Introduction & Module 1: Spotting Progression in MS: What Are You Missing?

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Introduction

Dr Marcello Moccia:

Welcome to this microlearning module series on spotting multiple sclerosis progression. My name is Marcello Moccia from the University of Naples, Italy.

One of the greatest challenges we face in clinical practice is recognizing progression from the early phases of multiple sclerosis. Progression can occur in the absence of relapses, and sometimes it involves subtle changes, including cognitive changes or findings that can only be detected on MRI.

This series has been designed to provide short, practical insights into how we can better identify the signals of progression. Across the modules, we will explore the tools available to us, the limitations of current approaches, and how emerging technologies can support more informed decisions, including the use of biological markers.

Our goal is simple: to help you feel more confident in recognizing progression earlier in MS and acting on it.

Welcome to Module 1: *Beyond Relapses: Uncovering PIRA*. Progression in MS does not always present with relapses, and in this module we will focus on how to recognize progression independent of relapse activity, or PIRA, and why it matters now.

You will explore this topic in more detail with our colleague and friend, Dr Arrambide, who will walk us through how PIRA presents in clinical practice and how we can recognize it more confidently.

Module 1: Beyond relapses – Uncovering PIRA

Dr Georgina Arrambide:

Hello everybody. I'm Dr Georgina Arrambide and welcome to this touchNEUROLOGY microlearning module series on progression in MS.

The scope of this module is to explore how progression in multiple sclerosis can occur independently of relapses, and how we can better recognize it in practice.

We are going to talk a little bit about the background. We have known for many years that inflammation and neurodegeneration overlap already in MS, even in the very early phases of the disease. However, it was only relatively recently that the terms relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) were proposed.

I think this differentiation became clearer following the introduction of high-efficacy treatments for MS.

One important point about progression independent of relapse activity is that it is not the same as secondary progressive MS. It can occur early in the disease course. For example, in the

Barcelona inception cohort study, we saw that around 25% of patients developed progression independent of relapse activity within a median follow-up of approximately seven years.

Of all these patients with PIRA, around 30% developed what we call early PIRA, which is progression independent of relapse activity occurring within the first five years of disease evolution.

What we see, then, is that PIRA helps us identify progression before the patient reaches what we know as secondary progressive MS, when it may already be too late for optimal intervention. Identifying it earlier in the disease course may allow us to better support these patients and potentially decrease the rate of disability accrual.

Another important aspect of PIRA is that it helps us identify different disease mechanisms driving disability. We know that RAW is related to relapses and possibly to new lesions, but there are other mechanisms of disability accrual that we are beginning to understand.

For example, when we started using high-efficacy treatments, we saw that we could control acute inflammation very well. However, some patients still progressed despite having no relapses or inflammatory activity on MRI.

This taught us that there are other mechanisms involved in disability accrual, such as chronic inflammation or perhaps purely neurodegenerative processes. Of course, age also plays a role. As we get older, repair mechanisms become less effective, and this itself can contribute to disability accrual.

Identifying these mechanisms helps us better understand the disease and recognize potential treatment targets in MS.

Of course, PIRA also has some limitations. First of all, there are varying definitions of PIRA. You need to take into account the baseline assessments, the event itself and the confirmation periods. Depending on the definition used, there may also need to be re-baselining if relapses or previous PIRA events occur in between assessments.

These definitions vary, although the roving-period definitions are being used more frequently because they appear to be more sensitive in identifying these events.

Another important point is that PIRA does not take MRI activity into account. Other definitions have therefore been considered, such as PERMA, where there is no MRI activity either — not only no relapses, but also no inflammatory activity visible on MRI.

This is important because, again referring to the Barcelona CIS cohort, we observed that around 50% of patients with PIRA developed what we would call active PIRA, meaning there was inflammatory activity visible on MRI. This suggests that inflammatory activity may still be contributing to disability in a way that is not entirely “pure” PIRA.

This is something we need to take into account.

We also have to remember that the definition of PIRA is based on the EDSS, which can be rater-dependent. It may also be difficult to account for variability related to factors such as heat sensitivity, where patients may temporarily experience worsening disability before later returning to their previous EDSS score.

In addition, we know that the EDSS is not particularly sensitive for upper limb dysfunction or cognitive impairment, both of which may also be important in PIRA.

Overall, I think we are moving towards a more unified definition of PIRA, which will be useful for clinical trials and observational studies. However, in day-to-day clinical care, we may need to remain more flexible and use the definition that is most sensitive for identifying potential progression while minimizing false-positive PIRA identification.

The key message here is that we need to pay close attention to what patients are telling us, even if those changes are not reflected in the score.

For example, there may be changes in functional systems that do not affect the EDSS score, or a patient may tell you that they can now only walk one kilometre, whereas a year ago they could walk five kilometres. This kind of change would not necessarily be captured by the EDSS.

We therefore need to take all of this into account.

Other tools that may help improve sensitivity, such as PROMs, imaging and body fluid biomarkers, will be discussed in the next modules.

For now, the take-home message is that there are different mechanisms beyond relapses that lead to disability accrual. PIRA, being a clinical definition, may encompass different pathogenic mechanisms.

Understanding these mechanisms may help us identify interventions that can decrease the risk of — or even prevent — disability accrual.