

Neonatal Epilepsy

“Essay”

Submitted for fulfillment of the requirements of M.Sc.degree in pediatrics

by

Dina Hossam El Din Hamed M.B.,B.Ch

Faculty of Medicine
Cairo University

supervised by

Prof. Dr. Zahraa Mohamed Ezz El Din

Prof. Of Pediatrics
Faculty of Medicine
Cairo University

Dr. Ranya Aly Hegazy

Lecturer of Pediatrics
Faculty of Medicine
Cairo University

Dr. Yasmine Amr Mansy

Lecturer of Pediatrics
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2007

ACKNOWLEDGEMENT

First of all, I would like to thank *Allah* the merciful and compassionate for making all this work possible and for everything that I have and everything I will ever be.

I have been honored and privileged to have worked under the supervision of such distinguished and great professors that many people would dream of having such a chance.

I would like to express my deepest gratitude to *Prof. Zahraa Mohamed Ezz El Din*, Professor of neonatology, Cairo University, for her unlimited support, valuable supervision and kind guidance. I thank her beyond words can convey. I hope I will be able to follow her footsteps.

I am deeply indebted to *Dr. Ranya Aly Hegazy*, she has been there for me from the beginning with her exceptional assistance, outstanding devotion, valuable time, enthusiastic encouragement and sincere guidance.

Words can not express my deep appreciation for *Dr. Yasmine Amr Mansy*. I m very thankful to her for her continuous support, and correction. I will always owe her so much.

Furthermore, I would like to convey my special thanks to all *the Staff members* in the Pediatric Hospital of Cairo University who taught me the true meaning behind being a doctor, and to *my dear colleagues* for their kind support.

SPECIAL DEDICATION

Last but not least I am deeply indebted to *my family (my father, my mother, my husband and my daughters "Mariam and Malak")* who were always there for me with their endless support and encouragement, they have always had faith in me. In fact I owe them everything that I am. To them I dedicate my work and to them I say **THANK YOU**

Abstract

Epilepsy is a serious brain disorder.

Neonatal seizures do not represent a homogeneous clinical entity and it can be difficult to distinguish epileptic from non-epileptic seizures when ictal semiology is not EEG related.

Neonatal seizures are difficult to detect, diagnose, and manage.

Treatment of seizures involves identifying and treating the underlying etiology of the seizure and appropriate use of pharmacologic interventions.

Key Words:

Neonatal seizures, Epilepsy.

CONTENTS

	<i>Page</i>
● Introduction and Aim of the work	1
● Review of literature:	
<i>Chapter 1:</i> Brain development	
Embryology.....	4
Brain malformations.....	15
<i>Chapter 2:</i> Pathophysiology of seizures.....	19
<i>Chapter 3:</i> Etiology of seizures.....	34
<i>Chapter 4:</i> Diagnosis of seizures.....	46
<i>Chapter 5:</i>	
Treatment of seizures.....	73
Prognosis of seizures.....	92
<i>Chapter 6:</i> Clinical approach to a case of seizure.....	96
● Summary	98
● References	100
● Arabic summary	113

List of Tables

<i>Tables</i>	<i>Page</i>
Table 1: Maturational factors modifying seizure susceptibility.....	32
Table 2: Classification of neonatal seizures based on electroclinical finding	
Table 3: Causes of neonatal seizures.....	42
Table 4: Idiopathic syndromes of clinical seizures in the newborn....	45
Table 5: Classification of neonatal seizures.....	49
Table 6: Differential diagnosis of neonatal seizures by peak time of onset.....	70-71
Table 7: Seizures versus jitteriness.....	72

List of Figures

<i>Figures</i>	<i>Page</i>
Figure 1: Neural tube.....	4
Figure 2: Brain vesicles-6th week.....	5
Figure 3: Early development of the brain.....	6
Figure 4: Development of the medulla oblongata.....	9
Figure 5(A): Development of the pons and cerebellum.....	10
Figure 5(B): Development of the pons and cerebellum.....	11
Figure 6: Diencephalon and telencephalon.....	13
Figure 7: A diagram showing the developmental course of human brain development.....	17
Figure 8 : Model of GABAergic action in neonatal seizures.....	24
Figure 9: The emergence of epilepsy from an ion channel gene mutation.....	31
Figure 10: Sample of a video-EEG tracing a full-term male infant with hypoxic-ischemic encephalopathy and seizures.....	56
Figure 11: EEG of a 5-day-old neonate, showing focal ictal pattern characterized by rhythmic sharp waves in the left rolandic region.....	58
Figure 12: EEG of a 5-day-old neonate on ventilator, showing "depressed brain seizure" characterized by less than one per second, low-amplitude sharp waves over the right hemisphere.....	59

Figure 13: EEG of a 3-day-old comatosed neonate with history of seizures, showing an electrographic "alpha band" seizure pattern without clinical accompaniment.....	60
Figure 14: Baby with a moderately abnormal background electroencephalogram (EEG) with more than 10 seizures an hour which were not detected with the cerebral function monitor (CFM) because they were of low voltage. (A) CFM trace (6 cm/h); (B) background EEG pattern; (C) seizures on EEG.....	62
Figure 15: Selective regional vulnerability determined according to age of insult.....	67
Figure 16: Evolution of brain injury as seen with MRI.....	68
Figure 17: The Children's Hospital recently participated in a multi-center international clinical trial studying the effect of cooling the brains of babies who were deprived of oxygen at birth.....	89
Figure 18: Baby wearing cap.....	89

List of abbreviations

AEDs: Antiepileptic drugs

ACh : acetylcholine

aEEG: Amplitude-integrated electroencephalogram

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

BFNC: Benign familial neonatal convulsions

BFN/IS: Benign familial neonatal infantile seizures

BINC: Benign infantile neonatal convulsions

Ca: Calcium

CBC: Complete blood count

CFM: Cerebral function monitor

CL: Chloride

CNS: Central nervous system

CRH: Corticotropinreleasing hormone

CT: Computed tomography

EAA: Excitatory amino acid

ECD : Electroclinical disassociation

ECl: Cl⁻ equilibrium potential

EEG: Electroencephalogram

EIEE: Early infantile epileptic encephalopathy

EME: Early myoclonic encephalopathy

EMG: Electromyography

FT: Full term

GABA: Gamma amino butyric acid

GABA-R: GABA receptors

GEFS+: Generalized epilepsy with febrile seizures plus

GLU-R: Glutamate receptors

ICEGTCS: Intractable childhood epilepsy with tonic-clonic seizures

ILAE: International league against epilepsy

IM: Intramuscular

IS :Infantile spasm

IV: Intravenous

K: Potassium

MRI: Magnetic resonance imaging

MCD: Malformations of cortical development

Na: Sodium

NAA: N-acetylaspartate

NKCC1: $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ cotransporter

NMDA: *N*-methyl-D-aspartate

NS: Neonatal seizures

PN: Postnatal day

PT: Preterm

SMEI: severe myoclonic epilepsy of infancy

SNR: Substantia nigra pars reticulata

Review of Literature

INTRODUCTION

Epilepsy is a serious brain disorder characterized by recurrent unprovoked seizures. Seizures are the most common neurological emergency in newborns (*Rennie and Boylan, 2003*). The incidence of seizures in the neonatal period is greater than in any other time of life with most seizures occurring within the first week of life (*Granelli and Mcgrath, 2004*). The incidence of seizures in infants born at term is 1.5 - 3.0 per 1000 live births; the incidence is even higher in preterm infants, ranging from 50 - 150 per 1000 live births. These figures are probably underestimations as these figures only include clinical and electroclinical seizures. The exact incidence of electroencephalographic, clinically silent seizures is as yet unknown(*Volpe, 2001*).

A significant percentage of neonatal seizures (NS), however, are symptoms of severe or progressive brain disease and prelude to development of neurological deterioration and epilepsy. Therefore, NS do not represent a homogeneous clinical entity and it can be difficult to distinguish epileptic from non-epileptic seizures when ictal semiology is not EEG related(*Mastrangelo et al., 2005*).

Seizures are the most frequent clinical sign of neurological dysfunction in the neonate(*Volpe, 2001*). Depending on the immaturity of the brain, seizures may disrupt the processes of cell growth, division, migration, myelination, receptor formation, and stability of the synapse, thus contributing to the neurological sequelae(*Scher, 2003*). The majority are occasional seizures, occurring as reactive events to acute insults, systemic diseases or disturbances, and subsiding soon after removal of the causative event(*Mastrangelo et al., 2005*).

Neonatal seizures are rarely idiopathic, therefore an extensive diagnostic workup is needed to establish the cause of seizures in newborn period(*Malik et al., 2003*). Most seizures are triggered by acute illness such as hypoxic ischemic encephalopathy, stroke, or infection; rarely are they triggered by epilepsy per se(*Clancy, 2006*). Determination of aetiology is highly critical because it affords the opportunity to treat specifically and also to make a meaningful prognostic statement(*Patrizi et al., 2003*).

Neonatal seizures(NS) are markers for time specific aetiologies during antepartum, intrapartum and neonatal time periods. Seizures with or without encephalopathic signs can represent a continuum of maternal, placental, fetal and neonatal risk factors and disease states(*Scher, 2006*).

The 1989 ILAE (international league against epilepsy) classification of epilepsy and epileptic syndromes was found unsatisfactory in newborns(*Arzimanoglou and Aicardi, 2001*). According to it, most of NS were classified under epilepsies and syndromes undetermined whether focal or generalized, with the exception of four rare but well defined electro-clinical syndromes: early myoclonic encephalopathy (EME), early infantile epileptic encephalopathy (EIEE), benign idiopathic neonatal convulsions (BINC), benign familial neonatal convulsions (BFNC). The 2001 ILAE proposed diagnostic scheme for neonates with epileptic seizures and with epilepsy which offers a variety of approaches to classification increasing its power to characterize individual patients in a less ambiguous manner with clear etiologic, therapeutic and prognostic implications(*Engel , 2001*).

Clinical experience suggests two major components to the relationship between brain development and epilepsy. First, the maturational state of the immature brain appears to generally decrease seizure threshold and to contribute to a different seizure phenotype from the adult brain. Second, certain forms of seizures, when present during development, may modify brain maturation, resulting in chronic epilepsy and or neurocognitive deficits(*Jensen, 1999*).

The first studies that reported on outcome of neonatal seizures showed a 20% incidence of evolution into epilepsy. When EEG monitoring was added to the clinical data, the rate of seizures predictive of epilepsy rose to 56%(*Pisani et al., 2004*). Neonates with a suboptimal Apgar score (5-minute Apgar Score less than 10) have a higher risk of epilepsy that lasts into adult life(*Sun et al., 2006*).

Aim of the work

The present research aims at providing an updated review of neonatal epilepsy. All aspects of the problem will be covered in a recent comprehensive way to shed light on this critical neonatal problem. Recent diagnostic approaches and therapeutic interventions will be reviewed.

BRAIN DEVELOPMENT

EMBRYOLOGY

At the third week, a thickening of the ectoderm appears known as the neural plate, which will form the neural groove which has two elevated edges called the neural folds.

The neural tube cranial to the fourth pair of somites develops into the brain. Fusion of the neural folds in the cranial region and closure of the rostral neuropore forms three primary brain vesicles from which the brain develops. the three primary brain vesicles form the:

- forebrain(prosencephalon)
- midbrain(mesencephalon)
- hindbrain(rhombencephalon)

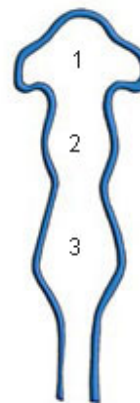


Figure1:Neural tube (cited from google images)

1.Prosencephalon

2.Mesencephalon

3.Rhombencephalon