The Role of MRI and Other Clinical Variables in Predicting the Etiology of Neonatal Seizures

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ABSTRACT:

BACKGROUND:

The first month of life is a time of increased risk of seizures; the prognosis largely depends on etiologic factors and the duration of convulsive activity.

OBJECTIVE:

To describe the spectrum of brain magnetic resonant imaging (MRI) findings with neonatal seizures.

PATIENTS AND METHODS:

Cross – sectional study conducted in Children Welfare Teaching Hospital /Medical City Complex. All full term neonates with a seizure were admitted to the Out -born Neonatal Care Unit or attending the Consultation Clinic and infants admitted to Pediatrics Neurology Ward who had history of fit during the neonatal period were included in the study (O -NCU) from January 1st to September 31st 2014.

RESULTS:

Eighty six neonates were included in the study, male: female ratio % o was 1.4:1. The mean age of presentation was 24 days (+18SD). Two-thirds of neonates presented in the first week and mainly in the first two days. The most common type of seizures was the subtle 15.1% within early or late presentation and less common (3.5%) were the autonomic. About half of the patients had abnormal Electroencephalography (EEG) study 49.1. Only 39.5% had normal MRI finding, about 60.5% had abnormal MRI, the most frequent abnormality was metabolic 15.1% and developmental 11.6%. The family history was positive in those who presented with seizures in first 14 days (early) in 30% , and more with those had metabolic etiology and no family history in case of vascular etiology. 89.5% of neonates had abnormal MRI finding in those who presented in the late period (p=0.003).

KEYWORDS Brain MRI; neonate seizures; Electroencephalography

INTRODUCTION:

One of the greatest advances in the investigation of epilepsy in the 20th century was the introduction of brain imaging. Neuroimaging has provided an extraordinary insight into the pathologic substrate of epilepsy, which is essential in determining probable course of the disease, appropriate treatment, surgical candidacy and likelihood of seizure freedom after surgical intervention. [1]

Brain magnetic resonant imaging (MRI) not only has higher sensitivity than computed tomography (CT) scan, but also better special resolution soft tissue contrast. In addition, it allows multiple planes imaging as well as function cerebral assessment through different techniques. All these characteristics make MRI the primary imaging modality for the evaluation of patients with epilepsy. MRI with dedicated epilepsy protocol increases even more the frequency with which epileptogenic lesions are identified. although protocols vary from institution to institution, most include axial and coronal oblique T2-weighted fast spin echo (FSE) and fluid attenuation inversion recovering (FLAIR) sequences, as well as coronal magnetization-prepared rapid acquisition gradient echo (MPRAGE) and/or spoiled gradient recalled echo(SPGR) volumetric dataset. [2, 3]

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AIMS OF STUDY:

To describe the spectrum of brain MRI findings with neonatal seizures and its diagnostic potential in determining the etiology of seizures and to correlate the neonatal seizures with clinical semiology, family history, age of presentation, EEG and MRI finding.

PATIENTS AND METHODS:

Study design:

The Cross–sectional study was conducted in Children Welfare Teaching Hospital /Medical City Complex during the year of 2014.

All term neonates with seizure admitted to the Out -born Neonatal Care Unit (O -NCU) or attending the Consultation Clinic at Children Welfare Teaching Hospital–Medical City Complex and infants admitted to Pediatrics Neurology Ward who developed fit during the neonatal period from January to September 2014 were included in the study. The O –NCU is considered a tertiary center for neonatal care that receive neonates from out-patient clinics and from other hospitals or centers.

Exclusion criteria

Neonates with fit due birth asphyxia, central nervous system (CNS) infections (meningitis & encephalitis), hypoglycemia, hypocalcaemia and hypomagnesaemia according to medical history and proved by investigation were excluded from the study. Neonates who were included in the current study but they did not complete their investigations especially the Electro encephalography (EEG) and Magnetic Resonant Image (MRI) were excluded from the study.

Data Collection;

History: The mothers or the neonate's companions were interviewed to collect the relevant information which included the age of the neonate, gender, age of the first attack of fit, family history of neonatal fit or, consanguinity.

Clinical semiology of fit:

The mothers or the care givers were asked to describe the attack briefly, the investigator will ask direct questions trying to classify the fit into: subtle, motor (tonic, clonic, multifocal, generalized, myoclonic) autonomic and non-paroxysmal attack, Care-givers were also instructed to videotape the seizure episode their baby during the events.

Medical examination: This included detailed general and neurological examination

Investigations

A. General investigations: complete blood picture and differential, serum electrolyte, liver function tests and renal function tests. Cerebrospinal Fluid (CSF), TORCH infection and metabolic study (available at the hospital's laboratories or some private laboratories) when indicated.

B. EEG: was done for all neonates who were included in the study and the results were classified into normal or abnormal depending on the background activity, presences or absence of epileptiform discharge, presences or absence of encephalopathy and presences or absence of hypsarrhythmia. The final decision was made by a specialist in neurophysiology.

C. MRI: was done for all neonates who were included in the study, and was done in the Institute of radiology and radiological department of nursery home hospital, using the SEMINS CONCERT 0.25T open magnate or SEMINS AVONTO 1.5T closed magnate.

Neonates were sedated with chloral hydrate 50mg/kg, or using the Ketamine (1.2mg/kg) + midazolam (0.1-0.2mg/kg) frequently each 15 mint.

The sequences included in the examination were:

T1: Axial, Sagittal

T2: Axial, Coronal

T2: FLAR, Coronal

T1 enhancement with contrast if ordered by the radiologist.

Magnetic resonance angiography (MRA), Magnetic resonance venography (MRV) if vascular etiology was suspected.

The contrast used was gadolinium, and the dose was 0.2mg/kg. 9 babies were examined with contrast.

The reports were done by the radiology specialist, and the cases were classified into: [4, 5]

Vascular etiology which include

A. Ischemia

B. Hemorrhagic

C. Vascular Malformation:

D. Cerebral arteries or vein thrombosis.

-Developmental: Metabolic: Multiple findings that did not fit any of the above mentioned pathologies

-Leukoencepalopathy: which mean white matter (WM) pathology as prominent T2-hyperintensity and prominent T1-hypointensity of affected WM relative to GM.

Intrauterine infections

Normal MRI

Statistical Analysis:

The data were coded and each questionnaire was assigned a serial identifier number. The data was then entered by the researcher into the computer using The Statistical Package for Social Sciences (SPSS) version 17.0.

Data were summarized using standard descriptive statistics, tables and graphs of categorical and numerical variables. Associations between categorical variables were assessed via chi-square. In all statistical analyses, a P value <0.05 was considered to be significant.

Ethical consideration:

The approval of the study proposal was obtained from the Iraqi Board for Medical Specialization.

The official agreement of Ministry of health (MOH) was obtained from the Research Ethical Committee in Ministry of Health – Iraq.

Limitations of the study

Difficulties faced by the investigator during the current study:

EEG and MRI were very difficult to arrange in the hospital and the cost of the test in the private sector was not acceptable by the majority of the families of the neonate.

At the MRI department the neonates were sedated or anaesthetized during the test whereas many researches stated that neonates can often be scanned without sedation during natural sleep induced by food, comfort and warmth often best after period of sleep deprivation. [4, 6]

RESULTS:

Eighty six neonates were included in the study. There were 50 males (58%) and 36 females with male: female ratio of 1.4:1 (table 1).

The mean age of the neonates at the interview was 24 days ± 18 SD.

It was found that the first attack occurred more during the first week of life; mostly during the first day (15%) and the second day (14%), and if early and late neonatal period is considered, table 1 showed that the first attack was during the first week of life (early neonatal period) in more than two thirds of neonates (69.8%) and during the late neonatal period in less than one third (30.2) of the neonates. The mean age at presentation was 8 days ± 8 SD.

Table two shows the seizure type according to the description of mothers or care givers i.e. semiology. It was found that subtle and motor clonic multifocal seizures were more than the other types of seizures (15.1% each) whereas autonomic seizure was found in only three neonates (3.5%).

EEG study was abnormal in 48.8% of neonates and 39.5% had normal MRI finding, 60.5% had abnormal MRI, the most frequent abnormalities were metabolic 15.1%, developmental 11.6% and vascular (9.3%) and the least frequent was leukoencephalopathy (2.3%) (Table 2).

Table 1: Frequency distribution of the study sample by socio- demographic variables

Variables	N	%
Age group (weeks)		
First week	16	18.6
Second week	16	18.6
Third week	19	22.1
Fourth week	8	9.3
>4 weeks	27	31.4
Total	**86**	**100.0**
Gender		
Female	36	41.9
Male	50	58.1
Total	**86**	**100.0**
Age at presentation (weeks)		
First week	60	69.8
Second week	7	8.1
Third week	10	11.6
Fourth week	9	10.5
Total	**86**	**100.0**
Family history of fits		
Negative	63	73.3
Positive	23	26.7
Total	**86**	**100.0**

Table 2: Epilepsy semiology, EEG and MRI findings

Variables	N	%
Seizure semiology		
Subtle	13	15.1
Motor clonic multifocal	13	15.1
Motor myoclonic	10	11.6
Motor clonic focal	9	10.5
Motor tonic generalize	9	10.5
motor tonic focal	8	9.3
Motor clonichemifocal	6	7.0
Motor spasm	6	7.0
Motor tonic multifocal	5	5.8
Non paroxysmal repetitive behavior	4	4.7
Autonomic	3	3.5
Total	**86**	**100.0**
EEG		
Normal	44	51.2
Abnormal	42	48.8
Total	**86**	**100.0**
MRI diagnosis		
Normal	34	39.5
Metabolic	13	15.1
Developmental	10	11.6
Vascular	8	9.3
Intracranial hemorrhage	7	8.1
Multiple findings	6	7.0
Infection	6	7.0
Leucoencephalopay	2	2.3
Total	**86**	**100.0**

For statistical analysis the age at presentation was classified into two groups (1-14) days and (15-28) days to overcome the problem of small sample size.

On studying the association of family history of fits, EEG result, MRI finding, epilepsy semiology with age at presentation (in days), showed that although positive family history was found in 29.9% of neonates who developed fits during their first 14 days of life compared to only 15.8% among those who developed the fits during 15-28 days of life yet the association was statistically not significant (table 3).

Age of presentation was significantly associated with any positive MRI diagnosis (P=0.003) and with Vascular/ hemorrhagic changes in MRI (P=0.019). Seizure semiology of motor clonic were higher among those who presented late and the association was statistically significant (P=0.008). The association between age at presentation and EEG finding was statistically not significant (table 3).

Table 4 shows the association between EEG results, family history, gender, epilepsy semiology with MRI diagnosis. It was found that although abnormal EEG was more among those with any positive MRI diagnosis, developmental and metabolic the association was only statistically significant among those with metabolic diagnosis on MRI (P=0.005), whereas normal EEG was more common among those with Vascular/ Hemorrhagic diagnosis on MRI with statistically significant association (P=0.002).

Positive family history of fits or neonatal deaths was higher than the negative among those with metabolic diagnosis on MRI with statistically significant association (P<0.001) whereas all those with Vascular/Hemorrhagic diagnosis on MRI gave no family history of neonatal fits or deaths and the association was statistically significant (P=0.009). The association between gender and MRI findings was statistically not significant, and although semiology of motor fits was higher than other types of semiology (Subtle and Non paroxysmal repetitive behavior/ autonomic) the association was statistically significant with any positive MRI diagnosis (P=<0.001) and Vascular/Hemorrhagic diagnosis on MRI (P<0.001) and failed to have statistical significance with developmental diagnosis on MRI (P=0.5).

Table 3: Association between family history, EEG result, MRI finding, epilepsy semiology and age at presentation (in days)

Variables	Age at presentation				
	1-14 days		15-28 days		
	N	%	N	%	P
Family history of fits					**0.22[NS]**
Negative	47	70.1	16	84.2	
Positive	20	29.9	3	15.8	
Total	**67**	**100.0**	**19**	**100.0**	
EEG					**0.71[NS]**
Normal	35	52.2	9	47.4	
Abnormal	32	47.8	10	52.6	
Total	**67**	**100.0**	**19**	**100.0**	
MRI diagnosis					
Any positive MRI diagnosis	35	52.2	17	89.5	0.003
Developmental	8	11.9	2	10.5	1[NS]
Metabolic	9	13.4	4	21.1	0.47[NS]
Vascular / hemorrhagic	8	11.9	7	36.8	0.019
Total	**67**		**19**		
Seizure semiology					
Subtle	10	14.9	3	15.8	1 [NS]
Motor clonic	17	25.4	11	57.9	0.008
Motor tonic	25	37.3	3	15.8	0.08[NS]
Motor myoclonic	9	13.4	1	5.3	0.45 [NS]
non paroxysmal repetitive behavior/autonomic	6	9.0	1	5.3	1 [NS]
Total	**67**	**100.0**	**19**	**100.0**	

Table 4: Association between EEG result, family history, gender, epilepsy semiology and MRI diagnosis

Variable	MRI diagnosis									
	Any positive MRI diagnosis		Developmental		Metabolic		Vascular/ Hemorrhagic		Total	
	N	%	N	%	N	%	N	%	N	%
EEG										
Normal	23	52.3	3	6.8	2	4.5	13	29.5	44	100.0
Abnormal	29	69.0	7	16.7	11	26.2	2	4.8	42	100.0
P (Chi-square)=	**0.11[NS]**		**0.19[NS]**		**0.005**		**0.002**			
Family history of fits										
Negative	39	61.9	8	12.7	2	3.2	15	23.8	63	100.0
Positive	13	56.5	2	8.7	11	47.8	0	0.0	23	100.0
P (Chi-square)=	**0.65[NS]**		**1[NS]**		**<0.001**		**0.009**			
Gender										
Female	20	55.6	4	11.1	7	19.4	4	11.1	36	100.0
Male	32	64.0	6	12.0	6	12.0	11	22.0	50	100.0
P (Chi-square)=	**0.43[NS]**		**1[NS]**		**0.34[NS]**		**0.19[NS]**			
Seizure semiology										
Subtle	4	30.8	1	7.7	1	7.7	0	0.0	13	100.0
Motor clonic	26	92.9	6	21.4	4	14.3	12	42.9	28	100.0
Motor tonic	19	67.9	3	10.7	8	28.6	2	7.1	28	100.0
Motor myoclonic	1	10.0	0	0.0	0	0.0	0	0.0	10	100.0
Non paroxysmal repetitive behavior/autonomic	2	28.6	0	0.0	0	0.0	1	14.3	7	100.0
P (Chi-square)=	**<0.001**		**0.28[NS]**		**0.11[NS]**		**<0.001**			

DISCUSSION:

The mean age of the neonates included in the current study was 24 days ± 18SD, those neonates were older than those included by Sabzehei et al [7] on studying the etiology, clinical types and short outcome of seizures in newborns admitted to Besat Hospital / Hamadan\ Iran (8.42 days ± 9.08Sd) which could be explain by the fact that the current study was conducted in a tertiary hospital that received referred cases from other hospitals unlike the Iranian study as they included only neonates who were born in the same hospital and admitted to the neonatal intensive care unit (NICU) and they reviewed their records for three years so their sample size was larger.

In this study males (58%) were more than females, nearly the same was found by Sabzehei et al. from Iran [8] as the males in their study represented 57% of the studied newborns and in North California [9] on studying both term and preterm neonates with seizure they noticed that seizure was more among males in both groups (57.3% and 50% in term and preterm infants respectively).

Regarding the age at presentation of first attack of seizure, more than two thirds of the studied neonates in this study developed fits during their first week of life, 15% during their first day and 14% during the second day of life, nearly the same was noticed by Sabzehei et al. [8] as early presentation (during the first three days of life) was found in 50% of neonates included in their study.

Although the time taken by the family to consult physicians ranged from (1-7) days to 29 days most of the families sought medical attention within a week from the index presentation reflecting the family awareness and care; besides, most of the etiological factors encountered in the current study usually presented early .

Family history of neonatal fits or neonatal death was positive in 26.7% of the studied neonates which was higher than what was found by Sabzehei et al. [8] as positive family history was found in only 4% of their studied neonates. This may be attributed to the fact that consanguineous marriages are still high in Iraq compared to other countries. A family history of neonatal convulsion may suggest that the infant has a genetic syndrome (neonatal epilepsy syndrome).

Many of these syndromes are considered benign and frequently disappear within the neonatal period. In the absence of other etiologies, a family history of neonatal seizures may suggest a good prognosis [10]. When age at first attack was considered, positive family history was more among those presented earlier (29.9%), as metabolic disorder and epilepsy syndromes which have genetic predisposition usually occur earlier than other etiologies. [11]

In our study the most common seizure types were subtle and motor clonic (15.1% for each), and if we collect all motor types of seizure they will reach 75% of all seizure semiology. Sabzehei et al, [8] showed that the subtle seizure was (38%) followed by tonic (29%), clonic (26%) and myoclonic(5.9%) and similar results were reported by Moayedi et al, [12] and Tekgulet et al, [13] in contrast to these results Sabzehei et al [7] who studies 101 neonates with seizure of whom 39.6% had both tonic and clonic seizures. Also, Kumar et al. [14] reported that multifocal clonic seizures 42.24% were the most common followed by generalized tonic 21.55%, subtle 8.19%, focal clonic 6.47% myoclonic only 0.86%. Volpe JJ et al [15] and Mizrahi &Kellaway [16] have reported subtle seizures as the most common type of neonatal seizures.

In most clinical settings including the NICU, seizure in newborns are identified by clinical observation. However, some of the clinically identified motor and behavioral phenomena characterized as seizures do not have simultaneous EEG correlate, thus overestimating neonatal seizures. Conversely many electrographic seizures are not accompanied by clinically observed alternation in motor or behavioral function, thus underestimating neonatal seizures. [14] In the current study EEG were abnormal in less than half of study sample 48.8% this could be attributed to the timing of EEG examination, because EEG examination is not available in our hospital and so the neonate will be referred to other facilities for EEG until after stabilization of the neonate, so they will have interictal EEG not ictal which yield more information.

The subject of electroclinical dissociation must be considered in certain subtle seizures, most generalized tonic, focal and multifocal myoclonic seizures, as they could have originated from the brain stem or spinal cord level, thus it is not surprising that many of these seizures do not have an EEG correlation. [17]

The abnormal MRI was found in 60.5% of neonate in our study sample with the most frequent anomalies being metabolic 15.1%, developmental 11.6% and vascular 9.3% and the least frequent etiology was leucoencephalopathy 2.3%. Similar results were obtained by Billetop A. et al, [18] on studying neonatal seizures, in Neonatal Intensive Care Unit, St Michael's Hospital, Bristol UK, during 2013, where they found that 64% had abnormal MRI finding with cerebral dysgenesis the most prevalent etiology followed by metabolic causes vascular (mainly the stroke). They also elicited that the negative predictive value of a normal MRI in survivors of developing any disability was 0.93. The only difference between the current and the above study was that metabolic causes were more common in the current study whereas neuro-developmental causes were more common in their study. This could be attributed to that the current study was performed in a tertiary center that receive many intractable neonatal seizure from other hospitals and health facilities and most of the intractable seizures were found to be of metabolic background. [19]

The percentage of seizures attributed to leukoencephalopathy was very low in the current study.

the current study and this was found by many researchers [6] this could be explained by the fact that the myelination is usually not completed after birth as it takes six months – two years to complete, and the WM disorders presented in the second year of life not early as GM disease.[20]

Tabban H. et al, [21] on studying the neonatal brain MRI findings at the Radiology Department in Hamad Medical Center- Qatar found that many antenatal, perinatal and early life risks face the immature developing brain and result in variable pathologies detected by brain MRI; the results of brain MRI were normal in 30% of neonates, vascular etiology was found in 35%, developmental in 20%, multiple findings in 9%, metabolic in 3% and very small percentage for infection and leukoencephalopathy.

This study was done in the radiology department to review all MRI reports and not only for those neonates who presented with seizure as those with seizure were not more than 17% of the studied MRI reports unlike the current study where all the included neonates were with neonatal seizure.

The current study showed that the neonates presented with seizure in late neonatal period have positive MRI findings more than those presented early, this could be explained by the fact that one of the commonest causes of fits during early neonatal period is neonatal epilepsy syndromes which have early onset of presentation, benign course, good prognosis, and usually with positive family history yet no neuroimaging abnormalities. [22]

The vascular etiology in the current study was more prevalent among those who presented in late neonatal period, and was significantly associated with MRI findings but not with family history nor EEG abnormalities which could be explained by the fact that vascular causes rarely have inherited pattern and most of vascular disorders presented with motor phenomena (mainly clonic seizure) which have been considered to be seizures are usually not associated with ictal EEG correlates. [22]

Regarding seizure semiology evidence revealed that semiology of clonic seizure was usually associated with abnormal EEG findings, subtle seizure was rarely associated with abnormal EEG findings, tonic and myocolinic were unusually associated with abnormal EEG findings, [6, 22]. Our findings were not consistent with this evidence because usually the EEG examination was performed interictally and it may need a larger sample size to reach a conclusion.

CONCLUSIONS:

1. More than two thirds of neonatal fits occurred during the first 14 day of life and mostly during the first or second day, even with the exclusion of hypoxic-ischemic encephalopathy and prematurity.
2. Gender had no impact on neonatal fits.
3. Positive family history was not a commonly associated finding with neonatal seizures, but if present, it was mainly associated with an early onset of presentation, with abnormal EEG findings and it was a good predictor only in those with metabolic cause rather than other etiologies.
4. A significant number of babies with neonatal seizures had MRI findings mostly in those who presented in late neonatal period, but if we consider the etiology, the vascular finding was more in late presentation whereas the metabolic and developmental changes more in those who presented early.
5. The motor seizures were more among all types with positive MRI findings. It is the common semiology in late presentation and its presence raises the suspicion of metabolic or vascular etiology.
6. EEG abnormality was not related to the age of presentation but the abnormality was still obvious in those who had developmental and metabolic, rather than vascualr causes.

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AUTHOR'S CONTRIBUTIONS;

Dr. Hula R. Shreef: A pediatric neurologist, who did the basic work of this research, chose the subject, collected the sample, collected the results and interpreted them and finally wrote a dissertation.
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Dr. Mohamed AL-Hilli: is the radiologist who put the guideline and sequences for the examination of the neonate and he was read all the radiological results.
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Dr. Husham Z. Hammoodi: Participate in the discussion and evaluation of data and review the manuscript as well as assist in coordinating the study, and participate in reading and improving the final manuscript.
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Dr. Mahjoob N. AL-Naddawi: he was the Supervisor, study conception and design.
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