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Original article

Failure of ketogenic diet therapy in GLUT1 deficiency syndrome

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ABSTRACT

Purpose: Epilepsy in GLUT1 deficiency syndrome is generally drug-resistant; ketogenic diet (KD) therapy is the mainstay of therapy, as production of ketones provides the brain with an alternative energy source, bypassing the defect in GLUT1. Failure of KD therapy and risk factors for failure have been sparsely published.
Methods: We performed a retrospective study of GLUT1DS patients with refractory epilepsy failing on KD therapy, to identify their clinical characteristics.
Results: Failure of the ketogenic diet was due to KD inefficacy (poor effect despite adequate ketosis), as well as intolerance and an inability to attain ketosis. Our cohort of seven patients in whom KD therapy failed stood out for their advanced age at seizure onset, i.e. almost 4 years vs 8 months in large series, female sex, as well as their advanced age at diagnosis and initiation of KD therapy. EEG recordings during KD therapy can aid in the assessment of effectiveness of the KD therapy.
Conclusions: GLUT1DS is generally described as a treatable disorder and existing case series do not provide details of treatment failure. In select patients with GLUT1DS, KD therapy fails, rendering GLUT1DS an essentially untreatable disorder. Failure of the ketogenic diet was due to KD inefficacy (poor effect despite adequate ketosis), as well as intolerance and an inability to attain ketosis. Failure to reduce seizure frequency with deterioration of the EEG findings should lead to consideration of cessation of KD therapy.

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Table 1 – Demographic/clinical characteristics.

Patient	Gender	Seizure onset (age)	Seizure type and seizure frequency	FSIQ (PIQ,VIQ)	Age at diagnosis	Diagnostic delay	Blood glucose (mmol/L)	CSF glucose (mmol/L)	Ratio CSF/blood glucose	CSF lactate (mmol/L)	*SLC2A1* gene mutation
1	F	3y0m	Absences, daily	85 (78, 94)	11y6m	8y6m	ND	ND	ND	ND	Missense, c.823G > A (p.(Ala275Thr)),[15] de novo
2	F	3y5m	Absences, hourly	82 (78, 88)	5y1m	1y8m	5.1	2.0	0.39	1.1	Missense, c.457C > T (p.(Arg153Cys)),[16] de novo
3	F	3y0m	Myoclonic absences, hourly, in the morning continuously	69 (64, 79)	10y9m	7y9m	5.1	2.7	0.53	1.3	No mutation
4	F	3y6m	Absences, hourly; Clonic seizures, yearly	83 (93, 83)	5y8m	2y2m	3.6[a]	2.3[a]	0.64[a]	1.0[a]	Nonsense, c.1164G > A (p.(Trp388.)), de novo
5	F	4y6m	Tonic seizures, myoclonic seizures, absences, all daily	54 (<55, 61)	13y9m	9y3m	4.9	2.7	0.55	1.1	No mutation
6	F	4y5m	Absences, hourly; myoclonic seizures, hourly; tonic-clonic seizures, only once	55 (56, 59)	14y5m	10y0m	3.9[a]	2.0[a]	0.51[a]	1.0[a]	Missense, c.418G > T (p.(Vall40leu)),[17] hereditary (father same mutation, with cognitive impairment and epilepsy in childhood)
7	F	4y0m	Absences, hourly	88 (100, 83)	5y2m	1y2m	4.9 3.4[a,b]	2.4 2.3[a,b]	0.49 0.68[a,b]	1.6 1.1[a,b]	No mutation

PIQ: performance intelligence score; VIQ: verbal intelligence score; FSIQ: full scale intelligence score; ND: not done; CSF: cerebrospinal fluid.

[a] CSF analysis was done while on KD therapy; these three patients all had asymptomatic hypoglycemia while on KD therapy.

[b] Cerebrospinal fluid analysis was repeated to exclude transient cerebral glucose deficiency in the absence of a *SLC2A1*gene mutation.

1. Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a metabolic encephalopathy caused by a decreased glucose transport into the brain.[1] GLUT1DS was first described in 1991 by De Vivo et al. in two patients with drug-resistant epilepsy, global developmental delay, movement disorder and acquired microcephaly.[1] Since then, the clinical spectrum has expanded to include ataxia, spasticity, chorea, cerebellar tremor, paroxysmal movement disorders and intellectual impairment in varied severity.[2,3] Mutations in the *SLC2A1* gene encoding GLUT1 are causative, as a defect in GLUT1 disables the transportation of glucose over the blood–brain barrier.[4] This results in low levels of glucose in the cerebrospinal fluid, i.e. hypoglycorrhachia. Thus, hypoglycorrhachia together with normal blood glucose levels provides the diagnostic clue for GLUT1DS.[5] In 90% of the affected patients, the diagnosis can be confirmed by mutational analysis of the *SLC2A1* gene. To date, more than 100 different mutations in the *SLC2A1* gene have been identified.[6]

Epilepsy is a key feature of the disorder in 85–90% of the affected individuals, with seizure onset generally before the age of two.[6] Many seizure types have been linked to GLUT1DS, including generalized tonic-clonic, absence, focal with and without impaired awareness, myoclonic, atonic, tonic and infantile spasms.[7,8] The majority of patients has more than one seizure type, with generalized tonic-clonic and absence seizures reported most frequently.[8]

Epilepsy in GLUT1DS is generally drug-resistant; ketogenic diet (KD) therapy is the mainstay of therapy, as production of ketones provides the brain with an alternative energy source, bypassing the defect in GLUT1.[2,6,9,10] KD therapy markedly reduces seizure frequency with reported success percentages ranging from 67 to 90% for complete seizure control, and 80–100% for significant seizure reduction.[6,8–11] Failure of KD therapy and risk factors for failure have been sparsely published. Hence, we performed a retrospective study of GLUT1DS patients failing on KD therapy, to identify their clinical characteristics.

2. Methods

We conducted a retrospective chart review of all children treated for GLUT1DS at the Academic Center for Epileptology, Kempenhaeghe & Maastricht UMC+, Heeze (ACE) and Radboud University Medical Center, Nijmegen, the Netherlands up to May 2018, in whom KD therapy failed to reduce seizure frequency. Ethics approval was obtained from the local institutional review board and informed consent was obtained from all patients' parents.

GLUT1DS was diagnosed either when analysis of the *SLC2A1* gene showed a pathogenic mutation and/or when cerebrospinal fluid (CSF) analysis met the criteria for GLUT1DS: a CSF glucose below the 10th percentile, a cerebrospinal fluid (CSF) to blood ratio below the 25th percentile and CSF lactate below the 90th percentile.[5]

Patients were treated according to the national KD therapy guideline.[12]

3. Results

3.1. *Clinical features*

This observational study included seven patients, all girls, out of a total of 70 patients with GLUT1DS seen in the past decade in our institutes (10%). The mean age at seizure onset was 3 years and 7 months; the mean age at diagnosis was 9 years and 6 months. The demographic and clinical characteristics of the patients are shown in Table 1. All patients clinically had generalized seizures. In all patients, pregnancy, delivery and neonatal period were uneventful. Their medical history, as well as findings of clinical examination, brain MRI results, metabolic and genetic testing, including whole genome

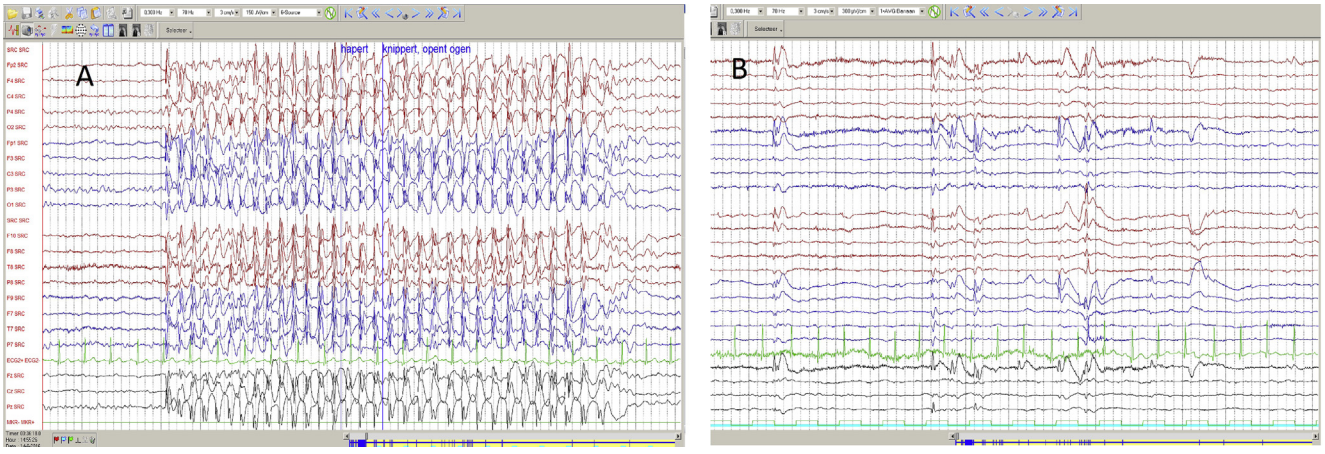

Fig. 1 – EEG before KD therapy showed isolated or series of generalized (poly)spike-and-wave discharges (2–3,5 Hz), predominant over the frontal cortex, with a duration of 1–13 seconds (A). Besides generalized discharges, (multi)focal epileptic discharges were present (B). 'Hapert' means falters, and 'knippert, opent ogen' means blinks, opens the eyes.

Table 2 – Ketogenic diet.

Patient	Ketogenic diet (KD)	Age at start KD therapy	Duration of KD therapy	Mean level of blood ketosis (mmol/L)	Seizure frequency in the first hour after awakening measured by EEG recording before/ during KD therapy	Adverse effects	Reason of KD discontinuation	Reason for failure KD	KD intolerance/ inefficacy/failure to achieve ketosis
1	MCT	11y10m	Currently 3y0m	>3	10/25	nausea, belching, abdominal pain	–	No seizure reduction (still daily absences) despite adequate ketosis	Therapy inefficacy
2	MCT	5y2m	Stopped after 3y8m	<1	33/continuously	diarrhoea, constipation, severe abdominal pain	Severe adverse effects	Severe adverse effects	Therapy intolerance
3	Classic KD	9y3m	Stopped within one week	–	30/NA	–	Behavioral problems (refusal to eat)	Compliance (behavioral) problems	Therapy intolerance
4	MAD, later switched to classic KD	5y8m	Currently 3y5m	>4	2/8	sometimes nausea, vomiting	–	No seizure reduction (still hourly absences) despite adequate ketosis	Therapy inefficacy
5	Classic KD, later switched to MCT	9y3m	Stopped after 1y8m	>3	8/8	sometimes constipation, abdominal pain, diarrhoea	Lack of seizure reduction	No seizure reduction (still hourly seizures) despite adequate ketosis	Therapy inefficacy
6	MCT	10y7m	Currently 3y4m, Previously 2y2m	1	60/60	sometimes diarrhoea	–	No seizure reduction, because adequate ketosis is not attained for unknown reasons	Failure to achieve ketosis
7	MAD, later switched to MCT	4y0m	Currently 1y7m, Previously 1y1m	>3	4/5	sometimes constipation	–	No seizure reduction (still hourly absences) despite adequate ketosis	Therapy inefficacy

MCT: Medium-Chain Triglyceride; MAD: Modified Atkins Diet; NA: not applicable.

sequencing, excluded other causes for their clinical manifestations.

3.2. EEG findings

EEG before KD therapy showed almost identical findings in all seven patients. All showed isolated or series of generalized (poly)spike-and-wave discharges (2–3,5 Hz), predominant over the frontal cortex, with a duration of 1–13 seconds (see Fig. 1a); in the first hour after awakening, the seizure frequency amounted to 2–60 seizures/hour. Besides generalized discharges, (multi)focal epileptic discharges were present in all patients (see Fig. 1b).

3.3. Treatment outcome

Table 2 summarizes the details of the KD therapy, its effect on seizure frequency, as well as reasons for failure. Ketogenic diet (KD) therapy was initiated at a mean age of 8 years. Four patients proved unresponsive to KD therapy (KD inefficacy, i.e. lack of effect despite ketone concentrations >3 mmol/L) and two did not tolerate KD therapy. One patient did not attain ketosis for unknown reasons. In the five patients tolerant to KD therapy, compliance to the KD therapy was generally good.

Despite failure to reduce seizure frequency, KD therapy was continued in these five patients because parents reported slight beneficial effects on concentration, alertness and cognitive functioning. One of these five KD tolerant patients with GLUT1DS also had a paroxysmal movement disorder which improved with KD therapy. The EEG recording though, showed an increase in seizure frequency, and frequency and/or duration of epileptic discharges on EEG in three out of five patients tolerant to KD, despite ketone concentrations >3 mmol/L; in two, the seizure frequency and frequency and duration of epileptic discharges in the EEG remained unchanged (Table 2).

Two patients (nr. 2 and 5) eventually fully stopped the KD therapy. For both, seizure frequency remained stable and there was no cognitive decline; patient 2 showed an increased frequency of paroxysmal exercise-induced dyskinesia. Despite this increase, both patient and her parents decided not to restart KD therapy for its lack of effect on seizure frequency and the major impact on their daily lives.

4. Discussion

GLUT1DS is generally described as a treatable disorder and existing case series do not provide details of treatment failure.[6,8–11] In select patients with GLUT1DS, KD therapy fails, rendering GLUT1DS an essentially untreatable disorder. In this small cohort, failure of the ketogenic diet was due to KD inefficacy (poor effect despite adequate ketosis), as well as intolerance and an inability to attain ketosis.

This cohort of patients with KD treatment failure stands out, compared to previously published series of KD treatment, for their advanced age at seizure onset (almost 4 years vs 8 months in large series[7]) and their long diagnostic and therapeutic delay. Early diagnosis and treatment are regarded as the most important factors that determine outcome.[13] In addition, all patients in our cohort are female, while normally there is no sex preference in this disease.[13] This suggests that advanced age at seizure onset and female sex might be risk factors for KD resistance. These assumptions should be tested in an explorative international multicenter study.

The study by Leary et al. showed that epileptiform discharges in the EEG were present in 67% of patients.[8] In other studies of GLUT1DS patients with a good response to KD therapy, epileptiform discharges in the EEG decreased in frequency or disappeared in 78–100%.[9,11] In our patients, KD inefficacy was further evidenced by the observation that EEG findings remained unchanged or even worsened during KD therapy. Therefore, EEG recordings prior and during KD therapy can aid in the assessment of effectiveness of the KD therapy.

Epilepsy in GLUT1DS is regarded as a direct result of the lack of glucose in the brain. As ketones serve as an alternative energy source for the brain, adequate ketone levels should solve the epilepsy problem. It is clear that in patients with KD therapy intolerance, the energy crisis of the brain persists as there are insufficient ketone bodies to serve as alternative energy source. In patients with KD inefficacy however, one would expect that the presence of adequate ketone levels should reduce or stop the epileptic seizures.

KD therapy failure in our small cohort suggests that this concept of reversible brain energy deficit in GLUT1DS does not suffice. Another argument against this concept is the observation that level of ketosis is not associated with the effectiveness of the ketogenic diet.[13]

For patients with KD intolerance and KD inefficacy, as well as those unable to reach ketosis, there is an urgent need for an alternative treatment. For all GLUT1DS patients, research into alternative treatment modalities is essential, because the adverse effects and impact of the KD also cause inconvenience in the ‘good responders.’ Moreover, there is a risk of late onset adverse effects caused by the KD, such as nephrolithiasis, cardiac complications and osteoporosis.[14]

We decided to continue KD therapy to circumvent glucose-driven brain metabolism and for the slight beneficial effects on concentration, alertness and cognitive functioning, and a decrease in frequency of paroxysmal movement disorder in one patient. Nonetheless, in the absence of an effect on seizure frequency and with deterioration of the EEG findings, we feel KD therapy is no longer justified for these children.

5. Conclusion

In conclusion, KD therapy can fail in patients with GLUT1DS. Failure of the KD is caused by intolerance, failure to achieve ketosis, or inefficacy, i.e. no effect despite adequate ketosis. Our small cohort of KD therapy failure stood out for their advanced age at seizure onset, diagnosis and initiation of KD therapy, and female sex. EEG recordings prior and during KD therapy can aid in the assessment of effectiveness of the KD therapy. Failure to reduce seizure frequency with deterioration of the EEG findings should lead to consideration of cessation of KD therapy.

Alternative treatment modalities for GLUT1DS are direly needed.

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Conflicts of interest

None of the authors has any conflict of interest to disclose and no funding was obtained for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.02.012.

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