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THERAPEUTIC KETOSIS IN THE TREATMENT OF GLUCOSE TRANSPORTER DEFICIT SYNDROME (GLUT1)

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Abstract

GLUT1 (Glucose transporter type 1) deficiency syndrome (GLUT 1DS) is caused by an impaired glucose transport into the brain mediated by GLUT1, the glucose transporter at the blood-brain barrier (BBB). This syndrome has a broad clinical spectrum, which includes drug-resistant infantile seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, ataxia and dystonia.

Lumbar puncture should be taken into account as the first diagnostic step. Thereafter, other procedures should be included, such as the mutational analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene. This applies especially to patients with highly suggestive clinical findings and low levels of cerebrospinal fluid glucose (<50 mg/dl or ratio <0.60).

Early diagnosis of GLUT1 plays a key role because it allows prompt initiation of treatment with a ketogenic diet (KD), which provides ketones as an alternative fuel to the brain. Compliance has been found to be much better in GLUT1 than in the other conditions for which KD treatment is indicated. KD should therefore be introduced early to satisfy energy demands of the developing brain and should be maintained into puberty.

Many clinical manifestations respond to a ketogenic diet, which is typically maintained from diagnosis in infancy or childhood until seizures subside in adolescence. However, it is important to note that there is little evidence that the diet has any significant impact on cognition and individual autonomy. Indeed, the effects on neurodevelopment and on movement disorders are less impressive.

Keywords: *GLUT1, epilepsy, Ketogenic Diet (KD), therapeutic ketosis.*

Introduction

GLUT1 deficiency syndrome was described for the first time in 1991 as a childhood epileptic encephalopathy with early onset (1). The classical phenotype ranges from mild motor and cognitive dysfunctions between seizures to severe neurological disability. In the most severe cases, patients are unable to speak or walk without support.

Glucose is the essential fuel for brain energy metabolism (2). GLUT 1DS is caused by an impaired glucose transport into the brain, mediated by GLUT I, the glucose transporter at the BBB (blood-brain barrier).

It is estimated that the adult brain consumes up to 25% of the body's total glucose supply at rest, while in the younger population it can use up to 80%. (3) GLUT1DS patients suffer from the following conditions: drug-resistant infantile seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, ataxia and dystonia (4). However, over the years, other clinical manifestations have been described, including paroxysmal exertion-induced dystonia, choreoathetosis, alternating hemiplegia, and migraine. Many patients (often those with the most disabling symptomatology) manifest brain hyper-excitation or deregulated excitability that translates into epilepsy. Atypical presentations include choreiform movements. The only genetic locus for GLUT1 known thus far is 1p34.2. (5)

The development of a series of animal models of the disease is expected to shed light on some standing questions.

GLUT 1DS is associated to different levels of cognitive impairment leading to dysfluency and expressive language deficits. In most patients, the CSF (cerebrospinal fluid)-to-blood glucose ratio is >0.50. (6) GLUT1DS diagnosis is usually achieved by means of molecular analysis of the SLC2A1 gene. Early diagnosis is key to start an early treatment with a ketogenic diet (KD), which is a high-fat, low carb diet mimicking the metabolic state of fasting. (6). Ketones employ a different transporter to access the CNS, providing the brain with an alternative source of fuel. This allows correcting the impaired brain energy metabolism and reducing the frequency of seizures, as well as the severity of the dystonic movement disorder. This mechanism relies on exogenous sources rather than on body fat for ketone production, so ketosis is maintained with no weight loss. Ketogenic diet proved to be a safe and effective diet during the past decades in drug-resistant childhood epilepsy (7). KD was developed by the Johns Hopkins University and it uses long-chain triglycerides (LCT fats). It consists of 4 g of fat to every 1 g of carbohydrate and protein combined (4:1 ration) with supplemental vitamins and minerals (7). Patients and caregivers are trained on how to measure and administer the diet. Therapeutic ketosis is usually monitored via urine and blood. The range of KD has increased significantly and it now includes other alternative diets, such as the low-glycemic index treatment (LGIT) (6).

From a technical point of view, treating GLUT 1DS with a ketogenic diet is not different from treating drug-resistant childhood epilepsy. Indeed, the diet has to be carbohydrate-restricted, tailored on the individual and supplemented with vitamins and minerals. However, the pathophysiological mechanisms are different. In drug-resistant childhood epilepsy, the mechanisms of how the diet works are still unclear, despite there is a better understanding of the anticonvulsant mechanisms (8). In GLUT 1DS, the KD plays a key role to provide alternative fuel; as mentioned above, KD should be introduced as early as possible when a diagnosis of GLUT 1DS is suspected. (2) GLUT1 deficiency syndrome should be taken into account in the differential diagnosis of any form of drug-resistant epilepsy (9). In infants, seizures usually have the following features: hypotonia, associated with brief, myoclonic limb jerks with a dazed expression.

Electroencephalography (EEG) recordings usually show multifocal spike discharges. In older children, seizures are usually myoclonic and generalized (10). Subjects with GLUT1DS usually have complex movement disorders with ataxia, dystonia, and chorea. These disorders are affected by different environmental stressors (11). Stressors include fasting, infections, prolonged exercise and anxiety. Epilepsy and movement disorders occur either separately or in combination. Severe motor disorders, including choreiform movements, have been observed without seizures (12).

Methods

A comprehensive literature review on KDs and relative anticonvulsant effect was conducted.

Results

A distinctive biomarker for GLUT1DS is low glucose concentration in CSF, also known as hypoglycorrhachia (13). This can be observed in other conditions, including infectious meningitis, mitochondrial diseases, and subarachnoid hemorrhage. Hypoglycorrhachia strongly suggests GLUT 1DS when these conditions are ruled out (6). In terms of diagnosis, lumbar puncture is the first step and should be performed on an empty stomach. In order to avoid stress-related hyperglycemia, blood samples used to assess glucose concentrations should be obtained immediately before the lumbar puncture. Initially, a CSF-to-blood glucose ratio of 0.33–0.37 (CSF concentration 40 mg/dl) was set as the cut-off value for a diagnosis of GLUT1DS in suspected cases. However, with the increasing recognition of milder allelic variants, higher values are now being applied. (6) This issue is still debated in literature. Weber et al. (14) suggest that milder phenotypes (especially those with movement disorders without epilepsy) can be associated with ratios of up to 0.59. Several attempts have been made to find a correlation between clinical severity and degree of hypoglycorrhachia, but there are still no conclusive results about this. This observation highlights that the normal range for CSF glucose levels have never been properly identified. This leads to the risk that some patients with normal glucose levels in the CSF might even go undiagnosed and untreated, so a molecular analysis of the SLC2A1 gene is an alternative gold standard for the diagnosis of GLUT1DS, when this condition is strongly suggested (9).

Discussion

It is interesting to highlight that Klepper and Leiendecker reported that about 30% in their cohort of 84 patients with low glucose concentration in CSF did not carry mutations; this suggests the existence of alternative disease mechanisms. In these patients with highly suggestive clinical findings and low CSF glucose, therapeutic ketosis should always be attempted. In the fasting state, brain glycogen storage is exhausted within minutes. The brain cannot use amino acids and fat to produce energy, so it switches to ketones as an alternative fuel. Ketones are generated in the liver from fatty acid degradation and enter the brain by the monocarboxylate transporter 1. The Ketogenic diet is a high fat, carbohydrate-restricted diet that mimics the metabolic state of fasting, used in drug-resistant childhood epilepsy. Novel indications for KD include disorders of brain energy metabolism such as pyruvate dehydrogenase deficiency and GLUT1DS. (15) Although, in epilepsy, the mechanism of action underlying the effectiveness of the KD is not yet clear, in GLUT1DS it essentially provides an alternative fuel source. The effectiveness of the KD in GLUT1DS might be increased by its anticonvulsant action. The vast majority of GLUT1DS patients are seizure free, allowing the withdrawal of anticonvulsant therapy (4). In the literature only a

few authors report that KD was not fully effective and antiepileptic therapy was not eliminated (16, 17). KD also proved to have a positive effect on movement disorders (18), including ataxia and dystonia. As reported above, therapeutic ketosis has a less significant impact on the developmental delay (4), but it is interesting to note that several authors have reported a significant increase in terms of alertness and activity in patients on KD. However, De Giorgis et al. (6) report that the introduction of KD in the first years of life in patients suffering from GLUT1DS guarantees a better outcome in terms of cognitive functioning. The developing brain needs energy, so KD should be started as early as possible in case GLUT1DS is suspected. The Modified Atkins Diet (MAD) is also well tolerated among patients and provides effective symptom control. This diet has additional strengths: it is easy to prepare and more palatable, which are strictly related to high compliance rates. Therapeutic ketosis has advanced considerably over the past years and it is currently taken into account as the first-line therapy in infantile spasms, myoclonic astatic epilepsy and status epilepticus. KD are being investigated for other illnesses, including neurological conditions, Alzheimer's Disease and cancer (19). Additional studies are required to fully understand the mechanisms by which metabolism-based therapies are so helpful in terms of anticonvulsant effects. In particular, KDs may be specifically effective in some epileptic syndromes, such as West syndrome, severe myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, febrile infection related epileptic syndrome, and drug-resistant idiopathic generalized epilepsies or refractory status epilepticus, as explained above (6). Short-term adverse events include the following: gastrointestinal symptoms, hyperlipidemia, and hypercalciuria, and frequently have mild severity in children and adults (20);
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potential long-term adverse effects include the following: nephrolitiasis, decreased bone density, and liver steatosis. Atherosclerotic effects remain a cause of concern. Patients on KDs should be monitored in specialized centers during the different stages of initiation, maintenance and withdrawal periods, in order to minimize adverse events and improve compliance. Although in recent years the majority of KD trials on children and adults with drug-resistant epilepsies are open-label, uncontrolled studies based on small samples, an increasing number of randomized controlled trials have provided better quality evidence on its efficacy (6). In line with the 2011 Italian consensus statement on KD therapy (21), the follow-up of GLUT1DS children and adults should include regular food and neurological assessments, and EEG tests should be performed at least five times during the first year of treatment, at baseline and after 3 months. Assessments should also include an assessment of cognitive and developmental levels, as well as blood and metabolic evaluations. With reference to adults, therapeutic ketosis can be helpful also in adulthood; even if epilepsy seems to disappear in adulthood, movement disorders persist. In addition KD may have neuroprotective effects (6). Additional measures may be included, such as pharmacological agents known to impair GLUT1 function. In conclusion, it is essential to diagnose this condition as early as possible to allow an early compensation through therapeutic ketosis: early identification of children with GLUT1DS is important to avoid submitting them to possibly ineffective or potentially detrimental treatments with antiepileptic therapies, and to make sure that young brains are provided with an alternative source of energy during a time of high cerebral metabolism. On the basis of the current knowledge in the literature, it is not possible to declare that the condition of GLUT1DS patients never deteriorates. The typical deficiency of glucose in the central nervous system, if allowed to persist for many years,

could be responsible for brain atrophy. This finding can be observed in Magnetic Resonance Imaging scans of these patients. And this condition can be responsible for a moderate but regular reduction of IQ (6). Ongoing research is required to shed light on the pathogenic mechanisms underlying different phenotypes. The availability of new animal models of GLUT 1DS and a growing cohort of patients could play a key role to provide answers to some of the many still open questions about this condition.

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