ASSESSMENT OF IDIOPATHIC GENERALIZED EPILEPSYCLINICAL ,EEG,AND MRS STUDIES

THESIS

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ABSTRACT

The determination of cognitive deficits as well as the use of advanced neuroimaging technique in epileptic patients is important especially in IGE because it reveals the possibility of seizures arise from focal brain pathology in what appear otherwise as generalized epilepsy syndromes.

Methods: Thirty IGE patients (10 with JME, 10 with GTC and 10 with CAE), and 10 healthy matched controls were submitted to a neuropsychological evaluation using a battery of psychometric tests for assessment of global intellectual functions, attention, memory, mental speed and information processing and to a single voxel MRS of Rt thalamus and prefrontal cortex measuring N-acetylaspartate (NAA) and NAA/creatine (Cr).

Results: Patients with IGE were found to perform worse than controls in all administered tasks with a significant correlation between the poor performance of the patients and the duration of the epilepsy or seizure frequency. A significant reduction of Rt thalamic and prefrontal cortex NAA and NAA/Cr ratio was observed in patients with IGE with a significant correlation between the change in neurometabolites of the patients and the seizure frequency. JME patients show significant reduction of NAA/Cr ratio in prefrontal cortex in comparison to other patients groups.

Discussion: This study shows evidence of impaired cognitive functions, in addition to neuronal dysfunction in the Rt thalamus and prefrontal cortex of patients with IGE, supporting the notion of abnormal thalamo-cortical circuitry as a substrate of seizure generation in this form of epilepsy. JME patients can show some frontal dysfunction, which may affect both epileptogenic features and cognitive processes.

KEY WORDS: Idiopathic generalized epilepsy, Cognition, Neuropsychology, Magnetic resonance spectroscopy, N-acetylaspartate, Thalamus, prefrontal cortex.

CONTENTS

LIST OF ABREVIATIONS

ADCME: Autosomal dominant cortical myoclonus and epilepsy

ADNFLE: Autosomal-dominant nocturnal frontal lobe epilepsy

AEDs: Antiepileptic drugs

ASE : Absence status epilepticus

BCECTS : Benign childhood epilepsy with centrotemporal spikes

BMEI: Benign myoclonic epilepsy in infancy

BNFCs : Benign neonatal familial convulsions

BNS: Benign neonatal seizures

BOLD: blood oxygenation level-dependent

CAE: Childhood absence epilepsy

CBC: Complete blood cells

CBZ: Carbamazepine

CHESS: chemical shift selective

Cho : Choline

CPT: Continuous Performance Test

Cr : Creatine

CSWS: continuous spike-and-wave during sleep

EEG: Electroencephalogram

EGMA :Epilepsy with generalized tonic-clonic seizures upon awakening

EGTCA: Epilepsy with generalized tonic-clonic seizures only

EM-AS : Epilepsy with myoclonic-astatic seizures

EME: Early myoclonic encephaloopathy

FAME : Benign adult familial myoclonic epilepsy

f MRI: Functional MRI

FS: Febrile seizures

FS +: Febrile seizures plus

GABA: Gamma-Aminobutyric acid

GEFS+: Generalized epilepsy with febrile seizures plus

Gln: Glutamine

Glu: Glutamate

GSWD: Generalized spike-wave discharges

GTCs: Generalized tonic-clonic seizure

HRBNT: Halstead-Reitan Battery of Neuropsychological Tests

HS: Hippocampal sclerosis

Hz: Hertz

IGEs: Idiopathic generalized epilepsies

ILAE: International League Agnist Epilepsy

IMT: incidental Memory Task

IPS: Intermittent photic stimulation

IQ: Intelligence Quotient

JAE: Juvenile absence epilepsy

JME: Juvenile myoclonic epilepsy

K-ARC: Kaufmanns Assessment Battery for children

LGS: Lennox-Gastaut syndrome

LKS: Landau-Kleffner

LTG: Lamotrigine

MAE: Epilepsy with myoclonic absences

MEG: Magnetoencephalography

MEI: myoclonic epilepsy of infancy

mI : Myo-inositol

MNCD: Mild Neuro Cognitive Disorder

MMSE: Mini-Mental state examination

MQ: Memory quotient

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

MRSI: Magnetic resonance spectroscopic imaging

MSI: magnetic source imaging

MTLE: Mesial temporal lobe epilepsy

MTR: magnetization transfer ratio

NAA: N-acetylaspartate

NMDA: N-Methyl D-Aspartate

NRT: Nucleus reticularis of the thalamus

PASAT: Paced Auditory Serial Addition Test

PET: Positron emission tomography

PFC: Prefrontal cortex

PHT: Phenytoin

PIQ: Performance scale of IQ

PMA: Perioral myoclonia with absences

PME: Progressive myoclonic epilepsies

ppm: Parts per million

PRESS: Point resolved spectroscopy

PTZ: pentylenetetrazol

QOL: Quality of life

RAVLT: Rey Auditory Verbal Learning Test

RT: Reaction time

SD: Standard deviation

SNR: signal to-noise ratio

SPECT: Single photon emission computed tomography

STEAM: stimulated –echo acquisition mode

SWD: spike and wave discharges

TE: echo time

TLE: Temporal lobe epilepsy

TPM: Topiramate

TR: repetition time

VIQ: Verbal scale of IQ

VOI: Volume of interest

VPA : Valproate

WAIS-III: Wechsler Adult Intelligence scale- III

WIS: Wechsler Intelligence scale

WISC: Wechsler Intelligence scale for children

WMS-r: Revised Wechsler Memory Scale

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INTRODUCTION

Magnetic resonance spectroscopy (MRS) is the only non-invasive diagnostic MRI technique that distinguished various metabolites on the basis of their slightly different chemical shifts or resonance frequency within the body. Although MRI and MRS are based on similar fundamental principles, many important differences exist between these two techniques. The major difference is that MRI produces visual images where as MRS obtains chemical information that may be expressed as numerical values. The distinction between MRI and MRS has now been blurred by the development of magnetic resonance spectroscopic imaging (MRSI), which provides metabolic information in an imaging format ***(Hammen et al., 2003).***

The major clinical use of MRS is to study the brain metabolites. High resolution (1H-MRS) spectra showed N-acetylaspartate (NAA), Choline (Cho), Creatine (Cr), gamma-Aminobutyric acid (GABA) and Glutamate. Difference in spectra has been noted between gray and white matter and between different regions of the brain. Immunohistochemical studies have suggested that NAA is localized exclusively in neurons and their processes throughout the CNS ***(Moffett et al., 1991; Simmons et al., 1991; Urenjak et al., 1993).***

Idiopathic generalized epilepsy (IGE) is characterized by the clinical triad of typical absences, tonic-clonic seizures and myoclonic jerks, with their onset in the first two decades. The neuroanatomical basis and the neurochemical abnormalities that underlay IGE are not fully defined that

means that the relationship between excitatory and inhibitory mechanisms in IGE remains uncertain (***Avoli et al., 2001; Bernasconi et al., 2003)***.

Experimental work in animal models of generalized epilepsy and clinical data in human with idiopathic generalized epilepsy indicate that thalamo-cortical circuit is involved in the generation of epileptic activity. While it is generally accepted that thalamo-cortical loop is abnormal in idiopathic generalized epilepsy, it is uncertain whether this loop is similarly affected among different IGE syndromes (***Savic et al., 2004)***.

A negative correlation has been found between NAA/creatine and the duration of epilepsy, and a relation between frequent generalized tonic-clonic seizures and low thalamic NAA concentrations. This suggests progressive thalamic dysfunction in patients with IGE (***Savic et al., 2000; Savic et al., 2004; Salmenpera and Duncan 2005)***.

AIM OF THE WORK

The aim of this study is to verify cognitive impairment in IGE patients, and to quantify the neurometabolites in two brain regions concerned with cognition; the thalamus and the prefrontal cortex, in a trial to find a possible link between neuronal dysfunction, evidenced by change in neurometabolites, and the presence of cognitive deficits in IGE patients, which may provide an objective basis to explain the prevalence of such cognitive impairment among epileptics. We also aim to correlate the findings with a number of epilepsy-related variables; as age at seizure onset, seizure frequency and duration of epilepsy.