



Prevalence of NMDA Receptor Antibody in Children with Autoimmune Encephalitis

Thesis

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Contents

	<i>Subjects</i>	<i>Page</i>
List of abbreviations.....	II	
List of figures.....	III	
List of tables.....	V	
• Introduction	1	
• Aim of the work	4	
• Review of Literature		
♦ Chapter (1): Encephalitis	5	
♦ Chapter (2): Autoimmune Encephalitis	27	
• Patients and Methods	50	
• Results	59	
• Discussion	87	
• Summary	99	
• Conclusion	103	
• Recommendations	104	
• References	105	
• Arabic Summary		

List of Abbreviations

ALT	: Alanine aminotransferase
NMDA	: N-methyl D-aspartate
CSF	: Cerebrospinal Fluid
CT	: Computed tomography
DCL	: Disturbed conscious level
EEG	: Electroencephalogram
ELISA	: Enzyme-linked immunosorbent assay
FLAIR	: Fluid attenuated inversion recovery
GABA	: G-aminobutyric acid
HHV6	: Human Herpesvirus 6
HSV	: Herpes simplex virus
ICU	: Intensive care unit
LGI1	: leucine-rich, glioma-B inactivated 1
LP	: Lumbar puncture
MR	: Magnetic resonance
MRI	: Magnetic resonance imaging
PANDAS	: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PLT	: Platelets

List of Figures

SLE : Systemic lupus erythematosus

VEEG : Video electroencephalogram

VZV : Varicella zoster virus

List of Figures

List of Figures

<u>No.</u>	<u>Figure</u>	<u>Page</u>
<u>1</u>	Demonstration of neuronal antibodies with immunohistochemical techniques.	29
<u>2</u>	A 17-year-old male patient with anti-NMDAR mediated encephalitis.	42
<u>3</u>	A 13-year-old girl with anti-NMDAR mediated encephalitis	43
<u>4</u>	A 9-year-old girl with positive serum anti-NMDAR antibodies.	44
<u>5</u>	Bar chart showing gender of the included infants and children.	60
<u>6</u>	Bar chart showing the mean ages of the included infants and children.	61
<u>7</u>	Bar chart showing body temperature among the included patients.	63
<u>8</u>	Bar chart GIT manifestations distribution of the study group.	64
<u>9</u>	Bar chart Neurological data of the included patients.	66
<u>10</u>	Bar chart of the MRI brain findings of the studied patients.	68
<u>11</u>	Bar chart showing EEG distribution of the studied group.	69
<u>12</u>	Bar chart showing the 4 months follow up of the studied patients.	70
<u>13</u>	Pie chart showing Hospitalization place of the studied patients.	71

List of Figures

<u>No.</u>	<u>Figure</u>	<u>Page</u>
<u>14</u>	Bar chart showing the percent of patients who had high and low anti NMDAR antibody titer.	76
<u>15</u>	Bar chart between high NMDAR antibody titre and low NMDAR antibody titre according to sex.	78
<u>16</u>	Bar chart between high NMDAR antibody titre and low NMDAR antibody titre according neurological data.	80
<u>17</u>	Bar chart between high NMDAR antibody titre and low NMDAR antibody titre according ALT	82
<u>18</u>	Bar chart between high NMDAR antibody titre and low NMDAR antibody titre according long term sequel.	84
<u>19</u>	Scatter plot negative correlation and significant between NMDAR titre serum and PLT. in patients group.	86
<u>20</u>	Scatter plot positive correlation and significant between NMDAR titre serum and Alt. in patients group.	87

List of Tables

<u>No.</u>	<u>Table</u>	<u>Page</u>
<u>1</u>	Common causes of encephalopathy.	8
<u>2</u>	Frequent differences between encephalopathy and encephalitis.	9
<u>3</u>	Possible etiological agents based on risk factors.	13
<u>4</u>	Possible etiological agents based on clinical presentation.	14
<u>5</u>	Causes of acute viral encephalitis.	15
<u>6</u>	Diseases mimicking viral meningo-encephalitis in children.	16
<u>7</u>	Differential diagnosis.	40
<u>8</u>	Comparison between groups according to demographic data.	60
<u>9</u>	Constitutional symptoms and symptoms indicating viral infections in the patients' group.	62
<u>10</u>	Neurological data distribution of the study group.	65
<u>11</u>	MRI brain finding of the studied group.	67
<u>12</u>	EEG findings of the study group.	69
<u>13</u>	Four months sequel of the studied patients	70
<u>14</u>	Place of hospitalization of the studied group	71
<u>15</u>	Laboratory data of the patients' group	72
<u>16</u>	Anti NMDA receptor antibody titer of the patients' group	73
<u>17</u>	Serum anti NMDA receptor antibody titer	74

List of tables

<u>No.</u>	<u>Table</u>	<u>Page</u>
	of the patients' group and control group	
<u>18</u>	Distribution of antibody titer among the patients' group	75
<u>19</u>	Relation between high NMDAR antibody titre and low NMDAR antibody titer according sex.	77
<u>20</u>	Relation between high NMDAR antibody titre and low NMDAR antibody titre according neurological data.	79
<u>21</u>	Relation between high NMDAR antibody titre and low NMDAR antibody titre according laboratory data.	81
<u>22</u>	Relation between high NMDAR antibody and low NMDAR antibody titre according long term sequel, hospitalization (ward/ICU).	83
<u>23</u>	Correlation between NMDAR antibody titre and other parameters, using Pearson correlation coefficient.	85

Introduction

Encephalitis refers to an inflammatory disorder of the brain resulting in altered mental status, seizures, or focal neurologic deficits, usually accompanied by signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings ranging from normal to extensive abnormalities. The causes of encephalitis are numerous, and most patients undergo extensive testing for infectious etiologies without discovery of a causative agent. **(Gable et al., 2009)**

The recent discovery that several forms of encephalitis result from antibodies against neuronal proteins has led to a definitive diagnosis in many of these cases. The antibodies target receptors and cell surface proteins involved in synaptic transmission, plasticity, or neuronal excitability, and associate with syndromes that despite being severe, frequently respond to immunotherapy. **(Lancaster et al., 2011)**

Autoimmune encephalitis is a type of encephalitis that can result from a number of autoimmune diseases including Rasmussen encephalitis, Systemic lupus erythematosus (SLE), Behcet's disease, hashimoto's encephalopathy and autoimmune limbic encephalitis. **(Bhalla et al., 2011)**

The most common presenting symptoms in children under the age of 12 years were abnormal behavior, seizures, and movement disorders. **(Titulaer et al., 2012)**

Anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis, also termed NMDA receptor antibody encephalitis, is an acute form of encephalitis which is potentially lethal but has high probability for recovery. It is caused by an autoimmune reaction primarily against the NR1 subunit of the NMDA receptor. **(Dalmau et al., 2008)**

This disorder has become a leading cause of autoimmune encephalitis in children and adolescents, with 40% of patients being younger than age 18 years. **(Dalmau et al., 2011)**

The disease had a higher incidence than its individual viral counterparts in patients <30 years. **(Gable et al., 2012)**

Anti-NMDAR encephalitis is increasingly recognized in children and appears to account for a major percentage of encephalitis cases, previously categorized as of unknown cause in such infants. Autoimmune anti-NMDAR encephalitis may be of unknown cause, post-infectious, paraneoplastic and as a manifestation of SLE. In



an individual patient, these autoantibodies may be to NMDAR (NR1), NMDAR (NR2) or both. Therefore, an appropriate assay testing for anti-NMDAR must cover both. **(Finne, 2013)**

Definitive diagnosis of anti- NMDAR encephalitis is established by demonstrating IgG antibodies to the NR1 subunit in patients' serum and CSF or CSF only and usually the CSF titre is higher than the serum titre. **(Dalmau et al., 2008)**



Aim of the study

Measurement of NMDAR antibody in CSF and serum samples in a cohort study of children presenting with acute encephalitis by ELISA technique.

Chapter 1:

Encephalitis

Encephalitis is an uncommon but potentially devastating neurological syndrome with different etiologies including direct central nervous system infection with different agents (most commonly viral) and those mediated by the immune system.(**Thompson et al., 2012**)

Encephalitis is a brain inflammation that over the long term can reduce neurologic health and cause disability and even death (**Schmidt et al., 2011**).

More than 100 infectious, post-infectious, and immune-mediated conditions can cause encephalitis, which occurs most often in infants and in adults >65 years of age (**Vora et al., 2014**).

Studies worldwide indicate that cause is unknown for 37%–85% of encephalitis cases and that recorded causes differ by region and implementation of systematized diagnostic algorithms (**Bitnun and Richardson, 2015**).

The management of patients with encephalitis has changed dramatically in recent years for several reasons including improved diagnostic and brain imaging

techniques, better antiviral and immunomodulatory treatments and more advanced neurointensive care and rehabilitation. It is important to recognize encephalitis because specific treatments given early can improve the outcome in certain case. **(Raschilas et al., 2002)**

Definition of encephalitis:

Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction. **(Tunkel et al., 2008)**

Although pathologic examination and testing of brain tissue is considered to be the “gold standard” diagnostic test for this syndrome, this is rarely done premortem due to potential morbidity associated with an invasive neurosurgical procedure. In the absence of pathologic confirmation, encephalitis has previously been defined on the basis of selected clinical, laboratory, electroencephalographic, and neuroimaging features **(Granerod et al., 2010)**

Encephalitis is characterized by brain inflammation as a consequence of direct infection of the brain parenchyma, a post-infectious process such as acute disseminated encephalomyelitis (ADEM) **(Bloch and Glaser, 2007)**, or a noninfectious condition such as anti-N-