Low-fiel**D** magn**E**ti**C** **R**esonance imaging of pulmonar**Y** **P**arenchyma changes associated wi**T**h confirmed **SARS-CoV-2** infection in children and adolescents

Brief title: Low-field Magnetic Resonance Imaging of Pediatric COVID-19 (DECRYPT)

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Sponsor:

Department of Pediatrics and Adolescent Medicine

University Hospital Erlangen
Friedrich-Alexander-University (FAU) Erlangen-Nürnberg
Pediatric Experimental and Translational Imaging Laboratory (PETI_Lab) Dr. med. Ferdinand Knieling
Loschgestr. 15
91054 Erlangen
Germany
Tel.: +49 9131 85-33118
E-mail: ferdinand.knieling@uk-erlangen.de

Study protocol

“DECRYPT_SARS-CoV-2“

Low-fiel**D** magn**E**ti**C** **R**esonance imaging of pulmonar**Y** **P**arenchyma changes associated wi**T**h confirmed **SARS-CoV-2** infection in children and adolescents

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2. Study title, version nmber, version date

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Version number

Version 1.4

Versionsdatum

09.08.2021

Protokollversionen

Datum	Version	Status	Änderungen
28.04.2021	1.0	Draft	correction Dr. Heiß
29.04.2021	1.1	Final version	
21.05.2021	1.2	Revision	Adjustments ethics
21.07.2021	1.3	Revision	Improvements ethics
09.08.2021	1.4	Translation	

3. Project summary

SARS-CoV-2 (Severe acute respiratory syndrome coronavirus type 2) is a new coronavirus and identified causative agent of COVID-19 disease. They predominantly cause mild colds but can sometimes cause severe pneumonia. The long-term consequences are still largely unexplained and misunderstood, especially in children and adolescents. The aim of this study is to assess the frequency of pulmonary parenchymal changes in pediatric and adolescent patients using low-field magnetic resonance imaging (LF-MRI) in the setting of proven past SARS-CoV-2 infection.

4. Responsibilities

Study lead

Dr. Ferdinand Knieling

Children's and Adolescents' Hospital
University Hospital Erlangen
Loschgestr. 15
91054 Erlangen
Tel. 09131 8533118
Email: ferdinand.knieling@uk-erlangen.de

Dr. Rafael Heiß

Institute of Radiology
Maximiliansplatz 2
91054 Erlangen
Tel.: 09131 85-36065
Email: rafael.heiss@uk-erlangen.de

Funders

Internal funds

5. Scientific background

SARS-CoV-2 (Severe acute respiratory syndrome coronavirus type 2) is a new coronavirus and identified causative agent of COVID-19 disease. They predominantly cause mild colds, but can sometimes cause severe pneumonia. While the molecular basis for the changes in lung tissue [1-3] or multi-organ involvement [4] have been described, the age-specific long-term consequences, especially in children and adolescents, remain largely unexplained and misunderstood today. Early publications from the primarily affected Chinese provinces described rather mild, partly asymptomatic courses in children [5]. This is consistent with the observation that the risk of severe COVID-19 disease increases steeply from the age of 70 years, and is also determined by the severity of obesity as well as other risk factors [6]. Developmental depended expression of tissue factors may be one reason for the relative protection of younger patients from severe courses of the disease [7].

However, it is now becoming increasingly clear that some individuals with milder initial symptoms of COVID-19 may suffer from variable and persistent symptoms for many months after initial infection - this includes children [8]. A modern low-field MRI is located in Erlangen, Germany. This technique has already been used to demonstrate persistent damage to lung tissue in adult patients after COVID-19 [9]. The device with a field strength of 0.55 Tesla (T) currently has the world's largest aperture (and is thus particularly suitable for patients with claustrophobia, among other things), a very quiet operating noise, and lower energy absorption in the tissue due to the weaker magnetic field than MRI scanners with 1.5T or 3T. This allows MRI imaging in a very wide pediatric population without the need for sedation.

The aim of this study is to assess the frequency of lung parenchymal changes by low-field gastric resonance imaging (LF-MRI) in past PCR-detected SARS-CoV-2 infection in pediatric and adolescent patients.

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6. Study objectives

Determination of the frequency of lung parenchymal changes by low-field magnetic resonance imaging (LF-MRI) in past PCR-detected SARS-CoV-2 infection in pediatric and adolescent patients.

Hypotheses:

- Lung parenchymal changes in pediatric and adolescent patients with positive SARS-CoV-2 infection can be detected by LF-MRI
- The patients with changes do not show clinical symptoms

Primary Objective:

- Determination of the frequency of lung parenchymal changes by LF-MRI.

Secondary Goals:

- Determination of the frequency of positive SARS-CoV-2 antibodies.
- Determination of the anamnestic frequency of clinical respiratory symptoms.

Study type

Prospective, monocentric, diagnostic study

7. Target figures

Primary Targets:

LF-MRT	Lung parenchymal changes

Secondary Targets:

Blood sample	SARS-CoV2-Antibody Mechanical cell properties (realtime deformability cytometry) Blood count
Clinical Features (via KIS)	Age Gender Weight Ethnicity Time of Infection (PCR result) Interval until LF-MRT Current medication Secondary Diagnoses Symptoms during COVID (e.g cough, shortness of breath, fever) Current symptoms (e.g cough, shortness of breath, fever)

8. Study Design

Monocentric / Multicentric

This is a monocentric study.

Studiy arms: intervention/control

All patients with inclusion criteria will receive a blood draw and MRI of lungs.

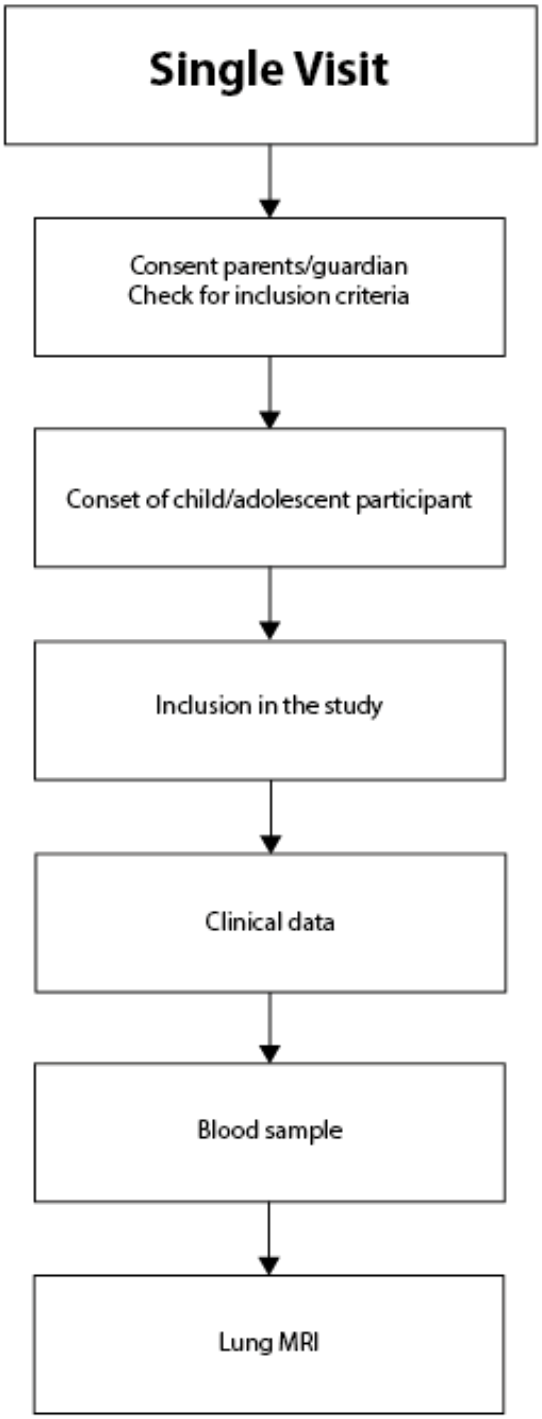
Randomization

Randomization is not provided.

Blinding

Blinding for the study is not possible. Blinding of the patients/test persons is not necessary.

Graphic representation of the study design



9. Study population

Inclusion and exclusion criteria

Inclusion criteria

- From 5 years to <18 years
- Positive SARS-CoV-2 infection confirmed by PCR

Excklusion criteria

- Acute SARS-CoV-2 infection and need for isolation.
- Necessary Quarantine
- Pregnancy
- Critical Condition
- MRI imaging rejection
- General contraindications to MRI examinations (e.g., electrical implants such as pacemakers or perfusion pumps etc.).

Quantity
It is planned to study n=58 patients.

Recruitment channels and measures

Patients (and parents) will be informed about participation in the study in an announcement via the hospital's homepage. This announcement describes the content, measures and duration of the study. Parents can then pre-register their child by phone or e-mail and will receive a call back for a specific appointment. If the child is willing to participate, a full explanation of the objectives and methods (especially the scientific/exploratory nature of the study), benefits and risks, and revocability of study participation will be provided. Patients of child and adolescent age are additionally informed and educated about the study and its procedure in an age-appropriate manner.

10. Course of study

Procedure for informing and obtaining consent

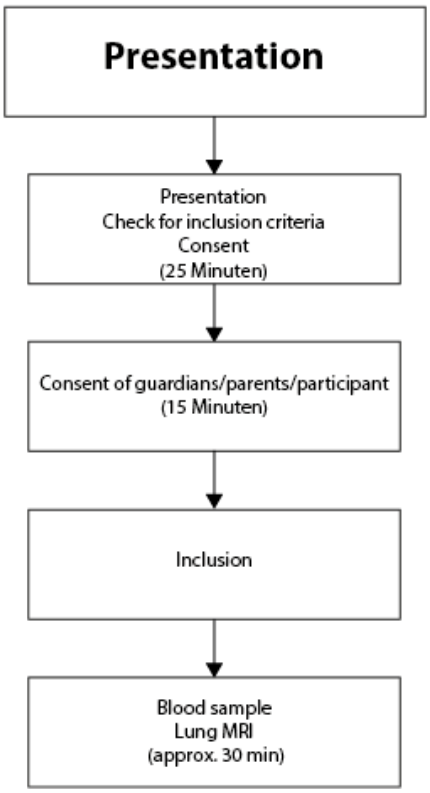
Patients or subjects can only be included in the study after written informed consent has been obtained. The written informed consent requires an oral and written explanation of the patients/test persons, as well as their parents or legal guardians, about the aims and methods (incl. scientific-explorative character of the study), benefits and risks as well as the revocability of the study participation. Children and adolescents are informed by means of age-appropriate, comprehensible patient information sheets. By giving written consent, the patients/participants

as well as their parents/guardians declare that they agree with the collection and storage of study-relevant data and their review by monitoring or authorities. It must be clearly conveyed to the study participant that withdrawal of consent is possible at any time and without any disadvantage. Furthermore, all study participants/subjects and parents/guardians are informed that this study is a purely scientific study without any current diagnostic or therapeutic benefit. In case of incidental findings, the study participants/test persons and parents/guardians will be informed and further clarification will be initiated if indicated.

The original consent form will be kept in the study folder at the study site. The patient/proband and parent/guardian will be given a copy of the patient information and consent form. The patient information and informed consent form can be found in the appendix of this study protocol.

Measures

After informing the patient/proband and parents/guardians, clinical data are collected and a blood sample is taken. After appropriate education of parents/guardians/patient, a native MRI examination (MRI examination without contrast medium administration) is performed after inclusion. The duration is about 20 minutes. This is performed exclusively without sedation. Patients can remain in a lying position during the examination. During the examination, patients are protected by hearing protection from the noise generated. To enable the patient to make himself/herself heard, he/she is given a bell button shortly before the examination begins; during the examination planning, communication is possible by means of an intercom system. In addition, the presence of a parent in the scanner room is possible during the entire examination time. The examination in the new 0.55 T MRI system does not differ in procedure and especially with regard to contraindications for an MRI examination from an examination in routinely used 1.5 or 3T devices. There is no intravenous administration of contrast medium and the images produced are not evaluated diagnostically.



Acquisition of the target variables

- MRI Imaging
- Antibody status from blood sample
- Determination of demograpic data

Timing and duration of the study for the individual subject/patient

For the individual patient, the duration of the study participation is 70 minutes. Approximately 40 minutes are allotted for education for study participants and parents/guardians and 30 minutes for the actual examination (blood sampling and MRI).

Total duration of the study

According to the number, the expected total duration of the study until the inclusion of the last patient is approximately 18 months.

11. Risk-benefit analysis

All study-related risks

Blood draw

The risks of blood collection include the development of bruises in the area of the injection site. There is a very small risk of local or general infection. In extremely rare cases, injury to a cutaneous nerve may occur, possibly even with a chronic course.

Magnetic resonance imaging

Unlike computed tomography, MRI does not use ionizing radiation, so no permanent side effects are expected.

More than 1 million MRI examinations at higher field strengths (1.5/3T) are performed annually in Germany. Provided that the general contraindications for MRI examinations are observed, no serious side effects occur. MRI is therefore one of the safest examination procedures.

The risks associated with an MRI examination emanate from the three main components of the MRI system.

Static magnetic field

The static magnetic field exerts forces and torques on ferromagnetic objects that can be so strong that the (mostly ferromagnetic) objects fly uncontrollably toward the magnet and hit patients and staff (missile effect). The magnetic forces are proportional to the field strength B and the field change with location (dB/dz). These risks are lower with the low-field MRI system. Risks are further minimized by providing safety training to operators and excluding patients with ferromagnetic implants from the study.

The gradient system

Gradient switching can cause the appearance of magnetic phosphenes and nerve and muscle cell stimulation. Rapidly switched gradients produce high magnetic field changes per time (dB/dt) that induce voltages in the body. If a current flows through the tissue via nerve endings, for example, this can result in so-called peripheral nerve stimulation. However, the manufacturer of the gradient system guarantees compliance with the limits for gradient switching times and amplitudes recommended in the IEC 60601-2-33 guidelines. Thus, nerve stimulation effects need not be considered further in the risk assessment of this study.

Another safety-relevant effect of gradient fields is noise caused by gradient switching due to current- and field-strength-dependent Lorentz forces in the gradient tube. These often unpleasant loud knocking noises occur especially during fast imaging processes where high

currents flow through the gradients. Noise levels can rise up to 115dB for 1.5T tomographs (background noise: approx. 78dB). Due to the lower magnetic forces at 0.55T, we expect lower noise levels. In addition, patients always wear hearing protection during the examination, so that the noise exposure remains well below the legal limit of 99 dB.

The high-frequency system

During the MR measurement, radiofrequency (RF) fields are sent into the human body, which are partially absorbed by the tissue and can lead to an increase in body temperature. The thermoregulatory response of human tissue to RF pulses has now been studied for 50 years. For example, using conservation of energy, it has been calculated that the body temperature of lightly clothed patients with undisturbed thermoregulation at room temperature increases by up to 0.6 °C with RF exposure of 4 W/kg (63 MHz, 1.5 Tesla). The assumed specific absorption rate (SAR) of 4 W/kg body tissue corresponds to the so-called "controlled mode first level" (IEC safety guideline), which is also used as an upper limit in routine clinical imaging. The magnitude of the actual temperature rise is generally smaller because skin cooling was not considered in the calculations (worst case scenario).

The body's energy production at rest is about 1.2 W/kg - equivalent to the energy conserved when wearing a thin sweater. Most healthy people are capable of compensating for 15 times this resting energy, and only a minimal increase in core body temperature occurs. Studies at 1.5 T have shown that RF absorption in humans leads only to the expected cardiac adaptation and does not cause adverse health effects. Theoretically, a 63 kg person is even capable of emitting 1296 W to the environment through the skin by cardiac adaptation (i.e., maximum increase in blood flow) - this would correspond to a SAR of 20.6 W/kg.

The same limits are observed with the 0.55 Tesla MRI system. At 0.55 Tesla, the wavelength of the radio waves used is significantly longer, so that the spatial distribution of the energy emission is more homogeneous and thus the risks tend to be lower.

Benefits associated with the study

The data obtained in the studies may provide essential insights into the course of SARS-CoV-2 infection in pediatric and adolescent patients.

The study may influence future clinical clinical management.

Discontinuation Criteria

Discontinuation criteria for the individual participant:

Particularly in light of the inclusion of pediatric and adolescent participants, study participation will be discontinued if MRI cannot be performed without sedation.

Study discontinuation for the individual participant will occur if:

- an event occurs that may lead to endangerment of the patient or the staff,
- the patient withdraws consent to participate in the study
- the patient does not comply with the instructions of the investigators and the operating personnel,

The patient can stop the examination at any time without giving any reason. For this purpose, a so-called bell button is available to the patient during the MRI examination, the activation of which gives a signal with which the patient can draw the attention of the physician/examiner to him/herself, even while the measurement is in progress. Furthermore, the patient is in contact with the examiner via microphone and headphones between the individual measurements and can thus also verbally request the termination of an examination. In addition, the presence of a parent in the scanner room is possible during the entire examination time. Study participants may also discontinue the study at any time before, during, and after all other study-related examinations without providing a reason.

Dropout criteria for the entire study:

There is no provision for discontinuation of the entire study.

Statement on medical justifiability

The examinations will be performed exclusively on an approved MRI device. The field strength used is significantly lower than the 1.5T and 3T scanners routinely used to date. The risks are low as described above, especially since no measures such as contrast agent application are foreseen. New diagnostic and clinical applications could arise from the trial implementation.

12. Biometrics

Exploratory Study

Samlple size calculation

With a sensitivity of 90%, specificity of 85%, precision of ±0.15 and a prevalence of 0.3 with a confidence level of 95% for a 10% dropout, the number of cases was n=58 (including dropout).

Statistical methodology

Continuous variables are reported as mean with standard deviation, categorical variables as numbers with percentages where appropriate. The occurrence of MRI changes is reported as a percentage of the population. For each clinical factor (vomiting, confusion, etc.), a relative risk (RR) and odds ratio (OR) of having an MRI change is calculated. 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 and Data protection

Data acquisition, storage

All raw data, such as patient records, represent source documents. Their availability is ensured for routine monitoring. The participation of individual patients or subjects in the study is documented, and the study director maintains an independent list to identify participating patients. This list included name and date of birth as well as study date and pseudonymization abbreviation of the patients and subjects. The study director is responsible for the quality of data collection and storage. Data storage (total data) is performed on computers or specially designated network drives at Erlangen University Hospital. Comparable to routine, imaging data are transferred to the protected PACS (Picture Archiving and Communication System).

Pseudonymization

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

Data transfer

The data will not be passed on to third parties.

The study results may be published anonymously, and it will not be possible to infer the identity of the participating individuals. The data will be kept for 10 years and then destroyed.

Revocation, data deletion

In case of revocation of the declaration of consent, data collected up to this point can be taken into account. The patient has the right to demand their destruction, provided that legal regulations do not prevent the destruction.

14. Handling biomaterials

The blood samples obtained are analyzed immediately after collection in the laboratory of the Children's and Adolescent Clinic and, if necessary, reserve samples are stored for 5 years.

15. Proband insurance

No insurance is provided due to low risk of study.

16. Signatures

Dr. med. Ferdinand Knieling
Director of Studies

Dr. med. Rafael Heiß
Director of Studies