Ketogenic diet: treatment of cerebral glucose transporter deficiency glut 1

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Abstract

Epilepsies in the neonatal period could be caused by inborn errors of metabolism; they are rare diseases, usually with intractable epileptic seizures. Some of these epilepsies have a specific treatment, like epilepsies that respond to vitamins or to the cerebral glucose transporter deficiency Glut 1.

We reported the case of a patient with deficiency of glut 1 and intractable epilepsy, treated with ketogenic diet that achieves complete control of the epileptic seizures.

Introduction

Several innate errors of metabolism present epileptic neonatal seizures that are treatable. These are uncommon diseases; they present alterations in neurodevelopment, long-term cognitive impairment that could be fatal if not controlled. These disorders can be divided in those that respond to treatment with vitamins such as pyridoxine dependent epilepsies, pyridoxal phosphate oxidase deficiency, folinic acid-responsive seizures, biotinidase deficiency and other metabolic epilepsies such as Glut 1 deficiency. Creatine deficiency syndrome, and phenylketonuria resistant to nutritional treatment [Surtees R and Wolf N, 2007].

The diagnostic of these diseases requires biochemical and genetics specialized studies, which may cause delay in the diagnostic, in many cases symptomatic treatments begin before the diagnostic has been confirmed due to the risk of death or severe neurological compromise of the patients.

Biotinidase deficiency is treated with the administration of biotin. It improves the epileptic seizures, the skin and neurodevelopment. Pyridoxine-dependent epilepsy is treated with the administration of
pyridoxine, parenteral and oral, depending on the clinical state of the patient; creatine deficiency is treated with creatine, arginine restriction and ornithine supplement, the GLUT 1 deficiency syndrome with ketogenic diet. GLUT1 DS, GID or the De Vivo disease (OMIM 606777) was described for the De Vivo in 1991 [De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI, 1999].

Glut 1 carries glucose through the blood-brain barrier; it facilitates glucose transportation across the luminal membranes of endothelium of the cerebral microcirculation and astrocyte plasma membrane. It is a cerebral metabolism disorder of genetic origin. Glut 1 transporter is a glycoprotein with 492 amino acids, with molecular weight of 45 a 55 K Da, it is expressed in vascular endothelium cells, blood-brain barrier, astrocytes and neurons, Glut 1 is encoded by the gen SLC2A1 which is composed by 10 axons, 9 introns, located in the short arm of chromosome 1 (1p35.31.30). It is an autosomal dominant disorder [Mueckler M, Caruso C, Baldwin SA et al, 1985].

This deficiency causes that the patients Glut 1 deficiency, does not have enough glucose to normal operation and brain growth [Schneider SA, Paisan-Ruiz C, Garcia-Gorostiaga I, Quinn NP, Weber YG, Lerche H et al, 2009].

**Clinical Manifestations**

In most of the reported cases, pregnancy and birth are normal and newborns are normal as well.

**Classic Form:**

Early –onset (0 to 24 months): It is presented with acquired microcephaly, refractory epilepsy to antiepileptic drugs, early epileptic encephalopathy, delay of psychomotor development, ataxia, dysarthria and spasticity. The symptoms generally get worse with fasting [Wang D et al, 2005]. Seizures start between the first and fourth months of age, other paroxysmal events such as apneas, abnormal ocular movements, opsoclonus, and non-epileptic paroxysmal events can precede epileptic seizures. The electroencephalogram shows multifocal spikes that tend to generalize.


Late onset: Over 25 months
The patients develop cognitive deficit with different degrees of severity, paroxysmal exercise-induced dyskinesia and epilepsy. There is no hepatomegaly, renal and hepatic function remains normal, plasma electrolytes, lactate, uric acid amino acids, and carnitine acyl carnitine normal as well. The no-classic phenotype usually has attenuated symptoms, intermittent ataxia, paroxysmal somnolence induced by exercise, hemiparesis, anomalies of the movement and the posture, sleep disorder, headache, varying degrees of cognitive alteration with or without epilepsy [Wang D, Pascual JM, Yang H et al, 2005; Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Maljevic S et al, 2008].

**Diagnostic**

The clinical symptoms lead to the diagnostic through the analysis in the cerebro-spinal fluid obtained by lumbar puncture. In the CSF glucose is abnormally low (less than 40 mg/dl) while in the blood is normal, CSF lactate is low or normal (less than 1.4 mmol). The rate between LCR glucose and plasma is less than 0.4. It is confirmed with search of mutations in the SLC2A1 gen, or functional testing as uptake of 3-O-metil-D-Glucose on erythrocytes lower than 50%, positron emission tomography (PET) revealed a global decrease in glucose uptake in the temporal cortex, in thalamus and basal ganglia [Pascual JM, Van Heertum RL Wang D, Engelstad K, De Vivo DC, 2002].

The delay in the diagnosis of Glut1 transporter deficiency syndrome occurs in ranges from months to years after the start of epileptic seizures. Brain imaging of MRI and CT may be normal or have slight nonspecific changes in the volume of cerebral cortex. As a differential diagnosis the Rett syndrome, Angelman syndrome, neuronal ceroid lipofuscinosis, opsoclonus myoclonus syndrome for neuroblastoma or paraneoplastic syndrome and epileptic encephalopathy with genetic origin are included [De Giorgis and Veggiotti P, 2013].

**Treatment:**
The ketogenic diet was introduced as a treatment for GLUT IDS in 1991. The treatment is based on the establishment of ketogenic diet in order to provide energy to the brain though the reproduction of ketones bodies, with the supplement of minerals, L-carnitine and vitamins.
The ketogenic diet must be started as soon as possible and must be kept at least through the adolescence. It is not used only in patients with epilepsy but also with movement disorders without epilepsy.

The response of the ketogenic diet in the classic phenotype in a study done in groups of 46 patients reported by W.G Leen is the following: 80% of patients began ketogenic diet, 62% of them were free of seizures and 24% had a decreased in the amount seizures [Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T et al, 2010].

The frequency or severity of the involuntary movements was reduced on a 40 % and at the 7% completely disappeared; a subjective improvement of cognitive function was reported after initiation of the diet [Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T et al, 2010].

The ketogenic diet contains medium chain triglycerides to optimize the antiepileptic response [Chang P, Plant N, Chen PE, Walker MC, Williams RSB, 2013], triheptanoin is a dietary supplement that boosts the brain anabolism and brain energy production [Chang P, Plant N, Chen PE, Walker MC, Williams RSB, 2013]. Some patients adapt themselves to brain glucose deficiency due to the permanent production of ketone bodies since early life, this excessive ketone bodies production provide an alternative energy substrate for the brain and it suggests a cerebral metabolic adaptation, with up regulation of monocarboxylic acid transporters (MCT1) at the blood- brain barrier induced by neuroglycopenia [Chenovard A, Vuillaume- Barrot SKA, 2014].

The ketones bodies are metabolized exclusively in the mitochondrial matrix to acetyl-coA go into the brain through a monocarboxylic transportation (MCT). The association with the deficiency of Co Q has been described, as a new factor on the pathogenesis of GID and its supplementation may be an adjuvant part of the treatment [Yubero et al, 2014].

The ketogenic diet is highly effective on the control of epileptic seizures due to the several action mechanisms proposed:

1. Reduction of the carbohydrates ingest and the activation of adenosine.
2. The activation of ATP sensitive potassium channels.

The effect of this diet is not clear for the neurologic development and more studies and monitoring are required [Danial N, Hartman A, Stafstrom CE, Thio L, 2013].

The barbiturates are inhibitors of the glucose transportation that make worse the symptoms of GLUT1D.

Clinical report
We report a Colombian 3 years old patient, female gender who has consult a pediatric neurologist; with drug resistant epilepsy, microcephaly and motor abnormalities. She began at her first month of age with multiple daily epileptic seizures, which describes tonic and myoclonic crisis (more than 100 per day) involuntary eye movements. She received different antiepileptic drugs to serum doses and levels in therapeutic ranges that included valproic acid, levetiracetam, vigabatrin, lamotrigine and clobazam.

She is the fifth daughter, with parents non consanguineous. The pregnancy and birth were normal, weigh, size at birth were normal as well and her other four siblings are normal.

The Glut 1 diagnostic was made at age of 2 years by measuring glucose in cerebro-spinal fluid and their relation with plasma glucose which was lower than 0.3 without alteration of lactic acid.

The tests of hepatic function, renal function, electrolytes, plasma glycaemia and uric acid were normal; amino acids chromatography, in plasma and urine were normal, organic acids normal and ammonium normal.

Brain images magnetic resonance were normal. Electroencephalogram showed hypsarrhythmia.

Started the ketogenic diet at 2 years 11 months of age, administrated by a gastrostomy tube with a special formula based on lipids: 92% of total calories, of which, 21% are MCT and 79% are LCT and a ketogenic ratio: 4:1, added with vitamins and trace elements for ketogenic diet on refractory epilepsy.

Evolution
At the first month of treatment the tonic seizure disappeared, keeping some myoclonic activity, after 6 months of treatment, she presented tree myoclonic crisis per day for less than one-second duration, there was no other type of seizure. After one year of treatment she was 8 myoclonic crisis per month.

Nowadays she is currently free of seizures.

During the strict follow up of the nutritional status, the results proved a proper gain of weight and size for the age. On admission, the patient had mild malnutrition but achieved, nutritional recovery.
Since the first week of treatment periodic quantification of ketone bodies in urine it remained, the electrolytes, cholesterol, triglycerides and plasmatic lipoproteins were normal. During the treatment, the patient has not showed any side effects related to the diet.
At the present time the patience has been 18 months of treatment with ketogenic diet, presenting tolerance and seizures control. The doses have been modified progressively, and the antiepileptic medicine quantity has been administrated with less sugar content.

**Discussion**

The epileptic encephalopathies of perinatal beginning, may have origin in treatable inborn errors of metabolism as GLUT 1 deficiency in some patients as the one that we reported; classical forms of presentation are submit. However, the diagnosis is delayed by the need for specialized biochemical tests. The clinical evolution is leading to the initiation of the treatment and clinical response with crisis controlling helps to confirm the diagnosis.

It is possible to achieve adequate nutritional contribution with ketogenic diet, in patients especially those who are fed by gastrostomy tube, due to their severe neurological compromise. These patients require constant clinical and biochemical monitoring. Adherence is one of the difficulties in maintaining long term ketogenic diet, nevertheless with personalized diets and adequate monitoring they can achieve individual therapeutic goals in each patient.

**Conclusions**

Deficiency of cerebral glucose transporter Glut1 is a rare disease with predominant neurological symptoms and refractory epilepsy, susceptible for treatment with ketogenic diet.
GLU1DS can be diagnosed in presence of clear hypoglycorrhachia with an optimal response to the ketogenic diet.
Currently specific ketogenic diet protocols have been developed for refractory epilepsy, which optimize the adherence and the achievement of therapeutic objectives in these patients.
Early Glut 1 deficiency diagnostic is important since it can be treated with a ketogenic diet.

**BIBLIOGRAPHY**

Chenovard A, Vuillaumier-Barrot SKA. A cause of permanent Ketosis: Glut1 Deficiency september 2014 JIMD Reports.


