Etiology of Neonatal Seizures and Associated Biochemical Abnormalities

Anoop Singh, R S Sethi, Om Shankar Chaurasiya, Anuj S Sethi
Department of Paediatrics, MLB Medical College, Jhansi

Original Research Article

ABSTRACT

A prospective observational study including neonates presenting with seizures admitted to neonatal intensive care unit (NICU) was done in tertiary level hospital ,Jhansi from October 2015 to November 2016 with objective to assess various etiological factors of neonatal seizures to study the biochemical abnormalities in neonatal seizures. The etiology of neonatal seizure, time of onset and its relation to etiology and associated biochemical abnormalities were established in each case. Out of 110 neonates studied, birth asphyxia was the commonest cause of neonatal seizures. Subtle seizures were most common type of seizures among patients of neonatal convulsion. Most of patients were term (62.7%) and most of seizures were observed in first 3 days of life (75.5%). Most common biochemical abnormality was hypoglycaemia followed by hypocalcemia, hyponatremia, hypernatremia, hypermagnesemia and hypomagnesaemia. In patients of birth asphyxia, most common abnormality was hypoglycaemia (17.77%) and hyponatremia (17.77%) followed by hypermagnesemia (16.6%). In patients of sepsis, hypoglycaemia (44.49%) was most common abnormality followed by hypocalcemia (18.57%). In IDM (Infant of Diabetic Mother) patients, hypoglycaemia and hypocalcemia was found in all patients. In subtle seizures most common abnormality was hyponatremia followed by hypoglycaemia while in tonic seizures, hypomagnesaemia followed by hypernatremia. In clonic seizures most common abnormality was hypoglycaemia and hypocalcemia.

KEY WORDS: abnormalities, hypernatremia, neonatal seizures, neonatal intensive care unit (NICU)

INTRODUCTION:

Neonatal seizure is the commonest neurological dysfunction in the neonatal period. It is a paroxysmal alteration in neurological function like motor, behaviour and/or autonomic function and can occur at any gestational age[1]. The neonatal central nervous system is particularly susceptible to seizures due to a combination of enhanced excitability, and low levels of the inhibitory neurotransmitter gamma amino butyric acid (GABA)[2].

Neonatal seizures are dissimilar to those in a child or adult because generalized tonic-clonic convulsion do not occur during the first month of life as the arborisation of axons and dendritic processes as well as myelination is incomplete.[3] Volpe has classified seizures in five clinical types-subtle, multifocal, clonic, focal clonic, generalized tonic , myoclonic [4].

Corresponding Author:
Dr Anoop Singh
721/E, Shree Ram Nagar Colony,
Basharatpur, Gorakhpur (UP) - 273004
Phone No.: +91 9889024130
E-mail: anoopsingh6108@gmail.com

The incidence rate of clinical seizures varies from approximately 1.1 to 8.5 per 1000 live births[5], with higher incidence in premature and low birth weight neonates. It may be up to 3.4% of neonatal intensive care unit admission[6]. The major causes of neonatal seizures are Hypoxic-Ischemic Encephalopathy (HIE), which represents about 50% of the causes of neonatal seizures. Metabolic abnormalities, infection, intracranial hemorrhage, developmental anomalies, and others like inborn errors of metabolism are other causes of neonatal seizures[7].

MATERIALS AND METHODS:

This prospective observational study included 110 neonates presenting in NICU of M.L.B. Medical College, Jhansi during the period from November 2015 to October 2016. Children inborn or outborn, term or preterm within 44 weeks of conception, born through either vaginal delivery or lower segment caesarean section, who presented with seizure within 28 days of their life were included in the study,

whereas.

Age of the patient more than 28 days, if neonate has taken any anti epileptic previously, recurrence of seizure , sample taken after administration of any drug were excluded.

There were a total of 858 admissions in SNCU during the period of study , out of these 178 newborns fulfilled our inclusion criteria.Only 110 of those were enrolled in our study , while 45 expired and 23 left against medical advice. The day of onset of seizures, type and the duration of the seizures were recorded. They were further classified according to Volpe's classification into multifocal, clonic, focal tonic and myoclonic. The vital signs of the baby were recorded. General physical examination and any disparity in head size and shape, skin lesions were noted. Gestational age was assessed according to New Ballard scoring. CNS examination was done and HIE was staged according to modified Sarnath's staging. Other systems were also examined.

The investigations included complete blood count, sepsis screening, peripheral smear, CRP and blood culture, blood glucose. Serum electrolytes were done on emergency basis; serum calcium, serum sodium, serum potassium, and serum magnesium were done using semi auto analyzer (by Colorimetric method). Lumbure puncture was performed and CSF analysis and culture was done. Chest X-ray and Ultrasound of cranium was done. CT scan, MRI and EEG was done as and when required.

RESULTS:

There were 110 neonates in our study with seizures admitted in NICU of M.L.B. Medical College.

Out of total 110 patients 69(62.7%) were term and 38 (34.5%) were preterm and only 3(2.7%) were post term. 48 patients(69.2%) out of term were male & 21 patient (20.8%) were female & 21 preterm(55%) were female and 17(48.7%).

The most common type of seizures in this study was subtle (41%) followed by tonic (33%), clonic (21%) & myoclonic (5%). Among patient of subtle seizures 61.37% had birth asphyxia, RDS 4(9%), bilirubin encephalopathy, 3 (6.1%) patients of metabolic disorder 2 (4.5%). Among patient of tonic seizures 45.94% patients were of birth asphyxia, 21.6% of sepsis, while 18.9% bilirubin encephalopathy and 5.4% of unclassified group.

Among patients of clonic seizures 39.17% patients were of sepsis, 26.08% of RDS, 8.6% of IDM and 8.6% of each bilirubin encephalopathy and unclassified group.

Among patients of myoclonic seizures, 50% patients were of sepsis and 16.66% of each birth asphyxia, metabolic disorders and RDS.

Onset of seizure on first day of life was seen in 53 neonates (48.18%), on second day 19(17.27%) and on third day 11(10%) neonates develop convulsion respectively. Late onset seizures were observed 13 neonates (11.8%). Overall 75% of seizures were observed to occur in first 3 days of life.

Onset of seizures on the first day was seen in 53 neonates among them most common etiology was birth asphyxia in 36 (67.9%) cases followed by RDS in 13 (24.52) case (Table 2).

On second day 19 neonates developed seizures among them 8 cases 42% were due to birth asphyxia, 3 were due to RDS and 15.82% were due to sepsis. On day 3, 11 neonates developed seizures, among them, 1 (8.09%) was due to birth asphyxia, 4 (36.4%) were due to sepsis, 2 (18.18%) due to RDS, 3 (27.27%) due to bilirubin encephalopathy, 1 case unclassified.

Most common biochemical abnormalities were hypoglycaemia 25.45%, followed by hypocalcemia 15.54%, while other abnormalities were hyponatremia in 14.54%, hypernatremia 13.6%, hypermagnesemia 7.2%, and hypercalcemia 1.8%. Most common biochemical abnormities in HIE patients were hyponatremia (17.77%), hypoglycaemia (17.77%) followed by hypermagnesemia (9.09%). Most common biochemical abnormality in sepsis was hypoglycaemia followed by hypocalcemia. In all patients of IDM hypoglycemia and hypocalcemia was found (Table 3). In subtle seizures most common abnormality was hyponatremia followed by hypoglycaemia. In tonic seizures most common abnormality was hypermagnesemia 18.91% followed by hypernatremia 16.2%, hypoglycaemia 16.2% (Table 4). In clonic seizures most common abnormalities were hypocalcemia 26.08% and hypoglycaemia 26.08%. In myoclonic seizures most common abnormality was hypoglycemia. No previous study regarding biochemical abnormality with type of seizures was found & so this data is need to be further evaluated.

DISCUSSION:

In our study male: female ratio was 1.89:1, which is similar to the result of Tanveer Nawab et al [8] & Tekgul H et al [9] which were 1.75 :1, 1.15:1 respectively. In our study maximum newborns were term babies (62.7%). Similar results were also seen in

Table 1: Co-relation of type of seizures with etiology (n=110).

Day	Birth asphyxia (n=45)		Sepsis (n=27)		RDS (n=18)		Bilirubin encephalopathy (n=8)		IDM (n=2)		Metabolic disorders (n=3)		Brain Malformation (n=2)		Unclassified (n=5)	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Subtle (n=45)	27	61.37	7	15.63	4	9	3	6.18	-	-	2	4.5	1	2.27	1	2.2
Tonic (n=36)	16	45.94	8	21.62	7	18.91	3	8.1	-	-	-	-	-	-	2	5.4
Clonic (n=23)	1	4.3	9	39.13	6	26.08	2	8.6	2	8.6	-	-	1	4.3	2	8.6
Myclonic (n=6)	1	16.66	3	50	1	16.66	-	-	-	-	1	16.66	-	-	-	-

Table 2: Co-relation of etiology with day of onset of neonatal convulsion (n=110).

Day	HIE (n=45)		Sepsis (n=27)		RDS (n=18)		Bilirubin encephalopathy (n=8)		Brain Malformation (n=2)		Metabolic disorders (n=3)		IDM (n=2)		Unclassified (n=5)	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Day 1 (n=53)	36	67.9	2	3.77	13	24.52	-	-	-	-	1	1.8	1	1.8	-	-
Day 2 (n=19)	8	42	3	15.8	3	15.8	2	10.52	2	10.52	-	-	1	5.2	-	-
Day 3 (n=11)	1	9.09	4	36.4	2	18.18	3	27.27	-	-	-	-	-	-	1	9.09
Day 4 (n=2)	-	-	1	50	-	-	-	-	-	-	1	50				
Day 5 (n=6)	-	-	3	50	-	-	1	16.66	-	-	1	16.66	-	-	1	16.66
Day 6 (n=2)	-	-	-	-	-	-	1	50	-	-	-	-	-	-	1	50
Day 7 (n=4)	-	-	3	7.5	-	-	1	25	-	-	-	-	-	-	-	-
Day 8 - 28 (n=13)	-	-	11	8.9	-	-	-	-	-	-	-	-	-	-	2	15.4

a study by Moayedi AR et al[10] which showed maximum cases were full term babies (81.2%) . Weight distribution: In our study 42.72% cases were of birth weight > 2500grams, 31.8% cases of 2500-1500 gm, 22.72% cases were of birth weight < 1500 gm while only 1.8% cases of were of birth weight < 1000 gm. This distribution was similar to Jasim et al 2[7], Sweta LM, et al [11], Sahana, et al 2014[6], which were 60%, 72% and 52% respectively for birth weight > 2500 gm.

Most common cause of neonatal seizures in present study was birth asphyxia 40.0% (45/100), second most common septicemia accounting for 24.54% (27/110) of cases. Third common cause was respiratory distress syndrome 16.36% (18/110). The least common cause was brain malformation 1.81% (2/110). These results were consistent with other studies like Shah G S[12] who found asphyxia was the most common cause (44%).

Table 3: Biochemical abnormalities in different types of seizures.

		Subtle N=45	Tonic N= 36	Clonic N= 23	Myoclonic N= 6
MAGNESIUM	NORMAL VALUE 1.6 -3.1 mg/dl N= 88	37 (82.2%)	26 (72.2%)	20 (86.95%)	5 (83.3%)
	HYPOMAGNESEMIA <1.6mg/dl N =7	4 (8.88%)	3 (8.33%)	0	0
	HYPERMAGNESEMIA >3.1 mg/dl N = 15	4 (8.88%)	7 (19.4%)	3 (13.05%)	1 (17.6%)
CALCIUM	NORMAL VALUE 0.8 – 1.45 mmol/L N =91	37 (82.1%)	32 (88.88%)	17 (73.91%)	5 (83.33%)
	HYPOCALCEMIA <0.8mmol/L N=17	6 (13.4%)	4 (11.11%)	6 (26.05%)	1 (16.66%)
	HYPERCALCEMIA >1.45 mmol/L N=2	2 (4.5%)	0	0	0
SODIUM	NORMAL VALUE 135 -145 mmol/L N=80	30 (66.7%)	27 (75%)	17 (73.91%)	6 (100%)
	HYPONATREMIA <135mmol/L N=16	9 (20%)	3 (8.3%)	4 (17.39%)	0
	HYPERNATREMIA >145mmol/L N=14	6 (13.4%)	6 (16.7%)	2 (8.69 %)	0
BLOOD SUGAR	NORMAL VALUE 40 -125 mg/dl N= 79	34 (75.5%)	27 (75.67%)	15 (65.21%)	3 (50%)
	HYPOGLYCEMIA <40 mg/dl N= 22	7 (15.5%)	6 (16.67%)	6 (26.08%)	3 (50%)
	HYPERGLYCEMIA >125 mg/dl N=9	4 (9%)	3 (8.10%)	2 (8.69%)	0

In the current study 5 cases of unknown etiology were due to lack of facility to diagnose. Onset of seizures : In our study maximum case of convulsion were seen in first 3 day of life 75.45% cases. Out of which 48.18% of total had convulsion of day 1 of life, 17.27% on day 2, 10% had on day 3 of life. 12% of total patients had convulsion between 4-7 day of life while 11.8% had convulsion between 8-28 days (late onset convulsion). This results was similar to AR Moayedi et al [10] in which 39% had seizures on day 1, 15.5% on day 2 and 12.7% on day 3, 12.7% between 4-7 day and 32.7% later. The study was similar to Adeebah et al [3], in which 50.8% of neonates had seizures within 3 days of age. Similar results were demonstrated by Sahana et al [6], Sabzehei et al [13], Fiaz et al [14].

In present study 75.45% cases had convulsion in first three days of life among them, 56% of birth asphyxia of which 69.8% cases present of day

Table 4: Biochemical abnormalities in different etiology of seizures.

		Birth Asphyxia N=45	Sepsis N = 27	RDS N=18	Bilirubin Encepha-lopathy N=8	Brain Malformation N= 2	IDM N=2	Metabolic DS N= 3	Unclassified N=5
MAGNESIUM	NORMAL VALUE 1.6 -3.1 mg/dl N = 87	37 78.86%	18 74%	16 88.9	6 66.7%	2 100%	2 100%	1 33.4%	5 100%
	HYPOMAGNESEMIA <1.6mg/dl N = 8	4 8.88%	4 11.11%	0	0	0	0	0	0
	HYPERMAGNESEMIA >3.1 mg/dl N = 15	4 8.88%	5 14.8%	2 11.11%	2 33.4%	0	0	2 66.6%	0
CALCIUM	NORMAL VALUE 0.8 – 1.45 mmol/L N = 91	38 84.4%	22 81.48%	15 83.3%	8 100%	2 100%	0	1 33.4%	5 100%
	HYPOCALCEMIA <0.8mmol/L N=17	5 11.9%	5 18.52%	3 16.67%	0	0	2 100%	2 66.6%	0
	HYPERCALCEMIA >1.45 mmol/L N=2	2 4.44%	0	0	0	0	0	0	0
SODIUM	NORMAL VALUE 135 -145 mmol/L N= 73	23 51.11%	20 74.07%	11 61.11%	8 100%	2 100%	2 100%	2 66.7%	5 100%
	HYPONATREMIA <135mmol/L N=16	8 17.7%	4 14.81%	3 16.66%	0	0	0	1 33.3%	0
	HYPERNATREMIA >150mmol/L N=21	14 31.12%	3 11.12%	4 22.23%	0	0	0	0	0
BLOOD SUGAR	NORMAL VALUE 40 -125 mg/dl N= 72	34 75.5%	12 44.44%	13 72.2%	6 75%	2 100%	0	0	5 100%
	HYPOGLYCEMIA <40 mg/dl N=28	8 17.77%	12 44.45%	4 22.22%	0	0	2 100%	2 66.7%	0
	HYPERGLYCEMIA >125 mg/dl N=10	3 6.6%	3 11.11%	1 5.55%	2 25%	0	0	1 33.3%	0

1 of life which was statistically highly significant.(p value<0.05). In late onset seizures, sepsis was the most common etiology. All patients of IDM presented within first 3 days. These findings were similar to Nawab et al February [8] in which on day 1,81.5% cases were of birth asphyxia, 3.4% cases of hypoglycaemia 5.1% due to other etiology and in late onset seizure (8-28 day) most common etiology was sepsis.

In subtle & tonic seizures birth asphyxia was observed to be the most common etiology followed by sepsis in clonic seizures most common etiology was sepsis followed by RDS. In myclonic seizures most

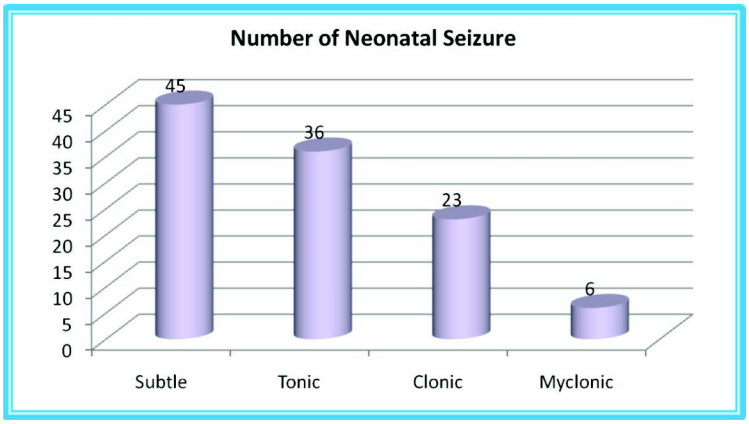

Figure 1: Type of Seizures (n=110).

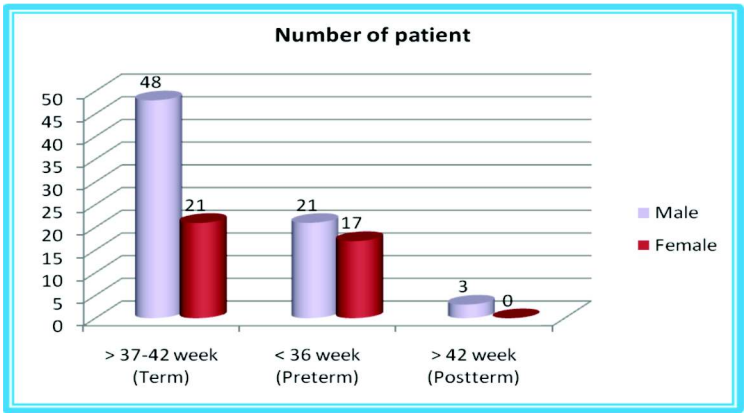

Figure 2: Gestational age and gender distribution of sample population (n=110)

common etiology was sepsis.

Most common biochemical abnormality was hypoglycemia 25.45% followed by hypocalcemia 15.45%. While other abnormalities were hyponatremia in 14.54%, hypernatremia in 12.5%, 13.6% hypermagnesemia and hypomagnesemia7.2% hyperglycemia 8 and hypercalcemia 1.8%. These finding were consistent with the observation of Fiaz et al [14] which were 23% for hypoglycaemia and 18% for hypocalcemia and Sabzehei MK et al [13] also demonstrated similar finding which were 19% for hypoglycaemia ,16.3% for hypocalcemia respectively. However these observations need further studies and confirmatory statistical analysis which were not applied here due to lack of ample sample size.

In patient of birth asphyxia 50% had no biochemical abnormality.Most common abnormalities were hypoglycaemia and hyponatremia followed by hypermagnesemia. Simultaneously multiple biochemical abnormalities were observed in 4.5% of HIE cases. With regard to sepsis 44% cases had no biochemical abnormality .Hypoglycaemia was most common abnormality followed by hypocalcemia 18.5% (44.44) which was highly significant. In 61.11% cases of RDS no biochemical abnormalities were seen. Most common finding was hypernatremia (22.22%) and hypoglycaemia (22.22%). In bilirubin encephalopathy 75% had no biochemical abnormality. Hypoglycaemia was the only biochemical abnormality in rest 25%. In cases of IDM all patients had hypoglycaemia and hypocalcemia.

CONCLUSION:

The recognition of the etiology for neonatal seizures is often helpful with respect to prognosis and treatment. The most common etiology for neonatal seizure is still hypoxic ischemic encephalopathy which can be prevented if proper antenatal and perinatal care is given. The time of onset of neonatal seizure many time indicates toward specific etiology (example; Onset of seizures within first three days is significantly associated with birth asphyxia). Biochemical disturbances occur frequently in

neonatal seizures either as an underlying cause or as an associated abnormality. Early recognition and treatment of biochemical disturbances are essential for optimal management and satisfactory long term outcome.

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