Metabolomics in Dravet syndrome

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Primary Objectives: 1. To assess the metabolic profile of patients with Dravet syndrome and identify metabolic variations that contribute to the pathophysiology of seizures and developmental delaySecondary Objectives:2. To assess the association...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON53973

Source
ToetsingOnline

Brief title
Metabolomics in Dravet syndrome

Condition

- Neurological disorders congenital
- Seizures (incl subtypes)

Synonym
Dravetsyndrome, severe epilepsy syndrome, Severe myoclonic epilepsy of infancy, SMEI

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Dravet Nederland/Vlaanderen;Ming-2 fonds

Intervention

Keyword: Dravet syndrome, Metabolic profile, Metabolomics, SCN1A-related seizure disorders

Outcome measures

Primary outcome

For all objectives the endpoint is the data from the metabolomics analysis. Per subquestion we will compare different patient groups.

To determine the metabolic profile of Dravet syndrome we will compare the data from the metabolomics analysis between the group with Dravet patients, the control group with other refractory epilepsies and the control group without epilepsy.

To determine the association between the metabolome and the severity of the disease we will compare data from the metabolomics analysis within the group with Dravet syndrome. We will divide the group with Dravet syndrome into three categories: severe, moderate and mild phenotype. The division will be based on

- Development: The classification severe to profound intellectual disability, moderate intellectual disability, mild intellectual disability will be based on the DSM V criteria18.

- Severity of epilepsy: will be based on frequency seizures and of incidence of status epilepticus. For both minor seizures (short absences, focal motor seizures and myoclonias) and major seizures (generalized tonic-clonic seizures, tonic seizures, focal seizures with impaired awareness, prolonged seizures) the frequency will be scored at the time of inclusion with points (score 4*=*daily

seizures, score 3*=*weekly seizures, score 2*=*monthly seizures, score 1*=*yearly seizures, score 0*=*seizure-free (> 1*year)). The incidence of status epilepticus will be scored as well. (score 3=> 6 per year, score 2= > 2 and < 6 per year, score 1 3= 1-2 per year, score 0=>1 year ago). The scores will be added per patient. The division into the three categories will be based upon the group mean scores.

- Number of ASM in current use: mild = 1 ASM, moderate= 2-3 ASM (ketogenic diet or vagal nerve stimulator is counted as 1 ASM), severe=>4 ASM
- Mobility, according to the Functional Mobility Scale. Mild= FMS score 5 or 6, moderate=FMS score 2, 3 or 4, severe= FMS score 1.

To determine the response to the ketogenic diet, we will compare responders and non-responders to the ketogenic diet within the group with Dravet syndrome and within the group with refractory epilepsy.

To determine the effect of specific treatments on the metabolome, we will compare patients who use certain ASM from the group with Dravet syndrome and the group with refractory epilepsy to patients who do not use this ASM from the same groups.

Per subquestion different metabolites will be of interest. To determine the specific metabolic profile of Dravet syndrome, we will take a broad look at the different metabolites, but we will be specifically interested in the energy metabolism and the neurotransmitter metabolism. These will also be the areas of interest when comparing the metabolome of Dravet syndrome to the control groups

and when comparing the different phenotypes within the Dravet syndrome. For the effect of treatment on the metabolome, the metabolites of interest differ. For the ketogenic diet the energy metabolism is of interest, for ASMs it depends on the pharmacological properties.

Secondary outcome

n/a

Study description

Background summary

To function optimally, the brain requires a large energy supply. In healthy individuals, the required energy is mostly derived from glucose metabolism, in the form of ATP1.Glucose metabolism is altered in epileptic brains. During seizures, the oxygen and energy consumption of the brain enhances due to the increase in demand. Post-ictal elevated lactate levels are common and are likely due to the mismatch in glycolysis and use of pyruvate1,2. Interictal FDG-PET imaging has shown glucose hypometabolism in epileptic foci without corresponding brain atrophy, indicating a permanently altered metabolic state in these brain regions3,4. The interictal reduced availability of ATP may contribute to seizure generation, since the post-ictal stabilization of ion gradients and membrane potentials, sufficient neuronal signal transduction and neuronal damage repair demands ample amounts of energy1Moreover, components of the second step of glucose metabolism, the tricarboxylic acid cycle (TCA cycle), function as building blocks for amino acids and proteins. Chronic depletion of these vital elements prevents neuronal repair as well as replenishing of neurotransmitters and may in part contribute to comorbidities of chronic epilepsy, such as cognitive regression. The role of impaired glucose metabolism in epileptogenesis has been affirmed in clinical practice, illustrated by the therapeutic success of the ketogenic diet in refractory epilepsy, which induces a metabolism shift to fatty acid metabolism5,6

The role of energy metabolism in epilepsy is however poorly understood and possibly differs per type of epilepsy. One of the epilepsy syndromes for which an altered metabolism has been suggested in earlier studies is Dravet syndrome. Dravet syndrome (DS) is a severe epileptic and developmental encephalopathy, presenting in the first year of life with prolonged generalized or unilateral tonic-clonic or clonic seizures, that progress to often therapy-resistant seizures over the course of the disease7). After the second year of life,

cognitive and motor development slows. In more than 80% of patients, DS is caused by a mutation in the SCN1A-gene, which codes for the alpha subunit of a voltage-gated sodium channel, predominantly expressed in GABAergic inhibitory interneurons, resulting in increased neuronal excitability8 . A longitudinal follow-up study compared FDG-PET scanning over time in three patients with an SCN1A-mutation to age- and gender matched controls and found normal cerebral glucose metabolism up until the first year of life but a gradual bilateral cortical glucose hypometabolism by the age of four, concurring with the clinical manifestation of cognitive regression. Interestingly, the three SCN1A patients showed similar patterns, suggesting a disease-specific process9. In a small study of fibroblasts in four Dravet patients a severe reduction in efficacy of the third step of glucose metabolism, the electron transport chain, compared to a control group was revealed. These defects were not seen in patients with a PCDH19 mutation with a similar phenotype10. A zebrafish model of Dravet syndrome demonstrated a decrease in the rate of glycolysis and of oxygen consumption, compared to wildtype, that was effectively resolved with the ketogenic diet11. A recent metabolomics analysis that was performed in Dravet mouse model revealed altered concentrations of several intermediates of glycolysis and the TCA cycle, indicating a shift in metabolism. Furthermore, an increased GABA-to-glutamate ratio was detected, a possible compensatory mechanism for increased excitability12.

Untargeted high-resolution metabolomics enables the profiling and analysis of thousands of metabolites. Over recent years, it has been applied in various fields of neuroscience to investigate biomarkers for disease and to identify metabolic pathways in pathophysiology. Research into biomarkers for mild cognitive impairment (MCI) en Alzheimer*s disease has shown promising results by identifying several candidate metabolites as prognostic factors13. For amyotrophic lateral sclerosis, metabolomics have been applied to elucidate the pathophysiological mechanisms13. In epilepsy, studies have applied metabolomics for various purposes. A comparative study between patients with different types of epilepsy and healthy controls could identify changes in the metabolic profile of patients with epilepsy in general, but could not distinguish types of epilepsy14. Comparing metabolic profiles of responders to non-responders to anti-seizure medication (ASM) did result in distinct characteristics15. However this difference was not observed in a different study in patients with newly diagnosed epilepsy16.
The heterogeneity of patients with epilepsy complicated the interpretation of results. Besides patient demographics such as age, gender and comorbidities, there is a large variety in seizure severity and use of different anti-seizure medication, that have an enormous influence on the metabolome.

Study objective

Primary Objectives:
1. To assess the metabolic profile of patients with Dravet syndrome and identify metabolic variations that contribute to the pathophysiology of

seizures and developmental delay

Secondary Objectives:
2. To assess the association between the metabolomics variations and response to treatment.
3. 3. To assess the effect of anti-seizure medication on the metabolome.

To achieve these objectives, we have formulated the following research questions.

For the primary objective 1:
a. What is the metabolic profile of patients with Dravet syndrome?
b. What are the differences in metabolic profile between Dravet patients, patients with other types of refractory epilepsy and patients without epilepsy?
c. Is there an association between specific metabolic variations and the phenotype in Dravet patients?

For secondary objective 2:
a. Is there an association between specific metabolic variations and the response to specific treatments, including the ketogenic diet?

For secondary objective 3:
a. What are the effects of commonly used anti-seizure medication, such as valproate, on the metabolome?

Study design

To assess the metabolomic profile in Dravet syndrome and to evaluate the effect of other factors on the metabolome, we will perform a case-control study in a cohort of patients with Dravet syndrome. As control groups, we will include patients with refractory epilepsies and a control group based on remnant samples available at the metabolic diagnostics section of the Genetic department of the UMC Utrecht.

Study burden and risks

With respect to potential benefits for participants: the aim of this study is to assess the metabolome of Dravet syndrome and to describe metabolic variations that can be linked to the severity of the phenotype and to responses to treatment. On a group level, this will increase our understanding of the pathophysiology of Dravet syndrome and may lead to improved therapeutic choices that may improve long-term outcome. On a broader level, elucidating the effect of anti-seizure medication and the ketogenic diet on the metabolome will improve our understanding of the method of action of these drugs and enable us to identify likely responders. The benefit for individual participants is possible improvement of treatment strategy based on metabolic profile.

With respect to group-relatedness: it is only possible to extend the knowledge of a genomic disorder (such as DS) by studying individuals with these specific disorders. As a large proportion of children and adults with genomic disorders has intellectual disability, the study needs to include participants who lack mental capacity to provide informed consent. The study cannot be carried out solely in patients who have capacity to provide informed consent. Therefore, the required criteria group-relatedness has been fulfilled for these patients.

With respect to burden, patients will be asked to undergo venepuncture on one occasion. This might give some discomfort or anxiety, in the worst case a vasovagal syncope might occur. We will ensure to minimize this risk by using personnel trained to work with mentally impaired subjects. No severe adverse events are to be expected from this procedure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Participants carry a SCN1A¬-mutation associated with a Dravet syndrome phenotype
OR
- Participants have refractory epilepsy other than Dravet syndrome and either use at least 2 anti-seizure medication or use at least 1 ASM and have a vagal nerve stimulator or are/were on the ketogenic diet (and a bloodspot was obtained before starting the diet)
OR
- Participants have undergone metabolic testing at the metabolic diagnostics section of the Genetic department of the UMC Utrecht after 2016 and remnant bloodsamples are available

AND
- Participants are living in the Netherlands

Exclusion criteria

- Patients with a variant of unknown significance (class III) in the SCN1A gene
- Patients with epilepsy caused by a mitochondrial disorder
- Patients who are currently on the ketogenic diet and for whom a bloodspot was not obtained before starting the diet
- Patients with an active infection at the time of blood retrieval
- Patients with substance abuse

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-06-2022
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	15-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-06-2023
Application type:	Amendment
Review commission:	METC NedMec

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	NL80025.041.21