University College London Hospitals NHS
NHS Foundation Trust
The National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG

Date:. 30th March 2016
Version 9.1
REC Reference Number: 07/Q0512/26

PATIENT INFORMATION SHEET

Study title: Investigation of human neurological ion channel or episodic neurological disorders

Chief Investigator: Professor Michael G Hanna
Principal Investigator: Professor Henry Houlden

You are being invited to take part in a research study of patients with neurological ion channel disorders or likely have a channel defect, thus affecting the synaptic pathway. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Ion channels are small pores in the membranes of the cells of the brain, muscle and nerve. They are usually part of the function of the synapse. They allow movement of charged particles (ions) across the cell membrane. Normal ion channel function is very important for the electrical signals that the brain, muscles and nerves depend upon to function.

Changes in the genetic code (known as genetic mutations) for ion channels or genes that interact or affect ion channels can result in abnormal function of that channel. Depending on the specific ion channel affected the features of these conditions can include muscle weakness, muscle stiffness, muscle twitching (myotonia or neuromyotonia), episodic ataxia and other forms of ataxia, episodic weakness in disorders such as myasthenia gravis, epilepsy or episodes of altered consciousness, migraine or rare headache disorders such as cluster headache and episodic pain, unusual sleep pattern or altered consciousness such as Kleine-Levin syndrome and sleep disorders such as parasomnias, and episodes of unsteadiness with walking. This covers a range of conditions of the muscle, spinal cord and brain.

The aim of our research project is improve our understanding of the clinical and genetic features of these conditions. We hope that this will allow us to work out better ways to diagnose and treat these conditions.

Why have I been chosen?

You have been chosen because your doctor feels your symptoms may be due to an underlying ion channel disorder, or you are a healthy person with no symptoms. If you are a healthy person you have been asked to participate in part or all of the tests involved in this study as your results will help act as a “control” against which to measure the findings from people with ion channel disorders.

Do I have to take part?

Taking part in the research is entirely voluntary. It is up to you to decide whether or not to take part.

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What is involved in the study?
If you did decide to participate it would involve the following simple things **(if you are being asked to participate because you are a healthy person you may only be asked to do one or some of these things)**:

1. Your history, examination findings and investigation results will be recorded in a research clinic visit of approximately 1 hour duration or during a routine clinical visit. In some instances patients may be examined at home or we may use letters from clinical colleagues. We may also ask you to complete an ethically approved questionnaire on your disorder. These data will be recorded in a secure database. If you attend clinic at the National Hospital for Neurology, this visit may be done in the context of your routine appointment. If you are not a patient at the National Hospital for Neurology then we will arrange a research clinic visit at your convenience, or these details may be sent to us by your treating doctor. Patients must be able to give informed consent themselves or through their next of kin. In patients below the age of 16 years we will obtain informed consent from the patient and also the parents or guardian. In these patients the blood sample will only be taken if other clinical tests are being carried out and there is blood leftover or if the patient gives a saliva sample. A skin biopsy will only be taken as part of the clinical evaluation and skin fibroblasts are left over from this and can be used or the smallest 2mm (a pinhead) skin biopsy will be taken if the individual is full aware and consents to the procedure. For the culture of fibroblasts or myoblasts written consent will be held by the PI in the laboratory that cultures the initial fibroblasts. In the case of deceased patients or where there is archival tissue that has already been used for a diagnostics and a report issued, this material may be used for genetic or functional analysis.

2. A video or photographs of your neurological examination may be taken. This may include videoing you walk, your eye movements, speech etc. Separate consent for this will be obtained.

3. Electrocardiogram (ECG): This test determines your heart rate and rhythm. You will be asked to expose your bare chest and electrodes will be taped onto your chest, wrists and feet. These will record your heart activity. This test takes approximately 10 mins.

4. We will perform simple electrical measurements on your nerves and/or muscles called nerve or muscle excitability studies. Nerve excitability testing involves administering electrical pulses to the median nerve at the wrist, recording the response in the muscle at the base of the thumb. Muscle excitability studies involve using small needles inserted into the muscle to look at how it responds to electrical stimulation. This can assess the manner in which ion channel disorders affect peripheral nerve and/or muscle function. The pulses are repeated over a period of approximately 10 minutes.

These tests may be performed in conjunction with routine nerve conduction studies and EMG (electromyography), which may be part of the standard investigations of patients with ion channel disorders. When performed together, these studies take between one and three hours. This would be done at a separate appointment to your clinic visit.

If you are on the medication acetezolamide, mexiletine or dichlorphenamide for your symptoms, we may discuss with you the possibility of withholding your medication for one day in order to perform
these studies, as the medication may affect the test's results. The decision to omit your medication for one day would be entirely voluntary, and we would discuss this fully with you beforehand.

5. A blood sample may be taken to test your DNA and/or RNA for possible changes in the genetic code. We will look at the genes in which genetic mutations may cause symptoms of ion channel disorders such as migraine, epilepsy, ataxia (in-coordination), sleep disorders, myotonia (stiffness) or periodic paralysis. This may also include sequencing all of your DNA or RNA specifically, but not exclusively looking at changes in your ion channels or interacting genes. Your sample will be stored for future testing in the event further genes are identified. Your samples are donated as a gift that may be retained for future research. Any new research will be reviewed by a research ethics committee but consent for future studies may only be required if the committee considers that the study is likely to substantially effect your interests.

Results of genetic tests performed on a research basis are not routinely made available. Should a result of interest be found, we are now able to validate research genetic results and you would be invited back for testing on a clinical NHS basis. If you are not a patient at the National Hospital for Neurology, we can arrange a follow up visit to discuss this, otherwise your GP or treating neurologist can be informed. Some insurance companies ask whether you have had gene studies to see if you suffer from hereditary disease or if you have undergone genetic testing. We keep details of any research results confidential. At the same time blood will be sent for biochemical analysis of your kidney function and electrolyte levels. This is so we can to evaluate any involvement in the condition or effects of medication you may be on.

6. A urine/hair sample may be collected during your visit for biochemical analysis.

7. If you have previously had a muscle biopsy performed as part of routine clinical care some of this tissue may remain stored. We may re-examine this tissue and perform additional tests on it to aid current and future research into the neurological channelopathies and episodic neurological disorders.

We may also ask for your consent to repeat or perform a muscle biopsy if you have not already had one. This will be to help us to further understand your condition and see how it is affecting your muscle. The biopsy will be examined under a microscope and additional laboratory tests may be done including collecting DNA or RNA from the sample to confirm your genetic diagnosis and/or investigate its effect on the muscle.
The biopsy will be taken under local anaesthetic. This tissue will be analysed at The Institute of Neurology in the UK. A biopsy is a procedure in which a small sample of tissue is removed. This can either be done by inserting a biopsy needle into your muscle (punch biopsy)_ or by removing a small cube of muscle approximately 0.5cm across from an open incision (open biopsy). This muscle sample is usually taken from the quadriceps muscle (upper outer thigh muscle) but other muscles are sometimes selected by your doctor (including arm muscles eg biceps or triceps or the calf muscle).

A needle biopsy (or punch biopsy) would be performed by a trained medical practitioner in sterile conditions. The skin over the biopsy site will be cleaned with an antiseptic solution and a numbing medicine (local anaesthetic) will be injected around the area which initially causes a stinging sensation lasting 5 to 20 seconds. The trained medical practitioner will insert the biopsy needle through your numbed skin in order take a sample from the muscle below. They will then withdraw the biopsy needle and apply firm pressure to the biopsy site for several minutes and until any bleeding has stopped. The opening in your skin will be closed with adhesive strips or stitches if necessary and a sterile bandage or dressing applied. Although the local anaesthetic will numb the skin you may feel a pushing or pulling sensation during the procedure which may be uncomfortable.
The biopsy site may be tender or sore for 2 to 3 days after your muscle biopsy.

An open biopsy, would be performed by a trained surgeon andthe procedure is usually performed in the operating theatre. The doctor doing the open biopsy will ask you to lie on your back or will position you depending on the muscle to be biopsied. He/she will sterilise the area where the biopsy will be taken from with an iodine or alternative cleaning solution. A numbing medicine (anaesthetic) will be injected around the area which initially causes a stinging sensation lasting 5 to 20 seconds. Once the area is numb a 2 inch cut is made through the skin. The surgeon then identifies the muscle and will apply further numbing medicine (local anaesthetic) over the surface before taking a very small piece of muscle. The numbing medicine will freeze the skin and reduce sensation in the muscle. Sometimes patients experience a pulling or pressing sensation as the muscle is removed and some patients find this uncomfortable. The procedure usually takes less than 10 minutes. After the surgery the biopsy the site will be covered with a sterile dressing and a bandage. The dressing should remain in place for 3-5 days. You should keep it dry. Sometimes stitches dissolve and do not need to be removed, but sometimes a stronger type of stitch is used, which will need to be removed. You will receive instructions as to which type of stitch you have.

For approximately 3 hours after the biopsy you should try to rest, ideally with the limb elevated on a pillow to prevent swelling and complications and to help healing. If possible, your journey home should avoid walking and you should be able to elevate your leg (for example sitting in the back of the car with the leg elevated on a pillow on the seat).

After 24 hours it is important to maintain mobility but try to avoid significant exercise or excessive walking one week. For example, you should be able to get around short distances but shouldn't plan walking long distances for a week.

Muscle biopsies are a common procedure and have a small number of risks, these include pain at the site of the biopsy when the anaesthetic wears off which should stop in a few days to weeks. You may have a small amount of bleeding, discharge, swelling or bruising around the wound but these go away after a few days. Rarely infection may occur as with any wound which may slow healing which may require treatment with antibiotics. Very rarely patients may have ongoing pain at the biopsy site or numbness over the scar which may require treatment. Also very rarely a haematoma may develop requiring further treatment. You will be given the standard UCLH muscle biopsy information leaflet which covers the procedure and possible risks in more detail.

8. You may have a skin biopsy taken if indicated. This will be used to see how your skin cells work and give us more information about how your disease affects you. The cells will be looked at under a microscope and grown as fibroblast cells to investigate how they work differently or

these cells may be changed and then differentiated into neuronal or other tissue lines that provide us with a better disease model. The procedure involves taking a small sample of skin usually taken from just above the ankle but can also be taken from other sites that your doctor selects (like the top of the thigh or forearm). Local anaesthetic will be given, and when the area is numb a small (3mm diameter) piece of skin will be removed using a small punch. No stitches are needed, and the wound heals over 7-10 days, generally becoming nearly invisible over a 4-6 weeks. A biopsy care sheet will be given to you after the biopsy so you know how to care for the site. This is a safe and widely used procedure but rarely side effects such as allergy to local anaesthetic, difficulties with healing, bleeding or skin infections may occur.

In some instances, we and our collaborators may change the fibroblast cells into induced pluripotent stem (iPS) cells in order to create better models of your disease. An iPS cell is a type of 'pluripotent' stem cell, which means that it can grow into most specialised cell types in the human body, such as nerve or muscle cells. They can be cultivated and survive indefinitely. Research using iPSC is particularly important for diseases where we know very little to advance our understanding as well as for the development of new drugs and methods. To promote further research on your disease, we may send cells derived from your donated samples to stem cell banks to generate and store iPS cells. These cells will be anonymised and stem cell banks will not have access to your personal information. The stem cell banks may then distribute the iPS cells to other researchers, where this is compliant with all relevant legal rules and regulations and approved as necessary by a research ethics committee. These cells will only be used for research and will not be used medically or transplanted.

You must explicitly give consent for generation of iPS cells from your samples by initialling box 9 on the consent form. If you would prefer your samples were not used to generate iPS cells, please do not initial that box.

You will be reimbursed for travel expenses in the event that you need to travel to the National Hospital for Neurology for a research visit.

What are the possible benefits of taking part?
We hope that participating in this study will help you by generating a greater understanding of **neurological ion channel disorders**, and possibly by identifying underlying causes. However, this
cannot be guaranteed. The information we get from this study may help us to treat future patients with such conditions.

What information will be held about the research subjects?
All the above information will be recorded in a central database, which will enable us to recognise patterns in these conditions and to track your genetic results **(if applicable)**. The only people who will have access to this data will be Professor Hanna, the medical research staff conducting this study, and doctors directly involved with your care (e.g. GP and treating specialist). Your confidentiality will be observed at all times. Professor Hanna is responsible for safety and security of
the data, which will be collected, stored at and processed by the Neuromuscular centre team at the Institute of Neurology, UCL. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address, date of birth and all identifiable information (including patient/hospital/NHS number) removed. However due to the "small pools" of

patients and researchers there may be a higher level of identifiability than other studies looking at more common conditions. That is to say that with knowledge of your unique clinical history, examinations findings or genetic information, your data might still be identifiable despite the removal of all demographic information. Therefore absolute 'anonymity' to participants cannot be assured. If you are a patient your GP and treating neurologist may be notified of your participation in this study.

What happens when the research study stops?
This study will continue indefinitely. If you wish to be informed of any results or information generated by the study which may affect you personally, please indicate this to the research team. We can alert you of any scientific publications arising from the study if you wish.

What if something goes wrong?
You have a right to complain through the UCLH complaints procedure. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns of this study, the normal National Health Service complaints mechanisms should be available to you.

What will happen to the results of the research study?
Results may be published in scientific journals and may be used as educational materials. Any of your data used in this manner would be anonymous. No identifying information would be released.

Can I withdraw from the study?
Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

Samples will be stored indefinitely. Should you decide to withdraw your consent or in the unlikely event that the samples are damaged in any way, the unused samples will be disposed in a respectful manner and incinerated. No further data will be collected if you have withdrawn your consent but it will not be possible to withdraw research data already obtained from the samples. Please note that any iPS cells already generated and associated data will not be destroyed and may continue to be used in research studies. This is because the process of making iPS cells is time-consuming and expensive. You are free to refuse consent for the generation of iPS cells from your donated samples.

Who has reviewed the study?
The study has been reviewed by the Joint National Hospital for Neurology and Institute of Neurology Research Ethics Committee.

Who can I contact for further information?
We would be happy to address any questions or issues that may arise.

Dr Emer O'Connor
Clinical Research Associate to Prof. Henry Houlden,
Department of Molecular Neuroscience,
Institute of Neurology, Room 904, Queen Square House,
Queen Square, London WC1N 3BG,
United Kingdom
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If you have any comments or concerns you may discuss these with local PI. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the local PIs. Please quote the UCLH project number at the top this consent form.

Thank you for agreeing to participate.

Professor M G Hanna BSc(Hon) MBChB(Hon) MD FRCP(UK)
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Director UCL Institute of Neurology