The Royal Society of Edinburgh

Lecture

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Multiple Sclerosis: has research got us to the end of the beginning or the beginning of the end?

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Report by Jennifer Trueland

Professors ffrench-Constant and Lubetzki described progress being made in finding treatments for relapsing and remitting multiple sclerosis and said we are on the cusp of a new era of treatments for the progressive form of the disease.

There have been major advances in understanding and treating multiple sclerosis in the last 15 years, said Professor Lubetzki, but the question which formed the title of the event – are we at the end of the beginning or the beginning of the end? – is not easy to answer.

She began by setting the scene: MS is a neurological condition which affects around 2.3 million people worldwide. Prevalence varies depending on where you are in the world – the closer to the Equator you are, the less likely you are to develop it. France has around 80,000 people with MS, out of a population of 64 million; a prevalence of 1.2 per thousand people, compared to a prevalence of 1.6 per thousand for the UK, which has around 100,000 people with the disease. In Scotland, however, prevalence is almost twice that of France, standing at 2.2 cases per thousand. People are usually diagnosed with MS when they are aged between 20 and 35, and it is three times more common in women than in men.

Professor Lubetzki spoke a little about how MS was first described, starting in 1822 with Augustus d'Este, a grandson of George III, whose condition was posthumously diagnosed due to perusal of his diaries, which catalogue his symptoms and the progression of the disease. By 1848, two pathologists had described the disease that would become known as MS, one in France and one in the UK. Even then, it was recognised that it is a disease of inflammation and degeneration.

As we understand it today, MS is a disease of the central nervous system in which, as part of an inflammatory process, the coating around the axons, or nerve fibres, is damaged. This coating is called myelin, and it protects and maintains the nerve fibres which are needed to carry messages between the brain and the rest of the body. Loss of this myelin leads to damage to the axons, which in turn causes progressive disability.

There are two patterns of symptoms of MS: relapsing and remitting, and progressive. Around 80% of cases begin with the relapsing and remitting form of MS (RRMS), in which symptoms such as attacks of numbness or weakness resolve themselves completely or incompletely. Around 50% of these will go on to develop the progressive form of the disease over the course of about 15 years. These have different causes: RRMS results from inflammation, whilst progressive MS results from irreversible nerve fibre damage. Treating these two forms of the disease is, therefore, not the same, explained Professor Lubetzki.

The causes of the inflammation that starts MS are complex and multifactorial. There is no single cause, but a number of factors, including genetics and environment, are implicated. It is also possible that a virus, or viruses, might be involved. The inflammation can be treated in a variety of ways, with a number of drugs available for RRMS that reduce the frequency and damage caused by relapses. There are more disease-modifying drugs coming on the market and they are getting better all the time. There are also drugs and therapies to help people manage their symptoms.

Professor Lubetzki said there have been more than 500 clinical trials since the 1990s, most of them on RRMS. “There are lots of drugs in development – it’s a new era,” she said. “But they only treat the inflammatory component of the disease.” The “next frontier” is finding drugs to treat the progressive phase. The goal is finding drugs where benefits outweigh the risks. There have been some small trials but all, so far, have failed, she said. However, some promising therapies are moving into phase 2 and 3 trials. “It’s an exciting era, with a lot to be done.”

Professor ffrench-Constant then went into more detail about what happens in progressive MS. He considered five questions: What has been damaged? Why has it happened? How might we treat it? Where have we got to so far? When will we finally succeed? Ultimately, he said, he was optimistic, but that’s not to say we have all the answers.

He began by talking about axon loss in MS. There is no single cause of this, but factors include ongoing inflammation, mitochondrial damage and persistent loss of myelin. As well as the acute inflammation associated with RRMS, there appears to be chronic inflammation, which manages to get through the blood–brain barrier. This is a problem, because anti-inflammatory drugs cannot (so far) breach that barrier. Additionally, when the mitochondria – the “cell batteries” – are damaged, it means the cells are no longer able to generate energy. The loss of myelin is the third and, some would argue, the most important, issue for axon loss, he said. Research has suggested that axons need myelin not just for protection, but also for energy. The nerve fibres are so long, so far away from the cell, that it’s the equivalent of a Eurostar train that would stretch from Edinburgh to the South of France. Therefore, they rely on the myelin sheath for energy. “If you lose myelin, and lose that source of energy, then the axon will be in big trouble,” he said.

To treat progressive MS, he said we need to do three things: first, prevent inflammation in the brain; second, protect axons that are already damaged; third, replace lost myelin. For the first, the problem is getting drugs over the blood–brain barrier to reach the inflammatory cells. There are research advances that would allow therapeutic antibodies to be delivered to the brain via the use of a transferrin receptor-based system.

For the second and third, the approach would involve reversing the energy failure by replacing myelin (remyelination), and a great deal of research has focused on this. We’ve known for around 30 years that myelin is formed by oligodendrocyte precursors, a type of stem cell. But we’re just beginning to get a better sense of what’s going on, and it’s more complicated than we thought, he said. If you look at the tissue to see what’s happening, you see that remyelination, or myelin repair, can already happen spontaneously in MS; so clearly, he said, there are stem cells in the brain. If we can get a better sense of how this happens, we might get a better idea of how we can effect the repairs.

Even where there are lots of oligodendrocytes present in lesions, remyelination doesn't always occur. This could be because it is somehow inhibited from happening. He cited research by Professor Lubetzki and others that suggests that re-expression of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) could inhibit remyelination.

Over the last few years, a number of targets have been found that might aid remyelination, and work is ongoing. The challenge, said Professor ffrench-Constant, is to turn promising targets into effective drugs.

So what is the answer to the question in the title of the event? It's complicated, he said. When considering the inflammatory stage of the disease, we're at the beginning of the end; we've got effective drugs, and they will get better.

The problem is, however, that you don't really know whether you were at the beginning until you (successfully) near the end. He, however, is confident that we are at the end of the beginning of finding treatments for progressive MS. He recalled doing his PhD studies in the 1980s when the first targets for disease-modifying drugs for RRMS were being identified; today they are being used to treat people. We're at a similar position with candidates for drugs for progressive MS. He hopes that we won't take as long to move to the treatment stage, because we've got "good tools" and we know an awful lot more about human cells than we did. We're also quicker at translating research into practice, particularly through the use of early-phase clinical trials – that is, testing the drugs on people. First-in-man experiments will increase, he concluded, and Edinburgh's Anne Rowling Centre will make a difference.

Questions

Questions covered a wide range of areas from connections between MS and other diseases to the role of nutrition.

Asked whether tick-borne Lyme disease could be a cause of MS, Professor Lubetzki explained that they are two different diseases, and there is no real data to allow her to provide a solid answer. It might be that Lyme disease could lead to relapse, so it might modify the disease, but not cause it.

Asked about whether deamination – loss of amino proteins – could be used as a biomarker, Professor ffrench-Constant agreed that it is an interesting idea. He also said there is no evidence that deamination is a cause of damage, because it is part of a much wider set of processes.

The speakers were asked their views on the relevance of mitochondrial DNA, which has also been linked to Alzheimer's disease. Professor ffrench-Constant said that, personally, he believes that the evidence on mitochondrial damage and MS is compelling, and that it is a very important target which might lead to a final common pathway for other neurodegenerative diseases.

The conversation then turned to genetics. Asked about the impact of being able to sequence the human genome – and whether or not the clinicians sequence their patients' genomes – Professor Lubetzki said that whilst genetics might account for a person's susceptibility to MS, there is no single gene causing the disease. A study in 2011 found around 1,000 genes that might make someone more susceptible, but the contribution of each gene would be small. They don't sequence patients' genomes because it wouldn't be of diagnostic value, she added.

Asked why women are more susceptible to the disease, Professor Lubetzki said that the simple answer is that we don't know, and that it is also the case that women are more likely to get other auto-immune conditions, such as rheumatoid arthritis.

Have there been studies with social scientists or anthropologists to discover causes behind the latitude gradient? Not that he knows, said Professor ffrench-Constant, but it might be interesting. It could be linked to genetics – people tend to settle at a latitude where they feel comfortable, but there is a suggestion that children who migrate take on the MS risk of the latitude they go to, whilst adults retain the risk of the country they left. There are many theories, he added.

Asked if there is work being done to find out what triggers the disease, Professor Lubetzki said there have been many attempts to find out, but that we simply don't know. It might even be that what we currently call MS is actually a number of different diseases, she added; the heterogeneity might be greater than we think.

Stem cell research in humans was next on the agenda. Professor ffrench-Constant said it is important to understand that there are two potential forms of research. A number of trials using stem cells to suppress the immune system are underway, but replacing stem cells in patients whose lesions do not have enough of them would be very difficult – even if it were possible – because you wouldn't be able to select which patients might benefit.

The final question was on nutrition, and whether it is possible to alter the course of the disease by eating or avoiding particular foods. Professor Lubetzki said there is no clear evidence linking diet with MS, but that there is some interest in the idea that faecal bacteria might have a role.

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