BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

Number **50**
2nd semester 2021

NEWSLETTER

Brain imaging in multiple sclerosis, yes... but with some added nuances!

This newsletter of the Charcot Foundation - Fighting multiple sclerosis focuses on magnetic resonance imaging (MRI). This is an area of science that is continually evolving. Dr Solène Dauby discusses her research in this field, with financial support from our Foundation.

While MRI is very sensitive when it comes to detecting abnormalities, it is not very specific as to their aetiology. Patients can be erroneously labelled with the diagnosis of MS when detecting small white matter abnormalities in the form of hyperintensities, which should not, however, be confused with MS lesions. These abnormalities may be due to micro-ischaemic disorders, may be congenital in origin, occur in people with migraine, diabetes or hypertension, etc.

By contrast, typical MS lesions are sometimes detected in people who undergo an MRI of the brain for a completely different reason, for example due to major headaches or head trauma. This is a "radiologically isolated syndrome", in people who will develop the disease in the coming years (30% develop it within 3 years) or who will never develop it: they are carriers but will not suffer from it. **The dilemma then arises: should we look at the images or at the persons who present symptoms and complaints?** We will only move forward with the images if we can be absolutely sure that they point to a disease and damage to the person's integrity.

There are also patients with a first MS attack, whose MRI reveals some typical, but millimetre-sized lesions, that will remain unchanged over time. They often are members of a family with an existing case of severe MS. These patients therefore do not need to be treated immediately and aggressively. Instead, they can be monitored, based on regular imaging and the decision to start therapy can be made only if this imaging worsens.

We must therefore be wary of an over-diagnosis of MS based solely on MRI and of over-treatment in spontaneously non-active and non-progressive forms of this disease. Obviously extensive and active lesions in imaging will also help us to start very aggressive treatments very early and very quickly nip this disease in the bud.

It is here that medicine becomes an art again, based on nuance instead of on algorithms that are blindly applied.

Professor Dr **Christian Sindic**
President

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Under the Patronage of Her Majesty The Queen

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Photo Credit: iStock & Shutterstock
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Keep your eyes open and look, keep looking, keep on looking: only in this way will you ever come to see.

Jean-Martin Charcot, born in Paris on 29 November 1825 and who died in Montsauche-les-Settons on 16 August 1893, was a French neurologist, professor of clinical neurological diseases at the Paris Medical Faculty and an academic.

As the discoverer of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that has gained its name in French medical literature, he is, along with Guillaume Duchenne, the founder of modern neurology and one of the great promoters of clinical medicine, a figure of positivism. In 1868, he was the first to describe multiple sclerosis.

FONDATION CHARCOT STICHTING

In 1987, the Charcot Foundation was founded by the Belgian MS Study Group, an association of Belgian neurologists with expertise in multiple sclerosis. Its aim: to overcome the disease through fundamental research.

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RESEARCH

MRI, a crucial tool for the diagnosis, prognosis and monitoring of patients

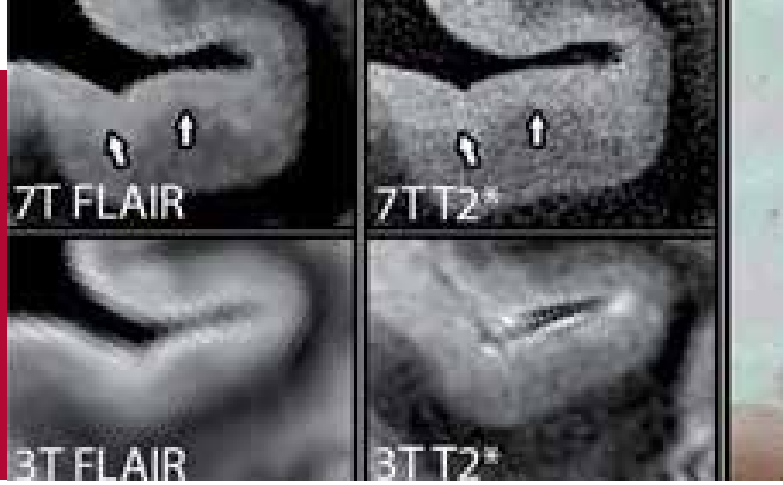
Multiple sclerosis is often described as an invisible disease or the disease of a thousand faces. MRI plays an important role in the diagnosis of this currently incurable disease. It can be used to confirm raised suspicions in addition to demonstrating the exact location and number of lesions.

Currently MRI plays a major role in the assessment and monitoring of patients with MS. It is a crucial tool for the diagnosis, prognosis and monitoring of these patients The changes that this disease induces in brain tissue are very complex and include inflammatory cell infiltration, the destruction of certain components of nerve cells (axons, synapses, etc.) and their sheaths (myelin), neuronal death, hypertrophy and the activation of other brain cells (astrocytes, microglia, etc.). Although we are unable to see these cells in detail, MRI can detect some of the secondary lesions associated with these phenomena. (1)

What determines the severity of the disease? The number of lesions or where the lesions are located?

This is a question that I often get from patients. It is quite easy and even tempting to imagine that a large number of lesions and substantial cerebral volume loss imply that the disease is more severe. It is not as easy as that, however. Observations have shown that the correlation between the number of lesions observed on conventional MRI (to which we have access in the clinic) and the disability in some patients is imperfect. In my opinion, there are two important reasons for this:

It is clear that the location of the lesions is a very important factor in determining the consequences that the lesion may have in terms of disability



Source: Kilsdonk and al Brain 2016. This image shows that 7T MRI can approximate the pathological appearance of cortical lesions.

Firstly, the brain is organised into different areas and the functionality of each of these areas is very different. Obviously, the location of the lesions is a very important criterion for the lesion's potential impact in terms of disability. A small lesion, in an important area of the brain (for example, used to move a limb), will have a much greater clinical impact than a larger lesion that is located in a more 'silent' area.

Secondly, conventional MRI only reveals part of the pathological processes of MS, and that is why we conceived this project. When we compare the MS lesions with MRI and then, under the microscope after autopsy, we observe several tissue changes that are linked to the disease but that are not visible with conventional MRI. Conceivably, the clinical condition and disability of a patient could thus worsen even though the MRI remains unchanged! This is probably due to these subtle changes, which conventional MRI cannot detect, but which are occurring in the brains of our patients. This is consistent with what we observe in progressive forms of this disease.

Are there other imaging techniques that can be used to identify MS (now and in the future)?

There are other imaging techniques that are used to study MS, but these are mostly being tested for research purposes. We also intend to use PET scans (2), more specifically to study the synapses as part of our study. But in clinical practice, MRI is used for the most part for clinical monitoring and to evaluate the effectiveness of a treatment.

Besides imaging techniques, we can also use clinical tests and objective measurements of specific parameters to visualise and assess this disease.

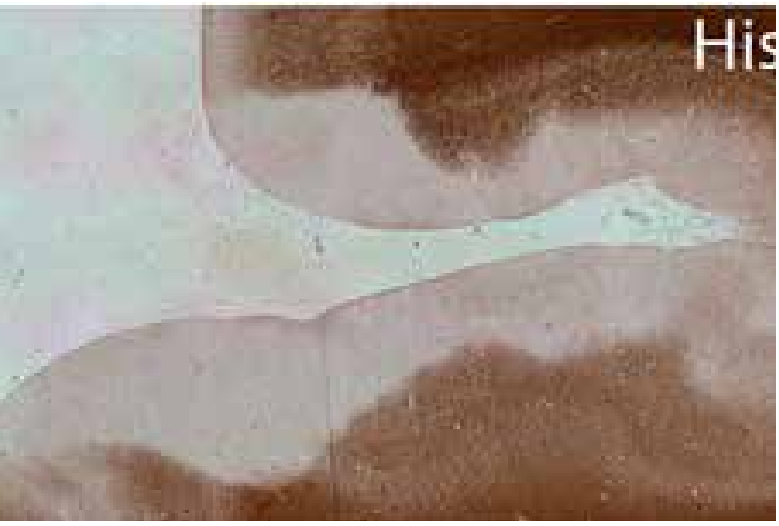
Does MRI also play a role in determining whether a patient should change treatments?

Yes, of course. In recent years, the management of MS has undergone significant changes, thanks to the advent of immunomodulatory therapies. Several studies have demonstrated that the functional prognosis (i.e. the patient's autonomy, his ability to walk, move, speak, etc.) is better when the disease is managed as early and as effectively as possible. MRI monitoring is crucial to managing patients as effectively as possible. We should therefore be able to adapt the treatment in step with the disease's potential aggressiveness. It is not uncommon to start a treatment and then switch to a more effective therapy because the disease progresses and new relapses eventually occur. Regular MRI follow-up can detect when treatment needs to be stepped up at the earliest possible stage.

Your research, which is funded by the Charcot Foundation, aims to clarify the correlation between what the MRI shows and the natural progression of the disease... Can you explain how you intend to do this?

As mentioned earlier, one of the current challenges in the treatment of MS is this imperfect correlation between lesions on conventional MRI and the patient's condition or progression. We know that conventional MRI does not detect everything and that we therefore miss certain phenomena, certain lesions. They explain this discrepancy.

Our research project aims to use two very advanced imaging techniques, namely 7T MRI (3) and PET scan. These two technologies will hopefully give us access to specific lesions and abnormalities that are not visible with conventional MRI.



We hope that by increasing our ability to detect brain abnormalities in patients, we can better correlate the images and clinical observations.

A new line of research focuses on remyelination. Can you explain how MRI or other imaging technology might contribute to this research?

A number of specific parameters that are studied using quantitative MRI (specific protocols used for MRI in research) have a correlation with the amount of myelin. Recently, researchers demonstrated that when you measure a quantitative parameter in MS patients called magnetisation transfer or MT, you can observe a correlation between the evolution and clinical data. In patients with a favourable course, the MT parameter in the lesions tends to increase.

Dr Solène Dauby
ULiège – Cyclotron Research Center

(1) MRI is a medical examination performed using strong electromagnetic fields. It produces 2D and 3D images of the body.

(2) PET scan is an imaging technique that studies the metabolic activity of tissues using a radioactive tracer like or analog to glucose.

(3) 7 Tesla MRI is a pioneering technique that provides enhanced images which can be used to map areas in the brain to the level of infra-millimetre resolution. Recently, 7T MRI demonstrated that MS, which until then was considered to attack the white matter of the brain only, is in fact also accompanied by lesions in the grey matter, which cannot be detected on conventional MRI.

- *More information and videos at www.fondation-charcot.org*
- *This newsletter is also available in FR and NL on our website.*

YOUR WILL CAN MAKE A DIFFERENCE

Has the Belgian Charcot Foundation ground to a halt this year? Far from it. Research into multiple sclerosis has continued unchanged. After all, our researchers know how many MS patients are counting on them to find a solution to a disorder that is still incurable. Their research was made possible by the money raised by the Belgian Charcot Foundation from its donors and testators. That is why we are counting on your help.

"There were two of us at home, my sister and me. When my sister was 30, she was diagnosed with MS. She'd just had another baby and people didn't know much about multiple sclerosis back then. The doctor said there was nothing to be done. Ten years later, she was in a wheelchair. As the years went by, she became more and more disabled. There was no real treatment at the time.

When my sister passed away last winter, we felt a lot of grief, but also regret that we hadn't been able to help her. My husband and I, unfortunately, never had children, so it made sense for us to think of my sister's children. I also felt it was important to make a legacy to the Belgian Charcot Foundation. The research they support helps bring about treatments. I'm so pleased that because of this research MS patients no longer have to end up in a wheelchair. I can only wish that my sister had lived to see this."

Claire M., Namur

"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"

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MRI
A technological breakthrough for the diagnosis of MS

Magnetic resonance imaging of the brain in multiple sclerosis (MS) was presented for the first time on 14 November 1981, when "The Lancet" published an article entitled "Nuclear Magnetic resonance imaging of the brain in multiple sclerosis", by Y. R. Young and his collaborators. These authors showed that CT (cranial X-ray computed tomography) scans of 10 patients with MS showed a total of 19 lesions altogether, while a further 112 lesions were shown on the MRI scans! This was the first time, in other words, that neurologists were able to ascertain the spread of the disease and the number of brain lesions during a patient's lifetime (the patient's "lesion load"). The team soon realised that most of these lesions were asymptomatic, in 'silent' areas of the brain.

Significant improvements have since been made in terms of the quality of the images and their resolution, by increasing the field strength of the magnets used (0.5 then 1.5 and finally 3 Tesla) and adapting this technique to the spinal cord. This gave us the opportunity to distinguish between old lesions and active inflammatory lesions (new lesions or reactivated old lesions) associated with blood-brain barrier leakage. A paramagnetic contrast product called gadolinium leaks into the active lesions. An active lesion may eventually (but not always) result in a permanent central necrosis called "black hole", due to demyelination and transsections of the nerve fibres.

> *"This made it possible to distinguish between old lesions from active inflammatory lesions.*

Since 2001, MRI has been used as part of the diagnostic criteria, based on the number and location of lesions, whether periventricular, cortical or juxtacortical, or in the cerebellum, brainstem or spinal cord. Finally, it also demonstrated something that neuropathology had already taught us, namely the presence of a central vein within MS lesions. The subpial demyelination sites, directly underneath the meninges, are still difficult to detect with conventional MRI.

Based on these images, prognostic criteria were formulated. Patients with lesions in the brainstem, cerebellum or lateral columns of the spinal cord have a poorer prognosis than patients who only have periventricular and hemispheric

lesions. Some (but not all) lesions have been detected within the cerebral cortex, in addition to those located in the white matter (myelinated fibres). Disease-induced brain atrophy can now be measured beyond the normal mean brain volume loss below 0.4% per year. More selective and localised atrophies also occur, in the corpus callosum for example, a bundle of myelinated nerve fibres that connects the two brain hemispheres, the thalamus and the cervical spinal cord. More recently, MRI revealed focal areas of meningitis corresponding with the presence of ectopic lymphocytic nodules in the meninges.

Thanks to MRI, scientists were also able to demonstrate the partial, albeit significant, effectiveness of Betaferon, the first interferon used to treat this disease. It prevented the development of new lesions, in addition to reducing the clinical relapse rate. This first study, which was published in 1993, did not yet use the contrast product gadolinium, which became the gold standard in all subsequent studies. Global brain atrophy, which is another reliable outcome measure of drug effectiveness, was first used in trials of Fingolimod (Gilenya). Slowing the speed of brain atrophy to the normal levels that are observed in any person was the desired (and in some instances achieved) goal in several recent trials of new treatments.

To date, conventional MRI is not very quantitative in terms of the overall lesion volume and the presence of active chronic lesions that progress insidiously without breaking down the blood-brain barrier. The latter, however, are very important in progressive MS. More recently, studies demonstrated that they are partially or totally surrounded by a thin border of iron-containing inflammatory cells.

> *“Slowing down this brain atrophy to the normal values observed in every human being is the goal pursued in several recent studies of new treatments*

As Dr Solène Dauby explains, however, this technology can bring us new data that will increase our knowledge of this disease, for example by using MRI systems with a magnetic field of 7 Tesla. This will make it possible to analyse and quantify loss of nerve cells, the rarefaction of synaptic connections, decreased nerve fibre density and, potentially, the remyelination of some of them, whether spontaneously or thanks to new treatments that are currently being tested in clinical trials.

Prof. Dr. Christian Sindic

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