pad InStat Software. Pearson's Chi-square test was applied to look for statistical significance. A p value < 0.05 was taken as significant.

3. Observations and Results

3.1 Incidence

Out of the 1412 babies admitted to the NICU (both inborn and outborn) over the study period, 75 developed seizures with an incidence of 5.3%.

3.2 Age of onset of seizures

A higher percentage of patients with 1st seizure occurring before 72 hours were found to have an abnormal EEG, USG and CT/MRI (14.70%, 14.28% and 50% respectively) as compared to later age of onset (5.12%, 5.00% and 34.6% respectively). There was no statistically significant difference between age of onset of seizures and EEG, USG and CT / MRI findings, therefore these findings in neonatal seizures were not influenced by age of onset of seizures (Table 1).

Table 1: Correlation of age of onset of seizures with EEG, USG and CT / MRI findings

Age of Onset	EEG		USG		CT / MRI	
	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
< 24 hrs ^	1 (14.29%)	6 (85.71%)	1 (14.29%	6 (85.71%)	2 (50%)	2 (50%)
24 - 72 hrs ^	4 (14.81%)	23 (85.19%)	4(14.29%)	24(85.71%)	11 (50%)	11 (50%)
4 - 7 days #	0 (0.00%)	17 (100%)	0 (0.00%)	17 (100%)	4 (36.36%)	7 (63.64%)
> 7 days #	2 (9.09%)	20 (90.91%)	2 (8.70%)	21 (91.30%)	5 (33.33%)	10 (66.67%)
Total	7 (9.59%)	66 (90.41%)	7 (9.33%)	68 (90.67%)	22 (42.31%)	30 (57.69%)

Gestational age, birth weight and gender were found to have no influence on EEG, USG and CT / MRI findings in neonatal seizures.

3.3 Etiology

Patients with perinatal asphyxia, intracranial infection and congenital malformation have a higher chance of EEG and USG abnormalities. USG abnormalities were also higher in neonates with intracranial hemorrhage.

3.4 Types of seizures

Multifocal clonic and multiple types of seizures had a greater association with EEG abnormalities as compared to other types. Focal and generalized clonic, myoclonic and subtle seizures (except orobuccal) had no correlation with EEG pattern.

USG and CT / MRI were abnormal in many of the clonic (multifocal and focal), generalized tonic and subtle limb movements. CT / MRI were also abnormal in most of the multiple seizures. Clonic seizures and USG as well as CT/ MRI abnormalities had a statistically significant association (Table 2).

Table 2: Correlation between Types of seizure and EEG, USG and CT / MRI findings

Type of Seizure		EEG		USG		CT / MRI	
		Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
Tonic		2 (9.09%)	20 (90.90%)	3 (12.50%)	21 (87.50%)	7 (46.67%)	8 (53.33%)
Clonic	Focal	0 (0.00%)	4 (100%)	1 (25.00%)	3 (75.00%)	3 (75.0%)	1 (25.00%)
	Multifocal	2 (33.33%)	4 (66.67%)	2 (33.33%)	4 (66.67%)	5 (100%)	0 (0.00%)
	Generalized	0 (0.00%)	1 (100%)	0 (0.00%)	1 (100.0%)	0 (0.00%)	1 (100%)
	Total	2 (16.66%)	9 (83.33%)	3 (27.27%)	8 (72.72%)	8 (80.0%)	2 (20%)
Myoclonic		0 (0.00%)	2 (100%)	0 (0.00%)	2 (100%)	0 (0.00%)	2 (100%)
Subtle	Ocular	0 (0.00%)	6 (100%)	0 (0.00%)	6 (100%)	0 (0.00%)	4 (100%)
	Orobuccal	1 (8.33%)	11 (91.67%)	0 (0.00%)	12 (100%)	1 (20%)	4 (80%)
	Limb	0 (0.00%)	8 (100%)	1 (12.50%)	7 (87.50%)	4 (50%)	4 (50%)
	Apnea	0 (0.00%)	3 (100%)	0 (0.00%)	3 (100%)	0 (0.00%)	2 (100%)
	Autonomic	0 (0.00%)	1 (100%)	0 (0.00%)	1 (100%)	0 (0.00%)	1 (100%)
	Total	1 (3.44%)	29 (96.66%)	1 (3.44%)	29 (96.66%)	5 (25%)	15 (75%)
Multiple		2 (25.00%)	6 (75.00%)	0 (0.00%)	8 (100%)	2 (40%)	3 (60%)
Total		7 (9.59)	66 (90.41%)	7 (9.33%)	68 (90.66%)	22 (42.31%)	30 (57.69%)

3.5 Status epilepticus

EEG, USG and CT / MRI studies revealed a higher incidence of abnormalities in patients with status epilepticus (17.39%, 16.67%, and 64.71% respectively) as compared to those without status epilepticus (6.00%, 5.88%, and 31.43% respectively). A statistically significant correlation was found between the occurrence of status epilepticus and CT/ MRI abnormalities (Table 3).

Table 3: Correlation between Status epilepticus and EEG, USG and CT / MRI findings

Status Epilepticus (SE)	EEG		USG		CT / MRI	
	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
With Status Epilepticus	4 (17.39%)	19 (82.61%)	4(16.67%)	20 (83.33%)	11(64.71%)	6 (35.29%)
Without Status Epilepticus	3 (6.00%)	47 (94.00%)	3 (5.88%)	48(94.12%)	11(31.43%)	24 (68.57%)
Total	7 (9.59%)	66 (90.41%)	7 (9.33%)	68(90.67%)	22(42.31%)	30(57.69%)

3.6 Need for antiepileptic drugs

Most cases of metabolic convulsions did not require antiepileptics. The chances of having abnormal EEG or USG findings were negligible in those patients not requiring antiepileptics. However, even in those patients not requiring antiepileptics, CT / MRI may pick up abnormal findings, especially lesions attributable to perinatal hypoglycemic insults (Table 4).

Table 4: Correlation between necessities of Antiepileptic drugs (AEDs) and EEG, USG and CT / MRI findings

Anticonvulsants	EEG		USG		CT / MRI	
	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
Required	7 (11.67%)	53 (88.33%)	7 (11.29%)	55 (88.71%)	19 (44.19%)	24 (55. 81%)
Not required	0 (0.00%)	13 (100%)	0 (0.00%)	13 (100%)	3 (33.33%)	6 (66.67%)
Total	7 (9.59%)	66 (90.41%)	7 (9.33%)	68 (90.67%)	22 (42.31%)	30 (57.69%)

3.7 Mortality

In 6 of the 8 neonates who expired, an EEG study was possible. 1 (16.67%) out of these were abnormal. 1 (12.5%) out of the 8 expired patients had abnormal USG findings. Only 6 (8.96%) out of the 67 who survived had abnormal EEG and USG findings. However, this difference was not statistically significant. In 4 of the 8 neonates who expired, a CT/MRI study had been possible, 2 (50%) out of which were abnormal. Among the survivors also, almost similar figure was found with 41.67% (20 out of 48) of the discharged patients who underwent a CT/MRI having abnormal findings.

4. Discussion

In the present study, the overall incidence of neonatal seizures among the NICU admissions was found to be 5.3%. Sattar *et al* [7] found an incidence of 4.8% among admitted neonates; this figure was similar to our study. From the classification of seizures based upon age of onset, we infer that the commonest period to develop the 1st seizure was within the 1st 72 hours of life. Hence, it is of vital importance to monitor infants closely during 1st 72 hours for any clinical manifestation of seizures.

Of the patients who had their first seizure within 72 hours of life, abnormal EEG and USG findings were noted in 29.1% each. As compared to this, in those patients with the first seizure occurring after 72 hours of life, 9.09% and 8.7% had abnormal EEG and USG findings respectively. Therefore, we recommend EEG and USG to be done in all patients with seizure onset before 72 hours. The gestational age, birth weight and gender were found to have no influence on EEG, USG and CT / MRI findings in neonatal seizures; this was comparable to the study of Sheth *et al* [8]

EEG abnormalities were found most commonly in multifocal clonic seizures (33.33%) followed by multiple seizures (25%). 9.52% patients with generalized tonic seizures and 8.33% patients with subtle orobuccal movements had abnormal EEG correlates. In all other types, EEG was normal. Clonic seizures had a higher association with USG abnormalities, the incidence being 25% in focal clonic convulsions and 33.33% in multifocal clonic convulsions. Similar to USG skull, CT/MRI abnormalities were also commonly detected in clonic convulsions, 100% of multifocal and 75% of focal clonic seizures. A significant statistical difference ($p < 0.05$) was found to exist when the incidence of USG and CT/ MRI abnormalities in clonic seizures was compared with that in other types of neonatal seizures; the reason could be related to the underlying etiology. We therefore strongly recommend doing a USG skull and CT/ MRI brain in all cases of clonic neonatal convulsions, especially multifocal and focal.

A significant number of generalized tonic seizures and subtle limb movements also had abnormal USG (12.5% and 12.5% respectively) and CT/MRI findings (46.67% and 50% respectively). None of the other seizure types were associated with abnormal USGs. Multiple types of convulsion were also associated with abnormal CT/MRI findings in 40% cases. The correlation was less (20%) in subtle orobuccal movements. The other convulsion types had normal CT/MRI studies. The findings of our study correlated with previous studies [9-11].

In this study, 32% neonates had status epilepticus. We did not come across any study which showed a correlation between status epilepticus in neonates and other factors of our interest in relation to neonatal seizures.

4 (17.39%) out of 23 EEGs done in patients with status epilepticus and 3 (6.00%) out of 50 EEGs done in patients without status epilepticus were abnormal. 4 (16.67%) out of 24 USGs in patients with status epilepticus and 3 (5.88%) out of 51 USGs in patients without status epilepticus were abnormal. Thus, a higher incidence of EEG and USG abnormalities were found in patients with status epilepticus as compared to those without status epilepticus. 64.71% of patients with status epilepticus had abnormalities on CT/MRI, while only 31.43% of patients without status epilepticus had abnormal CT/MRI findings, and this difference was statistically significant ($p < 0.05$).

In 13 patients (17.33%), convulsions subsided without anti-epileptic drugs, the etiology being metabolic (hypoglycemia and hypocalcemia) in 69.2% of these. All these 13 patients had normal EEG and USG skull findings. In 9 of these patients, a CT/MRI brain was done; 2 had findings suggestive of hypoglycemia and 1 was diagnosed to have left MCA infarct. We infer that most of the metabolic convulsions do not require anti-epileptic drugs and recommend that anti-epileptic drugs need not be used in cases of neonatal seizures with a proven metabolic etiology, especially hypocalcemia. We also infer that the chances of having abnormal EEG or USG findings are negligible in those patients not requiring anticonvulsants.

7 (11.67%) out of 60 EEGs done in patients requiring anti-epileptic drugs were abnormal. In our setup, due to non availability of an in-house NICU EEG facility, we could not perform ictal EEGs, which might have increased the yield of positive findings. Mises J *et al* studied 52 neonates suffering from disorders of amino acid metabolism, of which 3 had congenital hyperammonemia, none of whom had an abnormal EEG. Even in our study, the patient with congenital hyperammonemia had a normal EEG. In 5^{th} day fits, a typical interictal EEG pattern that appears in 60% of neonates is a discontinued theta rhythm. However in our study, the only infant with 5^{th} day fits had a normal EEG. None of the patients with sepsis, hypocalcemia, hyperbilirubinamia, intracranial hemorrhage showed abnormal EEG findings.

7 (11.29%) out of 62 USG studies done in patients requiring anti-epileptic drugs were abnormal. Patients with perinatal asphyxia, intracranial infection and congenital malformation were found to have a higher chance of EEG and USG abnormalities; this correlated with previous studies [12-15]. USG abnormalities were also higher in neonates with intracranial hemorrhage.

43 patients requiring anti-epileptic drugs underwent a CT/MRI and 19 (44.19%) of these had abnormal findings. These included 9 (64.28%) out of 14 patients with birth asphyxia, 3 (50%) out of 6 patients with intracranial infection and 2 patients each with sepsis (33.33%), hypoglycemia (33.33%), hyperbilirubinemia (40%), and intracranial hemorrhage (100%). Both the patients with congenital malformation (100%) and hyperammonemia (100%) had abnormal findings on CT/MRI. The study by Taghdiri *et al* found abnormal CT/MRI findings in 65% newborns, which were higher than our study [16]. The difference in their study could be due to the number of patients subjected to a neuroimaging study. Due to financial constraints and other reasons, we were not able to do a neuroimaging in every case, whereas in the aforementioned study, all the enrolled neonates underwent a CT brain.

Out of the 75 patients enrolled in our study, only 8 (10.66%) expired, 3 out of these had severe birth asphyxia, 3 had sepsis (out of these 2 also had associated birth asphyxia with severe PPHN), 1 had intracranial hemorrhage with suspected clotting factor deficiency and 1 had respiratory distress and systolic murmur with suspected PDA with CCF). The remaining 67 (89.33%) were successfully managed and discharged. There was no statistically significant difference observed between mortality and EEG, USG and CT/MRI findings. Thus, the abnormal EEG, USG or CT/MRI findings did not necessarily indicate a poor prognosis with regard to mortality.

EEG abnormalities have a consistent association with diffuse brain lesions. Burst suppression pattern on EEG was the commonest abnormal background activity in patients with HIE.IVH and dilatations of ventricles were picked up well on USG skull.HIE was the commonest abnormality picked up on a CT brain. Other lesions like infarcts, cerebral edema, meningitis / ventriculitis, lesions due to birth trauma and hypoglycemic brain injury were also detected. Brain injury due to kernicterus is detected in almost all patients in MRI brain as also congenital malformations and HIE. In cases of diffuse brain lesions like congenital malformations, encephalomalacia, intracranial infection, EEG findings correlate with the abnormal neuroimaging findings. There was a significant correlation between abnormal USG and CT / MRI findings.USG was not as sensitive as CT for picking up subarachnoid hemorrhage / intraparenchymal bleed, but picked up IVH equally well. USG was not sensitive in detecting cortical and subcortical abnormalities like infarcts and hypoxic / ischemic changes.

5. Conclusion

The commonest period for the development of the 1^{st} seizure is within the 1^{st} 72 hours of life. EEG provides a useful non-invasive test to diagnose neonatal seizures, yet its interpretation is influenced by variations in normal maturation process of brain. EEG abnormalities have a

consistent association with diffuse brain lesions. USG offers a rapid, inexpensive and fairly precise technique to evaluate many neonatal brain lesions, particulary in the early neonatal period. CT/MRI further adds to our knowledge in understanding the nature and extent of underlying intracranial pathology by revealing findings which are not easily picked up on USG skull. USG is advantageous over CT in patients who require repeated imaging, e.g. repeated therapeutic tapping and monitoring the change in size for intracranial abscess. USG is not as sensitive as CT for picking up subarachnoid hemorrhage, intraparenchymal bleed, cortical and subcortical abnormalities like infarcts and hypoxic / ischemic changes, but picks up IVH equally well.

EEG, USG and CT / MRI in particular are good diagnostic tools in neonates with status epilepticus. In neonates not requiring anticonvulsants, EEG and USG studies are usually normal, however CT / MRI may pick up abnormal findings, especially lesions attributable to perinatal hypoglycemic insults. USG is a very valuable, non-invasive, bedside, readily available diagnostic modality in newborns with perinatal asphyxia, intracranial infection, congenital malformations and intracranial hemorrhage. Most of the newborns with clonic seizures are found to have some underlying intracranial pathology, and hence, neuroimaging is strongly recommended in them. Abnormal EEG, USG or CT/MRI findings do not necessarily indicate a poor prognosis with regard to mortality.

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