Predisposing Risk Factors for Neonatal Seizures in Low Birth Weight Babies: Case Control Study

Uday C. Rajput[1*], L. S. Deshmukh[2]

[1]Assistant Professor, Department of Pediatrics, Government Medical College Miraj, Maharashtra, INDIA.

[2]Professor, In-charge, Neonatal Unit, Government Medical College, Aurangabad, Maharashtra, INDIA.

[*]Corresponding Address:

drudayrajput@gmail.com

Research Article

Abstract: **Objective:** To study the predisposing risk factors for neonatal seizures in low birth weight babies. **Design:** Prospective case control study. **Settings:** Neonatology Unit at tertiary care hospital. **Outcome measures:** Association of risk factors like preconceptional, postconceptional, antepartum, intrapartumand neonatal with neonatal seizures in low birth weight babies. **Results:**680 low birth weight neonatal babies were divided into two groups,340 low birth weight babies with neonatal seizures served as cases , 340 low birth weight babies matched for gestation, weight and sex without any seizures served as controls. Gestational age group of 34-37 weeks and birth weight between 1500-1750 gms had highest frequency of seizures 39.83% and27.80%respectively.All pre-conceptional factors, consanguinity, maternal height < 140 cm, maternal weight < 40 kg were significant risk factors for neonatal seizures. Unregistered/unbooked pregnancies, pre-eclampsia, eclampsia and maternal anemia were significant risk factors for neonatal seizures. Antenatal factors, magnesium sulphate to mother and maternal fever were significantly associated with neonatal seizures except premature rupture of membrane ($p>0.05$) and general anaesthesia ($p>0.05$).All intranatal factors were significantly associated with risk of neonatal seizures except cephalic, non-cephalic presentation ($p>0.05$) and induced vaginal delivery ($p>0.05$).All neonatal factors were significantly associated with risk of neonatal seizures except for sex, SGA and sepsis ($p>0.05$). **Conclusion:** We conclude that having the knowledge of these factors will help in careful monitoring for occurrence of seizures in low birth weight babies and proper early treatment. This will also help in reducing neonatal mortality.

Keywords: Neonatal Seizures, riskfactors, low birth weight.

Introduction

Seizures in the newborn period constitute a medical emergency and are the most common neurological symptom in the neonatal period. Seizures have adverse effect on neurodevelopment outcome of babies. Frequency of seizures is especially high in low birth weight preterm babies. Pathophysiology and risk factors for seizures differ in low birth weight preterm and term babies. In low birth weight babies areas of brain affected are also different as compared with term, specifically subcortical and white matter. Numerousprenatal, intranatal, postnatal factors has been implicated in association with seizures mainly in term babies. Although seizures in low birth weight babies are extremely important as they are usually subtle, which are likely to miss and associated with poor neurological outcome. To date there are only few studies to assess the risk factors especially in preterm low birth weight babies. Saliba *et al*[1] in large population based study has shown, strongest risk factor for seizures in low birth weight babies is decreasing birth weight (odds ratio 9.1) followed by male gender (odds ratio 1.8). Kohelet *et al*[2]also shown similar results. We undertook this case control study to evaluate the association of predisposing risk factors for seizures in low birth weight babies. As knowing the risk factors will help in prediction and early intervention of seizures in low birth weight babies.

Materials and Methods

This case control study was conducted in the Neonatal Intensive care of Government Medical College, a tertiary care hospital.

Selection of Subjects

The study was conducted on a total of 680 low birth weight neonatal babies, admitted to Neonatal Unit from December 2006 to December 2007. A total of 340 low birth weight babies with neonatal seizures served as cases .Seizures occurring at any time from birth to 28 day of life in hospital and witness by staffs or doctors were included in case group. Another 340 low birth weight babies matched for gestation, weight and sex without any seizures served as controls. Neonates with history of seizures but no directly observed clinical seizures were excluded from the study. Babies with birth weight less than 2500gms were termed as low birth weight. Very low birth weight was defined as less than 1500gms.Pretem birth was defined as any birth occurring before 37 weeks of gestation

Data sources

A structured from was filled for each case and control. Detail data was recorded for both case and control included parentral information, maternal pregnancy history, antenatal care, mother's age and parity. Antenatal

and intrapartum data had been recorded from the obstetric notes of the mothers. Along with above data detailed postnatal history and if any investigations done were recorded. Clinically seizures were chatageriozed into subtel, tonicfolcal, tonic generalized, clonic focal and clonic multifocal. Preconceptional risk factors studied were consanguinity, maternal height, maternal weight. Postconceptional risk factors studied were unregisterded, unbooked pregnancy, preeclampsia, ecclampsia, antepartumhaemorrage, maternal anemia. Antepartum risk factors studied were premature rupture of membranes, maternal fever, general anesthesia, magnesium sulphte. Intrapartum risk factors studied were presenting part, mode of delivery, place of delivery, meconium stained amniotic fluid. Neonatal risk factors studied were sex, need for resuscitation, small for gestation, respiratorydistress, jaundice, sepsis, polycythemia, necrotizingenterocolitis. In cases group, treatment details were recorded with special emphasis on number of anticonvulsant drugsrecived. Thorough neonatal examination was carried out at the time of admission and discharge. Babies were followed up till the time of discharge. Outcome was noted with reference to abnormal neurological examination at discharge or mortality.

Statistical Analysis:

The sample size was determined by carrying out a pilot study of risk factors on 80 newborn babies. The sample size was calculated to achieve a confidence interval (CI) of 95% and power of 80%. Calculated sample size was approximately 320 cases and 320 controls. 'P' value less than 0.05 was taken as statistically significant. Mean, averages, standard deviations and Odd's ratios were calculated for various parameters and risk factors. Calculations were done by using software Epi Info 2002. The approval of the ethical committees was obtained before the start of the study.

Results

During study period a total of 680 low birth weight babies were admitted to NICU. Out of which 340 low birth weight babies with neonatal seizures served as cases while another 340 low birth weight babies matched for gestational age and sex served as controls. Table I shows, cases and controls were comparable in terms of mean gestational age, mean birth weight and sex ratio. Mean day of onset of seizure was 5.5th day. Mean duration of hospitalization was more in cases as compared to controls. Most common type of seizures observed were subtle (50.26%) while clonic focal seizures (06.14%) were least common. A significantly higher incidence of seizures are associated with preterm gestational age .Gestational age group of 34-37 weeks has highest frequency of seizures and lowest frequency being in a group of 28-30 weeks. Highest frequency of seizures was observed in a babies having birth weight between 1500-1750 gms which was 27.8% (Refer Table II) Table III shows all preconceptional factors are significantly associated with neonatal seizures($p < 0.05$). All postconceptional factors are significantly associated with neonatal seizures except antepartum hemorrhage ($p>0.05$) Table V shows all antepartum factors are significantly associated with neonatal seizures ($p<0.05$) except premature rupture of membrane ($p>0.05$) and general anesthesia to mother ($p>0.05$). All intrapartum factors are significantly associated with neonatal seizures except cephalic, noncephalic presentation and induced vaginal delivery ($p>0.05$) {Refer table VI}. Table VII shows all neonatal factors are significantly associated with neonatal seizures except sex, small for gestational age and sepsis ($p>0.05$).

Discussion

Majority of low birth weight babies with risk factors had seizures during neonatal period. The study was able to demonstrate association of many preconceptional, postconceptional, antepartum, intrapartumand neonatal risk factors with neonatal seizures. The major strength of present study was large sample size with properly matched cases and controls. Limitation of our study was, we were not able to study the effect and association of risk factors with seizures in babies having neurological pathology like intra cranial bleed, meningitis, anomalies ect. But this data would not have any effect on association of risk factors we have studied. In our study highest frequency of seizures were observed among the gestational age group of 34-37 weeks (39.83%). Similar results were found in study by Aprino *et al*[3]. However, Kohelet *et al*[2] observed a significantly higher incidence of seizures with decreasing gestational age. (Refer Table II) Though, statistically increased risk of seizures among the premature infant is not surprising because premature infants are frequently exposed to the conditions that exposed them to damage or disruption of brain development,1 our observations did not support this hypothesis. In our study we did not observed any trend of seizures related to birth weight. In our study highest frequency of seizures was observed in babies having birth weight between 1500-1750 gms (27.80%){Refer Table II}.However, Kohelet *et al*[2] and Saliba *et al*[1] reported increased incidence of seizures with decreasing birth weight. This effect is probably related to prematurity. In our study we did not observed any correlation of seizures with birth weight, this could be chiefly due to small numbers of babies weighing < 1000 gms.

Table 1: General characteristics

Characteristics	Cases	Controls
Gestational age (wks.) Mean ± S.D.	34.84 ± 3.5	34 ±3.5
Sex Ratio : Male: Female	1.07:1	1.08:1
Birth weight (gms)		
Mean	1647.47	1646.70
Range	760-2460	800-2480
S.D.	±672.68	±402.59
Duration of Hospitalization (Days)		
Mean	10.52	8.62
Range	1-43	1-32
S.D.	±7.6	±5.6
Day of onset of seizure		
Mean	5.5	--
Range	1-17	

SD: Standard Deviation

Table 2: Frequency of neonatal seizures according to gestatinal age and birth weight

Gestational age (Wks.)	Subtle n(%)	Tonic focal n(%)	Tonic generalized n (%)	Clonic focal n(%)	Clonicmutifocal n(%)	Total n(%)
28-30	05(14.70)	14(41.17)	06(17.64)	06(17.64)	03(08.80)	34(09.09)
30-32	15(28.30)	19(35.84)	10(18.86)	03(05.66)	06(11.32)	53(14.17)
32-34	20(36.36)	14(25.45)	08(14.54)	06(10.90)	07(12.72)	55(14.70)
34-37	83(55.70)	21(14.09)	20(13.42)	04(02.68)	21(14.09)	149(39.83)
> 37	65(78.31)	02(02.40)	07(08.43)	04(04.81)	05(06.02)	83(22.19)
Gestational age (Wks.)						
28-30	05(14.70)	14(41.17)	06(17.64)	06(17.64)	03(08.80)	34(09.09)
30-32	15(28.30)	19(35.84)	10(18.86)	03(05.66)	06(11.32)	53(14.17)
32-34	20(36.36)	14(25.45)	08(14.54)	06(10.90)	07(12.72)	55(14.70)
34-37	83(55.70)	21(14.09)	20(13.42)	04(02.68)	21(14.09)	149(39.83)
> 37	65(78.31)	02(02.40)	07(08.43)	04(04.81)	05(06.02)	83(22.19)

Preconceptional Risk Factors

Consanguinity was a significant risk factor for seizures but could not find any study with similar observation. However, this association could be explained on the basis of higher incidence of inherited CNS disorders and malformations as well as inborn errors of metabolism.

Table 3: Preconceptional risk factors for neonatal seizures:

Risk factor	Cases (n=340) n (%)	Controls (n=340) n (%)	Odds ratio	95% C.I.	'p' value
Consanguinity					
▪ Yes	187(55.00)	114(33.52)	2.42	1.79-3.34	< 0.05
▪ No	153(45.00)	226(66.47)			
Maternal height < 140 cm					
▪ Yes	122(35.88)	94(27.64)	1.46	1.04-2.05	<0.05
▪ No	218(64.11)	246(72.35)			
Maternal weight < 40 kg.					
▪ Yes	193(56.76)	150(44.11)	1.66	1.21-2.28	<0.05
▪ No	147(43.23)	190(55.88)			

In our study maternal height < 140 cm was a significant risk factor for seizures. Similar observations were reported by Nadia *et al*[4] and Ellis *et al*.[5] In our study maternal weight < 40 kg was a significant risk factor for seizures. To our knowledge no other study had reported association of maternal weight with neonatal seizures.

In our study unregistered and unbooked pregnancies were significantly associated with neonatal seizures .Similar observations were noted by Nadia *et al*[4], Ellis *et al*[5] and Aprino *et al*[3].In our study incidence of antepartum hemorrhage (APH) was higher in cases as compared to controls. However, it did not reached statistical significance.

Postconceptional Risk Factors

Table 4: Postconceptional risk factors for neonatal seizures

Risk factor	Cases (n=340) n (%)	Controls (n=340) n (%)	Odds ratio	95% C.I.	'p' value
Unregistered Pregnancies					
▪ Yes	157(46.17)	39(11.47)	6.62	4.38-10.04	< 0.05
▪ No	183(53.82)	301(90.88)			
Unbooked pregnancies					
▪ Yes	211(62.05)	125(36.76)	2.81	2.04-3.89	< 0.05
▪ No	129(37.94)	215(63.23)			
Antepartum hemorrhage					
▪ Yes	42(12.35)	30(08.82)	1.46	0.86-2.46	> 0.05
▪ No	298(87.64)	310(91.17)			
Pre-eclampsia					
▪ Yes	89(26.17)	47(13.82)	2.20	1.47-3.33	< 0.05
▪ No	251(73.82)	293(86.17)			
Eclampsia					
▪ Yes	56(16.47)	15(04.41)	4.27	2.29-8.08	< 0.05
▪ No	284(83.52)	325(95.58)			
Maternal anemia					
▪ Yes	202(59.41)	148(43.52)	1.90	1.38-2.67	< 0.05
▪ No	138(40.58)	192(56.47)			

Various authors found that APH was a significant risk factor for neonatal seizures [4, 6, 7]. As APH is a risk factor for preterm delivery and subsequent neonatal complications. In our study both Pre-eclampsia and eclampsia were significantly associated risk factors for neonatal seizures .Similar observation were reported by Nadia *et al*[4] and Aprino *et al*[3].In our study maternal anemia was significantly associated with neonatal seizures. Patterson *et al*[6], observed that maternal anemia as a risk factor for neonatal encephalopathy which could lead to seizures.

Antepartum Risk Factors

In our study incidence of premature rupture of membrane was higher in cases as compared to controls. However, it was not statistically significant [OR=1.41, p>0.05)]. In our study maternal fever was significantly associated with neonatal seizures Maternal fever has been shown to be significant risk factor for neonatal seizures by various authors [4,7,8]. In our study general anesthesia to mother was not associated significantly with neonatal seizures.

Table 5: Antepartum risk factors for neonatal seizures

Risk factor	Cases (n=340) n (%)	Controls (n=340) n (%)	Odds ratio	95% C.I.	'p' value
Premature rupture of membrane					
▪ Yes	75(22.05)	57(16.76)	1.41	0.94-2.10	>0.05
▪ No	265(77.94)	283(83.23)			
Maternal fever					
▪ Yes	68(20.00)	43(12.64)	1.73	1.12-2.67	<0.05
▪ No	272(80.00)	297(87.35)			
General anaesthesia to mother					
▪ Yes	25(07.35)	25(07.35)	1.00	0.54-1.85	>0.05
▪ No	315(92.64)	315(92.64)			
Magnesium sulphate to mother					
▪ Yes	57(16.76)	15(07.35)	4.36	2.34-8.24	<0.05
▪ No	283(83.23)	325(92.64)			

In our study magnesium sulphate to mother is significantly associated with neonatal seizures. This could be possibly related to the increased chances of neonatal depression and need for resuscitation predisposing the babies to hypoxic ischemic insult.

Intrapartum Risk Factors

In our study presentation (Cephalic/noncephalic) was not significantly associated with neonatal seizures. In our study as compared to induced labour, the spontaneous labour was significantly associated with neonatal seizures .This could be because of the close monitoring in the induced labour as compared to spontaneous labour. However, induced labor has been found to be significant risk factor for neonatal encephalopathy [5,7]. In our study instrumental delivery was significantly associated with neonatal seizures Nadia *et al*[4] and Ellis *et al*[5] reported similar results .We observed significant association of

cesarean section and neonatal seizures Similar observation was reported Kohelet *et al* [2]andSaliba *et al*[1]In our study delivery at home and hospital both were significantly associated with neonatal seizures.

Table 6: Intrapartum risk factors for neonatal seizures

Risk factor	Cases (n=340) n (%)	Controls (n=340) n (%)	Odds ratio	95% C.I.	'p' value
Cephalic Presentation					
▪ Yes	264(77.64)	268(78.82)	0.93	0.64-1.37	>0.05
▪ No	76(22.35)	72(21.17)			
Noncephalic presentation					
▪ Yes	76(22.35)	72(21.17)	1.07	0.73-1.57	>0.05
▪ No	264(77.64)	268(78.82)			
Instrumental delivery					
▪ Yes	37(10.88)	20(05.88)	1.95	1.07-3.58	<0.05
▪ No	303(89.11)	320(94.11)			
Caesarean section					
▪ Yes	182(53.52)	39(11.47)	8.89	5.88-13.48	<0.05
▪ No	158(46.47)	301(88.52)			
Spontaneous vaginal delivery					
▪ Yes	164(48.23)	239(70.29)	0.39	0.28-0.55	<0.05
▪ No	176(51.76)	101(29.70)			
Induced vaginal delivery					
▪ Yes	57(16.76)	42(29.70)	1.43	0.91-2.25	>0.05
▪ No	283(83.23)	298(87.64)			
Home delivery					
▪ Yes	144(42.35)	194(57.05)	0.55	0.40-0.76	<0.05
▪ No	196(57.64)	146(42.94)			
Hospital delivery					
▪ Yes	196(57.64)	146(42.94)	1.81	1.32-2.48	<0.05
▪ No	144(42.35)	194(57.05)			
Meconium stained liquor					
▪ Yes	39(11.47)	31(9.11)	1.29	0.76-2.19	<0.05
▪ No	301(88.52)	309(90.88)			

However Saliba *et al*[1] reported that, hospital delivery was a independent risk factor for neonatal seizures. we observed meconium stained amniotic fluid as a significant risk factor for neonatal seizures Similar observation was noted by various studies[5,6,7,9].

Neonatal Risk Factors

Our study shows gender difference was not significantly associated with neonatal seizures Aprino*et al*[3] and Kohelet *et al*[2] had similar observations. We noted need for resuscitation was significant risk factor for neonatal seizures. Similar observation was noted by Kohelet *et al* [2.] In our study a respiratory distress syndrome was significantly associated with neonatal seizures. Similar observation was noted by Kohelet *et al*[2]. In our study jaundice was significantly associated with neonatal seizures similar observation was noted by Aprino *et al*[3]. In our study necrotizing enterocolitis was observed as a significant risk factor for neonatal seizures .Similar observation was noted Kohelet *et al*[2]. In our study polycythemia was observed as a significant risk factor for neonatal seizures .To the best of our knowledge no other study has reported this association. In our study we found sepsis had no significant association with neonatal seizures. However, infants with septicemia/septic meningitis may have convulsions because of direct brain damage due to central nervous system infection and associated increase chances of hypoglycemia, circulatory abnormalities, electrolyte imbalance, predisposing baby for seizures[10].Though the incidence of SGA babies was higher in cases as compared to controls it was not statistically significant. However, Saliba *et al*[1]observed that term SGA infants were about two times as likely to have seizures as infants who were appropriate for gestational age. We conclude that having the knowledge of these factors will help in careful monitoring for occurrence of seizures in low birth weight babies and proper early treatment. This will also help in reducing neonatal mortality. However more studies can be done by using regression analysis for studying the association of risk factor individually.

Table 7: Neonatal risk factors for neonatal seizures

Risk factor	Cases (n=340) n (%)	Controls (n=340) n (%)	Odds ratio	95% C.I.	'p' value
Male ▪ Yes ▪ No	176(51.76) 164(48.23)	177(52.05) 163(47.94)	0.99	0.72-1.35	>0.05
Female ▪ Yes ▪ No	164(48.23) 176(51.76)	163(47.94) 177(52.05)	1.01	0.74-1.38	>0.05
Need for resuscitation ▪ Yes ▪ No	61(17.94) 279(82.05)	33(09.70) 307(90.29)	2.03	1.26-3.28	<0.05
Small for gestational age ▪ Yes ▪ No	41(12.05) 299(87.94)	31(09.11) 309(90.88)	1.37	0.81-2.30	>0.05
Respiratory distress syndrome ▪ Yes ▪ No	172(50.58) 168(49.41)	140(41.17) 200(58.82)	1.46	1.07-2.0	<0.05
Jaundice ▪ Yes ▪ No	200(58.82) 140(41.17)	124(36.47) 216(63.52)	2.49	1.81-3.43	<0.05
Necrotizing enterocolitis ▪ Yes ▪ No	30(08.82) 310(91.17)	12(03.52) 328(96.47)	2.65	1.28-5.58	<0.05
Sepsis ▪ Yes ▪ No	131(38.52) 209(61.47)	128(37.64) 212(62.35)	1.05	0.75-1.43	>0.05
Polycythaemia ▪ Yes ▪ No	16(04.70) 324(95.29)	06(01.76) 334(98.23)	2.75	1.0-7.96	<0.05

Conclusion

Neonatal mortality and morbidity can be reduced by having the knowledge of risk factors like, preconceptional, postconceptional, antepartum, intrapartum and neonatal with neonatal seizures in low birth weight babies.

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