INFORMATION SHEET FOR ADULT PATIENTS

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

PRINCIPAL INVESTIGATOR COORDINATING CENTER

Dr. Josep Dalmau
Neuroimmunology Unit, Neurology Department
CENTER: Hospital Clínic de Barcelona (Barcelona, Cataluña)
Research Group in Neuroimmunological Diseases
CENTER: IDIBAPS-Hospital Clínic, Barcelona

INTRODUCTION

"We are writing to inform you about a research study in which you are invited 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 with Dr. Josep Dalmau (contact phone number 93 227 1738), who is responsible for project coordination. Additionally, you may consult with any person you deem appropriate."

VOLUNTARY PARTICIPATION

Participation in this study is voluntary, and you can choose not to participate or change your decision and withdraw consent at any time without affecting your relationship with your doctor or the treatment you 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.

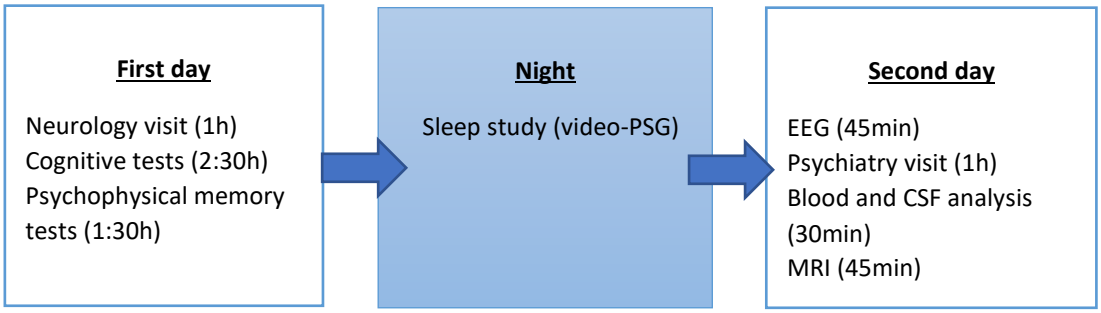
The disease you have is called anti-NMDA receptor encephalitis and was recently discovered in 2007. It is a condition in which the body's immune system attacks a protein called NMDAR in brain cells called neurons. This attack is caused by antibodies produced by the body itself. The antibodies disrupt 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 knowledge of symptoms throughout the disease. This assessment will be conducted during hospital visits and remote visits via video conference. During the visits, various specialists (neurologists, psychiatrists, neuropsychologists, sleep specialists) will speak with you and conduct medical tests to assess the presence of cognitive problems (memory, attention, perception, and language), psychiatric issues (mood variations and behavior), and sleep disorders. Additionally, a brain MRI, an electroencephalogram (EEG), and a sleep test will be performed. A lumbar puncture will be conducted during the first and last visits to study cerebrospinal fluid. All these tests conducted in the hospital (except for the lumbar puncture for cerebrospinal fluid analysis during the first and last in-person visits) are part of routine practice for monitoring the recovery of anti-NMDAR encephalitis. However, in this study, they will be conducted in a more planned manner and will include the analysis of a greater number of biological variables. It is known that antibodies can persist in 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 relapse (which typically occurs in 15-20% of patients). Regarding remote visits, they will include clinical evaluations via video conference (which have been implemented as part of routine practice due to the COVID-19 pandemic), the psychophysical tests described below (a novel aspect not typically performed in regular 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 you are experiencing, but not in a systematic manner as we will develop now).

In total, participation in the study includes: 8 visits over 18 months (3 in-person visits and 5 via video conference), as well as a cognitive rehabilitation program during the first year.

- For the 3 in-person visits, you will be required to travel to the 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 2 days and will include the tests indicated in the schedule below, except for the cerebrospinal fluid (CSF) analysis, which will be performed only 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.
- Another two visits (the second and 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) by courier to record brain activity during sleep and while playing a game on the tablet (lasting around 10-15 minutes). You will be asked to use the device daily for one week before returning it to the hospital via 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 cognitive functions (attention, memory, mental processing speed) and help you return to your normal life sooner. You will perform exercises tailored to your needs, adjusted by a cognition specialist, using your computer or an iPad tablet provided by us, according to your preference. The sessions will last 45 minutes, twice a week for the first 6 months of the study, once a week for the following 3 months, and once every two weeks for the remaining 3 months.

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

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

It is possible that you may not receive specific benefits from participating in the study. However, the study has been designed considering the potential benefits of an intensive cognitive rehabilitation program specifically tailored to your needs, as well as close clinical monitoring by a highly specialized team in your disease. 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. 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, along with a detailed report of these findings.

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

An LP is an outpatient procedure in which a small needle is inserted, under local anesthesia, between the vertebrae (bones) in the lower part of the back, below the spinal cord, to obtain a small amount of CSF.

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.

Other tests that involve potential risks, although very low in probability and also very mild, include: 1) Brain magnetic resonance imaging (MRI): Some participants may experience claustrophobia or be bothered by 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 it is

similar to routine blood tests; 3) EEG: Very occasionally, some participants may report mild irritation in the area of the scalp where electrodes were placed, which usually resolves within a few hours without any intervention; and 4) Psychophysical tests of memory and remote overnight EEG recording: These tests may cause mental fatigue during the time required for concentration in performing the exercises (which will be prevented and mitigated by any member of the technical team), require a certain amount of dedicated time (15 minutes daily for one week), and interfere with nighttime rest (during the evaluation week). However, it is expected that participants will adapt to the device (worn as a cap). The remaining tests performed in this study do not pose any health risks to the participant or 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, you will receive treatment based on your doctor's decision and 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

Participating in this study involves the analysis of blood and cerebrospinal fluid (along with the samples obtained for clinical reasons and two additional lumbar punctures during follow-up). If there are residual clinical samples of serum and cerebrospinal fluid from the diagnosis of the disease (obtained during your hospitalization in the acute phase of the disease), they may be used to expand the analysis. The samples will be stored and identified only with a code in the Neuroimmunology Laboratory of IDIBAPS-Hospital Clínic until they are used for the objectives of this study. Once completed, any remaining samples will be destroyed unless you sign a separate consent form allowing them to be stored and used in future research. If any relevant information is obtained that could affect your health or that of your family, you will be notified if you wish.

CONSENT FOR ADULT PARTICIPANTS

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

Version 3, December 30th, 2022

I, (participant's full name) _____,

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 to carry out similar research projects to the present one or in the same research area.

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

□YES □ NO

2. I agree to the use of the residual clinical samples of my serum and cerebrospinal fluid from the diagnosis of the disease to expand the analysis:

□YES □ NO

3. I agree to undergo the two proposed lumbar punctures in the study:

□YES □ NO

4. I wish to be informed of any research-derived information that may be relevant to my health:

□YES □ NO

Participant's Signature: Investigator's Signature:

Date: ____/____/_____ Date: ____/____/_____