

Particular Features of Neonatal Seizures Populational Study

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Abstract— The characteristic features of the neonatal seizures is determined by the anatomical and physiological peculiarities of the human brain in the perinatal period. Current data point towards an excessive depolarization as the underlying mechanism of neonatal seizures. We conducted a retrospective population-based study whose objective was to identify the etiologic factors, predisposing and prognostic predictors of neonatal seizures, by recording epidemiological data, data regarding antenatal or perinatal pathology, clinical aspects of neonatal seizures, neurological syndrome severity, and complications during the follow-up. 206 children were enrolled in the study, all with neonatal seizures in their medical records and born in the Sibiu, Medias and Cislădie Maternity Hospitals between January 1995 and December 2005. The incidence of neonatal seizures was double in males. The postmature male newborns showed a significantly higher birth weight than the female newborns. Although the boys presented an early onset seizure, the average seizure duration was lower. The hypoxic-ischemic encephalopathy, intracerebral hemorrhage, and symptomatic infections are the primary etiological factors for girls and the metabolic context, for boys. The female gender was associated with increased rates of mortality and morbidity compared to male gender. In the case of late complications, the mental retardation predominates in female gender and the attention deficit hyperactivity disorder in male gender .

Index Terms—Complications, etiology, gender, neonatal seizure, risk, predictors.

I. INTRODUCTION

The diagnosis of neonatal seizures (major signs of neurologic dysfunction) is more difficult due to their clinical and electroencephalographic characteristic features [1]-[3].

The particular aspect of the neonatal seizures is caused by the anatomical features of the human brain in the perinatal period: 1. evolving neuronal migration and layering, 2. incomplete myelination in the efferent cortical systems 3. ongoing synaptogenesis, 4. physiological peculiarities of the developing brain. In the limbic system and cortex, the excitatory synapses mediated by glutamate, develop before the inhibitory ones, so an increased susceptibility to seizures in the immature neurons (compared to the mature neurons) of the hippocampus and cortex is recorded. There are also

deficient inhibitory mechanisms due to the insufficient development of the substantia nigra [4]-[8]. Common in the term newborns are the subtle seizures without any corresponding EEG discharges, of nonepileptic nature, considered as a probable epiphenomenon of a severe encephalopathy [9],[10].

Current data point towards an excessive depolarization as the generating mechanism of neonatal seizures, secondary to the: 1. Na-K-dependent pump failure, 2. ATP diminishing, 3. Excitatory neurotransmitter excess, 4. inhibitory neurotransmitter deficit associated with a relative excess of the excitatory neurotransmitters, 5. cell membranes changes with increased permeability for sodium. The substrate of these changes is generally represented by hypoxia, ischemia, hypoglycemia, hypocalcemia, hypomagnesemia or pyridoxine dependency [4]-[8].

In the management of neonatal seizures, the accurate identification of the etiology is a primary objective, which can lead to an etiologic-orientated therapy that may limit the central nervous system dysfunction and may therefore provide an optimal control of seizures and improve the prognosis [11].

Identifying the risk factors (extreme gestational ages-postmaturity/prematurity, male gender, maternal diabetes, preeclampsia, maternal obesity, maternal smoking, extreme birth weights and others) is essential for prevention of neonatal seizures [12], [13].

II. OBJECTIVE

The objective of this study was to identify the etiologic factors for the neonatal seizures, the risk factors or predictors for further neurological complications by recording epidemiological data, data on antenatal or perinatal pathology, seizure aspect, neurological syndrome severity and complications during follow-up.

III. MATERIAL AND METHODE

We conducted a retrospective population-based study selecting the data regarding the children with neonatal seizures, born in the period January 1995 to December 2005 in the Maternity Hospitals from Sibiu, Medias, and Cislădie towns. They had been examined in the neonatal period and followed up in the Neurology Department, Outpatient Care Unit of the "Gheorghe Preda" Psychiatric Hospital and Pediatric Hospital Sibiu.

We included in the study only patients who met the age criteria (seizures in the first 44 weeks of the postmenstrual

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period) and the clinically appropriate Volpe definition (subtle seizures, clonic, tonic or myoclonic seizure) [4];

The data necessary for the study were obtained from the recorded birth observation charts of the mothers and newborns and from the neurological follow-up sheets. We collected from the database informations regarding gender, environment, birth weight, gestational age, associated maternal diseases, postnatal adaptation including mortality (onset, duration, aspect, recurrence, responsiveness to treatment), neurological status (severity of the neurological syndrome applying the Sarnat classification depending on the level of consciousness, neuromuscular control, complex reflexes, seizure occurrence). We also evaluated late neurological complications: psychomotor delay, cerebral palsy, hydrocephalus, epilepsy.

Analysis of the recorded data was performed using descriptive statistics such as average, standard deviation, percentage, or by applying statistical techniques to determine the type of distribution (Kolmogorov-Smirnov, histogram type graphics), statistical tests for comparing two samples (T-test, Mann-Whitney, binomial test), statistical tests to determine the association between two variables (Chi-square test). We considered a significance level of $p < 0.05$, the data were recorded in Excel 2013 and processed using SPSS, version 20 [15],[16].

IV. RESULTS AND DISCUSSIONS

From 1 January 1995 until 31 December 2005 Sibiu, 48.377 live births were registered in the Maternity Hospitals from Sibiu, Medias and Cisnădie towns. In this period 206 cases of neonatal seizures have been identified in the database, the overall incidence in the studied group being 4.25 %.

In the first stage we studied the frequency of neonatal seizures relative to gender, rural or urban background and gestational age. These occurred with a *2 times higher frequency in boys* compared to girls, boys 68.9% (N=142), girls 31.1% (N=64) $p=0.000$, regardless of background: a) urban, male gender 70% (N=86), female gender 30% (N = 37) and $p=0.000$; b) rural, male gender 67% (N=56), female gender 33% (N=27), and $p=0.002$. The higher frequency in boys is preserved regardless of gestational age: a) premature males 63% (N=40), females 37% (N=23) and $p = 0.043$, b) at term born males 68% (N=80) 32% females (N= 37) $p=0.000$, c) postmature males 85% (N=22) 15% female (N=4), $p=0.001$.

Our results correlate with the current data in the literature concerning certain gender features of the neurotransmitter effects in the neonatal period. Such experimental studies on mice indicate a prolonging depolarizing effect on the GABAergic receptor in male gender compared to female gender. This change correlates with the different expression of the NKCC2 KCC1 channels in relation to the gender. This feature may play an important role in the longterm sex-specific differences of the neonatal seizures and in the neonatal brain susceptibility to insults [17].

In the second phase, we analyzed birth weight

according to the gestational age and gender. No significant differences were observed for newborns on term, between the two genders regarding birth weight; the mean average weights for males was $M = 3155g$ ($SD = 522.96$, $N = 80$) and for females $M = 3044g$ ($SD = 395.99$, $N = 37$), $p = 0.205$. In *premature and postmature patients statistically significant differences were observed between the two genders in terms of birth weight, with a lower weight in girls compared to boys* (Fig.1). Thus, for premature infants the mean average weights recorded for males are $M = 2092g$ ($SD = 572.46$, $N = 40$) and for females $M = 1697g$ ($SD = 588.14$, $N = 23$) with $p = 0.011$. In the case of term newborns we recorded an average weight of $M = 3642g$ ($SD = 396.45$, $N = 22$) for males and $M = 3137g$ ($SD = 292.61$, $N = 4$), $p = 0.024$ for females, in both cases with an over 500g weight difference.

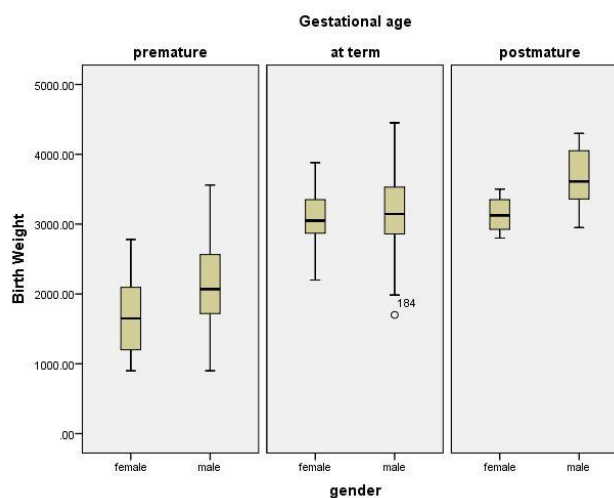


Fig.1- Average birth weight in relationship to the gestational weight and gender

Our results corresponded to the other available studies results, which associated masculine gender, especially the premature age with an increased risk of developing neonatal seizures [12],[18]-[20]. Some studies provided conflicting data according to which not the gender, just the low birth weight is associated with an increased risk of seizures in the neonatal period. This aspect suggests an establishment of a priority for preventive measures by reducing the rate of preterm or low weight births [21]-[23].

The literature data are inconclusive in terms of newborns birth weight associating neonatal seizures in relation to the gender [24]. In this category of patients there were reports of a lower birth weight for males, associating an increased risk for prematurity [22]-[35]. In our study the lower birth weight in females corresponds to the physiological parameters of growth.

Low birth weight is an important risk factor in triggering neonatal seizures for the term, postmature or premature neonates (for which a weight less than 1500 grams is considered significant). The severity of the intraventricular bleeding involved in the etiology of neonatal seizures is directly correlated with the intrauterine growth restriction [6].

In the third stage we evaluated the **risk factors** for neonatal seizures and concluded that *the fetal distress is a significant seizure trigger*. Acute fetal distress was associated

with almost half of the newborns: with 48.6% (N=67) in male and 53.2% (N=33) in female newborns with neonatal seizures. The acute chronic fetal distress occurred in 31.5% of newborns with 31.2% (N=43) in male newborns and 32.3% (N= 20) in female newborns while the chronic fetal distress in 8.5% of newborns with 9.4% (N=13) in males and 6.5% (N=4) in females. In 10% of neonates there was no fetal distress in male gender 10.9% (N=15) and female gender 8.1% (N=5).

We haven't noticed any differences between genders in terms of fetal distress (Chi-square test, p=0.805). Our results are similar to those in the literature associating acute or chronic fetal distress with early-onset neonatal seizures (intrauterine growth restriction, abnormal quantity of amniotic fluid, changes in heart rate, poor perinatal adaptation with pH < 7 in the umbilical cord blood, and others) [27]-[28].

The *etiological factors* of neonatal seizures regardless of gender were represented by brain disorders associated with cerebral dysfunction and seizures during the neonatal period: a) hypoxic-ischemic encephalopathy (HI), b) brain hemorrhage (HC), c) symptomatic infections in the neonatal period (inf), d) metabolic causes (Metab), e) maternal drug use (drug), f) antenatal or perinatal stroke (AVC) (Table 1). Our results are similar with those of all other clinical trials, which incriminated the perinatal asphyxia as the most common cause of neonatal seizures regardless of the gestational age [29]-[33]. Therefore Volpe identified the hypoxic-ischemic encephalopathy as the primary cause of neonatal seizures in 60-65% of cases but the percentage varies according to the different authors [4,34]. Other etiologies vary in frequency depending on the study [33], [35]-[36]. Brain hemorrhages is more common in the preterm group [34],[37].

Table 1. Distribution of cases according to the etiology of neonatal seizures and gender

ETIOLOGY	Females N (% etiology; % gender)	Males N (% etiology; % gender)
HI (91;45.7%)	25 (27.5%; 41.7%)	66 (72.5%; 47.5%)
HC (18; 9%)	5 (27.8%; 8.3%)	13 (72.2%; 9.4%)
HI+HC (37;18.6%)	16 (43.2%; 26.7%)	21(56.8%; 15.1%)
Inf.(5;2.5%)	3 (60.0%; 5.0%)	2(40.0%; 1.4%)
HI+inf (12; 6%)	3 (25.0%; 5.0%)	9(75.0%; 6.5%)
Malformation. (5; 2.5%)	2 (40.0%; 3.3%)	3(60.0%; 2.2%)
Drug (2; 1%)	0	2(100.0%; 1.4%)
Metab. (23; 11.6%)	4(17.4%; 6.7%)	19(82.6%; 13.7%)
inf+HI+HC (4; 2%)	2(50.0%; 3.3%)	2(50.0%; 1.4%)
AVC (2; 1%)	0	2(100.0%;1.4%)

We have observed differences between the two genders. Thus, factors such as *hypoxic-ischemic encephalopathy, intracerebral hemorrhage, symptomatic neonatal infections prevailed in female gender:*a) males 15.1% (N=21), b) females 26.7% (N=16). Infectious diseases are divided between genders with 1.4% (N=2) males and 5% (N=3) females. The association of infectious diseases with hypoxic ischemic encephalopathy and intracerebral hemorrhage was recorded in 1.4% (N=2) males and in 3.3% (N=2) females. The *metabolic causes prevailed in males*

13.7% (N=19) as compared to 6.7% (N=4) females. We haven't found any literature data regarding a gender-specific predilection for a certain etiology of neonatal seizures.

In the *assessment of the severity of the hypoxic-ischemic encephalopathy by gender* we applied for the analysis of the neurological syndrome severity, the Sarnat Grading Scale: three grades (easy, moderate or severe) based on several criteria: awareness, muscle tone, complex autonomic functions, seizure, and duration.

The moderate *neurological syndrome prevailed* in 63% (N = 126) of all patients. The proportion was 64.5% males (N = 89) and 59.7% females (N=37). The severe form was reported in 37% (N=74) of all patients of which 35.5% (N = 49) of the involved newborns were males while 40.3% (N = 25) females. In 6 patients (2.9%) no records in this respect were noticed. We haven't obtained any statistical significant differences between genders in terms of the neurological syndrome (Chi-square test, p = 0.309).

Available studies in the literature indicate the Sarnat staging and the EEG as significant factors in evaluating the prognosis of patients with neonatal seizures. The low-grade hypoxic-ischemic encephalopathy (as classified by Sarnat) evolves usually with a normal neurological development, and the severe forms with significant morbidity and mortality (75-80% of survivors will present neurological sequelae) [38].

Further we characterized *in relation to gender, the responsiveness to therapy, seizure recurrence and seizure aspect (onset, type and duration)*.

In the female newborns the seizure onset occurred on average in the first 73.50 hours (SD =105.18, min=1, max=480, N= 59) with an *earlier onset in the male newborns*, on average in the first 43.41 hours (SD=61.33, min=1, max=500, n=137). *The difference was statistically significant* (p=0.044).

According to Volpe's classification the neonatal seizures are grouped into subtle seizures, clonic, tonic, myoclonic seizures. Applying the above mentioned clinical classification according to the gender we have not identified a statistically significant association between gender and seizure type. For both genders we have found in approximately equal proportions: a) subtle seizures in male gender 76.1% (N = 108), female gender 76.6% (N = 49), p=0.544, b) clonic seizures in male gender 45.8% (N = 65), female gender 48.4% (N = 31), p=0.419, c) tonic seizures in male gender 31% (N=44), female gender 26.6% (N=17), p = 0.319, and d) myoclonic seizures in male gender 23.2% (N = 33) and female gender 20.6% (N = 13), p = 0.414 (Table 2).

Table 2. Distribution of neonatal seizures based on the clinical appearance and gender

Seizure type	Male		Female		p-value
	absent	present	absent	present	
Subtle	34 69.4% 23.9%	108 68.8% 76.1%	30.6% 31.2% 23.4%	49 31.2% 76.6%	0.544
Clonic	77 70.0% 54.2%	65 67.7% 45.8%	33 30.0% 51.6%	31 32.3% 48.4%	0.419
Tonic	98 67.6% 69%	44 72.1% 31.0%	47 32.4% 73.4%	17 27.9% 26.6%	0.319
Myoclonic	109 68.6% 76.8%	33 71.7% 23.2%	50 31.4% 79.4%	13 28.3% 20.6%	0.414

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Although some studies did find correlations between the clinical aspects of neonatal seizures, gestational age and etiology, we have not been able to identify associations between gender and seizure type.

The *average duration of seizures* (measured in hours) in female *preterms* (M = 31.38, SD = 83.18, min=1, max= 480, N=42) *was higher than in male preterms* (M=17.87, SD =40, min=1,max=240, N=99). The results are supported in our study by the predominance of the severe hypoxic-ischemic encephalopathy in female preterms, knowing from the current literature data, the association of neonatal seizures and hypoxic-ischemic encephalopathy (it was present especially in women). The results are inconsistent with the outcomes of other available studies which described in female preterms superior adaptation mechanisms to hypoxia due to the elevated catecholamine levels [39]. Our result could be explained by the other available studies which support a longer duration of the seizure secondary to the severe hypoxic-ischemic encephalopathy [40], cerebral malformations or central nervous system infections [41].

Analyzing the *recurrence of seizures* at more than 24 hours after obtaining the therapeutic control, we found the recurrence of seizures in 42.2% (N=27) of female newborns and in 48.9% (N=69) male newborns (p=0.228). We didn't find any substantial studies that support a higher rate of recurrence in relation to the gender.

The importance of gender in the assessment of risk, regarding *acute complications (mortality) and late complications (neurologic sequelae)*, showed in both cases a *predominance of immediate and late complications in girls*.

The death rate was higher (double) among girls 12.5% (N = 8) comparing to boys 7% (N=10) but with not statistically significance, p = 0.154. This result is preserved *regardless of the rural or urban background*: a) for urban provenance the percentage for the male gender was 8.1% (N=7) and 13.5% (N=5) for the female gender respectively, but with no statistical significance between genders p = 0.270, b) for rural provenance the percentage was 5.4% (N = 3) for male gender and 11.1% for the female gender (N=3),with no statistical significance between genders p=0.299. The higher mortality rate is maintained *regardless of the gestational age*. In preterm newborns the proportion for male gender was 12.7% (N=7) and 20% for female gender(N=6),with no statistical significance between genders p = 0.278. In term newborns the proportion for male gender was 3.4% (N=3) and for female gender 5.9% (N=2) also with no statistical significance between genders p = 0.433.

About half of female newborns 48.4% (N = 32) *presented sequelae* with a 10% lower rate than in males 37.3% (N = 53) and the tendency to statistical significance (p = 0.089)(Table 3).

Table 3. Frequency of neurological sequelae in relation to gender

		Females (N ; % sechele; % gen)	Males (N ; % sechele; % gen)	Chi Squar e test
Epilepsy N=30 14.6%	absent	51 (29% ; 79.7%)	125 (71% ; 88%)	0.211
	Epilepsy	11 (50% ; 17.2%)	11 (50% ; 7.7%)	
	Febrile seizures	2 (28.6% ; 3.1%)	5 (71.4% ; 3.5%)	
	Status epilepticus	0	1 (100% ; 0.7%)	
Mental Retardatio n N=51 24.7%	absent	47 (30.3% ; 73.4%)	108 (69.7% ; 76.1%)	0.063
	Mental retardation	16 (42.1% ; 25%)	22 (57.9% ; 15.5%)	
	ADHD	1 (7.7% ; 1.6%)	12 (92.3% ; 8.5%)	
Motor delay N=71 34.6%	absent	39 (28.9% ; 60.9%)	96 (71.1% ; 67.6%)	0.333
	Motor delay	8(27.6% ; 12.5%)	21 (72.4% ; 14.8%)	
	Cerebral Palsey	17(40.5%;26.6%)	25 (59.5% ; 17.6%)	
Hydroceph alus N=24 11.7%	Absent	53(29.1%;82.8%)	129(70.9%; 90.8%)	0.234
	Ventriculo megaly	5 (50% ; 7.8%)	5 (50% ; 3.5%)	
	Hydroceph alus	6 (42.9% ; 9.4%)	8 (57.1% ; 5.6%)	

Differences between genders in terms of the types of sequelae were:

- 17.2% of female newborns had epilepsy and 7.7% of male newborns but without any statistical significance p = 0.410.
- 25% of female newborns had mental retardation while only 8.5% of the male newborns associated hyperactivity disorder with attention deficit, the difference being statistically significant for the male gender (p = 0.022).
- 26.6% of female newborns had cerebral palsy and only 17.6% of the male newborns, with no statistical significance (p = 0.194).

Our results are similar to those of other studies which declare mental retardation, motor delay and epilepsy as the most common complications [42]. No literature data were identified in confirming a preference for the type of neurological complications in relation to the gender.

Although in our study *epilepsy, cerebral palsy, mental retardation are all complications that are associated more frequently to female newborns, a statistically significant correlation could be established only with mental retardation. Males evolve more frequently with hyperactivity disorder.*

Our results confirm an increased risk of mortality and later neurological complications in female gender although the literature data are inconclusive. In antithesis, there are a few studies that correlate male gender with an increased rate of mortality and consequently with a poor prognosis [25], [43]-[45]. In the case of a hypoxic event in premature babies some studies support a better prognosis for girls ,which is explained by the superior defense mechanisms (increased discharges of catecholamines) [39]. Our results associated the female gender with a higher rate of neurological complications probably due to the etiology of neonatal seizures. In our study the cerebral dysfunction for female newborns is secondary mainly to the hypoxic-ischemic encephalopathy (HI) and to intracerebral hemorrhage, with other studies confirming the hypoxic-ischemic encephalopathy and braindysgenesis with a worse prognosis

for immediate and delayed complications compared the other etiologies[32]. Applying the classification of Sarnat regarding the severity of hypoxic-ischemic encephalopathy in patients with neonatal seizures, the male gender is associated mainly with a moderate neurological syndrome while the female gender with an increased incidence of the severe neurological syndrome and therefore with a higher mortality risk. We also recall in our study a lower birth weight for the female newborns as an additional risk factor for complications [4], [43], [45].

Neonatal seizures may have an early and long-term impact on neurocognitive processes, especially in the case of the immature, developing brain. Whether one get immediate control of the neonatal seizure, the risk of early mortality and subsequent neurocognitive impairment and epilepsy still remains significant [46]. Identifying the etiology is essential in assessing the risk of neurological sequelae (epilepsy, cerebral palsy, psychomotor delay, behavioral problems). It is important to know that the cerebral malformations, intraventricular hemorrhage, strokes and the severe hypoxic-ischemic encephalopathy determine an increased risk of late morbidity [4],[32],[45]. Alongside the mentioned clinical factors, the electroencephalographic and severe imaging abnormalities are followed by a worse prognosis [29],[43],[46].

Regarding the higher occurrence of attention deficit hyperactivity disorder, especially in males, this is probably due to the increased recurrence rate of neonatal seizures among boys.

Current study results confirm for the recurrent neonatal seizures an aberrant reorganization of the neural networks, altered synaptogenesis with second cognitive dysfunction [47]. No gender differences could be established in terms of birth weight, fetal distress, neurological syndrome, types of seizures and seizure recurrence.

V. CONCLUSION

The study group analysis of patients with neonatal seizures in relation to the gender showed that the male newborns are correlated with 2 times higher frequency of neonatal seizures regardless of the provenance and gestational age, with an earlier onset of the seizures in relation to female newborns and with a mainly metabolic etiology of the seizure. On follow up, the boys are less exposed to neurological sequelae with predominant attention deficit hyperactivity disorder. Regarding the *girls*, we observed in preterm and postterm newborns statistically significant differences between the two genders in relation to birth weight (500g lower in females) and a primary etiology of seizures represented mainly by hypoxic-ischemic encephalopathy, intracerebral hemorrhage, symptomatic infections. The girls are also exposed to a longer average duration of neonatal seizures and to a higher neurological sequelae (especially mental retardation) and mortality risk.

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