Clinical, electrophysiological, and neuroimaging predictors for antiseizure medication in infants with neonatal clinical seizures

İpek Dokurel Cetin[1], Seda Kanmaz[2] , Hasan Tekgul [2]

1. Ataturk City Hospital, Pediatric Neurology, Balikesir, Turkey, 2. Ege University Faculty of Medicine, Pediatric Neurology, İzmir, Turkey

INTRODUCTION

Seizures occur more often in the neonatal period than at any other time of life and they could indicate the presence of a potentially treatable etiology. Most neonatal seizures are acute provoked / symptomatic seizures, occurring as a consequence of a specific identifiable etiology.

The classifications of neonatal seizures are performed according to new ILAE-2020 classification and Volpe classification. However early treatment of all types of neonatal seizure : clinical, electro-clinical, and electrographic seizure is essential. After a succesful seizure control, the discontinuation of antiseizure drugs in seizure-free infants is main goal due to the possible long-term side effects of drugs.

In this retrospective study, we aimed to determine the clinical predictors in infants with neonatal seizures for the antiseizure medication (ASM).

PATIENTS & METHODS

The study cohort consisted of 652 infants with neonatal clinical seizures followed in two instutitions between 2005 and 2021.

From the patients' charts, the clinical parameters (demographics, etiology, and seizure semiology in neonatal period), electroencephalography characteristics, and magnetic resonance imaging findings were recorded.

The cohort was divided into two groups with ASM follow-up period at 2 years of age**; group I (infants with ASM)** and **group II (infants without ASM).**

Univariate and multivariate analyses were performed for the predictive value of the clinical-demographic variable, EEG characteristics, and MRI findings. The possible factors identified with univariate analyses, were further entered into Cox regression analysis, with backward selection, to determine the independent factors of continuation of ASM treatment in infants.

RESULTS

The demographic data of the cohort and predictors for ASM discontinuation is seen in Table I. The duration of ASM of infants with seizure-free was 4.4±3.3 months. and infants with ASM therapy was 18.5±6.3 months (p=0.001). 63.5%(n=414) of the cohort was male. Univariate analysis revealed that certain clinical parameters (birth weight, seizure semiology, duration of ASM, polytherapy), EEG characteristics, and MRI findings are valuable clinical predictors for ASM continuation in infants with neonatal seizures (Table 1).

Multivariate analysis with the Cox regression model predicted the following parameter significantly associated with the continuation of ASM treatment in infants with neonatal seizures: politherapy of ASM at the NICU discharge, abnormal EEG characteristics, and abnormal MRI findings (Table II).

Table II. Predicted variables of the continuation of ASM treatment in infants with neonatal seizures

	HR	95% CI	P Value
Dualtherapy/Polytherapy at the NICU discharge	1.5	1.2-1.8	<0.001
Abnormal EEG between 1-3 months of age	1.6	1.3-1.9	<0.001
Abnormal MRI at the 4-8 months of age	1.3	1.1-1.6	<0.001

EEG:Electroencephalogram, MRI:Magnetic resonance imaging

CONCLUSION

Our cohort study revealed the most valuable three predictors for the continuation of ASM treatment in infants with neonatal seizures; (1) Dualtherapy/Polytherapy at the NICU discharge, (2) abnormal EEG between 1-3 months of age, and (3) abnormal MRI at the 4-8 months of age.

REFERENCES

1. Glass HC, Soul JS, Chang T, et al. Safety of Early Discontinuation of Antiseizure Medication After Acute Symptomatic Neonatal Seizures [published correction appears in JAMA Neurol. 2021 Jul 1;78(7):882]. JAMA Neurol. 2021;78(7):817-825

2. Osmond E, Billetop A, Jary S, et al. Neonatal seizures: magnetic resonance imaging adds value in the diagnosis and prediction of neurodisability. Acta Paediatr 2014; 103:820

3. Dizon MLV, Rao R, Hamrick SE, et al. Practice variation in anti-epileptic drug use for neonatal hypoxic-ischemic encephalopathy among regional NICUs. BMC Pediatr 2019; 19:67

4. Glass HC, Shellhaas RA. Acute Symptomatic Seizures in Neonates. Semin Pediatr Neurol 2019; 32:100768

Table I. Clinical, electrophysiological and neuroimaging predictors for antiseizure medication in infants with neonatal clinical seizures (univariate analysivs)

Variables	Group I: N=253(38.8%)	Group II: N=399(61.2%)	Total Cohort	P value
Birthweigth(grams), Mean±SD	2715.3±932.4	2869.4±850.3	2812±883.8	.045*
Clinic Seizure Semiology-ILAE-2020				
Tonic	90	71	161(25.2%)	.001†
Clonic	45	92	137(21.4%)	
Myoclonic	24	35	59(9.2%)	
Epileptic Spasms	16	8	24(3.8%)	
Subtle	53	133	186(29%)	
Sequential	22	49	71(11.1%)	
Unclassified	0	2	2(0.3%)	
Etiology Structural				
HIE	97	167	264(40.5%)	.267†
Vascular	42	42	84(12.9%)	
Brain Malformations	39	15	54(8.3%)	
Genetic	26	39	65(9.9%)	
Infection	26	118	144(22.1%)	
Metabolic	17	10	27(4.1%)	
Unknown	6	8	14(2.1%)	
ASM at the NICU discharge				
Monotherapy	165	345	510(78.3%)	.001†
Dualtherapy/Polytherapy	88	53	141(21.7%)	
EEG the most pathologic EEG between 1-3 months of age				
Normal	41	221	262(40.2%)	.000†
Abnormal	212	178	390(59.8%)	
Focal epileptiform activity	79	53	132(20.2%)	
Abnormal background	27	39	66(10.1%)	
Excessive sharp transients	73	79	152(23.3%)	
Burst suppression pattern	33	7	40(6.1%)	
MRI at the 4-8 months of age				
Normal	64	220	284(43.7%)	.001†
Abnormal	186	179	368(56.3%)	
Ischemia/Hemorrhage	38	72	110(%16.9)	
Periventricular leukomalacia	39	27	66(10.2%)	
Multicystic encephalomalacia	51	19	70(10.8%)	
Corpus Callosum abnormalities	14	12	26(4%)	
Delayed Myelination	36	38	74(11.4%)	
Hydrocephalus	7	7	14(2.2%)	
Cortical Dysplasia	1	4	5(0.8%)	

Missing data for the variable "Clinic Seizure Semiology": 12 (1.8%).
Missing data for the variable "ASM at the NICU discharge": 1 (0.2%).
Missing data for the variable "MRI at the 4-8 months of age": 3 (0.46%).
ASM:Antiseizure medication, EEG: Electroencephalogram,HIE: hypoxic ischemic encephalopathy, MRI:Magnetic resonance imaging, NICU:Neonatal intensive care unit,
* Student's t-test was used to compare parametric variables.
†Mann-Whitney U test was used to compare non parametric variables.