BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

Number **53**
1st Semester 2023

NEWSLETTER

Fundamental research: essential to achieving our objectives

We have four therapeutic objectives:

Our first therapeutic objective is **to prevent the onset of the disease** through a better understanding of genetic susceptibility as well as environmental factors that are also necessary for the outbreak of the disease. Genetic studies enable us to understand better the mechanisms of the disease depending on the genes involved, while the Epstein-Barr virus infection is currently receiving the most attention among the environmental factors in trying to understand how it modifies the immune system of people predisposed to develop MS.

Our second therapeutic objective is **to prevent relapses** caused by invasion of the central nervous system by immune cells of blood origin. What are these immune cells? What are their characteristics? What are the factors that cause their activation and expansion? Even though we currently have increasingly potent drugs to prevent relapses, their action mechanism is not always fully understood and their targets are probably not yet sufficiently specific to MS.

Our third therapeutic objective is **to prevent the progression** of the disease even in the absence of a relapse, since there is persistent inflammation within the central nervous system itself that leads to nerve fibre degeneration and nerve cell death. To that end, we need to know more about the cells responsible for this chronic inflammation, and be able to deactivate them with drugs that can enter the nervous system through the blood-brain barrier.

Our fourth therapeutic objective is **to repair existing lesions**, and therefore to understand and quantify the mechanisms of demyelination and remyelination, to stimulate the latter, in particular the oligodendrocytes and their precursors which are responsible for the synthesis of myelin. The three articles in this issue of our newsletter discuss this in more detail.

As you may have garnered, these therapeutic objectives are increasingly well defined but still require a great deal of analysis and a better understanding of the complex mechanisms responsible for the disease. This is why fundamental and translational research remains so important, and can be conducted fully in our country only with the support, help and backing of all our donors.

Prof. Dr. Christian Sindic

President

Belgian Charcot Foundation
Public interest foundation

Under the Patronage
of Her Majesty The Queen

Avenue Huart Hamoir, 48
B - 1030 Brussels
Phone: +32 2 426 49 30
info@fondation-charcot.org
NN 468 831 484

Photo Credit: iStock & Shutterstock
Responsable publisher: I. Bloem
Av. Huart Hamoir, 48 - 1030 Brussels

ONLINE GIFT

www.fondation-charcot.org
BE43 0001 6000 1601

Join us on **Facebook**

YOUR BEQUEST WILL ENABLE RESEARCHERS TO GO FURTHER AND FASTER

Thinking about your will is never easy. We'd all like to have a say after we go and decide for ourselves what will happen to our estate.

This is what Jacqueline told us: "*With time, I've come to have a different take on life. I'm 75, I have grandchildren, and I'd like them to have the best possible future. My sister has MS and the whole family feels strongly about the issue. So obviously, when I began to consider where to leave my estate, I included a legacy to the Belgian Charcot Foundation, to pay for MS research and help beat the disease. That way, I'll carry on supporting the Foundation as I've been doing for several years now.*" Jacqueline B.

Why choose to make a donation in your will to the Belgian Charcot Foundation?

- because multiple sclerosis is still incurable and very often evolves into a disability and disrupts the lives of thousands of people
- because all the efforts we can make now bring us closer to the solutions: stopping the disease, repairing its damage and one day beating it completely
- because we commit ourselves to invest your donation completely in MS research.

Do you have any questions? We will answer you in complete discretion.

"I would like to help overcome Multiple Sclerosis and I would like to make a gift in my will or living trust to the Belgian Charcot Foundation"

☐ I would like to receive free documentation

☐ I would like to be contacted without any obligation

My (mobile) phone number: .....

My personal details ☐ Mrs. ☐ Mr.

First name: .....

Name: .....

Street: .....

Number: ..... Box: ..... Postcode: .....

City: .....

E-mail (optional):

.....

Please send this reply form in a stamped envelope to:
Belgian Charcot Foundation - Mrs Isabelle Bloem
48 Avenue Huart Hamoir - 1030 Brussels - Belgium
or by e-mail to : isabelle.bloem@fondation-charcot.org

The Belgian Charcot Foundation respects the law on the protection of your personal data. The information collected through this form will only be used to answer your request for information about gifts and wills. More information in our privacy statement at

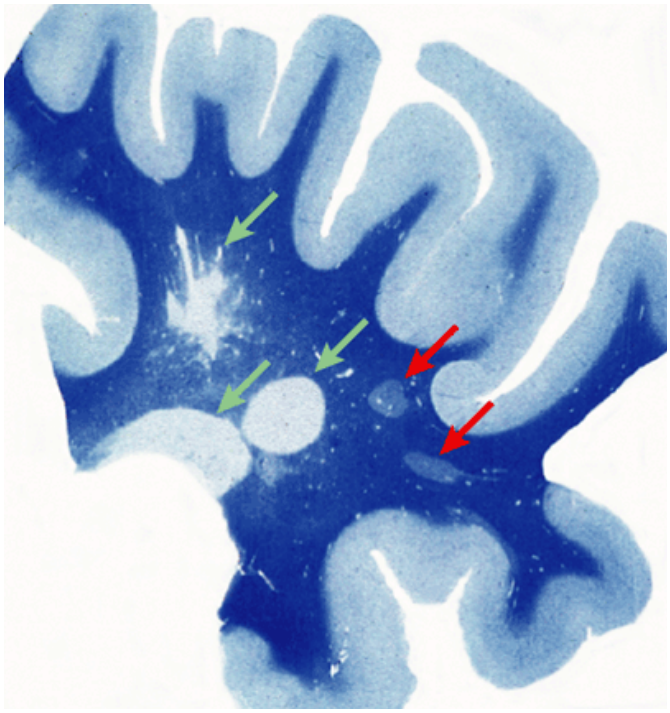
www.fondation-charcot.org

Remyelination of MS plaques: ultimate goal or illusion?

The myelin sheath that surrounds and insulates nerve fibres is a membrane with a very particular composition, consisting of 70% lipids and 30% proteins. This proportion is the opposite of what is observed in the other membranes of the body's cells. All membranes are very sensitive to oxidation phenomena which destroy them and any inflammatory reaction is accompanied by the release of oxidising products.

And the shadow plaques?

Is there spontaneous remyelination in the brain of patients suffering from MS? The answer is a resounding YES. Such spontaneous remyelination was suggested by the work of Olivier Périer and Anne Grégoire in 1965, two Belgian researchers who used electron microscopy for the first time to study MS lesions. In 1970, John Prineas and his colleagues definitively confirmed that such remyelination was present. The new myelin sheaths are thinner than normal, but they again make it possible for



© Nature Reviews / Neuroscience

Histological section of a fragment of cerebral hemisphere obtained at autopsy from an MS patient:
in light blue, the cerebral cortex containing some myelin
in dark blue, the compact myelin of the white matter
green arrows: three demyelinated plaques with clear contours
red arrows: two partially remyelinated plaques = "shadow plaques"

nerve impulses to be transferred close to normal. These remyelinated plaques are called "shadow plaques". Several studies have since then shown that this remyelination can vary substantially from one person to another, as well as from one area of the brain to another in the same person. For example, a study of 51 autopsies showed extensive remyelination in 20% of patients, ranging from 60 to 96% of the total number of lesions. It has also been shown that remyelination was more frequent and more complete in recent plaques and in plaques located in the cerebral cortex. Conversely, very old plaques, located around the ventricles or in the cerebellum showed little or no sign of remyelination. We do not yet understand the causes of these differences between individuals and between different brain sites at this time.

What are the factors involved in blocking remyelination?

Unfortunately, there are many factors and they interact, making it difficult to find the best therapeutic target. They include:

- The persistence of low-grade inflammation in the periphery of old plaques, which are then called "chronic active". These are activated macrophages that continue to destroy the myelin sheaths at the periphery of the lesion, causing a slow increase in their diameter. These macrophages often contain highly toxic iron atoms. They also contain a lot of fat and myelin fragments, which keeps them in a pro-inflammatory state. They release oxidising and neurotoxic substances. This inflammation cannot be visualised by an injection of gadolinium during an MRI scan.

- A cicatricial hypertrophy of astrocytes which replace the destroyed myelin and make the brain tissue hard and "sclerous".

- A degeneration of nerve fibres that have lost their myelin sheaths, that may be deformed, and have a reduced capacity to produce energy molecules.

- An insufficient number of oligodendrocyte precursor cells (OPCs) and/or their incapacity to develop into mature oligodendrocytes capable of synthesising new myelin sheaths around nerve fibres.

How could we stimulate remyelination?

Needless to say, prevention is always better than cure and the first thing is to prevent the appearance of new plaques and therefore new areas of demyelination, thanks to our current anti-inflammatory drugs, which are increasingly more powerful: they make it possible to prevent the appearance of more than 90% of the active plaques that take up the contrast medium in MRI.

The most daunting challenge at the moment is to block the chronic inflammation around the older plaques, i.e. to block the activity of macrophages in the periphery of the lesions and more diffusely throughout the brain. There is also a population of lymphocytes that have diffusely invaded the brain tissue, whose inflammatory activity must be blocked. We therefore need drugs that can penetrate the blood-brain barrier in sufficient doses in the nervous system to achieve this goal.

Another challenge is to stimulate the OPCs to develop into mature oligodendrocytes and re-synthesise myelin sheaths. Such stimulation may require the delivery of growth factors or differentiation factors through genetically modified regulatory lymphocytes, small nanomolecules or extracellular vesicles capable of crossing or short-circuiting the blood-brain barrier.

Such drugs with remyelinating potential should in any case be administered very quickly from the onset of the disease, concurrently with the anti-inflammatory drugs available to us in order to prevent the degeneration of nerve fibres and sclerosis by hypertrophic astrocytes.

In conclusion, remyelination of MS plaques is potentially feasible and is the subject of much research, as attested by the projects of many of the Foundation's 2023 laureates.

Professor Emeritus Christian Sindic, President

The references of all the studies cited are available on request from the Belgian Charcot Foundation.

With the support of

Degroof Petercam

Imaging remyelination in MS

Myelin is a special membrane enveloping axons which, by acting as a protecting insulator for electrical cables, allows for a rapid transmission of the electric signal along the axons and provides them with a trophic/nutritional support.

In Multiple Sclerosis (MS) a dysregulated immune response attacks myelin sheets in the brain and spinal cord, leading to a progressive damage of axons and subsequent loss of neurons (the cells bearing axons). Damaged neurons cannot properly conduct the electrical impulses needed to carry motor, sensitive, balance and other important information within the brain and away from the brain to the rest of the body. This explains why neuronal damage/loss represents the major substrate of clinical-neurological disability in MS.

> *"Neuronal damage/loss represents the major substrate of clinical-neurological disability in MS*

Within the brain and spinal cord, myelin is formed by specific cells called oligodendrocytes, which repeatedly wrap their lipid-rich cellular membrane around axons to form the myelin sheet. Following the inflammatory-driven myelin damage typically observed in MS plaques, oligodendrocytes and their progenitors cells can sometimes regenerate the previously damaged myelin sheets in a process called "remyelination". Restoring myelin in MS can improve axonal conduction speed and metabolic support, thus preventing clinical disability deterioration, or even promote recovery of neurological functions.

Tracking the MS demyelination/remyelination process in vivo (vs. ex vivo observation of myelin status in autopsy tissue) is of pivotal importance for the development of new remyelinating drugs.

Several advanced quantitative and semi-quantitative magnetic resonance imaging (MRI) techniques have shown promise to depict myelin content within MS plaques. However, many of these MRI techniques lack myelin specificity and require long protocols that are not widely available, limiting their use to specialised MS research centres. Recent evidence from literature suggests that some modified T1 sequences obtained in MRI could be used to track MS demyelination and remyelination, and could be potentially used to measure myelin content and stratify patients in MRI based clinical trials. T1 mapping together with other T1 relaxometry techniques may be the most adequate tool for inclusion into clinical practice. T1 sequences are indeed the most suited for examining the normal anatomy of the brain. In addition to MRI, positron emission tomography (PET) imaging offers the unique opportunity to specifically track myelin content using radiotracers that directly bind to myelin. However PET imaging is relatively invasive, is expensive and is not available in the large majority of MS centres worldwide.

In summary, imaging myelin in MS is fairly accurate nowadays, but often requires specialised imaging techniques that are not widely available. In the near future, standardisation of imaging protocols across different MS centres is required in order to ease the development of neuroprotective-remyelinating strategies for MS patients.

Prof. Pietro Maggi, MD, PhD, UCLouvain

Measuring remyelination

Measuring central nervous system (CNS) functions using evoked potentials

MS is associated with functional alteration of multiple nerve information transmission pathways in the CNS. Whereas demyelination is one of the cardinal elements of the disease, it is associated, very rapidly, with a loss of nerve fibres (axonopathy). In the acute phase, a conduction block decreases the speed of propagation of the nerve impulse, and it is difficult to detect a loss of nerve fibres. The development of conduction over time makes it possible to put things in perspective. Neurophysiological techniques (evoked potentials - EPs) make it possible to measure the conduction parameters of several central nervous pathways, afferent (to the cerebral cortex) or efferent (to the spinal cord).

Therapeutic trials have in recent years been conducted in humans with drugs that may provide neuroprotection or promote the remyelination of nerve fibres injured by the inflammatory process. These trials are the result of research conducted in animals in inflammatory and non-inflammatory demyelination models. Blocking inflammation with drugs available today also allows for natural remyelination, which may explain a partial functional improvement.

There are many parameters that influence the accuracy of EP measurement techniques. It is essential to standardise the methodology so that it can be used in practice in a group of patients with inflammatory lesions that can vary greatly in severity and topography.

Visual evoked potentials (VEPs) are the most commonly used

In theory, all the procedures for neurophysiological studies could be used to assess remyelination. However, the more complex the pathways explored, which also involve multiple levels of potential damage (brain, brainstem, spinal cord), the more variable the results that may negate the real benefit obtained at the level of a single individual. It is therefore mainly the visual pathways, which are very frequently affected in MS, that are studied to assess remyelination.

> *“It is therefore mainly the visual pathways, which are very frequently affected in MS, that are studied to assess remyelination*

The disease may involve the optic nerve itself but also the pathways connected to it (optic radiations). VEPs were among the first to be recorded over 50 years ago. They capture the electrical response induced in the occipital cortex by a simple retinal stimulation of a small portion of the visual field. Multifocal VEPs (mfVEPs), which are much more recent, have significantly improved the accuracy of the measurements thanks to a wider stimulation of the visual field and a far more efficient quantification of the activation of the occipital cortex. They have been used in some studies to measure the impact of drugs that promote remyelination.

VEPs as a measuring instrument of remyelination

Opicinumab (a LINGO-1 inhibitor that blocks the development of oligodendrocytes) has shown partially favourable results with this technique.

Clemastine (an antihistaminic product) is another drug that has been shown to have a favourable effect on remyelination of the optic pathways based on neurophysiological measurements. Studies are underway to test different strategies for promoting remyelination (VISIONARY-MS with nanoparticles and CCMR

Charcot Fund 2023

to test the combination of Metformin and Clemastine) in situations of chronic MS-related lesions.

It is necessary in fact to dissociate the response of the CNS to an acute aggression (such as optic neuritis) from chronic situations. The kinetics of the use of a drug is an essential element in obtaining its effect in the initial phase, whereas its mechanism of action may be completely different in chronic, fixed situations. The combination of several functional, neurophysiological and imaging methods is probably a way forward to gain a better understanding of the real impact of a drug that promotes CNS repair.

In summary, neurophysiological techniques have become very useful in measuring functional disturbances linked to MS lesions. They can be used to quantify disorders of nerve impulse transmission in different pathways. Optical conductions are the simplest to explore and have proven to be useful in drug trials that may promote remyelination.

Professor Dominique Dive,
University Medical Centre, Sart-Tilman, Liège

The 2023 Charcot Fund jury selected 12 projects led by university teams across the country. The budget allocated to them is €621,824. **Half of these research projects target remyelination**. Deciphering and controlling the repair processes of this myelin would be a tremendous breakthrough.

Understanding the mechanisms of the disease is crucial to overcoming MS. In university laboratories and research centres, budgets for multiple sclerosis research are available but are limited. Every year, many research teams turn to the Belgian Charcot Foundation.

Progress in research requires excellence and resources.

> *We have excellence, help us provide the means. Together, let's invest to beat multiple sclerosis*

The Belgian Charcot Foundation is the only independent institution in Belgium to provide exclusive support for MS research. See all research projects on :

www.fondation-charcot.org

20 KM OF BRUSSELS – 28 MAY 2023

Run with the Charcot Team to fund MS research days.

REGISTER HERE

€7 A MONTH FOR ONE YEAR = ONE DAY OF RESEARCH

DONATING €7 A MONTH BY STANDING ORDER REALLY SUPPORTS RESEARCH INTO MS IN BELGIUM

BE43 0001 6000 1601

Gifts of €40 or more are tax deductible.