Selecting Outcome measures for MITOchondrial disease in children (the SO-MITO study)

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Primary Objective: *Which outcome measure should we use to measure disease severity and disease progression in this specific group?*To test the feasibility (% of patients who were able to complete the test) of the selected outcome measures.To test...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Inborn errors of metabolism
Study type	Observational invasive

Summary

ID

NL-OMON38137

Source
ToetsingOnline

Brief title
Selecting outcome measures for mitochondrial disease in children

Condition

- Inborn errors of metabolism

Synonym
Mitochondrial disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ZonMW,mogelijk NutsOhra

Intervention

Keyword: Mitochondrial disease, Outcome measures, Pediatrics

Outcome measures

Primary outcome

Per test, per patient group:

* The percentage of patients who were able to complete the test

* The inter-rater reliability of one assessor

* The intra-rater reliability of two assessors

* The test-retest reliability after two weeks

* The correlation between parameters pre-specified per disorder (see paragraph 7.1)

* The correlation between these parameters over time (including a VAS-score for the patient*s and parents* experience on disease severity and disease progression)

Secondary outcome

Per patient group:

* The SD and clinically significant difference (minimal important change; * 2 points difference on the 11-item VAS scale of disease severity of both patient and parents and/ or * 2 point difference on the 11 item VAS-scale of disease progression of both patient and parents in the same direction as the effect of the study parameter) of the two most reliable instruments

* The time to complete the inclusion of all patients (calculated from the day the study starts recruiting).

* A description of the clinical symptoms, with focus on the functional

abilities and challenges

* The correlation between the concentration of several biomarkers and

functional abilities and general disease severity

Study description

Background summary

In recent years, there is more and more interest in the treatment of mitochondrial dysfunction by e.g. antioxidants1-4. However, the quality of these studies is widely criticized, since most studies are of inferior scientific quality and have insufficient sample size5, 6. One of the aspects of scientifically sound research in mitochondrial disorders we are currently focusing on is the selection of clinically relevant and scientifically robust outcome measures for children.

Our approach and past research
In Figure 1 you can see our approach. After an inventory of the most burdensome symptoms rated by patients and their parents7, we*ve reviewed the literature for available instruments which were previously able to measure these aspects reliably in disorders with similar symptoms and limitations8. In this review, we*ve presented a toolbox of 33 instruments which, in our opinion, are the most promising instruments to measure disease severity and disease progression in children with mitochondrial disorders. However, there is no experience with these instruments in children with mitochondrial disorders yet.

The challenge of selecting outcome measures for mitochondrial disease
Internationally, there is a huge demand for so-called *common data elements* for diseases like mitochondrial disease (http://www.nlm.nih.gov/cde/) . This is an extremely challenging task, since mitochondrial disorders are extremely heterogeneous. Since mitochondria are present in virtually every cell of the human body, virtually every organ can suffer from mitochondrial dysfunction. Mostly, mainly the most energy-consuming organs are affected, including the brain, muscle, heart and eye in every conceivable combination and severity. For example, a patient with Leigh syndrome, the prototype paediatric mitochondrial disease, may suffer from severe psychomotor retardation, dystonia, brainstem failure and responds poorly to his environment, whereas a patient with Kearns-Sayre syndrome suffers from chronic progressive external ophthalmoplegia, muscle weakness, retinopathy, but may for example be able to attend school. From a molecular perspective, more than a hundred genetic defects causing mitochondrial disorders are known (and many more are to be found using whole exome sequencing), causing a wide variety of biochemical

defects with their corresponding cellbiological consequences9. From a clinical perspective, there is a very poor genotype-phenotype correlation, even between siblings10. Moreover, the traditionally used and well-defined syndromes (Leigh syndrome, MELAS syndrome, etc) may have many different underlying molecular mechanisms.

Patient inclusion
One of the many questions that has to be answered before we can recommend certain outcome measures to be used in clinical trials in children with mitochondrial disease, is if we should select patients for intervention studies based on biochemical or phenotypical characteristics. Please see Figure 2 for a summary of the pro*s and con*s of both approaches. In this study, we aim to use both perspectives to group patients. For the clinical syndromes, we chose to include the well-characterized mitochondrial syndromes, such as Leigh syndrome, MELAS syndrome, Kearns-Sayre syndrome and Barth - and Sengers syndrome. The patients in the other group will be included based on their biochemical data and subsequently be classified into three clinical subgroups: myopathic and encephalo(myo)pathy patients, based on strict criteria.

Study objective

Primary Objective:
Which outcome measure should we use to measure disease severity and disease progression in this specific group?
To test the feasibility (% of patients who were able to complete the test) of the selected outcome measures.
To test the reliability (inter-rater reliability, intra-rater reliability, test-retest reliability) of the selected outcome measures.
To test the validity (correlation with predefined anchors and between parameters measuring the same construct) of the selected outcome measures.
To test the responsiveness over time of the selected outcome measures.

Secondary Objectives:
Is it feasible to use this group for intervention studies?
To determine the SD and the minimal important difference by the patient for the two most reliable outcome measures and determine the sample size for future studies
To determine the time to complete the patient inclusion

What are the functional abilities and challenges of the specific groups (which should be given more attention to in clinical practice)?
To determine the clinical spectrum of the phenotypes, with a specific focus on the function abilities and challenges

What is the value of the commonly used biomarkers for mitochondrial dysfunction as an outcome measure in intervention studies?
To determine the correlation between the commonly used biomarkers for

mitochondrial dysfunction and the functional capacities and disease progression in this group

Study design

This study is an observational study, in which the observation is performed using several instruments which were previously selected to be promising tools to measure disease severity and disease progression in children with mitochondrial disorders 8.

Patient inclusion and protocol selection
Patients will be included from two perspectives: the syndromal and the biochemical approach. The patients with a well-characterized syndrome (see paragraph 4.2) will be included in the syndromal group. Patients with a well-characterized mitochondrial dysfunction in combination with a classical mitochondrial phenotype (see paragraph 4.2) will be included in the biochemical group. The patients within the biochemical group are classified into the myopathic and the encephalopathic group (the clinical subgroups) based on their clinical symptoms. For the patients within the syndromal group, the syndrome is classified into a specific clinical subgroup, so all patients with the same syndrome perform the same tests. Each of the two clinical subgroups has its own toolbox of instruments measuring the functional abilities of the patient. For each syndrome, a number of instruments will be added (syndrome specific toolbox) based on the syndrome specific complaints and symptoms in this group. See also paragraph 5 for the methods and a description of the toolboxes.

Study design
These instruments will be used a time x, time x + 2 weeks and time x + 9 months, see Figure *. The patients will be seen by two experienced assessor (paediatric pediatric physiotherapists), who will both keep their own CRF. The examinations will be videotaped and, where possible, be scored again after 4 weeks to determine inter-rater reliability. Test-retest reliability will be tested by measuring at time x and at time x + 2 weeks. Patients will be phoned two days prior to the second assessment to ask if the disease has been stable since the previous assessment. If not, they will not be seen at time x + 2 weeks, but at x + 9 months and at x + 9.5 months. Responsivity will be tested by seeing the patients again at x + 9 months. At all visits, patients, parents, assessors and the physician are asked how they estimate certain aspects of the disease severity of the patient, see attachment *.

Study burden and risks

Patients will be seen at the outpatient clinic of the assessors three times. This means that they will not be able to attend school during that day. Since these patients have a mitochondrial disorders and tired easily, it is possible that they will be more tired during the week. Also, it is known that patients

with mitochondrial disease may suffer from muscle aches after exercise. Since we will test the limits of the patients* possibilities, this will probably also be the case after our examinations. The risks of serious complication of the individual tests are however, in literature and in our experience, negligible. We have deliberately chosen for instruments measuring the abilities in daily life and not for strenuous test such as the maximal exercise test, because these tests are probably too burdensome to the patients. The burden will also be minimized by a balanced programme, including regular pauses and alternation between exercise tests and more quiet tests, see attachment *.

On every visit to the outpatient clinic, after all tests are performed, blood will be drawn for biomarker analysis. We will try to make this as comfortable as possible (e.g. using emla cream), but it may still be a burden for the children. We draw blood at the end of the day because of this may be a traumatic experience for the child.

For parents, there will also be a burden, by taking 3 days off. Since we give a detailed programme including information on all three days, we think that parents may be able to make a decision for themselves.

Since we aim to test paediatric measurement instruments, this study cannot be performed in adults. We think this study is relevant to all children with mitochondrial disease, since studying future compounds in a homogenous, well-characterized cohort of patients using feasible, reliable and valid instruments increases the likelihood that valid conclusions will be drawn according to the effect of the treatment. Also, this study is an expression of our aim to advocate scientifically sound research in orphan diseases, which is sadly still rare.

This study will give a good overview of the patient*s health state and it might give a better overview over the patient*s problems than can be obtained in a regular outpatient visit. Therefore, a summary letter with the findings of this study will be sent to all physicians caring for the patient. This may be beneficial for the coordination of the care around the patient.

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

* 2-17 years old at the inclusion date and
* Biochemical group (see paragraph 4.2.2 of the protocol)
o mitochondrial dysfunction in muscle biopsy AND a mitochondrial phenotype and/or
o a confirmed pathogenic mutation, in case of mtDNA mutation in sufficient heteroplasmy to explain phenotype, agreement on pathogenicity between two physicians working in different centres
* Syndromal group (see paragraph 4.2.1 of the protocol)
o Fulfilling the criteria of the specific syndrome
o A confirmed pathogenic mutation or biochemical defect (only in Leigh)

Exclusion criteria

* Insufficient knowledge of the native language spoken in the hospital the child is seen in
* It is expected that the studies will be too burdensome for the patient or the family
* End-of-life expected within 3 months from the initiation of the study
* Other disabling disease

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	150
Type:	Anticipated

Ethics review

Approved WMO

Date:	08-04-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL47373.091.13