NON PHARMACOLOGICAL TREATMENT OF EPILEPSY

Essay

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SUMMARY AND CONCLUSION

Drug resistant epilepsy is an everyday challenge facing neurologists owing about one third of patients with epilepsy. Those who did not achieve complete seizure control for 12 consecutive months with the first two or three Anti-epileptic drugs were given the predictive diagnosis of refractory or drug-resistant epilepsy, 20 % of those with generalized epilepsy and around 35% of those with partial epilepsy.

Since about one third of epilepsy is refractory to pharmacological treatment new modalities of treatment have emerged in recent years, many of these being non-pharmacological as epilepsy surgeries, deep brain stimulation (DBS), transmagnetic stimulation (TMS), vagal nerve stimulation and life style modification such as ketogenic diet and sleep therapy as well as gene and cell therapy which are still under trials.

The ketogenic diet could be considered the first treatment for epilepsy ever used with historical background since patients were put into strict fasting, ketogenic diet is achieved by too low a proportion of carbohydrate and too high a proportion of fat which inturn resembles fasting. The mechanism of action is not very well understood yet the efficacy of this treatment is very well established and studied with 30 to70 percent of patients having more than

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List of Abbreviations

Abbrev.	Meaning
AA	Arachidonic acid
AAVs	Adeno- associated viral vectors
ABA	Applied Behavioral Analysis
AChE	Acetyl Choline Esterase
ADK	Adenosine Kinase
ADT	After Discharge Threshold
AEDs	Antiepileptic Drugs
ANT	Anterior Nucleus of Thalamus
ATP	Adenosine Triphosphate
BDNF	Brain- Derived Neurotrophic Factor
BLA	Basolateral Amygdala
BP	Bis-phosphate
CA1	Cortical Area 1
CN	Cranial Nerves
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
DBS	Deep Brain stimulation
DHA	Docosahexaenoic acid
DNA	Dioxynucleic acid
DPCPX	8 cyclopentyl- 1,3- dipropyl- xanthine
ECT	Electro- Convulsive Therapy
ED	Epileptiform Discharge
EEG	Electro-encephalogram
EMG	Electro-myograhy
EPA	Eicosapentaenoic acid
ES	Embryonic Stem Cell
ESC	Embryonic Stem Cell

List of Abbreviations

Abbrev.	Meaning
ESNPs	Embryonic Stem Cell Derived Neural Precursor Grafts
FDA	Food and Drug Administration
Fepsp	Functional Excitatory Postsynaptic Potentials
FF	Fimria- fornix
FGF	Fibroblast Growth Factors
Fmri	Functional Magnetic Resonance Imaging
GABA	Gama- amino Butyric Acid
GAD	Glutamic Acid Decarboxylase
GEE	Generalized Estimating Equations
GLUT	Gltamine
GSH	Glutathione
HFV	Human Foamy Virus
hNT	Human Neuro-committed Teratocarcinoma
HSV	Herpes Simplex Virus
Hz	Hertez
ICU	Intensive Care Unit
IPG	Internal Pulse Generator
IV	Intravenous
KA	Kainic Acid
KD	Ketogenic Diet
LC	Locus coeruleus
MCT	Medium Chain fatty acid
MRI	Magnetic Resonance Imaging
MS	Medial Septum
MT	Motor Threshold
NA	Nor Adrenaline
NCP	Neuro Cybernetic Prothesis

List of Abbreviations

Abbrev.	Meaning
NE	Norepinephrin
NINDS	National Institute of Neurological Disorders & Stroke
NO	Nitric Oxide
NPY	Neuro peptide Y
NTS	Nucleus of the solitary tract
OCD	Obsessive Compulsive Disorder
6- OHDA	6 Hydroxy Dopamine
OSA	Obstructive Sleep Apnea
OSAS	Obstructive Sleep Apnea syndrome
PB	Parabrachial nucleus
PC	Pyriform Cortex
PDA	Personal Digital Assistant
PET	Positron emission Tomography
PUFAs	Poly-unsaturated Fatty Acids
QOL	Quality of Life
Raav	Recombinant Adeno Associated Virus
RMT	Resting Motor threshold
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
Rtms	Repetitive Trans Magnetic Stimulution
SCPs	Slow Cortical Potentials
SD	Sleep Deprivation
SE	Status Epilepticus
SMA	Sensorimotor Area
SMR	Sensorimotor Rhythm
SNr	Substantia nigra pars reticulata
SPECT	Single- photon emission computed tomography

List of Abbreviations

Abbrev.	Meaning
SVZ	Sub Ventricular Zones
TES	Trans cranial Electric Stimulation
TLE	Temporal lobe epilepsy
TMS	Trans cranial Magnetic Stimulation
UCPs	Uncoupling Proteins
VDB	Vertical limb of the diagonal band of Broca
VNS	Vagal Nerve Stimulation

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INTRODUCTION

Epilepsy or correctly a seizure is defined in physiological terms, being "the name for occasional sudden, excessive, rapid and local discharges of grey matter". It is more difficult to offer a comprehensive clinical definition of epileptic seizures because of varied clinical manifestations produced by neuronal discharge. However an epileptic seizure can be defined as an intermittent and stereotyped disturbance of consciousness, behavior, emotion, motor function or sensation that on clinical grounds is believed to result from cortical neuronal discharge ***(Chadwick, 2009).***

Despite problems with differing definitions of epilepsy and case ascertainment methods, there is remarkable agreement about epidemiology of epilepsy in different populations in the developed world. Incidence rates vary in the range of 20-55 /100000 per year were as the prevalence for active epilepsy is in the range of 4-10/1000 ***(Sander, 2003).*** Twenty to thirty per cent of patients with epilepsy never achieve remission they have refractory epilepsy that is associated with psychosocial handicap ***(Jacoby et al., 1996).***

Epilepsy is refractory when seizures are so frequent or severe that they limit the patient's ability to live life fully according to his or her wishes or necessitate the use of medications that, although effective, produce adverse effects. In spite of medical therapy, seizures persist in approximately

20 percent of patients with primary generalized epilepsy and 35 percent of those with partial epilepsy ***(Devinsky, 1999).***

Since about one third of epilepsy is refractory to pharmacological treatment new modalities of treatment have emerged in recent years, many of these being non-pharmacological as epilepsy surgeries, deep brain stimulation (DBS), transmagnetic stimulation(TMS), vagal nerve stimulation and life style modification such as ketogenic diet and sleep therapy, which will be considered as the main issue of our review.

Families of children with epilepsy now ask about the ketogenic diet at clinic visits. Is it effective and safe to use for treatment of epilepsy? ANSWER: The ketogenic diet can be considered an option for children with intractable epilepsy who use multiple antiepileptic drugs. It is a treatment of choice for seizures associated with glucose transporter protein deficiency syndrome (ie, De Vivo disease) and pyruvate dehydrogenase complex deficiency. The diet's strictness, unpalatability, and side effects limit its use, adversely affecting patients' compliance and clinical efficacy ***(Rogovik and Goldman, 2010).***

Most seizures can be controlled by a single antiepileptic drug but sometimes seizures are drug-resistant. The review of trials found that VNS is effective when used with one or more antiepileptic drugs to reduce the number of seizures for people with drug-resistant partial epilepsy. Adverse effects

were hoarseness, cough, and neck pain ***(Privitera et al., 2002).***

TMS is a non-invasive brain stimulation technique which, over the last 25 years, has greatly expanded from a simple method for stimulating the motor cortex to an invaluable tool with multiple researches, diagnostic and even therapeutic applications. In this review, we discuss the use of repetitive TMS as a means of suppressing cortical hyper excitability in drug-resistant epilepsies. The theoretical background and the experimental evidence in favor of this novel therapeutic approach are presented, and a number of open-label and controlled studies in patients with various forms of focal epilepsy are reviewed. It is concluded that, although the therapeutic effects of repetitive TMS in epilepsy appear rather limited, further clinical testing of this rapidly evolving technology is warranted ***(Kimiskidis, 2010).***

Surgical treatment emerges as a therapeutic option for refractory status epilepticus (RSE) in children. Surgical approaches for RSE include focal cortical resections, hemispherectomies, multiple subpial transections, and rarely corpus callosotomy and vagal nerve stimulator implantation. Resective surgery has shown immediate- and long-term benefits in cases of definite localization of the epileptogenic focus by electrographic and imaging data ***(Vendrame and Loddenkemper, 2010)***.

Since the development of DBS for Parkinson's disease, DBS has been suggested as a treatment option for various other neurological disorders. Stimulation of deep brain structures for refractory epilepsy appears to be a safe treatment option with promising results. As research on the evaluation and optimization of DBS for refractory epilepsy may be difficult and unethical in patients, studies on animal models of epilepsy are indispensable. Various brain structures and specific nuclei such as the basal ganglia, the cerebellum, the locus coeruleus and temporal lobe structures have been investigated as target areas for DBS. Additionally, a wide variety of stimulation parameters are available, with a range of stimulation frequencies, pulse widths and stimulation intensities. This review provides an overview of the relevant literature on studies of DBS for epilepsy. Knowledge gained from animal studies can be used to answer questions regarding the optimal brain targets and stimulation parameters in human applications ***(Wyckhuys et al., 2009).***

Approximately 30% of epilepsies are believed to be idiopathic or of genetic origin. Most of them are complex diseases with both genetic and environmental causation; however autosomal dominant monogenic epilepsies have also been identified, with the majority resulting from polymorphism in ion channels. A mutation in the nicotinic acetylcholine receptor α4 was the first autosomal defect identified in epileptic patients with nocturnal frontal lobe epilepsy .Since then, more than 12 mutations associated with channelopathies have been identified. Results from