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Changing Epidemiology and Clinico-Etiological Profile of Neonatal Seizures in a Tertiary Care Teaching Hospital after a Period of 20 Years: A Comparative Study

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Abstract

Background: Seizures are the most frequent sign of neurological dysfunction in the neonatal period. We studied the incidence, clinical types and etiological factors in neonatal seizures and change/s in the epidemiology of neonatal seizures in the last 2 decades by comparing data from a study done 20 years earlier. *Methods*: It was a prospective observational cohort study conducted in a tertiary care teaching hospital in north India from November 2016 to October 2017. 7303 neonates were recruited and of these, 66 (0.9%) had clinical seizures at the time of presentation. Complete demographic details, relevant clinical information and investigations were recorded in the pretested Performa and analysed. *Results*: The overall incidence of neonatal seizures was 0.9% (66/7303). The incidence of seizures was 0.44% (29/6589) among Inborn and 5.1% (37/714) among Out born neonates. Incidence in ELBW, VLBW, LBW and normal birth weight was 2.5%, 4.4%, 0.62% and 0.84% respectively. Male preponderance was observed with a male to female ratio of 1.44:1. Forty-five (68.18%) neonates had seizures in the first 96 hours of life. Out of 142 seizure episodes in 66 neonates, subtle seizure 68 (47.9%) were the most common clinical type followed by focal clonic 27 (19%) and multifocal clonic 27 (19%). Etiological profile revealed perinatal asphyxia in 14 (21.2%), meningitis in 13 (19.7%), hypocalcemia in 12 (18.2%), hypoglycemia in 8 (12.1%), intracranial bleed in 6 (9.1%), hypernatremia in 4 (6.1%) and acute bilirubin encephalopathy in 4 (6.1%). IEM (1.5%) and CNS malformation (1.5%) were observed in 1 patient each. Cause of seizures could not be ascertained in 3 (4.5%) patients. *Conclusions*: Perinatal asphyxia and HIE still remains the commonest cause of neonatal seizures despite significant advancements in perinatal and neonatal care although incidence has decreased when compared to the statistics 20 years back. Biochemical abnormalities still are an important and manageable cause of neonatal seizures.

Keywords: Neonatal Seizures; Perinatal Events; HIE; Biochemical.

Introduction

Neonatal seizures are one of the few neonatal neurologic conditions that require immediate medical attention. Seizures are most frequent sign of neurological dysfunction in the neonatal period. Neonatal seizures can be defined clinically as paroxysmal alteration in motor activity, behaviour or autonomic function that results from abnormal electrical activity of brain in neonatal period [1]. Seizures are more frequent in neonatal period than any other period of life due to predominace of excitatory influences in the developing brain.

Knowledge of etiology of neonatal seizures and institution of etiology specific therapy is essential not only for the control of seizures but also to achieve better neurological outcome in long term. There have been significant improvements in maternal and child health over past two decades in India. Early and better management of obstetrical emergencies has influenced

the incidence of birth asphyxia and seizures. Similarly the implementation of standard protocols of NRP for resuscitation, advancements in intensive care services and better management of sick as well as preterm neonates is expected to be reflected, in the changing epidemiology and outcome of various neonatal problems including neonatal seizures. The present study was a comparative study to determine any change in the epidemiology of neonatal seizures during the last 2 decades by comparing the observations of this study to a similar study conducted in the same institution 20 years back

Material and Methods

The present study was an observational prospective cohort study conducted from November 2016 to October 2017, in a tertiary care level teaching hospital. After approval from the IEC and obtaining written and informed consent from parents, all the subjects from birth to 28 days of life who presented with clinical seizures, observed and documented by trained resident doctor on duty were recruited in the study. Neonates who were admitted with complaints of abnormal body movements by caretaker and had no seizures during the hospital stay, term neonates more than 28 days at time of presentation and preterm neonates more then 44 weeks of PMA were excluded.

All demographic and clinical information were recorded in a pretested performa. Antenatal information such as maternal age, gravida and parity, booked/unbooked status, no of antenatal visits, period of gestation, history of systemic illness, drug intake during pregnancy, history of infections including TORCHES group, PIH and GDM were recorded. History of perinatal events such as term/ preterm labour, antenatal steroids with time of administration, onset of labour pains, decreased fetal movements, APH, PROM, maternal fever, chorioamnionitis, foul smelling or meconium stained liquor were also recorded. Labour and resuscitation room events such as duration of labour, presentation, mode of delivery, forceps or ventouse application, emergency or elective LSCS, perinatal asphyxia, traumatic delivery, resuscitation records and apgar scores, indication for NICU admission, duration of hospital stay, complications and condition at the time of dischage were recorded in the performa. Baseline characteristics of all neonates e.g. age at the time of admission, sex gestational age and birth weight were documented. Weight at the time of admission, length and head circumference were recorded by standard techniques. Lubchenco intrauterine growth charts were used for intrauterine growth status to classify neonates in LGA, AGA and SGA. Ponderal index was used to classify SGA babies in symmetrical or asymmetrical IUGR.

All newborn studied were subjected to estimation of blood glucose, total and ionised calcium levels, phosphorus, alkaline phosphatase, serum sodium, potassium, chloride, magnesium and cranial ultrasound. Additional investigations were guided by history, clinical examination and previous investigations and included serum bilirubin, blood group, DCT, sepsis screen, blood culture, CSF examination, renal or liver function tests, screening for congenital infections (TORCHES), screening for IEM and CT or MRI of brain as indicated.

Seizures as observed at the time of presentation by the trained resident doctor on duty were recorded and classified according to Volpe's [10] classification. The duration, clinical type and medications given were recorded for each seizure episode.

Results

A total of 7303 neonates were enrolled in the present study. Inborns were the patients born at our facility in KNH while those refferred to IGMC from elsewhere were labelled as Outborns. Out of 7303, 6589 (90.22%) were Inborn and 714 (9.78%) were outborn babies, of these 66 neonates presented with seizures, 29 (43.9%) from Inborn group and 37 (56.1%) from outborn group. Overall incidence of neonatal seizures was 0.9% being higher in Outborn group (5.1%) as compared to Inborn group (0.44%) and the difference was statistically significant (p value <0.01).

Out of total 7303 neonates studied, 3927 (53.77%) were males and 3376 (46.23%) were females. Incidence of neonatal seizures was 0.99% and 0.79% in males and females respectively with a male to female ratio of 1.44:1 and the difference was not stastically significant. 45 (68.18%) manifested seizures within first 96 hours of life while 58 (87.8%) had seizures within first 7 days of life.

Based on the gestational age, the subjects were divided into 4 subgroups, Early Preterm (<34 completed weeks), Late preterm (34-36+6weeks), Fullterm (37-41+6weeks) and Post term (>42 completed weeks). Out of 7303, 454 (6.22%) were early preterm, 1300 (17.8%) were late preterm, 5530 (75.22%) were full term and 19 (0.26%) were post term neonates. The overall incidence of neonatal sizures was 3.08%, 0.69% and 0.78% in the early preterm, late preterm and fullterm neonates, which was significantly

higher in early preterms as compared to late preterm and fullterm neonates (p value<0.0001). Further analysis revealed that among the Inborns (n=6589) the incidence was significantly higher in early preterms(2.3%) as compared to late (0.54%) and fullterm (0.29%) (p value <0.0001). Among the Outborn group (n=714) incidence was 5.2%, 1.6% and 6.7% in early, late and fullterm group respectively which was significantly higher in both early preterm and fullterm groups as compared to late preterm (p value <0.05).

Out of total 7303 neonates, 4634 (63.45%) were of normal birth weight, 2381 (32.6%) were LBW, 248 (3.4%) were VLBW and 40 (0.55%) were ELBW. Overall incidence of neonatal seizures was 0.84%, 0.63%, 4.4% and 2.5% in Normal, LBW, VLBW and ELBW groups respectively. The incidence was significantly higher in VLBW and ELBW group (with p value <0.001) as compared to other two groups. Among the Inborns (n=6589), the incidence in Normal weight, LBW, VLBW and ELBW groups was 0.3%, 0.3%, 4.4% and 3.2% respectively. Among the Outborn (N=714) the incidence in Normal weight, LBW and VLBW groups was 7.2%, 2.9%, and 4.5% respectively.

In the present study, 53 (80.3%) subjects had only single clinical seizure type whereas 13 (19.7%) had multiple types of seizures. Of the total 142 seizure episodes, 68 (47.9%) were subtle, 27 (19%) were focal clonic, 27 (19%) were multifocal clonic, 17 (12%) were generalised clonic and only 3 (2.1%) presented with myoclonic seizures.

The analysis of etiological factors revealed perinatal asphyxia in 14 (21.2%), CNS infection in 13 (19.7%), hypocalcemia in 12 (18.2%), hypoglycemia in 8 (12.1%), intracranial bleed in 6 (9.1%) hypernatremia in 4 (6.1%), acute bilirubin encephalopathy in 4 (6.1%), IEM in 1 (1.5%) and CNS malformation in 1(1.5%) patient whereas cause of seizures could not be ascertained in 3 (4.5%) subjects.

Further analysis of the cause of seizures among the Inborns (n=26) revealed perinatal asphyxia in 8 (27.6%), CNS infection in 5 (17.2%), hypoglycemia in 4 (13.8%), hypocalcemia in 4 (13.8%) IC Bleed in 3 (10.3%), hypertnatremia in 2 (6.9%) and acute bilirubin encephalopathy in 1 (3.4%). Among the Outborns(n=37) etiology of seizures included hypocalcemia in 8 (21.6%), CNS infection in 8 (21.6%), perinatal asphyxia in 6 (16.2%), hypoglycemia in 4 (10.8%), IC Bleed in 3 (8.1%), acute bilirubin encephalopathy in 3 (8.1%), hypernatremia in 2 (5.4%), IEM in 1 (2.7%) and CNS malformation in 1 (2.7%). Cause of seizures could not be ascertained in 2 (6.9%) inborn and 1 (2.7%) ouborn patients. The commonest cause of seizures was perinatal asphyxia (27.6%) among Inborns and CNS infection (21.6%) and hypocalcemia (21.6%) in among Outborns.

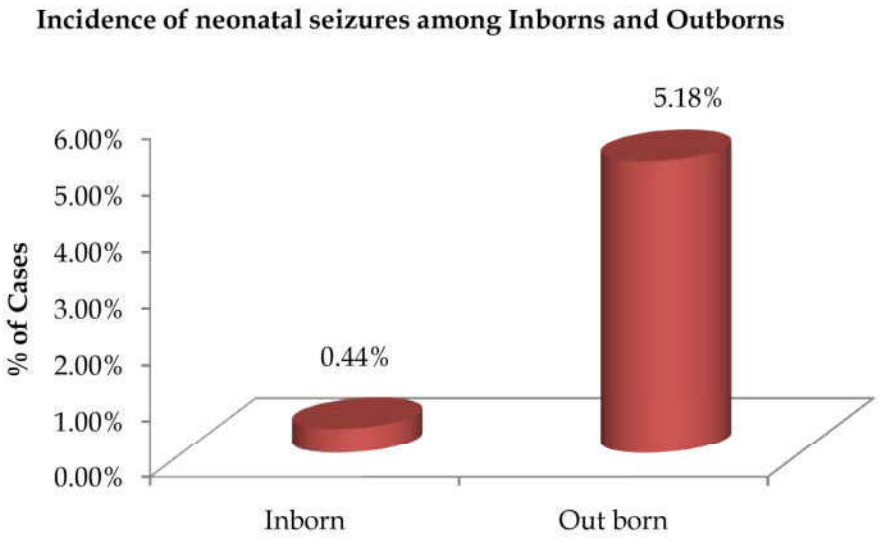
There were 13 (19.7%) cases with meningitis, 8 (61.54%) from outborn and 5 (38.46%) in the inborn

Table 1: Etilogical profile of seizures in Outborns vs Inborns

Etiology of Seizures	Inborn/Out born		Total
	Inborn	Out born	
Perinatal asphyxia	8	6	14
	27.6%	16.2%	21.2%
Hypoglycemia	4	4	8
	13.8%	10.8%	12.1%
Hypocalcemia	4	8	12
	13.8%	21.6%	18.2%
Hypernatremia	2	2	4
	6.9%	5.4%	6.1%
Meningitis/sepsis	5	8	13
	17.2%	21.6%	19.7%
Acute bilirubin encephalopathy	1	3	4
	3.4%	8.1%	6.1%
IC Bleed	3	3	6
	10.3%	8.1%	9.1%
IEM	0	1	1
	0.0%	2.7%	1.5%
Structural malformation	0	1	1
	0.0%	2.7%	1.5%
Could not be found	2	1	3
	6.9%	2.7%	4.5%
Total	29	37	66
	100.0%	100.0%	100.0%

Table 2: Comparision of results to similar studies

	Sood A et al 1997	Sudia S et al. 2013-14	Bagla et al. 2015-16	Present study 2016-17
Incidence %	1.3	2.16	1.19	0.9
Male:female	-	1.73:1	2.27:1	1.44:1
Commonest seizure type	Subtle(39%)	Subtle(63.33%)	Subtle(38.9%)	Subtle(47.9%)
Commonest Causeof seizures	Perinatal asphyxia(38.9%)	Perinatal asphyxia (53%)	Perinatal asphyxia(36.1)	Perinatal asphyxia(21.2%)
Commonest biochemical abnormality	Hypocalcemia (11.5%)	Hypocalcaemia (6%)	Hypoglycemia (8.3%),	Hypocalcemia (18.2%)
CNS infection	20.34%	10%	22.2%	19.7%

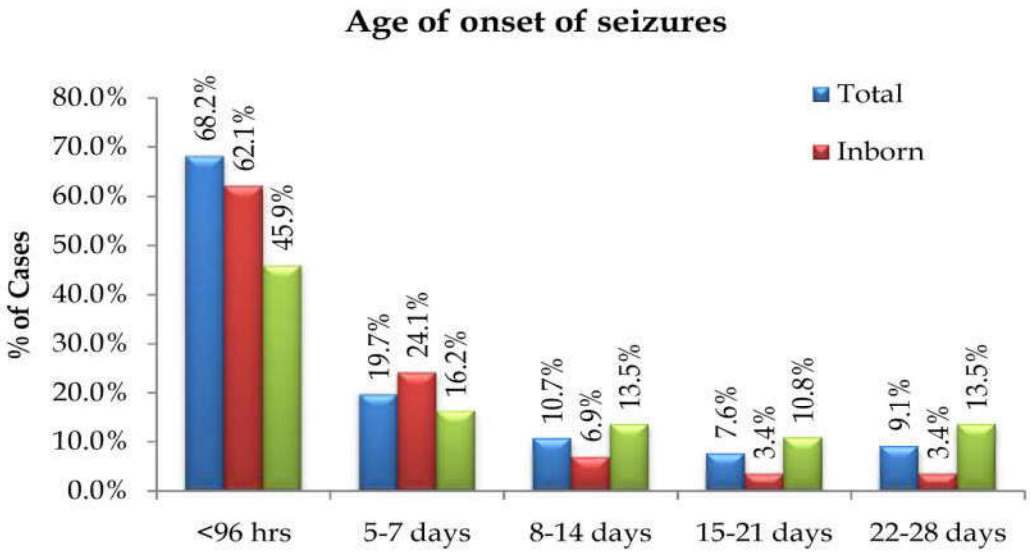


Graph 1:

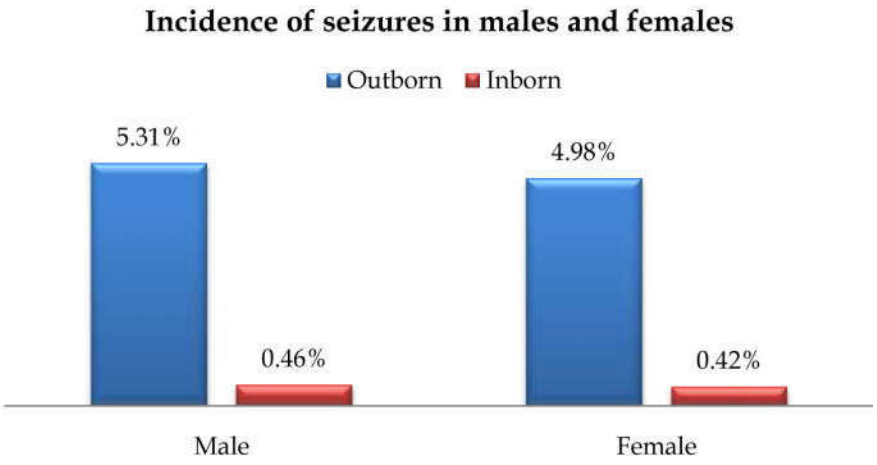
group, blood culture revealed growth in 8 (61.5%) patients. NLF was present in 3 (37.5%), Burkholderia cepacia in 2 (25%) and 1 (12.5%) each for Acinetobacter, E coli and Klebsiella spp. 1 patient had evidence of hydrocephalus on neuroimaging.

Biochemical abnormalities were present in total 31 (46.9%) patients in present study. In 21 (31.8%) patients biochemical abnormalities were the primary cause of seizure whereas in 10 patients these were associated with other conditions (6 patients with perinatal asphyxia, 3 with meningitis and 1 with IC Bleed). Hypocalcemia was the most common metabolic abnormality associated with seizures in the present study and was observed in 12 cases (18.2%). Early onset hypocalcemia was documented in 4 (33.3%), whereas late onset hypocalcemia was observed in 8 (66.7%) cases. 10 (83.33%) cases had only hypocalcemia while 2 (16.66%) had hypomagnesemia associated with hypocalcemia. Vitamin D levels were done in all patients with primary hypocalcemic seizures, 6 (50%) neonates were vitamin D deficient, 2 had insufficient level (16.7%) and 4 (33.3%) had normal levels of viamin D. 1 (8.3%) patient had primary hypoparathyroidism. Hypocalcemia was the commonest biochemical abnormalty in perinatal asphyxia and was documented in 3 (21.2%) patients. Hypoglycemia was observed in 8 cases (12.1%) as primary cause of seizures (5 neonates were preterm while 3 were term). It was also documented as associated abnormality in 2 cases with meningitis and 1 case of perinatal asphyxia.

Hypernatremia was found in 4 (6.1%) patients and all 4 had hypernaremic dehydration with pre renal AKI. Hyperphosphatemia and hypomagnesemia was observed in 2 patients each (3%) and hyponatremia was observed in only 1 (1.5%) subject. Intracranial bleed was observed in 6 cases (9.1%), 2 had classic HDN, 1 had CNS infection and 3 preterm neonates had spontaneous intraventricular bleed. 1 patient with IEM (Non ketotic hyperglycinemia) had seizures refractory to poly AED.



Graph 2:



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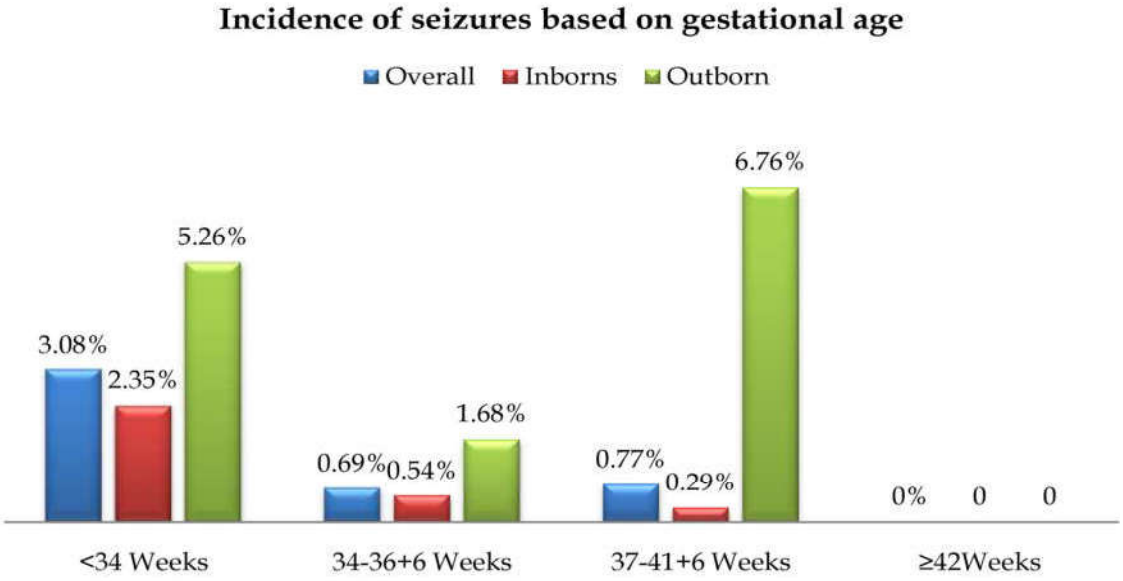

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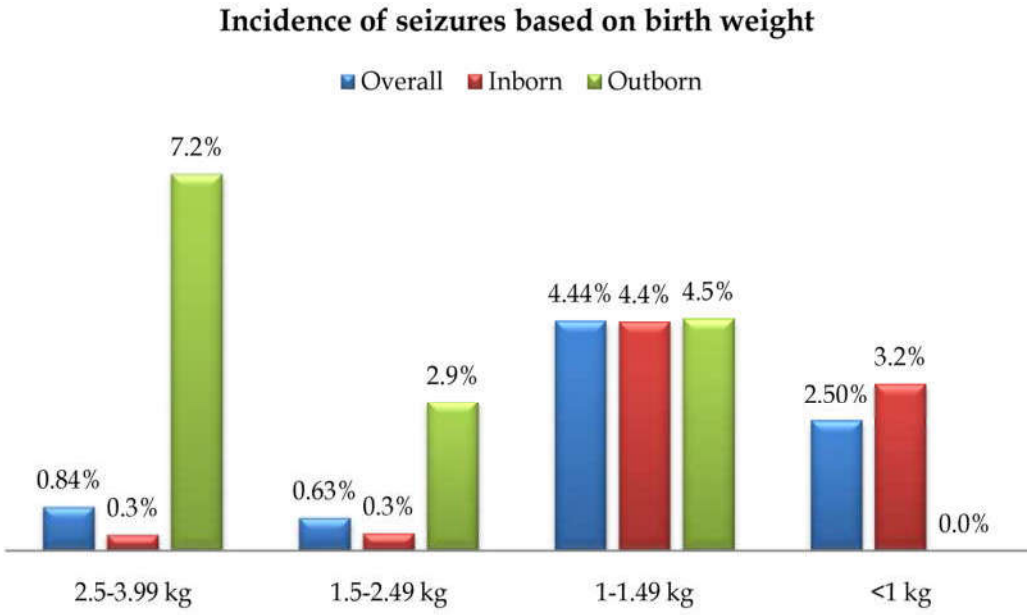

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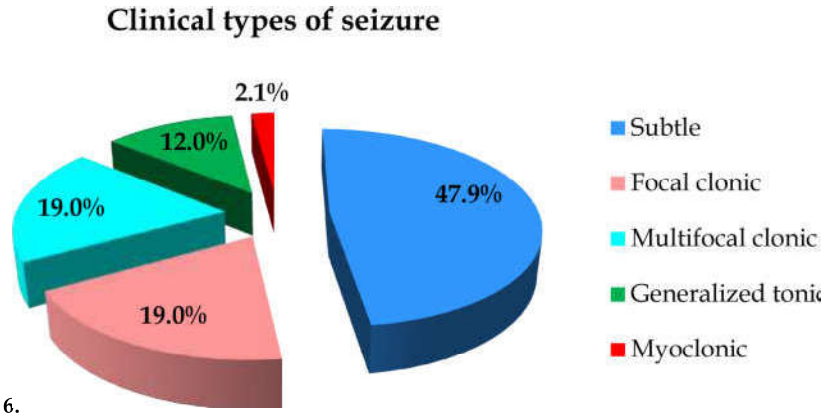
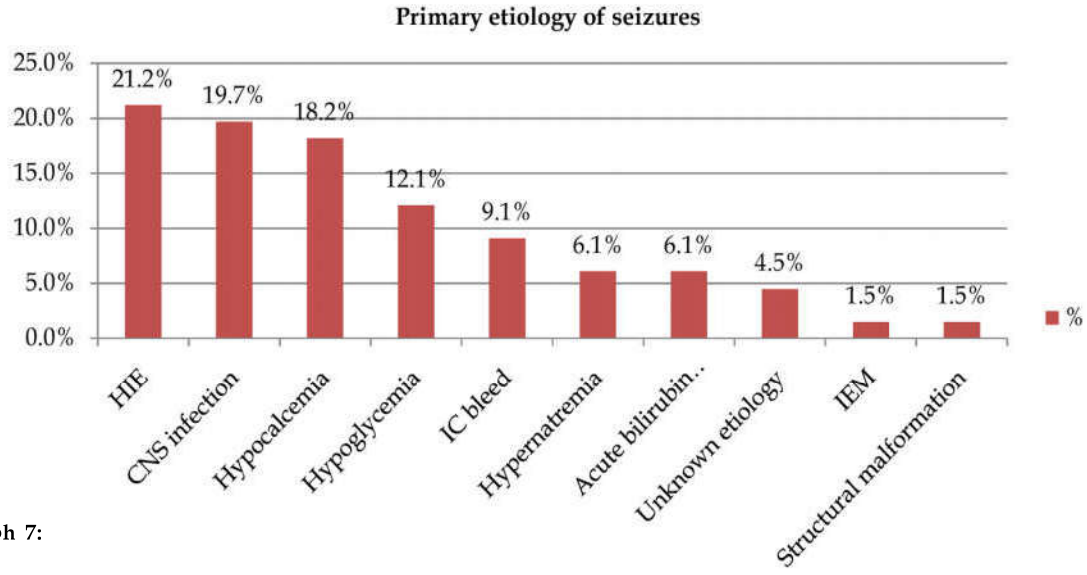


Graph 6.



Graph 7:

Discussion

Overall incidence of neonatal seizures was 0.9% (Inborns-0.44%, Outborns-5.1%) in the present study. NNPD [6] data from 18 tertiary care units across India has reported incidence of 1.03% which is comparable to this study. Similar results were also reported by Kumar et. al. (1.16%) [3] Sudia S et. al. (1.17%) [4] and Bagla J et. al. (1.19%) [5]. The incidence of neonatal seizures has declined in our institution over last 2 decades when compared to the results of Sood A et. al. [2] from 2.14% to 0.9% which can be partly attributed to significant improvement in neonatal and intensive care services during this period.

The Incidence of neonatal seizures observed in the present study was 3.08%, 0.69% and 0.77% in Early, Late preterm and Full term neonates respectively whereas NNPD [6] has reported incidence of 0.84% in term and 2.08% in preterm neonates which is comparable to our study.

Overall incidence of neonatal seizures observed in present study was 0.84%, 0.63%, 4.4% and 2.5% in Normal, LBW, VLBW and ELBW groups respectively. NNPD [6] has reported incidence of 0.8% in normal and 3.61% in VLBW neonates which is comparable to our study.

Incidence of neonatal seizures in the present study was 0.99% and 0.79% in males and females respectively with a male to female ratio of 1.44:1, whereas a much higher incidence in males as compared to females was reported by Sudia S et. al. [5] (1.73:1) and Bhatt S et. al. [7] (2.37:1). This male preponderance reported in some studies can be partly due to early medical attention seeking behaviour for male babies.

Out of the total 142 seizure episodes, 68 (47.9%) were subtle, 27 (19%) were focal clonic, 27 (19%) were multifocal clonic, 17 (12%) were generalised clonic and 3 (2.1%) were myoclonic seizures. The studies conducted by Mizrahi and Kellaway [8], Scher et. al. [9], Volpe JJ et. al. [10] and Bagla J et. al. [5] had reported subtle seizures as the most common clinical type of neonatal seizures whereas Kumar et. al. [3] have reported multifocal clonic as the most common clinical type.

Incidence of perinatal asphyxia and HIE as cause of neonatal seizures as reported by various studies like Sood et. al. [2] (38.9%) and Kumar et. al. [3](44.4%), Legido A et. al. [11] (35%) is more as compared to present study (21.2%) which can be partly explained by improvements in perinatal and neonatal care during the last 2 decades.

Meningitis was documented in 13 (19.7%) patients in the present study which is comparable to reported by Sood A et. al. [2] while Sudia et. al. [4] (10%) and Kumar et. al. [3] (7.77%) reported a lower incidence of CNS infection. The higher incidence of meningitis in present study may be due to the fact that our institution serves as referral centre for sick neonates.

Hypocalcemia was the most common primary metabolic abnormality responsible for seizures in the present study and was observed in 12 (18.2%) cases. Similar results had been observed by Kumar et. al. [3] (24.7%). In the present study hypoglycemia was observed in 8 (12.1%) patients which is comparable with Sood et. al. [3] and Kumar et. al. [3]. Hypernatremia was observed in 4 (6.1%) patients and all 4 subjects had hypernatremic dehydration with pre-renal AKI. Madhusudan K et. al. [14] reported hypernatremia in 3 cases (2.5%) which is comparable to the present study.

Neurosonography revealed IC Bleed in 6 (9.1%) cases in this study which is comparable with results of Bushra et. al. [13] (9%) Sahana et. al. [12] in (5%). Cause of seizures could not be found in 4.5% cases in present study which is comparable to results of Sahana et. al. [12] (4.58%).

Comparison of similar studies with the results of the present study, it is evident that the incidence of perinatal asphyxia has decreased in our institution but the metabolic derangements and CNS infection are still responsible for a good proportion of cases of neonatal seizures.

Conclusion

We conclude that incidence of perinatal asphyxia as cause of neonatal seizures has decreased significantly in last 20 years from 38.9% to 21.2%. Incidence of CNS infections continue to be still high (19.7% in the present study as compared to 20.3% in 1997). Therefore there is need to reinforce strict infection control measures, hygiene and to promote exclusive breast feeding. Late onset hypocalcemia is the another important cause of neonatal seizures in the late neonatal period (3rd and 4th week), therefore calcium and vitamin D supplementation to both mother during pregnancy and lactation as well as baby should be advocated and instituded. 2 of our outborn, home delivered, subjects had IC Bleed due to classic HDN, so hospital delivery should be encouraged and all neonates must be administered vitamin K at birth. Where other investigations fail to reveal a cause or metabolic cause is suspected,

screening for IEM should be done. Clinical monitoring of seizures should be supplemented with video EEG monitoring if possible to detect only electrographical seizures.

Conflict of Interest: None

Financial Suppoert: None

Ethical responsibilities of authors: The paper is our original unpublished work and it has not been submitted to any other journal for reviews.

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