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Brief Communication

GLUT1-deficiency syndrome: Report of a four-generation Norwegian family with a mild phenotype

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ABSTRACT

Introduction: Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare metabolic encephalopathy with a wide variation of clinical phenotypes. Familial variants are often milder than *de novo* cases, and may therefore remain undiagnosed. The aim of this study was to characterize the clinical course of GLUT1-DS in a four-generation Norwegian family where the oldest generations had never received any treatment.
Method: Through interviews and clinical investigations, we characterized a family of 26 members, where 11 members had symptoms strongly suggesting GLUT1-DS. All members were offered genetic testing of the *SLC2A1* gene. Affected members were offered treatment with ketogenic diet, and the effect of the treatment was registered.
Results: We sequenced the *SLC2A1* gene in 13 members, and found that 10, all with symptoms, had the *c.823G>A* (*p.Ala275Thr*) variant. All affected members had experienced early-onset epilepsy, paroxysmal exercise-induced dyskinesias, and most had mild learning disability. Moreover, some had symptoms and signs of a distal neuropathy in addition to reduced sense of orientation and excessive daytime sleep. Their load of symptoms had decreased over the years, although that they never had received any treatment. Nevertheless, those who started dietary treatment all experienced an improved quality of life.
Conclusion: We report a four-generation family with GLUT1-DS where the disease has a mild course, even when untreated. In addition to classical GLUT1-DS features, we also describe symptoms which have never been reported in GLUT1-DS previously. As such, this family extends the phenotypic spectrum of GLUT1-DS and underlines the importance of diagnosing also relatively mildly affected patients, even in adult life, as they also seem to benefit from dietary treatment.

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1. Introduction

Glucose is the main source of energy in the brain. To be available for the brain, glucose has to cross the blood-brain barrier, and this passage is dependent on the transporter protein GLUT1 [1]. GLUT1 is encoded by the gene *SLC2A1* on chromosome 1. A heterozygous mutation in *SLC2A1*, either arisen *de novo* or inherited in an autosomal manner [2–4], gives rise to a metabolic encephalopathy, *i.e.* glucose transporter type 1 deficiency syndrome (GLUT1-DS) [5].

The classical presentation for patients with GLUT1-DS is early-onset epilepsy, developmental delay, microcephaly and movement disorders (paroxysmal exercise-induced dyskinesias) [6–8]. However, milder phenotypes with only movement disorders or mild carbohydrate-responsive symptoms have also been reported [9–13].

To counteract the insufficient energy supply to the brain, the treatment of choice in GLUT1-DS is the classical ketogenic diet (KD) [14]. This is a diet with high-fat, low-carbohydrate, and moderate protein intake [15]. Fat metabolizes to ketone bodies, which can cross the blood-brain barrier and serve as an alternative fuel for the brain [16]. Studies have also indicated that the modified Atkins diet (MAD) is effective in these patients, and is often offered to adult patients or patients that are not able to comply with the classical KD [17,18].

Here we present a four-generation Norwegian family with GLUT1-DS which in addition to classical symptoms exhibits signs and symptoms not previously associated with GLUT1-DS. The aim of this study was to characterize this family clinically and genetically.

2. Material and methods

2.1. Genetic analyses

Deoxyribonucleic acid (DNA) was extracted from venous blood using Autopure LS from Qiagen, Cologne, Germany. (http://www.quiagen.com/Products/Automation/AutopureLS.aspx).

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All exons and exon-intron boundaries of the *SLC2A1* gene were sequenced in the proband, and thereafter the relevant fragment in exon 6 was sequenced in subsequent family members.

In addition to the ten affected members, three siblings were genetically tested; two healthy and one with Asperger and Tourette's syndromes.

2.2. Patients

At our center, the proband (IV-1) was diagnosed with GLUT1-DS in March 2014. The family history revealed several other possibly affected family members, who were described to have epilepsy and movement disorders. During the next two years, we mapped a family of 26 members, of whom 11 had symptoms strongly indicating GLUT1-DS. One of these 11 members was deceased. The demographic and clinical data were collected retrospectively from clinical investigation of the patients, the patients' medical records, and from phone interviews.

Informed consent was obtained from all patients or their relatives. The project is approved by the the Regional Committee for Medical and Health Research Ethics in South East of Norway.

2.3. Treatment

None of the 10 patients had previously received any treatment. After having been diagnosed with GLUT1-DS, they were offered treatment with the classical KD or MAD.

2.4. Neuropsychological testing

Only the youngest children (VI-1, 2, 3, and 7) were tested neuropsychologically before and 6–12 months after diet initiation. The remaining six members were not systematically tested.

The clinical information was obtained from interview by clinicians at follow-up at the epilepsy center or by phone.

3. Results

A pedigree of the family is shown in Fig. 1. All 10 affected members had the c.823G>A (p.Ala275Thr) variant. Demographic and clinical data from these members are summarized in Table 1. The three siblings (IV-4, IV-6, IV-8) did not have the variant.

Nine of the 10 affected family members have had paroxysmal exercise-induced dyskinesia (PED), leading to inactivity in most of them. All adult patients reported that they had an apparently unusual urge for sweets, resulting in poor dental health. Those diagnosed with epilepsy had been treated with anti-seizure drugs for many years before they were diagnosed with GLUT1-DS. None of the family members were diagnosed with neurological conditions other than epilepsy.

In three patients, the clinical information was sparse. Patients II-2 and II-3 were interviewed by phone. They both declined treatment and no clinical examinations were undertaken. However, they both reported having symptoms from childhood, which improved with intake of carbohydrates. Patient III-4 lives abroad and was unable to provide detailed information.

4. Discussion

We have clinically and genetically characterized 10 members from a four-generation Norwegian family with GLUT1-DS. Both members of the first generation are deceased, but according to other family members, I-2 had increased need of daytime sleep and exercise-induced dyskinesias.

The course of the disease in this family is unusually mild in the three first generations, even when untreated. The affected family members live outside institutions; some are married and have children. This supports the notion that the phenotype of familial GLUT1-DS is often milder than in sporadic, *de novo* cases [7,19]. However, none of them have a vocational training, and they are unemployed. Furthermore, two of the family members in the fourth generation seem to have a more severe course of the disease. Patient IV-1 is autistic with major speech problems, and patient IV-5 is developmentally delayed. It is difficult to state if the symptoms are due to GLUT1-DS or a comorbid condition.

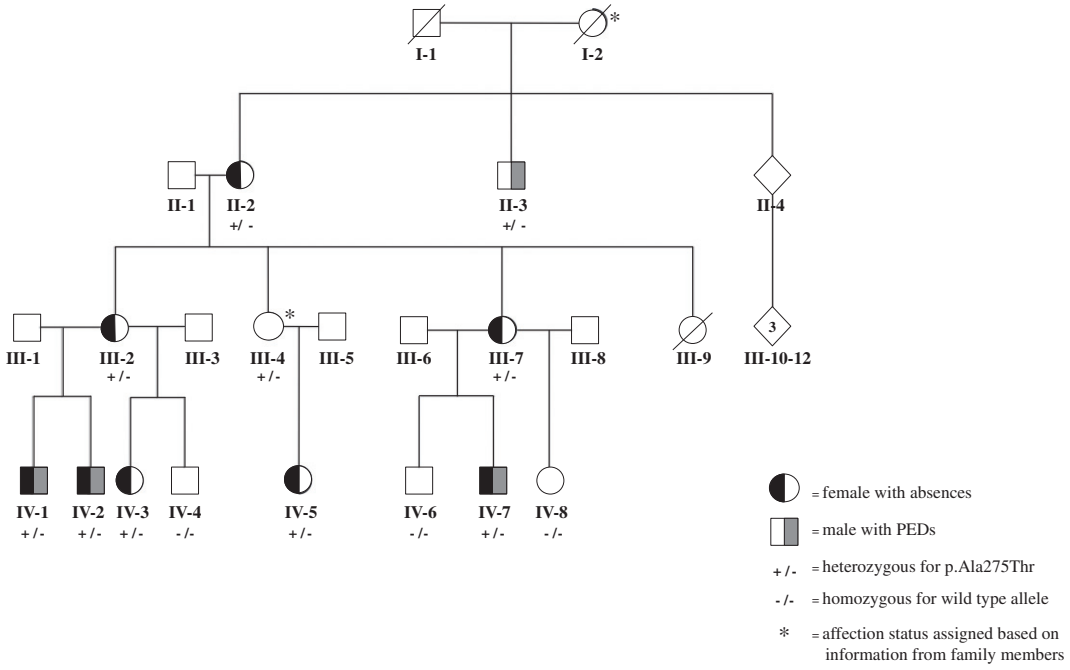

Fig. 1. The figure shows the pedigree of a four-generation Norwegian family with GLUT1-DS caused by a missens mutation in c.823G>A (p.Ala275Thr). + denotes mutation, − denotes wild type, PED = paroxysmal exercise induced dyskinesia.