

Glucose Transporter-1 (GLUT1) Deficiency Syndrome in Infants

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَأَنْزَلَ اللَّهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ تَكُنْ
تَعْلَمُ وَكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيمًا

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List of Abbreviations

<i>Abbrev.</i>	<i>Full term</i>
ACTH	: Adreno-corticotrophin hormone
AEDs	: Antiepileptic Drugs
CAE	: Childhood absence epilepsy
CC	: Corpus callosum
CSF	: Cerebro-spinal fluid
CT	: computerised tomography
EEG	: The electroencephalogram
EMS	: Extended metabolic screening
FDG	: fluoro-deoxy-glucose
FH	: Family history
GABA	: γ -aminobutyric acid
GEFS+	: Generalized epilepsy with febrile seizures plus
GLUT	: Glucose transporter
GLUT1-DS	: Glucose transporter-1 deficiency syndrome
HTLV	: Human T-lymphotropic virus
ICU	: Intensive care unit
IGE	: Idiopathic generalized epilepsy
ILAE	: International League against Epilepsy
IQ	: intelligence quotient
IVIG	: Intravenous immunoglobulin in Epilepsy
LGID	: low-glycemic index diet
LP	: lumbar puncture
MAD	: Modified Atkins diet
MRI	: Mental retardation
MSI	: Magnetic source imaging
MST	: Multiple subpial transections

List of Abbreviations *(Cont.)*

<i>Abbrev.</i>	<i>Full term</i>
NAD	: No abnormality detected
NICE	: The National Institute of Clinical Excellence
PCR	: polymerase chain reaction
PED	: paroxysmal exertion-induced dystonia
SD	: Standard deviation
SE	: Status epilepticus
SLC2	: Solute carrier family 2
SPECT	: Single photon emission computed tomography
TLE	: Temporal lobe epilepsy
USA	: united States of America
VNS	: Vagus nerve stimulation
WHO	: World Health Organization

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Introduction

In 1991 GLUT1 deficiency syndrome (GLUTDS) was first described as an early-onset childhood epileptic encephalopathy caused by impaired glucose transport across the blood-brain barrier and into brain cells (*De Vivo et al., 1991*). Defects in the facilitated glucose transporter GLUT1 resulted in low CSF glucose levels termed hypoglycorrachia. The majority of patients carry mutations in the SLC2A1 gene encoding the GLUT1 transporter. The classical phenotype of an early-onset epileptic encephalopathy rapidly expanded, to date the complex clinical pheno-type includes an epileptic encephalopathy with complex movement disorders in variable combinations, paroxysmal events, specific seizure types, and adult manifestations. The low glucose concentration in the cerebrospinal fluid (CSF) termed hypoglycorrachia represents the biochemical hallmark of the disease and thus the diagnostic gold standard .

There is a classical manifestation of GLUT1DS: intractable epilepsy within the first six months of life followed by global developmental delay and a complex movement disorder (*Klepper and Leiendecker, 2007; Leen et al., 2010*). Symptoms may increase on fasting and improve on carbohydrate intake reflecting the cerebral energy deficit (*Brockmann et al.,*

2001). Seizures are of various types and often not controlled by anticonvulsant medication (*Klepper et al., 200*).

When GLUT1DS is suspected, the essential diagnostic step is to perform a controlled lumbar puncture. Patients should fast for 4-6 h to achieve a glucose steady state within the CSF compartment. The diagnosis of GLUT1DS by means of a lumbar puncture is confirmed if: CSF glucose concentration is < 2.2 mmol/l (<40 mg/dl) (*Rotstein and De Vivo, 2010*) GLUT-1DS was diagnosed also with CSF glucose 60 mg/dl especially with milder phenotypes and with patients with movement disorders without epilepsy (*Suls et al 2008, Sul s et al 2009, Mullen et al 2010, Weber et al2008*). And it was recommended that all patients with normal blood glucose concentration and CSF glucose concentration lower than 60 mg/dl should perform molecular genetic testing of SLC2A1 (*Wang et al., 2002*), (exclude prolonged seizures/status epilepticus or hypoglycemia) concentrations of CSF cells, protein, and CSF lactate are normal (exclude CSF infection). CSF lactate is never elevated in GLUT1DS (*Klepper and Leiendecker, 2007; Leen et al., 2010*). The ratio of CSF glucose vs. blood glucose concentration can be an additional biomarker and should be <0.45 . Blood glucose should be determined immediately before the lumbar puncture to avoid stress-related hyperglycemia (*Klepper and Leiendecker, 2007*).

The ketogenic diet remains the therapy of choice for GLUT1DS. It mimics the metabolic state of fasting but maintains ketosis by the utilization of nutritional fat rather than body fat. In the setting of hypoglycorrhachia ketones serve as an alternative fuel to the brain and effectively reverse the cerebral energy crisis. The response to a classical 4:1 or 3:1 (fat: carbohydrate and protein) ketogenic diet in most patients will be impressive with immediate seizure control and improvement motor and cognitive function (*Klepper and Leindecker, 2007; Klepper et al., 2005; and Leen et al., 2010*). The modified Atkins Diet (MAD) represents restricts of carbohydrates to 10 g/day (15 g/day in adults) while encouraging high fat foods (*Kossoff and Dorward, 2008*). It is similar in fat composition to a 0.9:1 ketogenic ratio (fat: carbohydrate and protein) diet, with approximately 65% of the calories from fat sources. In GLUT1DS MAD has been used successfully (*Ito et al., 2008*). The low glycemic index diet liberalizes the extreme carbohydrate restriction of the KD but restricts the type of carbohydrate containing foods to those that produce relatively small changes in blood glucose (*Pfeifer et al., 2008*).

Aim of the Work

To try to find the prevalence of glucose transporter type 1 deficiency syndrome in infants with intractable epilepsy.

Part (I): Epilepsy and Intractable Epilepsy

1- Epilepsy

► Introduction

As a result of advances in technology and enhanced medical knowledge, children with chronic diseases that were previously fatal in early childhood now survive to be young adults. Chronic childhood illnesses have, therefore, become one of the primary health priorities that need intensive research. These diseases vary widely in their nature and severity, their influence on the child's behavior, daily activity, normal growth, and their interference with scholastic achievement. Among the important childhood chronic diseases is epilepsy (*Isaacs and Sewell, 2003*).

► Epidemiology and morbidity indices

● *Incidence by seizure type*

Seizure types vary in incidence. Generalized tonic clonic or various types of partial seizures dominate about 75% of childhood epilepsy syndromes and partial seizures seemed to occur more often than generalized seizures (*Kotsopoulos et al., 2002*). Absence epilepsies account for approximately 15% and other generalized epilepsies account for only 10%. This latter group consists of the majority of the

catastrophic syndromes, including West syndrome, Lenox-Gastaut syndrome, and severe myoclonic epilepsy of infancy (*Camfield et al., 1996*).

● **Worldwide distribution**

Around 50 millions people worldwide have epilepsy with nearly 90% of them are found in developing regions (*WHO, 2009*). In developed countries the incidence of epilepsy varies between 50 and 100 per 100,000 persons per year (*Kobau et al., 2007*).

The incidence rates are higher in developing countries due to exposure to higher risks of permanent brain damage like CNS infection, head trauma, perinatal complications and malnutrition in addition to different population demographic characteristics, poor antenatal care, and lower standards of epilepsy care (*Hopkins and Shorvon, 1995; Leary et al., 1999; Tellez-Zenteno et al., 2004*). However, seizure prevalence may be under-reported because of reluctance to disclose a potentially stigmatizing condition (*Jacoby, 2002*).

In Egypt, *Mekky (1981)* studied the epidemiology of epilepsy and reported a prevalence of 4.1 per 1000 population and the highest prevalence was in the age group 10-19 years reaching 7.4 per 1000. *El-Afify (1981)* studied epilepsy in El-Sahel Teaching Hospital and reported a prevalence of 9.8 per 1000 population, whereas *El-Khayat et al. (1994)* studied the

epidemiology of epilepsy among Egyptian infants and children and reported a prevalence rate of 3.5 per 1000.

In Upper Egypt, Assiut Governorate, the prevalence of epilepsy was reported by *Shawki (1995)* to be 12.9 per 1000 population, while *Massoud (1997)*, in his study on 195 school children in Cairo, reported a lower overall prevalence of 1.9 per 1000.

Kandil et al. (2007) conducted a hospital-based study to evaluate the frequency and pattern of childhood epilepsy in Upper Egypt among population with age range from birth to 18 years. They found that 48% had age ranges from 12-18 years, 78% were rural residents and 62.2% were illiterate. About 70% had age at onset of 5.9 ± 3.5 years. Parental consanguinity was reported in 41% and family history of epilepsy was reported in 17.3%.

The incidence and prevalence of epilepsy in some developed and developing countries, Arab, African, and tropical countries are illustrated in (**Appendix I**).

- *Age*

Epilepsy is the second most common chronic neurological disorder after stroke affecting approximately 0.5–2% of the population (*Boon et al., 2001*). It is estimated