INFORMATION SHEET FOR LEGAL GUARDIAN/PARENT OF PATIENTS UNDER AGE OF 18

Title of the study: Antibody-mediated NMDA receptor encephalitis: symptoms, biomarkers, and mechanisms of the prolonged recovery stage

PRINCIPAL INVESTIGATOR COORDINATING CENTER

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INTRODUCTION

We are reaching out to inform you about a research study in which we invite your child and you, as their legal guardian and companion, to participate. The study has been approved by a Research Ethics Committee, in accordance with current laws. If you have any questions or need clarification after the explanation, you can speak with any member of the team or contact Dr. Josep Dalmau (contact phone: 93 227 1738), who is responsible for coordinating the project. Additionally, you may consult with other individuals you deem appropriate.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary, and you have the right to choose not to participate or to change your decision and withdraw consent at any time. Your decision will not affect the relationship with your child's doctor or the treatment they receive.

GENERAL STUDY DESCRIPTION:

We invite you to participate in a research study led by Dr. Josep Dalmau from the Neurology Department at Hospital Clínic Barcelona.

The disease your child has is called anti-NMDA receptor encephalitis, and it was discovered recently in 2007. It is a condition in which the body's immune system attacks a protein called NMDAR in brain cells called neurons. This attack is caused by antibodies produced by the body itself. The antibodies disrupt the function of NMDAR and are believed to be a primary cause of the disease's symptoms. The antibodies are found mainly in the cerebrospinal fluid (CSF), which surrounds the brain and spinal cord. Occasionally, the antibodies are also found in the blood, but they are less reflective of the disease's symptoms. Patients with anti-NMDA receptor encephalitis always have antibodies and other abnormalities in the CSF, particularly in the early stages of the disease. It is believed that the presence of these antibodies and other proteins related to inflammation or neuronal dysfunction persist for many months in the CSF and may be associated with the persistence of certain symptoms of the disease.

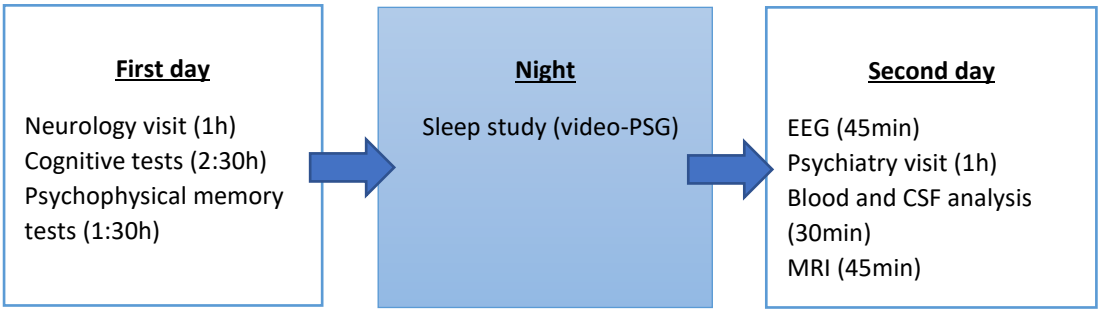
It is known that people who suffer from this type of autoimmune brain disease experience alterations in cognitive functions, behavior, and sleep habits that persist for months after the

acute phase of the disease. However, the exact cause of these alterations and the most appropriate treatment are not yet known. Similarly, the need to prolong immunotherapy and the factors that help predict the prognosis for patient recovery are also unknown.

The general purpose of this research is to improve our understanding of the symptoms throughout the course of the disease. This assessment will be conducted during hospital visits and remote visits through video conferencing. During the visits, various specialists (neurologist, psychiatrist, neuropsychologist, sleep specialist) will speak with you and your child, and your child will undergo medical tests to evaluate the presence of cognitive problems (memory, attention, perception, and language), psychiatric symptoms (mood variations and behavior), and sleep-related issues. Additionally, a brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and sleep test will be conducted. During the first and last in-person visits, a lumbar puncture will be performed to study the cerebrospinal fluid. All these tests conducted at the hospital (except for the lumbar puncture for cerebrospinal fluid analysis during the first and last in-person visits) are part of the routine practice for monitoring the recovery of anti-NMDA receptor encephalitis. However, in this study, they will be conducted in a more planned manner, including the analysis of a greater number of biological variables. It is known that antibodies can persist in the cerebrospinal fluid for many months, but it is unknown whether their levels and the levels of other markers (called neurofilaments) can predict complete recovery or the possibility of disease relapses (which occur in around 15-20% of patients). As for the remote visits, they will include clinical evaluations via video conferencing (which have been implemented in routine practice due to the COVID-19 pandemic), psychophysical tests described below (a novel aspect not typically performed in routine care), and a cognitive rehabilitation program in collaboration with the Institut Guttmann (with whom we already have experience in their cognitive stimulation program for patients with the type of encephalitis your child has, but not in a systematic manner as we will develop now).

In total, your child's participation in the study includes 8 visits over 18 months (3 in-person visits and 5 via video conferencing) and a cognitive rehabilitation program during the first year.

- For the 3 in-person visits, you and your child will be required to travel to Hospital Clínic in Barcelona (first visit, second visit at 6 months, and third visit at 12 months; there will be no cost to you). Each of these visits will span over 2 days and includes the tests outlined in the diagram below, except for the cerebrospinal fluid (CSF) analysis, which will only be performed on your family member during the first and third visits.



- The 5 video conference visits will be distributed over the 18-month study period (3 during the first year and 2 during the last 6 months):

  - Two of these visits (the first and fourth) will assess cognitive functions and each will last approximately 40 minutes. The first video conference will take place after the first visit in Barcelona, and the other will occur one year later.
  - Two additional visits (the second and the third) will assess psychiatric functions, and each will last approximately 15 minutes. These two video-conferences will take place approximately 3 and 9 months after the first visit in Barcelona. After each of these visits, you will receive a portable device (iPad tablet) at your home (sent by courier) to record brain activity during sleep and while performing a task designed as a game on the tablet (duration of about 10-15 minutes). Your child will be asked to complete the exercise on the tablet daily for one week. At the end of the week, you will return the tablet to the hospital using the coordinated courier service.
  - The last video conference visit will include a cognitive evaluation (45 minutes) and a psychiatric evaluation (20 minutes) on separate days, according to your convenience. Portable devices will not be used during this visit.
- The cognitive rehabilitation program (conducted online from home) aims to enhance the recovery of your child's cognitive functions (attention, memory, mental processing speed) and help them return to their usual activities sooner. Your child will perform exercises that a cognition specialist will tailor to their needs, using either their computer or an iPad tablet provided by us, according to their preference. The sessions will last 45 minutes and will be conducted twice a week during the first 6 months of the study, once a week for the following 3 months, and once every two weeks for the subsequent 3 months.

Throughout the study, both for the cognitive evaluation exercises and the tasks with the portable device, you will have telephone or video-conference support from a child and adolescent neuropsychologist from the research team who will help you with any questions or issues you may have.

Due to this remote follow-up part of the study, we appreciate your participation and collaboration in helping coordinate the video-conference and/or telephone tests and visits with your child, as well as your support in motivating and engaging your child to successfully complete the clinical evaluations and cognitive rehabilitation exercises.

We also ask for your help in taking care of, maintaining, and using the technological instruments that we will provide you with while they are in use, as well as coordinating their return to the hospital. Without a doubt, throughout this process, you will have our contact and support whenever it is needed.

The study will include data collection during all follow-up visits with your doctor. Additionally, clinical data on the progression of your disease will be collected to correlate it with the study results.

A total of 20 adolescents and adults from across Spain are expected to participate in this study. You will be asked to report any neurological symptoms that occur during the study and may be important to your doctor.

The data obtained in this study will be compared to data collected from patients with the same disease, anti-NMDA receptor encephalitis, who did not undergo cognitive rehabilitation. This

comparison aims to investigate the usefulness of this treatment and determine if the detected alterations in these patients are also related to abnormalities in synapses or connections between neurons.

BENEFITS AND RISKS OF PARTICIPATING IN THE STUDY

As the legal guardian or parent of the participant, it is possible that you may not directly receive specific benefits from your participation in the study. However, the study has been designed considering the potential benefits of an intensive cognitive rehabilitation program specifically tailored to the needs of your child, as well as close clinical monitoring by a highly specialized team in their disease and pediatric neurology. The validation of the effectiveness of this treatment will only be possible at the end of the project, and at this time, it is speculative. However, the more adherent your child is to the treatment and cognitive rehabilitation program, the better data we will obtain during the study, allowing us to continue providing them with the most specific treatment possible to their needs, with the goal of helping them improve their symptoms, providing support when needed, and trying to help them return to their normal routine as soon as possible. Additionally, you will have quick and direct access to the medical team of the study, who have extensive experience in treating children and adolescents, in order to facilitate close clinical monitoring and address any doubts that may arise.

On the other hand, identifying the exact parameters of cognitive deficits and behavioral alterations could benefit other patients in the future and contribute to a better understanding and treatment of this encephalitis. Additionally, you will have access to the results obtained from cognitive performance tests, clinical evaluations, neuroimaging, and neurophysiological assessments (electroencephalogram, sleep study), along with a detailed report of the findings.

The only invasive procedure your child will undergo is two lumbar punctures (LP) to obtain cerebrospinal fluid (CSF) samples during the first and third (last) in-person visits. However, you and your child can choose to participate in the full study without undergoing this procedure.

The study of cerebrospinal fluid (CSF) provides valuable information for the study of many neurological diseases, especially autoimmune diseases that affect the brain. CSF is useful because it bathes the brain and spinal cord, making it the best source of information about neurochemical and immunological changes that may be occurring in the brain, as the blood does not reflect as specifically what is happening in the central nervous system. The study of CSF allows the detection of antibodies directed against neuronal proteins that cause autoimmune encephalitis, enabling diagnosis, as well as the detection of other markers indicative of neuronal damage, inflammation, and alterations in immune function in the brain. Knowing the degree of damage to the nervous system caused by antibodies is essential for predicting the recovery's evolution, the risk of sequelae, and the ability to benefit from appropriate treatment.

IS A LUMBAR PUNCTURE PAINFUL? There are two parts at the beginning of the LP procedure that may cause some discomfort. Firstly, during the administration of local anesthesia, you may feel a few seconds of stinging or burning sensation when it is injected. You will feel a sense of pressure when the needle is inserted, and there is usually brief and mild pain when the needle passes through the tissue surrounding the region where the cerebrospinal fluid is located. The discomfort throughout the procedure is minimal to moderate.

WHAT ARE THE RISKS OF LP? When an experienced physician performs the LP, as is the case in this study, the risks are minimal, and it involves little discomfort. There is a small possibility of developing a headache after the procedure. LPs are performed using a special needle designed specifically for this procedure, which causes less pain at the puncture site, and the risk of post-LP headache is low. If a patient develops a headache, it usually improves within a few hours and can be relieved by drinking fluids. Rarely, the headache may persist for more than 24 hours and require additional treatment. The potential and generic risks of the procedure include infection and bleeding in the puncture site or within the subarachnoid space. While these complications are potentially significant, the likelihood of developing them is minimal, and they would be appropriately treated. There is no risk of paralysis. There is a possibility that some patients may not directly benefit from the LP, but for those patients with relapses or unfavorable clinical progression, this test will help guide the therapeutic decisions of the medical team, as the titers of NMDAR antibodies in the CSF, but not in the blood, have clinical correlation.

It is important to note that there are potential risks associated with some of the tests, although the probability and severity of these risks are very low. These risks include: 1) Brain magnetic resonance imaging (MRI): Some participants may experience claustrophobia or discomfort due to the noise of the machine, but the test can be terminated at any time; 2) Blood analysis: There is a very low risk of infection, dizziness, or bleeding, but these risks are similar to routine blood tests; 3) Electroencephalogram (EEG): In very rare cases, some participants may experience mild irritation in the area of the scalp where electrodes were placed. This irritation typically subsides within a few hours without requiring any specific treatment; 4) Psychophysical memory tests and remote nocturnal EEG recording: These tests may cause mental fatigue during the time spent concentrating on the exercises (which the technical team will try to prevent and mitigate), require a certain amount of time dedication (15 minutes per day for a week), and potentially interfere with nighttime rest during the evaluation week. However, it is expected that participants will become accustomed to wearing the device, which is worn like a cap.

Regarding your involvement, there is a possibility that your child's participation in this project may require a certain demand of your time and dedication. You may also experience mental fatigue related to your involvement in the neurological and psychiatric evaluations of your child and the remote tasks.

It is important to note that the remaining tests conducted in this study do not pose any risk to the health of your child or yourself, nor do they have any adverse effects.

ALTERNATIVE TREATMENTS

Currently, the long-term treatment for autoimmune encephalitis is not clear. If you choose not to participate in the study, your child will receive treatment based on the decision of their doctor and according to standard practice.

CONFIDENTIALITY

Hospital Clínic de Barcelona, with VAT number 0802070C, as the data controller, informs you that the processing, communication, and transfer of personal data of all participants will comply

with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights. The legal basis for the processing of your data is the consent you provide at this moment, in accordance with Article 9 of Regulation (EU) 2016/679.

The data collected for these studies will be identified only by a code, and no information that could identify the participants will be included. Only the study doctor and authorized collaborators will be able to link the data collected in the study to your medical history.

Your identity will not be accessible to anyone else except in the case of a medical emergency or legal requirement. Health authorities, the Research Ethics Committee, and authorized personnel appointed by the study sponsor may have access to your personally identifiable information when necessary to verify study data and procedures, but always maintaining confidentiality in accordance with current legislation.

Only encoded data, which will not contain any information that can directly identify the participant (such as name, initials, address, social security number, etc.), may be transferred to third parties and other countries. In the event of such transfer, it will be for the same purpose of the described study and confidentiality will be ensured.

If encoded data is transferred outside the EU to entities related to the participating hospital, service providers, or collaborating researchers, your data will be protected by safeguards such as contracts or other mechanisms established by data protection authorities.

In addition to the rights provided by previous legislation (access, modification, opposition, and cancellation of data, deletion under the new Regulation), you can now also restrict the processing of inaccurate data, request a copy of the data, or have them transferred to a third party (data portability) for the data you have provided for the study. To exercise these rights or if you want to know more about confidentiality, you should contact the principal investigator of the study or the Data Protection Delegate of Hospital Clínic de Barcelona at protecciodades@clinic.cat. You also have the right to contact the Data Protection Agency if you are not satisfied.

The data already collected cannot be deleted, even if you withdraw from the study, to ensure the validity of the research and comply with legal obligations and medication authorization requirements. However, no new data will be collected if you decide to stop participating.

The Investigator and the Sponsor are required to retain the data collected for the study for at least 10 years after its completion. Subsequently, personal information will only be retained by the healthcare center for your healthcare purposes and by the sponsor for other scientific research purposes if the patient has given consent, and if permitted by law and applicable ethical requirements.

COLLECTION AND USE OF BIOLOGICAL SAMPLES

Participation in this study involves the analysis of blood and cerebrospinal fluid (CSF) samples from your child (alongside the samples obtained for clinical purposes and two additional lumbar

punctures during follow-up). If there are remaining clinical samples of serum and CSF from the diagnosis of the disease (obtained during hospitalization in the acute phase of the illness), they may be used to expand the analysis. The samples will be stored in the Neuroimmunology Laboratory of IDIBAPS-Hospital Clínic, identified only with a code, until they are used for the purposes of this study. Once the study is completed, any leftover samples will be destroyed unless you sign a separate consent for their storage and use in future research. If any relevant information that could affect the health of your child or other family members is obtained, you will be notified if you wish.

CONSENT FORM FOR LEGAL GUARDIAN/PARENT OF PATIENT UNDER THE AGE OF 18

Study Title: "Anti-NMDA Receptor Encephalitis: Symptoms, Biomarkers, and Mechanisms of Prolonged Recovery Stage"

Version 3, December 30th, 2022

I, (full name of the legal guardian/parent) _____,

have read the information sheet provided to me about the study.

I have had the opportunity to ask questions about the study.

I have received sufficient information about the study.

I have spoken with: (investigator's name) _____.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

- Whenever I want.
- Without having to provide an explanation.
- Without this decision affecting my medical care.

In accordance with the applicable laws, I declare that I have been informed of the existence of a file or processing of personal data, the purpose of collecting such data, and the recipients of the information.

I give my consent for the processing of:

- ✓ My personal data to carry out the research project.
- ✓ My personal data and those of my child will be used to carry out similar research projects to the present one or in the same research area.

1. I freely give my consent for my child to participate in the study.

□YES □ NO

2. I freely give my consent to participate in the study as the legal guardian/parent of the underage participant.

□YES □ NO

3. I agree to the use of the remaining clinical samples of serum and cerebrospinal fluid obtained during the diagnosis of the disease of my child for further analysis.:

□YES □ NO

4. I agree to the two lumbar punctures being performed on my child as proposed in the study:

□YES □ NO

5. I would like to be informed of any research findings that may be relevant to my child's health.

□YES □ NO

Signature of the father/mother/legal guardian

Date: ____/____/_____

Investigator's Signature:

Date: ____/____/_____