Tandem Mass Spectrometry In Patients with Drug Resistant Epilepsy

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List of Abbreviations

Abb.	Full term
AED	Antiepileptic drugs
ASDs	Antiseizure drugs
CAH	congenital adrenal hyperplasia
DALYs	Disability adjusted life years
DBS	Dried blood spot
DRE	Drug resistance epilepsy
GLUT1	Glucose transporter type 1
IE	Intractable epilepsy
MCAD	Medium-chain Acyl-CoA Dehydrogenase
MSU	maple syrup urine
MTS	Mesial temporal sclerosis
NBS	Newborn screening
PDH	Pyruvate dehydrogenase
SUDEP	Sudden unexpected death in epilepsy
TLE	Temporal lobe epilepsy
VNS	Vagus nerve stimulation

INTRODUCTION

Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. It is important to note that no seizure frequency requirement is necessary to meet the definition. Thus, an individual with one seizure per year can be regarded as treatment resistant ***(Kwan and Golyala, 2017)*.**

The development of pharmacokinetic (metabolic) and pharmacodynamic (functional) tolerances may explain the loss of efficacy of almost all first-, second-, and third-generation AEDs with prolonged use. This phenomenon may be a significant reason for medication failure in some patients ***(Enid and Farrell, 2016).***

Drug-responsive epilepsy in which the patient receiving AED regimen has been seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer ***(Kwan and Golyala, 2017).***

Inherited metabolic abnormality was a common influential factor in the pathogenesis of IE, especially in infantile spasms. Screening of inborn metabolic abnormality in children with IE should be conducted as early as possible, to achieve early treatment and improve their prognosis ***(Lui et al., 2016).***

Inborn error of metabolisms are a collection of rare genetic diseases that generally result from a deficiency of an intracellular component (e.g., an enzyme or transporter) of a metabolic pathway, resulting in an accumulation of a substrate or intermediate in a pathway and/or reduced ability to synthesize essential compounds. Often the central nervous system (CNS) is affected, leading to neurological disease ***(Emma et al., 2014).***

Although these disorders are individually rare, collectively they account for a significant portion of childhood disability and deaths. Most of the disorders are inherited as autosomal recessive whereas autosomal dominant and X-linked disorders are also present. The clinical signs and symptoms arise from the accumulation of the toxic substrate, deficiency of the product, or both. Depending on the residual activity of the deficient enzyme, the initiation of the clinical picture may vary starting from the newborn period up until adulthood ***(Ezgu, 2016).***

The following clues should raise the suspicion of an inherited metabolic disorder: the marriage is consanguineous; there is a history of recurrent abortion; there is a history of unexplained neonatal death in sib-lings especially associated with acidosis, coma, and convulsions, picture like encephalopathy; a sibling has been diagnosed as suffering from

an IEM. In certain developed and developing countries, neonatal screen for metabolic disorders allows diagnosis and treatment in the pre-clinical phase, so that the adverse consequences of such disorders can be prevented. Metabolic disorders for which newborn screening are conducted include phenylketonuria (PKU), galactosaemia, maple syrup urine disease (MSUD), homocystinuria, and biotinidase deficiency ***(Vairo et al., 2017).***

Aim of the Work

The aim of this study is to detect the inherited metabolic abnormalities in children with drug resistant epilepsy to provide early diagnosis and treatment.

Chapter 1
INTRACTABLE EPILEPSY

Epilepsy

The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome ***(Fisher et al., 2015).***

Types of epilepsy

- Seizure type

Seizures are classified into focal onset, generalized onset, and unknown onset (***Fisher et al., 2017).***

- Epilepsy type

Generalized Epilepsy, the patient would typically show generalized spike-wave activity on EEG. Individuals with generalized epilepsies may have a range of seizure types including absence, myoclonic, atonic, tonic, and tonic-clonic seizures ***(Nordli, 2016).***

Focal Epilepsies include unifocal and multifocal disorders as well as seizures involving one hemisphere. A range of seizure types can be seen including focal aware seizures,

focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic-clonic seizures. The interictal EEG typically shows focal epileptiform discharges, but the diagnosis is made on clinical grounds, supported by EEG findings ***(Nordli, 2016).***

Combined Generalized and Focal Epilepsies patients who have both generalized and focal seizures. The diagnosis is made on clinical grounds, supported by EEG findings. The interictal EEG may show both generalized spike-wave and focal epileptiform discharges ***(Nordli, 2016).***

The term "*Unknown"* is used to denote where it is understood that the patient has Epilepsy but the clinician is unable to determine if the Epilepsy Type is focal or generalized because there is insufficient information available. This may be for a variety of reasons. There may be no access to EEG, or the EEG studies may have been uninformative ***(Fisher et al., 2017).***

- Epilepsy syndrome

An epilepsy syndrome refers to a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together. It often has age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation, and sometimes prognosis. It may also have distinctive comorbidities such as intellectual and

psychiatric dysfunction, together with specific findings on EEG and imaging studies. It may have associated etiologic, prognostic, and treatment implications. It is important to note that an epilepsy syndrome does not have a one-to-one correlation with an etiologic diagnosis and serves a different purpose such as guiding management. There are many well-recognized syndromes, such as childhood absence epilepsy, West syndrome, and Dravet syndrome ***(Nordli, 2016).***

- Idiopathic Generalized Epilepsies

The IGEs encompass four well-established epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clonic Seizures Alone (formerly known as Generalized Tonic-Clonic Seizures on Awakening but modified in recognition that seizures can occur at any time of day ***(McTague et al., 2016).***

- Self-limited focal epilepsies

Typically beginning in childhood. The most common is self-limited epilepsy with centrotemporal spikes, formerly called "benign epilepsy with centrotemporal spikes." Others included in this broad group are the self-limited occipital epilepsies of childhood, with the early-onset form described by Panayiotopoulos and the late-onset form by Gastaut. Other self-limited frontal lobe, temporal, and parietal lobe epilepsies have

been described with some beginning in adolescence and even adult life ***(Guerrini and Pellacani, 2012).***

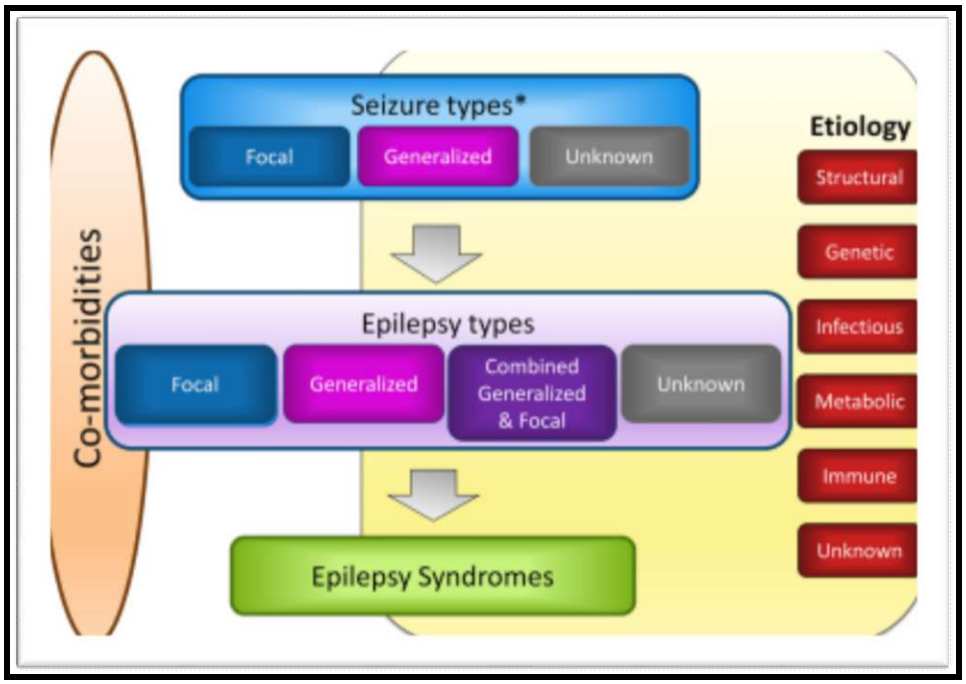

Figure (1): Framework for classification of the epilepsies ***(Fisher et al., 2017).***

Intractable Epilepsy

Epidemiology

The prevalence of epilepsy in developed countries ranges between 4 and 10 per 1, 000 individuals per year with much greater prevalence rates in developing and resource-poor countries and some estimates at greater than 130 per 1000 individuals per year ***(Laxera et al., 2014)***

Epilepsy is a common neurological disorder that affects over 70 million people worldwide. Despite the recent