Dietary treatment of children with Angelman Syndrome and refractory epilepsy

Published: 03-05-2016
Last updated: 19-04-2024

Primary objective: - 50% seizure reduction or more at 3 months of dietary treatment .Secondary objectives: -level of ketosis on KD and MAD.-number of patients maintaining >50% seizure reduction on MAD.-number of withdrawals (not able to continue...

Ethical review	Approved WMO
Status	Pending
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON43592

Source
ToetsingOnline

Brief title
Dietary treatment in Angelman Syndrome

Condition

- Neurological disorders congenital
- Seizures (incl subtypes)

Synonym
Angelman Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: KInderneurologie
Source(s) of monetary or material Support: subsidie is aangevraagd bij Angelman

Foundation en stichting Coolsingel

Intervention

Keyword: Angelman Syndrome, children, dietary treatment, refractory epilepsy

Outcome measures

Primary outcome

- 50% seizure reduction or more after 3 months of dietary treatment.

Secondary outcome

-observation of level of ketosis during dietary treatment. ketosis will be

measured on daily basis by parents

-improved EEG outcomes.

-maintaining or improved QoL.

-maintaining patient related growth curves.

-safety by closely monitoring of side effects of AED and dietary treatment.

-feasibility by monitoring behavior, feeding difficulties and parental stress

by questionnaires .

-protocol compliance.

Study description

Background summary

Angelman syndrome (AS) is a rare genetic neurodevelopmental disorder characterized by impairments in cognitive, neurological and motor functioning leading to a postulated neurological and behavioural profile. Its prevalence among children and young adults is estimated at 1:24.580 new borns[
AS has been recognized during 1960*s by paediatrician Dr. Angelman who published his landmark report on *puppet children* in 1965 with the discovery of which became known as the *happy puppet syndrome*. The name Angelman syndrome was introduced in 1982 .

The phenotype features are mouthing behaviour, sleep difficulties, fascination with water, absent or minimal speech development, abnormal electroencephalogram results, epilepsy and ataxic of broad based gait. Additional features as feeding difficulties, gastrointestinal reflux, hand flapping, easily provoked laughter, short attention span, hyperactivity and microcephaly are described in 63-80% of the cases .
AS is caused by the lack of UBE3A gene expression from the maternally inherited chromosome 15 due to various 15q11-q13 abnormalities.
Over 90% of patients with AS develop epilepsy. Many different seizure types are seen and non- convulsive status epilepticus is common.

Ketogenic diet treatment in refractory epilepsy in children:
Despite the availability of a large number of anti epileptic drugs (AED) seizures in 50% of children with AS do not respond adequately or children suffer from serious side effects from pharmacological treatment. These children are in need of additional treatment options. The latest Cochrane review based on data from several clinical trials show the ketogenic diet (KD) to be a successful, non-pharmacological, treatment option in treating seizures in children with refractory epilepsy. Various studies showed an efficacy rate in the range of 27-62% at three months after diet initiation, with success being defined as >= 50% seizure reduction. Most studies reported success rates at three months and to a lesser extend at 12 months after diet initiation. Reported efficacy rates at 12 months range between 9-83%.
Treatment with KD is compliance demanding and requires a high degree of medical and dietetic monitoring because of its side effects and limits. On KD ketone bodies appear in the blood which proves the metabolism has switched from carbohydrate buring to fat burning for energy supply. To achieve and maintain this delicate metabolic balance the menu's have to be calculated and prepared strictly on a daily basis by parents. It takes efforts to incorporate this diet into daily life. Therefore efforts were made to design dietary regimes that are more liberal as the Modified Atkins Diet (MAD) and LGID. Studies mention parents and caregivers of patients do confirm these diet to be more liberal . On LGID the intake of fat and protein is calculated, the carbohydrates with glycemic index > 50 are restricted. On MAD only the carbohydrates are restricted, the intake of fat and protein being ad libitum, this gives parents the opportunity to be flexible and to adjust to their child*s personal needs and capabilities. These diets do not achieve a notable level of ketosis but still seizure reduction is achieved.
The KD is based on high intake (90 energy%) of long chain fat (LCT). Medium chain fat (MCT) utilizes fast and more ketone bodies than LCT, which may benefit efficacy of the diet and makes it possible to maximize the amount of carbohydrates into the diet. When adding MCT into the diet becomes more diverse and palatable.
Recent research indicates decanoic acid (C10) as part of MCT fat may mimic the mitochondrial proliferation associated with the KD. This suggests adding MCT benefits efficacy on seizure reduction.
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Refractory epilepsy in AS:
In children with AS epilepsy starts often in infancy and generally before the age of 4. Although no direct correlation is proven between epilepsy severity and degree of cognitive impairment, recurrent and prolonged seizure activity in AS has been hypothesized to have a large impact on cognitive outcomes.]. In a significant proportion of patients (23-77%) seizures are inadequately responding to well dosed pharmacological treatment with AED of first choice and/or a combination of AED. Several studies and retrospective chart reviews report monotherapy of valproate or clonazepam or both drugs in combination to be most effective Additionally used AED are phenobarbital, topiramate, carbamazepine, lamotrigine and levetiracetam with a lower efficacy.

Ketogenic diet in AS:
Non-pharmacological treatment options like the KD and LIGD have produced promising results in reducing seizures in children with AS.
Two case reports of children with AS show a almost immediate and notable success of KD on seizure reduction [
A prospective trial of the LGID in small cohort of six children (mean age 3.3 y) with AS, showed a > 80% seizure reduction in five of them after four months of treatment. After one year five patients maintained having > 90% seizure reduction
As the underlying working mechanism of the KD treatment is not fully understood yet, the question arises how important it is to reach ketosis to achieve seizure reduction. Patients do not achieve a significant level of ketosis whilst on the more moderate types of KD like LGID or MAD. Past studies have shown that ketosis does not improve seizure outcome with the LGID
Using the LGID and MAD is described by parents and caregivers (from AS patients and children with refractory epilepsy) as more palatable and easier to incorporate in daily life than the original KD. This is important, taking into account the behavior and feeding difficulties seen in AS. There are no studies on MAD in AS.

Experience dietary treatment i fn Erasmus Medical Center Sophia Children's Hospital Rotterdam:
Since 2001, 155 young children with refractory epilepsy have started the KD (all types of diets) in Erasmus MC Sophia Children*s hospital. Among them, four children with AS started LGID. This type of diet was chosen based on previous publications .Of our parents, one stopped the LGID after three months due to lack of efficacy. Three patients achieved moderate seizure reduction after one month LGID treatment, which did not improve further over time. Of these three patients, two showed significant improvement after switching over to KD and one reached seizure freedom after adding 10 energy% MCT fat to the LGID diet. Most parents still had the need for close monitoring the daily intake, diet calculation and preparation
Four patients with refractory epilepsy and behavior problems started MAD and were all able to reach > 50% seizure reduction.
Feedback from parents of our AS patients shows that switching over to the KD to

try improving seizure reduction was accepted very well by the patients and seemed not to increase the level of parental stress. Also to our experience the MAD fits better to Dutch eating habits than LGID and parents had the opportunity to be more flexible and adjust to the needs and capacities of their child on daily basis.

Based on literature and our clinical exiperiences the aim of our study is to maximize the effect on seizure reduction of dietary treatment but minimize the burden for patients and parents by starting strictly (with ketosis) and end easy (with decreased ketosis).

Study objective

Primary objective:
- 50% seizure reduction or more at 3 months of dietary treatment .

Secondary objectives:
-level of ketosis on KD and MAD.
-number of patients maintaining >50% seizure reduction on MAD.
-number of withdrawals (not able to continue any dietary treatment and/or insufficient seizure reduction after 3 months of dietary treatment)
- quantification of growht deviation (both height for age and weight for height)
-(change of) level of parental stress and coping during different study periods.
- incidence, kind of feeding difficulties
- change in eating behaviour during study periods, acceptance of change in diet.
- incidence, kind of behaviour problems and change in behaviour during study periods.
- changes of QoL during study periods.
- incidence of adverse effects (i.e gastro-intestinal problems, constipation, vomiting)
- toxicity (i.e. adverse events CTCAE grade >= 2).

Study design

This concerns a prospective trial of 10 months consisting of an observational period of 1 month followed by randomized trial of 3 months. After this period an additional observational study of 6 months is performed.

Intervention

During study patients use adequately dosed AED in depended to kind of study group.
First period:
After a run-in period of 1 month in which patients follow normal diet and AED will be continued and optimized whenever necessary, randomization

will take place.

Second period; 3 months
Randomisation into
1. Diet group: KD (5 energy% carbohydrates), containing 15 energy% MCT fat and AED.
2. Control group: continue normal diet (patient related) .

Third period: 3 months
1. Diet group;
- patients with > 50 % seizure reduction switch to a MAD (10 energy % range 20-40 grams carbohydrates), energy from fat and protein is unrestricted,
15 energy% MCT fat supplemented.
- patients with < 50% seizure reduction terminate dietary treatment and restart their
normal diet.
2. Control group ;
- patients with < 50 % seizure reduction start postponed KD (5 energy% carbohydrates), 15 energy % MCT fat .

Fourth period: 3 months
1. Control group:
- patients with > 50% seizure reduction switch to a MAD (10 energy % range 20-40 grams carbohydrates), energy from fat and protein is unrestricted,
15 energy% MCT fat supplemented.
- patients with < 50% seizure reduction terminate dietary treatment and restart their
normal diet.
- Patients from diet group continue MAD for additional 3 months

Study burden and risks

During the trial period of 10 months all patients will be closely monitored by a specialized dietitian and specialized nurse. During both dietary treatments adverse effects are seen like constipation, deviated lipid profile, nausea, food refusal, low blood sugar. These effects are in general temporarily, mild and seldom reason for diet termination. The patient related possible risks of the KD are classified as moderate and on MAD are classified as low based on a previous explorative studies . Based on the fact this study concerns young children with psychomotoric retardation the overall classification of this study is moderate.
During the study period efficacy, safety, feasibility, QoL, (eating) behavior, parental stress and compliance will be assessed by registering the effect on seizures, adverse effects of standard AED treatment and dietary treatment and

protocol compliance.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Angelman syndrome (genetically proven)
- > 2 year
- < 18 year
- minimum 10 seizures per month
- Able to use > 50% of energy need by oral food.
- Written informed consent by parents
- AED use

Exclusion criteria

- < 2 years.
- > 18 years.
- on KD or LGID treatment during the past 6 months.
- overweight: weight /height : > +2.5 SD or BMI >30
- underweight : weight/height; < - 2.5 SD.
- fully or partial (> 50% of energy need) tube feeding dependent.
- deviated lipid profiles

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2016
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Date:	03-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL55145.078.15