Report on GLUT1 Deficiency Syndrome Conference

Chicago, US, July 24th 2009

By W.G. Leen, MD

‘GLUT1 deficiency: from the beginning to now and beyond’

Dr. D.C. de Vivo (Professor of Pediatrics, Colombia University, New York) opens the conference with an overview on GLUT1 deficiency syndrome (GLUT1DS) from 1991, when diagnosis of GLUT1DS was first made, until now. He describes the process of glucose metabolism in the brain. Glucose is transported across the blood-brain barrier into astrocytes and neurons by GLUT1 and GLUT3. In astrocytes, glucose is metabolized into energy, glycogen, or lactate. Neurons use glucose, lactate or ketones as source of energy.

Erythrocyt uptake studies are still being performed in the US as a screening tool for GLUT1DS. In 100% of the patients with a lowered GLUT1 uptake in erythrocytes a mutation in the GLUT1 gene was found, while in patients with a normal glucose uptake only 1 patient had a mutation in the GLUT1 gene (a missense mutation that effected the efflux of glucose, whereas in other GLUT1DS patients the influx and efflux are affected).

Dr. de Vivo emphasizes that although we have learned a lot about GLUT1DS in the past years, many aspects remain to be clarified. We do not yet understand the large phenotypic diversity in GLUT1DS. He hypothesizes whether breast milk may be neuroprotective in GLUT1DS, as breast milk is high in fat. A reactive astrocytosis is seen in the brain of GLUT1DS mice from day 21-90 after birth (after they start suckling).

Dr. de Vivo pleads for improved diagnostics, and underlines the ‘MFLP’ of many doctors (‘morbid fear of lumbar puncture’). Because GLUT1DS is a treatable disorder and the ketogenic diet may even improves outcome, newborn screening can be justified in the future. A screening tool for this purpose, however, is yet unavailable. He hopes that in the future a more effective treatment or even cure for GLUT1DS will be found. Maybe there will be a role for stem cell biology in future treatment of GLUT1DS, some patients with GLUT1DS already had a stem cell transplantation, but at this moment there is not enough scientific evidence and the potential risks are too big to justify stem cell transplantation in GLUT1DS.

‘GLUT1DS in the laboratory and in the clinic 2009-2019’

Dr. J. M. Pascual (Principal investigator of the University of Texas Southwestern Medical Centre) describes that some parts of the brain are more affected in GLUT1DS than other parts and that the brain of a child consumes three times more energy than an adult brain. Nuclear magnetic resonance (NMR) studies in GLUT1DS mice can help us understand the changes in brain metabolism in GLUT1DS. He plans to use MRI to conduct NMR studies not only in mice, but also in GLUT1DS patients. This technique is safe, noninvasive, and can give us information on neurotransmitters, oxygen use, brain development and structure, and treatment efficacy in GLUT1DS.

Dr. Pascual hopes that there will be some breakthroughs in the years to come. He wants to clarify the metabolic changes in GLUT1DS before the end of next year.

‘How the brain works and seizes in GLUT1DS’

The energy paradox in the brain in GLUT1DS is discussed by L. Good (electrical engineer and postdoctoral researcher in the laboratory of dr. Pascual). We generally assume that when the brain receives less glucose, it produces less energy and therefore the neurons will be less active. But why then do seizures occur in GLUT1DS? The two most important neurotransmitters in the brain are
glutamate (excitation) and GABA (inhibition). The balance between these neurotransmitters is very important. The excitability of the brain of GLUT1DS mice was measured by EEG recordings before and after carbohydrate intake. When less glucose was available, the level of excitation of the brain was reduced, but the level of inhibition was much more reduced, thereby creating an imbalance between excitation and inhibition.

On EEG recordings, a striking ‘peak and wave’ pattern of 3 per second is seen in GLUT1DS mice. This pattern can only be found if the cortex and thalamus are both involved.

In the future, Good hopes to clarify the mechanism of how the ketogenic diet alleviates seizures in GLUT1DS. Furthermore, he hypothesizes that antiepileptic drugs with an effect on GABA function may reduce seizures in GLUT1DS. On the other hand, he realizes that antiepileptic drugs such as barbiturates with a known effect on GABA function are also known to reduce GLUT1 function and therefore should not be used in GLUT1DS.

‘How glucose and ketone bodies are useful to the brain: lessons from GLUT1DS’

Dr. I. Marin-Valencia (pediatrician and postdoctoral researcher in the laboratory of dr. Pascual), explains how glucose and ketone bodies supply the brain with energy. Although the brain contains only 2% of the total body weight, it consumes 20% of the energy in the resting state. This energy is metabolized from glucose and is used for signaling function in the brain. Ketone bodies are produced in the liver from fat and are alternative fuel for the brain in starvation. In the newborn, ketone bodies play a significant role in fueling the brain. This is probably the reason why GLUT1DS does not manifest during the first months of life.

The distribution of glucose consumption in the brain can be visualized by cerebral positron emission tomography. In GLUT1DS, a diminished cortical glucose uptake is seen with more severe hypometabolism in the mesial temporal regions and thalami.

Some experiments are being performed with GLUT1DS mice and control mice using NMR. After the administration of a magnetic active substance, 13C-glucose, the metabolites derived from glucose are analyzed. The aim of future research is to determine the biochemical mechanisms underlying GLUT1DS.

‘Movement disorders in GLUT1DS’

The aspect of movement disorders in GLUT1DS is discussed by dr. M. Rotstein (Postdoctoral Clinical Fellow at the University of Columbia). Movement disorders are very common in GLUT1DS. A video-based research showed that dystonia is seen in 86% of the patients, mild chorea in 75%, tremor during movement in 70%, and myoclonus in 16% of the patients.

Walking abnormalities are seen in 89% of the patients and consist of spasticity (12%), ataxia (35%), a combination of ataxia and spasticity (35%), and dystonia while walking (5%).

Movement disorders can be intermittent in GLUT1DS. These non-epileptic paroxysmal events occur in 28% of the patients and consist of episodes of ataxia, weakness, dystonia, and chorea. Most patients display a combination of these symptoms. Episodes can last minutes to hours and occasionally last several days. Frequency of the paroxysmal movement disorders ranges from daily to monthly. The most common triggers for paroxysmal movement disorders in GLUT1DS are physical activity and tiredness. Other causes are: noncompliance with the ketogenic diet, fasting, emotional stress, sleep deprivation, excitement, and anxiety. Movement disorders in GLUT1DS are treated with the ketogenic diet. The diet has been reported to diminish severity and frequency of movement disorders. The movement disorders also respond to feeding in general.

The reason movement disorders are common in GLUT1DS is related to the diminished amount of glucose that is found in the basal ganglia, thalamus and cerebellum on PET-scan in GLUT1DS patients. Paroxysmal movement disorders are probably caused by the combination of less glucose transport into those parts of the brain and additional stress which causes a relatively energy deficit. Recently, a nonclassical phenotype of GLUT1DS has been described of paroxysmal exercise induced dyskinesia (dystonia and chorea after exertion). Another nonclassical phenotype has just been
identified: in a patient with alternating hemiplegia of childhood (AHC) a mutation in the GLUT1 gene was found.

‘Cognitive and behavioral skills in GLUT1DS’

Ms. Hinton (neuropsychologist) reports on the results of cognitive and behavioral tests in GLUT1DS patients. The intelligent quotient (IQ) varies in GLUT1DS patients from 40 to 110, with the majority of patients having an IQ between 55-70. Overall, GLUT1DS patients score more than 2 standard deviations below normal. Cognition is correlated with neurological score in GLUT1DS. There is no proven association between cognitive performance and age or gender. Communication difficulties are common in GLUT1DS. Patients often poorly articulate and have a dysfluent speech. Receptive language skills are stronger than the expressive language skills in most GLUT1DS patients.

The adaptive behavior of GLUT1DS patients is correlated with the intellectual function. Socialization skills are a relative strength in GLUT1DS. Overall, adaptive behavioral skills are more than 2 standard deviations below normal. There is no evidence of any characteristics in the behavior of GLUT1DS patients. Poor attention is common, and some behavioral problems have been described especially during adolescence, but no consistency is found.

The Kaufmann Assessment Battery for Children (KABC) demonstrates that sequential information processing is a relative strength in GLUT1DS patients compared to the spatial integration. This means that repetition is a good way to learn for children with GLUT1DS. When we look at the change over time, we see that developmental gains are made. The relative level of function compared with children of their age remains stable. There is no evidence of a progressive decline in cognitive function over time. Cognitive function is thereby not correlated with the deceleration of the head growth.

Therapeutic options in relation to the cognitive problems are speech therapy, learning by repetition, providing structure and teaching in a playful manner.

‘The ketogenic diet in GLUT1DS’

Ms. B. Zupec-Kania (Consultant of the Charlie Foundation) and Ms. D. Koeningsberger (Pediatric Nurse Practitioner in Nutrition and Gastroenterology) discuss the ketogenic diet in GLUT1DS. Adequate ketosis is reached when the ketones in the blood (beta-hydroxybutyrate (β-OHB)) is 4-5 mmol/L. To optimize the β-OHB it is important to monitor the β-OHB and increase the ratio of fat to carbohydrate and protein until β-OHB becomes 4-5 mmol/L. It is also important to maintain the correct total daily calorie intake and to avoid obesity, since ketosis is more difficult to reach in obesity. But enough calories need to be consumed to ensure linear growth (height). Be careful with too much calorie intake from vitamin supplements. Young children can become ketotic with lower fat to carbohydrate and protein ratios than older children.

Parents and doctors must be aware of the possible complications of the ketogenic diet. Cholesterol and triglycerides can become elevated over time if the diet contains only saturated fats. In older children cream and butter must therefore be replaced by polyunsaturated fats (oils, sesame see, peanut oil). A second complication is osteoporosis. Risk factors for developing osteoporosis are low mobility, too little vitamin D, and some antiepileptic drugs interfere with the vitamin D metabolism. To avoid osteoporosis, the diet must be supplemented with elemental calcium. Furthermore, ketotic patients have an increased risk of kidney stones. To prevent kidney stones ensure an adequate fluid intake and supplement calcium. Other supplements that are necessary with the ketogenic diet are a complete vitamin and mineral tablet, which must contain iron, L-carnitine (a nutrient that helps fat turn into energy), alpha lipoic acid (this has been shown in the laboratory –at very high doses) to normalize glucose by correcting the defect), and selenium.
Answers to the questions of the parents support group

Are there children with paroxysmal movement disorders during exercise observed in the US?

Dr. Rotstein (Postdoctoral Clinical Fellow at the University of Columbia) states that he has seen paroxysmal movement disorders, such as exercise induced dyskinesias, in classical GLUT1DS patients. He observes this type of movement disorder not especially after puberty, but in children of all ages, also in younger children. These symptoms are seen in boys and girls. He hypothesizes that the onset of the symptoms during puberty in the patients on a ketogenic diet may be related to noncompliance with the ketogenic diet, or the need for a higher fat to carbohydrate and protein ratio to maintain an adequate ketosis in older children. It is observed in the US that patients develop more seizures during puberty, which also might be related to noncompliance with the diet or maybe there is an influence of hormones.

An observation by dr. de Vivo (Professor of Pediatrics, Colombia University, New York) is that girls appear to be more symptomatic at younger age, and catch up with the boys during puberty. This is not scientifically proven yet. It might be related to the hormonal state. In the newborn, the estrogen level is higher in boys than in girls, during puberty the estrogen level becomes higher in girls. Estrogen is known to increase the level of GLUT1 transporter expression.

The treatment of choice of the paroxysmal movement disorders is the ketogenic diet. If the diet is already started, a higher ratio should be tried. The movement disorders also respond to feeding in general. Medications that are used for dystonia or chorea in other disorders are an option if the ketogenic diet does not reduce the symptoms enough, but this has not been tried in any of the US patients yet.

What is the US experience with language delay and development?

Ms. Hinton (neuropsychologist) reports on the results of cognitive and behavioral tests in GLUT1DS patients (see also the general report of the conference). In summary, GLUT1DS patients score more than 2 standard deviations below normal on cognitive function and behavioral skills. Receptive language skills are stronger than the expressive language skills in most GLUT1DS patients. Developmental gains are made over time. The relative level of function compared with children of their age remains stable. There is no evidence of a progressive decline in cognitive function over time.

What are the routine checkups for GLUT1DS in the US?

No standard protocol exist for routine checkups in GLUT1DS in the US. Ms. Koeningsberger (Pediatric Nurse Practitioner in Nutrition and Gastroenterology) strongly advises to have regular scheduled blood test in patients who are on the ketogenic diet (complete blood count, lipid profile, hepatic profile, metabolic panel, calcium, magnesium, phosphorous, selenium, manganese, betahydroxybutyrate, and a complete urine test including calcium). These blood tests should be done every two months during the first 6 months. Thereafter it should be done every 6 months.

Is the modified Atkins diet used in patients with GLUT1DS?

In the US GLUT1DS patients are treated with the ketogenic, and not the modified Atkins, diet, as far as dr. de Vivo and Ms. Koeningsberger know. According to Ms. Koeningsberger it is impossible to reach an adequate ketosis with the Atkins diet. A β-OHB level of 1-1.5 mmol/L might be reached, but it is necessary to maintain 4-5 mmol/L. She states that a modified Atkins diet maybe better than no diet at all, but an adequate level of ketosis can never be reached. The ketogenic diet is very important in the
first decade in life for maintaining and developing a correct brain structure. Later in life, the diet becomes important for an adequate brain function.

Dr. de Vivo discusses if specific anti epileptic drugs are preferred in GLUT1DS. There are no particular anti epileptic drugs helpful in GLUT1DS. Some medications, however, must not be used in GLUT1DS, such as barbiturates. Valproic acid should not be used in patients who are on a ketogenic diet, because valproic acid inhibits fat oxidation. Diamox and topiramate should also not be used in patients on the diet, because they increase the risk of kidney stones.

Is there a new therapy for GLUT1DS?

At this moment, the only therapy for GLUT1DS is the ketogenic diet. Studies are being performed to search for alternatives for the ketogenic diet. Maybe there will be a role for stem cell biology in future treatment of GLUT1DS, dr. de Vivo mentions, some patients with GLUT1DS already had a stem cell transplantation, but at this moment there is not enough scientific evidence and the potential risks are too big to justify stem cell transplantation in GLUT1DS. Alpha lipoic acid has been shown in the laboratory –at very high doses- to normalize glucose by correcting the defect. It is, however, not scientifically proven that alpha lipoic acid normalizes the glucose uptake defect in GLUT1 patients. But it is recommended to supplement the ketogenic diet with alpha lipoic acid (starting dose 10mg/kg/day; increase the dose if it is well tolerated and no gastrointestinal symptoms occur). Treatment of GLUT1DS with ACTH has been tried, but, although the short term effect of ACTH is an elevated blood sugar level with higher levels of GLUT1 transporters and less symptoms, in the long run, GLUT1DS patients become worse with a high blood sugar level. For behavioral problems and attention deficits in patients with GLUT1DS, sometimes stimulant medication, which is also used in ADHD, is started, with good effect in some patients.

How can we improve the cooperation between the parents support groups (Europe / US)?

Parents in the US contact each other on Yahoo Groups at http://groups.yahoo.com. European parents are welcome to join the group (just search for ‘GLUT1DS’ and create an account). The GLUT1DS conference was organized by two active parents of the parents support group in the US: Jennifer and Sal Lazar (duogolf@comcast.net). Parents in Europe are welcome to contact them as well.

Recommended websites::

http://groups.yahoo.com
www.charliefoundation.org (especially for recipes)
www.milestonesforchildren.org (fund raising projects)