LETTER

Transition from ketogenic diet to triheptanoin in patients with GLUT1 deficiency syndrome

INTRODUCTION

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) causes cerebral energy deficiency due to altered transport of glucose across the blood brain barrier and into astrocytes.[1] Its main phenotype combines developmental delay, permanent motor dysfunction and paroxysmal neurological manifestations.[1] In addition, GLUT1-DS may solely consist of paroxysmal manifestations such as seizures or exercise-induced paroxysmal dyskinesia.

Ketogenic diet is the primary treatment of GLUT1-DS with clear efficacy on seizures and non-epileptic motor manifestations,[1] but it has severe constraints. Ketogenic diet failure has been occasionally reported due to poor tolerance, inefficacy or failure to achieve ketosis,[2] emphasising the need for alternative therapeutic options. Triheptanoin is a triglyceride containing three 7-carbon fatty acids, which provides acetyl-coenzyme A (CoA) and propionyl-CoA, two key carbon sources for the Krebs cycle.[3] Treatment with triheptanoin resulted in a dramatic and sustained reduction of non-epileptic paroxysmal events in a group of GLUT1-DS patients who were not on ketogenic diet.[4 5] Here, we evaluated the long-term effect of triheptanoin in four GLUT1-DS patients with persistent paroxysmal manifestations while on ketogenic diet.

MATERIAL AND METHODS

We enrolled four GLUT1-DS patients (table 1) who reported persistent paroxysmal events while on ketogenic diet (trial registration number NCT02014883). Three adults and one child's legal guardian signed a written informed consent for participation in this study sponsored by INSERM.

The study was divided into baseline, transition from ketogenic diet to triheptanoin (transition), short-term evolution (short term) and long-term follow-up (long term) with triheptanoin. A flow chart is presented in online supplementary file 1. This study had the same design than our previous works with triheptanoin in GLUT1-DS.[4 5] During the baseline phase, patients had to maintain their usual ketogenic diet. During the transition phase, triheptanoin was gradually introduced by replacing a portion of the usual fat intake by triheptanoin. Importantly, the lipid amount was kept unchanged. During the short-term phase, patient's total fat content was progressively reduced to 40%–45% of usual daily calorie intake with triheptanoin accounting for about 30% of daily calorie intake. Patients were evaluated after 6 months and then on a yearly basis for 3 years (long-term phase).

Patients and their caregivers filled a comprehensive diary during the study to record all paroxysmal events and their approximate duration.[4 5] The evaluating physician reviewed diaries at each visit and grouped paroxysmal events into motor and non-motor manifestations. The primary endpoint was the total number of paroxysmal manifestations normalised over a month. Secondary endpoints were: the mean duration and number of motor manifestations, and the clinical global impression severity and change scales. Safety was verified at each visit. Compliance was assessed by a trained dietician and monitored according to plasma levels of triheptanoin-derived metabolites.[4 5]

RESULTS

The transition period was difficult for three patients with mild worsening of

Table 1 Baseline characteristics of GLUT1-DS patients and changes in outcome variables

	P1	P2	P3	P4	Mean (SD)
Sex	M	F	M	F	
Age	26	19	17	24	21.5 (4.2)
Lipid % at baseline	87	70	39	85	
Event types	LL dystonia. Dysarthria. Fatigue.	LL dystonia.	Ataxia. Confusion. Fatigue.	LL dystonia. Dysarthria. Fatigue. Headache.	
Reasons for enrolment	Poor KD tolerance	Numerous paroxysmal events	Poor KD compliance	Numerous paroxysmal events	
Total events					
Baseline	1.5	3.0	2.0	6.5	3.3 (2.3)
Transition	11.0	3.0	3.5	5.0	5.6 (2.7)
Short term	9.5	3.5	3.0	3.0	4.8 (3.2)
LT – 6 months	--	3.0	1.0	2.5	2.2 (1.0)
LT – first year	--	2.2	0.7	0.7	1.2 (0.9)
LT – second year	--	3.4	0.3	14.4	6.1 (7.4)
LT – third year	--	1.8	0.4	2.1	1.4 (0.9)
Motor events					
Baseline	1.0	2.5	1.0	3.5	2.0 (1.2)
Transition	8.5	3	0.5	5.0	4.3 (3.4)
Short term	9.5	3.5	0.5	3.0	4.1 (3.8)
LT – 6 months	–	3.0	0.3	2.3	1.9 (1.4)
LT – first year	–	2.2	0.2	0.7	1.0 (1.0)
LT – second year	–	3.3	0.2	14.4	6.0 (7.5)
LT – third year	–	1.7	0.1	2.1	1.3 (1.1)

GLUT1-DS was defined by low cerebrospinal fluid to blood glucose ratio and an *SLC2A1* missense mutation. Patient P1 reported few paroxysmal events on a well-followed ketogenic diet initiated 4 years prior to the study, but his quality of life was heavily impacted by his diet. Patients P2 and P4 reported numerous events despite ongoing ketogenic diet with good compliance for 3 and 8 years, respectively. Patient P3 was partially compliant to a KD started 4 years prior to the study and experienced paroxysmal events. Total and motor paroxysmal events are expressed per month. Values are mean and SD between brackets.
F, female; KD, ketogenic diet; LL, lower limbs; LT, long-term follow-up; M, male.

motor (P4) or non-motor (P3) manifestations in two patients and an increase of both manifestations in patient 1 (table 1). Patient 1 quit the study at the end of the short-term period as his paroxysmal manifestations remained more frequent, severe and prolonged as compared with baseline. The other three patients (P2, P3 and P4) were stable during the short-term period and were followed-up for 3 years.

The total number of events and the number of motor events decreased over 3 years for patients P3 and P4 while they remained stable for patient 2 (table 1, online supplementary file 1). At the end of the second year of follow-up, patient 4's events temporarily increased due to major diet deviations (fast-acting sugars intake). We renewed our dietary recommendations and subsequently observed a reduction of her paroxysmal events (table 1, online supplementary file 1). Triheptanoin also reduced the mean duration of total paroxysmal events between baseline and both short-term and long-term follow-up periods (online supplementary file 2).

Plasma C5-keto acids significantly increased once triheptanoin was introduced reflecting its proper metabolism (data not shown).

DISCUSSION

Three out of four patients were able to transition from ketogenic diet to triheptanoin and were willing to pursue triheptanoin for 3 years. A sustained reduction of total events, and particularly of motor events, was observed in two patients over 3 years. We also observed that the mean duration of the remaining events decreased with triheptanoin. Patients felt that they benefited from treatment with triheptanoin and objected to return to a ketogenic diet.

We previously reported a dramatic and sustained reduction of paroxysmal events in GLUT1-DS patients who were on a normal diet before being treated with triheptanoin.[4 5] The present study suggests that triheptanoin can improve movement disorders in GLUT1-DS patients manifesting persistent paroxysmal manifestations while on ketogenic diet. However, difficulty in switching diets was the main issue. One patient was eventually unable to switch from his ketogenic diet to triheptanoin due to worsening of his condition during the first months, illustrating the challenge of the initial switching period. This increase of paroxysmal events suggested that patient 1 was strongly dependent to ketone bodies as triheptanoin provides less ketone bodies than ketogenic diets.[3] Further studies are warranted to investigate the best way for transitioning patients from ketogenic diets to triheptanoin. A longer transition phase may be appropriate allowing for a more gradual reduction of the lipid ratio in the diet.

Limitations of this study include the absence of statistics due to the very small number of patients and its open label design. We only evaluated a few GLUT1-DS patients who had an unsatisfactory outcome under ketogenic diet or were unable to fully comply with ketogenic diet requirements. Hence, our findings provide no indication that triheptanoin may be a relevant option for patients whose symptoms are well controlled on ketogenic diet. Conversely, triheptanoin may be considered for GLUT1-DS patients with persistent paroxysmal manifestations on ketogenic diet and/or patients who fail to be compliant to ketogenic diet. In 2018, an industry-sponsored phase 3 trial with a short-term design of 2-month treatment was discontinued, contrasting with our findings. In our experience, proper dietary instructions, compliance and monitoring are mandatory for triheptanoin to provide its best efficacy.[4 5]

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