New Imaging Biomarkers for Muscular Diseases - Multispectral Optoacoustic Imaging in Spinal Muscular Atrophy (MSOT_SMA)

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Protocol Version 2.3 – 07.11.2019

Study protocol

MSOT_SMA

Non-invasive molecular imaging of muscle degeneration in spinal muscular atrophy

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2. Study titel, version number, version date

Study title

Non-invasive molecular imaging of muscle degeneration in spinal muscular atrophy

Version number

Version 2.3

Version date

7.11.2019

Protocol versions

Date	Version	Status	Changes
02.04.2019	1.0	Outline	
23.04.2019	2.0	Final application	Adaptation formulations, correlation with ultrasound
03.06.2019	2.1	Amendment	Specification of ultrasonic measurement parameters
02.10.2019	2.2	Amendment	specification clinical testing, adjustment of muscle regions
07.11.2019	2.3	Amendment	Application specialist deleted

3. Project summary

Neuromuscular diseases do often already present in the neonatal period and manifest with muscle hypotonia and weakness. Associated diseases are caused by numerous pathologies in the central nervous system (brain and spinal cord), the peripheral nervous system or the skeletal muscle. Spinal muscular atrophy (SMA) is a pathology of the central nervous system characterized by the degeneration of motor anterior horn nerve cells in the spinal cord or lower brain stem, which lead to progressive muscle weakness and atrophy. The clinical spectrum of all subtypes of the disease is broad, but in almost all cases the therapeutic options are limited to supportive therapy and palliative measures to prevent or alleviate complications such as spinal deformities or respiratory insufficiency. In the course of the disease, patients lose their motor neurons and thus their original skeletal muscle mass. In the muscle itself, a histological loss of the nerve and muscle fibers as well as a fatty remodelling can be observed. Most patients show normal cognition and consciously experience the course of their disease. In particular, the infantile development of SMA is lethal after only a few years of life.

Since 2016 (USA) and 2017 (European Union), the drug Nusinersen (Spinraza®, Biogen) has been available for the treatment of children and adults with SMA. It contains an antisense oligonucleotide, which is supposed to increase the expression of the usually in SMA reduced "survival motor neuron protein". In the ENDEAR study, the study used for FDA approval, 40% of children in the treatment arm achieved significant improvements in the area of motor milestones, while no child in the control group achieved this. Further positive effects were also reported in older children and adolescents as a result of the CHERISH study. The drug is administered intrathecally (in the spinal fluid). The first three doses were administered at intervals of 14 days and the fourth at intervals of 30 days. Subsequently, maintenance therapy is administered at intervals of 4 months. According to the Joint Federal Committee, the annual therapy costs currently amount to 310,877.58 € to 310,942.95 € - internationally, Spinraza® ranks second among the most expensive drugs in the world.

Whether patients benefit from this therapy can only be assessed clinically so far. To date, there are no prospective markers available that can predict a response or indicate therapeutic changes. Since 2017, a multispectral optoacoustic tomograph (MSOT) with an extended emission spectrum (660nm-1300nm) has been available to the University Hospital Erlangen through a DFG grant for large-scale equipment. MSOT imaging is similar to conventional sonography in that a transducer is placed on the skin and energy is supplied to the tissue by pulsed laser light instead of sound. On a macroscopic level, this leads to a constant change of minimal oscillations of individual tissue components. The resulting sound waves can then be detected by the same transducer. Previous studies have shown that the

quantitative determination of hemoglobin can be used to obtain information on blood circulation and inflammatory activity. In the extended spectrum, in contrast, not only hemoglobin and its oxygenation stages but also other biomarkers such as collagens and lipids can be detected. As already shown in preliminary work on Duchenne muscular dystophy, the method is very sensitive and correlates significantly with the corresponding clinic. In the light of progression of the spinal muscular atrophy, this method would for the first time allow a non-invasive and quantitative determination of the molecular composition of muscle tissue in affected patients. In this first pilot study, it will be investigated whether differences in muscular composition are also observed in spinal muscular atrophy. In the future, this could serve as a completely new method to provide information about the course of disease or response to therapy.

4. Responsabilities

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Children's Hospital Erlangen, Else-Kröner-Fresenius Foundation (Else-Kröner-Fresenius Memorial Scholarship Ferdinand Knieling)

5. Scientific background

Spinal muscular atrophy (SMA) is an autosomal-recessive disorder, characterized by progressive muscle weakness and atrophy. Spinal muscle atrophy has an incidence of 1/10,000 with an estimated carrier frequency of 1/50 (Sugarman 2012, McAndrew 1997, Pearn 1978). The condition is caused by a homozygous deletion or mutation in the survival motor neuron 1 (SMN1), resulting in reduced expression of the survival motor neuron (SMN) protein. This leads to the degeneration of motor neurons in the spinal cord and brain stem (Lefebvre 1995, Prior 2010). A nearby related gene, survival motor neuron 2 (SMN2), also produces the SMN protein, but due to aberrant splicing around 85-90% of translated protein are truncated and non-functional and rapidly degraded in the cell (Mailman 2002); remaining 10-15% are functional (Butchbach 2016), partially compensating the loss of SMN1 by SMN2 protein synthesis (Hsieh-Li 2000). Individuals with a higher copy number of SMN2 do in general have a milder phenotype (Mailman 2002, Butchbach 2016).

The various forms of SMA are differentiated according to distribution pattern, onset of disease, disease severity and hereditary pattern and are generally designated according to the muscle groups mainly affected (Pearn 1973, https://www.dgm.org/muskelerkrankungen/spinale-muskelatrophie). A large number of similar, much rarer forms are known that can be associated with additional dysfunctions. The non-proximal spinal muscle atrophies are also very rare and do usually not lead to significant limitations of vital functions at the onset of adulthood. However, the vast majority (approx. 90%) of patients belong to the group of so-called proximal SMA, which is characterized by the onset of muscle weakness in muscle groups close to the trunk (above all thigh and hip muscles, later also arm and shoulder girdle involvement). Proximal SMA is divided into different subtypes, which are primarily defined according to the onset of the disease, the learned motor skills and life expectancy.

Spinal muscular atrophy type 0, also called prenatal onset SMA, describes the most severe form of SMA as it presents before birth with decreased fetal movements. Neonates are born with severe hypotonia and weakness, areflexia, facial weakness, joint contractures, difficulty swallowing and respiratory failure on examination. Life-expectancy is greatly reduced, most patients die within the first 6 months of age (Dubowitz 1999, MacLeod 1999).

Spinal muscular atrophy type 1, also called Werdnig-Hoffman disease or infantile SMA, is the most common type of SMA. Symptoms usually exhibit at birth or before 6 months of age. Infants present with hypotonia (proximal more than distal limbs, legs more affected than arms) with poor head control (“floppy baby”), reduced or absent tendon reflexes and are never able to sit unassisted. Patients may show a bell-shaped thorax, paradoxical breathing,

swallowing weakness and tongue fasciculations. Cognition is not affected. Disease is usually fatal prior to 2 years of life due to respiratory failure (Finkel 2014, Thomas 1994).

Spinal muscular atrophy type 2, also called Dubowitz disease or intermediate SMA, presents usually between 6-18 months of age. This form tends to manifest with progressive leg weakness, which is worse than weakness in the arms, hypotonia and in a great percentage of patients areflexia. Comorbidities are related to muscular weakness and include scoliosis and joint contractures, as well as possible restrictive lung disease due to intercostal muscle weakness. Cognition is normal in affected patients (von Gontard 2002). Children with SMA type 2 are able to sit unassisted but are never able to walk independently. Life expectancy is reduced, but most patients live until adulthood (Fried 1971, Hausmanowa-Petrusewicz 1985, Imai 1995).

Spinal muscular atrophy type 3, also called Kugelberg–Welander disease or juvenile SMA, usually manifests after 12 months of age. Patients suffer from a proximal muscle weakness, which is more pronounced in the legs than in the arms. Individuals are able to walk unassisted, however at some point a wheelchair may be needed. Unlike SMA type 2, these patients do usually not suffer from orthopedic comorbidities or respiratory muscle weakness. Cognition and life expectancy are normal within this group. (Kugelberg 1956, Meadows 1969, Zerres 1997).

Spinal muscular atrophy type 4, is the mildest form of disease with an onset in adulthood, often at age 30 or later. Patients present with mild muscle weakness in the legs, that may procced to the arms. A small number of patients may require wheelchair assistance. Cognition and life expectancy is normal (Pearn 1978, Tsukagoshi 1965, Piepers 2008).

Extensive research has been done over the last two decades to develop an effective treatment strategy for SMA. Nusinersen (Spinraza®, Biogen), the first approved drug for the treatment of SMA, has been available since December 2016. This is an antisense oligonucleotide drug that leads to an increased production of full-fledged functional SMN protein. It is administered directly intrathecally as it does not cross the blood-brain barrier. Several studies showed improvements in motor function and survival in patients treated with Nusinersen, where early treatment was necessary to maximize the benefit of the drug. Long-term data are still pending. Several other promising therapeutic approaches, including gene therapy for SMA, are currently under development.

There are currently no prospective markers available that can predict early muscle degeneration, disease progression, therapy response or therapeutic changes. Since 2017, the University Hospital Erlangen (Deparment of Medicine 1, Department of Pediatrics) has a multispectral optoacoustic tomograph (MSOT) funded by the DFG. This allows non-invasive, quantitative imaging of the composition of target tissues in the non-sedated child, comparable to sonography. This is of particular importance in this patient group.

In MSOT, similar to conventional sonography, a transducer is placed on the skin and instead of sound, energy is supplied to the tissue by means of pulsed laser light. This leads to a constant change of minimal expansions and contractions (thermoelastic expansion) of individual tissue components or molecules. The resulting sound waves can then be detected by the same examination unit. Previous studies have shown that the quantitative determination of hemoglobin can be used to obtain information on blood flow and inflammatory activity in the intestine from patients with Crohn's disease (Waldner, Knieling et al. 2016, Knieling, Neufert et al. 2017) (Waldner 2016, Knieling 2017). In the newly configured device (Acuity Echo, iThera Medical GmbH, Munich, prototype) an extended spectrum of laser light can be used, which ultimately not only enables the detection of haemoglobin and its oxygenation stages, but also the detection of further markers such as collagen and lipid. [redacted]

Figure 1 - MSOT principle (a), experimental preliminary work (b), and first time representation of collagen in vivo (c)

Figures 1 and 2 show exemplary MSOT images. In the light of the progression and the sometimes severe course of SMA, this method would for the first time allow a non-invasive and quantitative determination of the molecular composition of muscle tissue. In this first pilot study in patients with SMA, it will now be investigated whether the differences in the muscle composition of healthy volunteers and SMA patients in the early stages can be quantified and whether this could simultaneously be used as marker during therapy with Nusinersen. In the future, this could generate a completely new, non-invasive method to evaluate endogenous biomarkers for therapy response.

Figure 2 - Feasibility of 3D MSOT image (a) and diagnostic quality (b).

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6. Study objectives

To establish a spectral profile of muscle tissue based on multispectral optoacoustic tomography (MSOT) of patients with spinal muscular atrophy and healthy volunteers.

Hypotheses:

- The optoacoustic spectrum of patients with spinal muscular atrophy compared to healthy volunteers is different
- The quantitative fraction of lipid signal in muscles determined by MSOT differs in patients with spinal muscular atrophy compared to healthy volunteers
- The quantitative fraction of collagen signal in muscles determined by MSOT differs in patients with spinal muscular atrophy compared to healthy volunteers
- The quantitative fraction of hemo-/myoglobin in muscles determined by MSOT differs in patients with spinal muscular atrophy compared to healthy volunteers
- The quantitative fraction of oxygenated/deoxygenated hemoglobin in muscles determined by MSOT differs in patients with spinal muscular atrophy compared to healthy volunteers
- There are no side differences in patients with SMA and healthy volunteers.

Primary study objective:

- Comparison of the optoacoustic spectrum determined by MSOT in patients with SMA and healthy volunteers

Secondary study objectives:

- Comparison of the quantitative lipid signal fraction determined by MSOT in patients with SMA and healthy volunteers
- Comparison of the quantitative fraction of collagen signal determined by MSOT in patients with SMA and healthy volunteers
- Comparison of the quantitative fraction of hemo-/myoglobin signal determined by MSOT in patients with SMA and healthy volunteers
- Comparison of the quantitative fraction of oxygenated/deoxygenated hemoglobin determined by MSOT in patients with SMA and healthy volunteers
- Correlation of lipid content determined with MSOT with disease duration/patient age
- Correlation of collagen determined by MSOT with disease duration/patient age

- Correlation of haemoglobin/myoglobin content determined by MSOT with duration of disease/patient age
- Correlation of oxygenated/deoxygenated hemoglobin determined by MSOT with duration of disease / patient age
- Correlation of lipid content determined with MSOT with age-related functional muscle tests (Hammersmith Infant Neurological Examination (HINE)/ The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend)/expanded Hammersmith functional motor scale (HFMSE)/ Revised Upper Limb Module (RULM)/ &-Minute-Walk Test (6-MWT)))
- Correlation of collagen determined with MSOT with age-dependent functional muscle tests (HINE/ CHOP Intend/ HFMSE/Revised Upper Limb Module/6-MWT)
- Correlation of hemo-/myoglobin content determined with MSOT with age-dependent functional muscle tests (HINE/ CHOP Intend/ HFMSE/Revised Upper Limb Module/6-MWT)
- Correlation of oxygenated/deoxygenated hemoglobin determined with MSOT with age-related functional muscle tests (HINE/ CHOP Intend/ HFMSE/Revised Upper Limb Module/6-MWT)
- Measurement of signal differences in right / left comparison
- Correlation of MSOT ultrasound image (RUCT) with standard sonography

Study type

Since no data exists so far to support the hypothesis of this study, it is an explorative study / pilot study.

7. Target parameters

All measurements with MSOT are performed over the proximal and distal limb muscles in a right-left comparison (leg proximal: Musculus quadriceps, distal: Musculus triceps surae; arm proximal: Musculus biceps, distal: Forearm flexors) in healthy subjects compared to patients with SMA.

Primary target:

Optoacoustic Absorption Spectrum of Muscle.

This target is measured non-invasively by MSOT.

Secondary targets:

Quantitative lipid signal (in arbitrary units)

Quantitative collagen signal (in arbitrary units)
Quantitative hemo/myoglobin signal (in arbitrary units)
Muscle oxygenation (in %)
Ratio of lipid to hemo/myoglobin signal or collagen to hemo/myoglobin signal
These target values are collected non-invasively using MSOT.

Diameter, number of nerve fibers (peripheral nerves, median nerve, ulnar nerve, ischiadic nerve)
Muscle texture (Heckmatt score, echogenicity)
These target values are determined by means of B-image sonography.

Clinical scores for determining muscle strength consisting of:

Patients < 2 years and patients ≥ 2 years with inability to sit:

- Hammersmith Infant Neurological Examination (HINE)/ The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend)

at age ≥ 2 years and ability to sit in a wheelchair additionally:

- Revised Upper Limb Module (RULM)

Patients ≥ 2 years and sitting ability:

- expanded Hammersmith functional motor scale (HFMSE)/ Revised Upper Limb Module (RULM)

in case of ability to walk additionally:

- 6-minute walking test

< 2 years	≥ 2 years with inability to sit	≥ 2 years and ability to sit in a wheelchair	≥ 2 years and ability to sit	≥ 3 years and ability to walk
HINE Section 2	HINE Section 2	HINE Section 2		
CHOP Intend	CHOP Intend	CHOP Intend		
		(HFMSE)	HFMSE	HFMSE
		RULM	RULM	RULM
				6MWT

These target values are clinically determined at presentation.

Age
Sex
Weight
Skin color
Ethnic Background
Disease duration
Current medication

These target values are either available in the electronic patient file or they are collected at presentation for the study.

8. Study design

Monocentric / multicentric

This is a monocentric study with matched collectives (age, gender).

Study arms: intervention/control

Interventions are not planned. A comparison is made between healthy volunteers and patients with SMA. The study procedure is identical for all volunteers and patients.

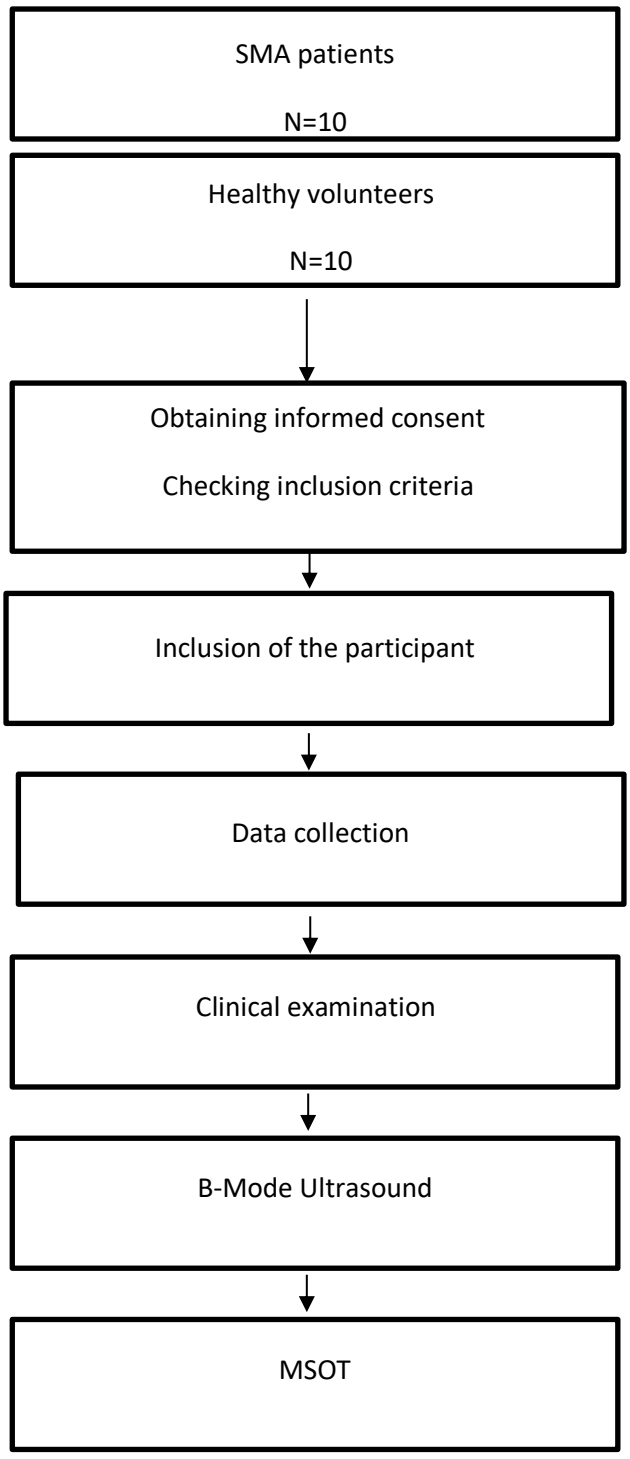
Randomization

Randomisation is not planned. The allocation to the groups is based on the known diagnosis (SMA) and controls (subjects).

Blinding

Blinding for the examination is not possible due to the often clear clinical appearance. Blinding takes place during the measurement and evaluation of the data. Blinding of the patients/test persons is not necessary.

Graphical presentation of the study design



9. Study population

Inclusion and exclusion criteria

Preliminary phase

Inclusion criteria:

SMA patients:

- Genetically Confirmed SMA Type I-III
- From birth
- Independent from current therapy

Healthy controls:

- From birth, matched (age, gender) to SMA collective

Exclusion criteria:

SMA patients:

- Pregnancy
- Tattoo on skin to be examined

Healthy controls:

- anamnestic or other signs of myopathy
- pregnancy
- Tattoo on skin to be examined

Patient/control number

As this is a pilot study, an exact case number calculation is not possible. It is planned to study a total of 10 healthy volunteers and 10 patients with SMA.

Recruitment routes and measures

Patients (and parents) are informed about the possibility of participating in the study in the context of an elective presentation in the Department of Neuropediatrics in our pediatric Clinic. If the patient is willing to participate, he/she will be fully informed about the aims and

methods (especially about the scientific/explorative character of the study), benefit and risk and revocability of the study participation. Patients in childhood and adolescence will also be informed and educated about the study and its procedure according to their age.

Healthy volunteers are recruited in the outpatient department of our Pediatric Clinic. Acutely ill or unstable patients are not recruited. In the preliminary phase, volunteers are parallelised with the SMA collective in terms of age and sex.

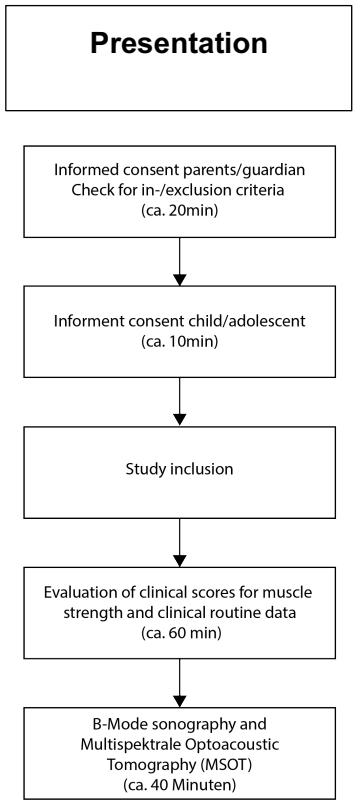
10. Study course

Procedure for informing about and obtaining consent

Patients or test persons can only be included in the study after a written consent has been given. The written declaration of consent requires oral and written information of the patients/test persons as well as their parents or legal guardians about goals and methods (incl. scientific-explorative character of the study), benefit and risk as well as revocation of participation in the study. Children and adolescents are informed by means of age-appropriate, comprehensible patient information sheets. By giving their written consent, the patients/test persons and their parents/guardians declare that they agree to the collection and storage of study-relevant data and their verification by monitoring or authorities. The study participant must be clearly informed that the declaration of consent can be withdrawn at any time and without any disadvantage. Furthermore, all study participants/test persons and parents/guardians are informed that this study is a purely scientific study without any current diagnostic or therapeutic benefit.

The original of the declaration of consent will be kept in the study folder at the place of study. The patient/control and the parents/guardian receive a copy of the patient information and declaration of consent. The patient information and the consent form are attached to this protocol

Measurements



After informing the patient / control and parent / guardian and obtaining consent, clinical scores are collected to assess muscle strength according to age (Hammersmith Infant Neurological Examination (HINE)/ expanded Hammersmith functional motor scale (HFMSE)/ The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend)/ Revised upper Limb Module (RULM)/6-minute walking test (6-MWT)). Subsequently, MSOT imaging is performed on 4 anatomical regions in all study participants: Upper/lower arm and upper/lower leg on predefined muscle groups. (Leg proximal: Musculus quandriceps, distal: Musculus triceps surae; arm proximal: Musculus biceps, distal: Forearm flexors). The examination is analogous to sonography over the corresponding skin layers without further invasive procedures. The anatomical region can be localized by means of built-in B-image sonography; the corresponding optoacoustic signals can then be conducted. The duration per anatomical region is limited to 5 minutes; this corresponds to a maximum of 20 minutes for both upper extremities and 20 minutes for both lower extremities. Patients can remain in a relaxed posture during the examination, without the need for breathing maneuvers or similar assistance.

Recording of target parameters

- Clinical evaluation of muscle strength by HINE/HFMSE/CHOP Intend/RULM/6-MWT
- Non-invasive in-vivo measurement of lipid, collagen, myo/hemoglobin content and oxygenation by MSOT
- Determination of routine data (duration of disease, current medication) from electronic patient file in Soarian

Time schedule and study duration for the individual patient/control

For the individual patient, the duration of the study participation is 130 minutes. Approximately 30 minutes are spent on education for study participants and parents/guardians, 60 minutes on clinical (routine) testing of muscle strength, and 40 minutes for the actual examination.

Total duration of study

Depending on the number of patients, the expected total duration of the study up to the inclusion of the last patient is approximately 12 months.

11. Risk-benefit analysis

All study-related risks

Based on the classification criteria for medical devices (Directive 93/42/EEC, Annex IX), the optoacoustic system of iThera Medical corresponds to Class IIa:

- Active diagnostic device
- non-invasive
- Temporary use (<60 min)

No CE certification is available for this research device (current type designation according to imprint: Acuity Echo). A conformity assessment procedure in the sense of the MPG is not intended or planned by the manufacturer at the present time. It is therefore a purely scientific pilot study. There is no dependency on the manufacturer, all diagnostic and analytical procedures are available to the study directors on site. The cooperation with the company is regulated in a separate contract drawn up by the legal department before the start of the study.

Adherence to energy levels

The laser safety and maximum permitted radiation dose for irradiation with laser pulses is regulated in the laser standards ANSI and IEC 60825. The MSOT system meets these standards and therefore remains below the MPE (maximum permissible exposure) limits for skin irradiation and is therefore considered safe.

Temperature increases due to MSOT in tissue

Optoacoustic imaging does not result in any significant temperature increase in the tissue. The absorption of a laser pulse in the tissue results in a local transient temperature increase of a few millikelvin. Depending on the duration of the examination and the skin type of the patient, temperature increases occur typically in the range of less than one degree Kelvin.

Histological changes in tissue

Histological changes in the target tissue and surrounding structures are neither expected nor have they been observed in previous preclinical and clinical studies.

Slight, reversible redness or warming might occur in very sensitive skin.

Such side effects are to be noticed at any time by the test person or doctor; the examination can then be interrupted or aborted. In any case, no irreversible damage is to be expected.

In general, the near infrared light used in the MSOT can lead to retinal damage if the eye is irradiated. In order to prevent this, test participants and examiners will wear appropriate laser safety glasses during the examination.

Since the data obtained is not used to interpret diagnostic results, there is no risk of possible misdiagnosis or incorrect display of data in this exploratory pilot study.

No other risks exist for this study, nor have we described any risks based on our own preliminary data.

Benefits associated with the study

The data obtained in the studies may provide important insights into the pathomechanism of SMA. The possible quantitatively determinable differences could be used in the future as a monitoring method for a therapeutic response or prognosis of this disease.

Termination criteria

Termination criteria for the individual participant:

Especially in light of the background of the inclusion of children and adolescents, participation in the study is discontinued if the skin becomes conspicuously warm or reddened. The examination time per anatomical region is limited to 5 minutes, so that these events are very unlikely.

Due to the short duration of the study participation, no other discontinuation criteria are planned.

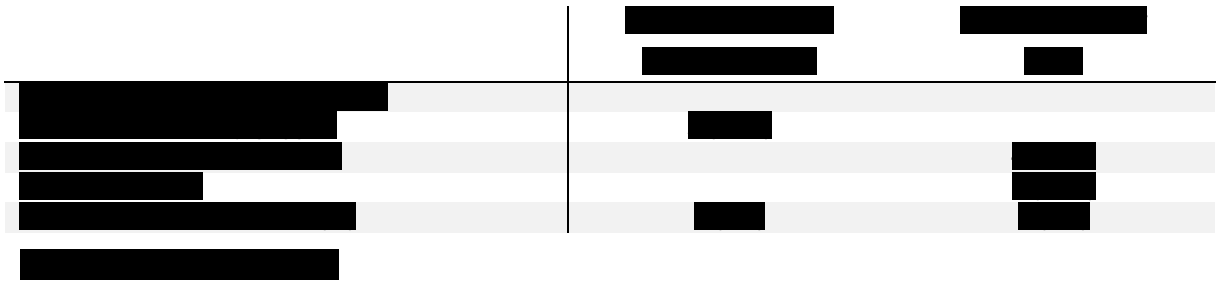
Termination criteria for the whole study:

A termination of the entire study is not planned.

Statement on medical justifiability

Based on previous experience in children with Duchenne muscular dystophy and healthy controls, the risk of the occurrence of unwanted events is stratified as extremely low.

[redacted]



In this study no central organs are examined, but only extremities are measured - this leads to a further significant reduction of a possible residual risk.

Particularly in light of the background of completely new therapeutic approaches, we hope that this method will provide us with a child-friendly diagnostic tool for the treatment of these complex diseases. Since these diseases and their therapy are only relevant in childhood, no comparable adult collectives are available.

12. Biometrics

Explorative study: explanation of the statistical methodology, justification of the selected number of cases

Case number calculation:

As this is a pilot study and no information on the expected differences between the different groups is available yet, no case number calculation was performed. The number of cases given represents an estimate or is within the appropriate range for a pilot study.

Statistical methods:

Continuous variables are given as mean values with standard deviation, categorical variables as numbers with percentages if necessary. The MSOT parameters are compared using a two-sided, unpaired t-test with the same deviations. If the standard deviation is unequal, a correction according to Welch may be applied. Furthermore, ROC analyses (Receiver Operator Characteristics) between healthy/ill persons are planned. Genetics serve as the gold standard. Correlations are indicated by the Pearson coefficient. All statistical tests are performed on both sides and a p-value of <0.05 is considered statistically significant. All analyses are performed using GraphPad Prism (version 7.00 or later, GraphPad Software, La Jolla, CA, USA), RStudio (version 1.1.456 or later, RStudio Inc., Boston, MA, USA) or IBM SPSS Statistics (version 24 or later, IBM Corp., Armonk, NY, USA).

13. Data management und and data protection

Data acquisition and storage

All raw data, such as patient files, are source documents. Their availability is ensured for routine monitoring. The participation of the individual patients or test persons in the study is documented. The study leader maintains an independent list for the identification of the participating patients. This list containes the names and date of birth as well as the date of examination and pseudonymisation codes of the patients and subjects. The study leader is responsible for the quality of data collection and storage. The data storage (complete data) takes place on computers or specially designed network drives of the University Hospital Erlangen. The raw imaging data (no patient-related data) are stored on dedicated servers of iThera Medical GmbH.

Pseudonymisation

Prior to a scientific analysis of the materials and data of this study, all information will be pseudonymized according to the guidelines of the Federal Data Protection Act.

Data transfer

In this study, data transfer is only intended for the MSOT raw data. The company iThera Medical GmbH will work with this data to ensure adequate recording quality and to develop algorithms for evaluation. The data will only be passed on pseudonymously on encrypted physical drives. The data will not be used for later approval of the prototype used. The cooperation is explicitly regulated by the legal department before the start of the study (an additional agreement to the service contract can be found in the appendix).

The study results can be published anonymously, whereby it will not be possible to draw conclusions about the identity of the participating persons. The data will be kept for 10 years and then destroyed.

Revocation, data deletion

If the declaration of consent is revoked, data collected up to this point can be taken into account. The patient has the right to demand that the data be destroyed, provided that legal provisions do not prevent such destruction.

14. Handling of biomaterials

No biomaterials are obtained.

15. Insurance

The participants of the study are insured via the group contract of the CCS Erlangen.

16. Signatures

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Study director

Prof. Dr. med. Regina Trollmann
Study director

Prof. Dr. med. Maximilian Waldner
Technical implementation

Prof. Dr. h.c. Dr. med. W. Rascher
Clinic director