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www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring the Role of IgG Autoantibodies in Idiopathic Inflammatory Myopathies (IIM)

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. This medical industry feature, titled "Exploring the Role of IgG Autoantibodies in Idiopathic Inflammatory Myopathies (IIM)," is sponsored by argenx. Here's your host, Dr. Brian McDonough.

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Dr. McDonough:
This is *NeuroFrontiers* on ReachMD, and I'm Dr. Brian McDonough. Today, we'll be discussing the role of IgG autoantibodies in idiopathic inflammatory myopathies—also known as IIM or myositis—and how they're reshaping both our approach to diagnostic classification and our understanding of the pathogenesis.

Joining me is Dr. Julie Paik, who's an Associate Professor of Medicine and Co-Director of the Myositis Center at Johns Hopkins University in Baltimore, Maryland. Dr. Paik, welcome to the program.

Dr. Paik:
Thank you, good to be here.

Dr. McDonough:
Well, to start us off, Dr. Paik, can you give us an overview of IIM and who tends to be affected by these conditions?

Dr. Paik:
Sure. IIMs are a group of rare autoimmune diseases primarily defined by inflammation of skeletal muscle, which then leads to muscle weakness. These conditions are systemic in nature, so we may also see inflammation affecting the skin, joints, lungs, GI Tract , and also the heart.[1]

And in terms of who's affected, the incidence increases with age, with the peak age of incidence around 50 years, based on available data from North America and also in Europe. Inclusion body myositis is more common in men, while most other subtypes tend to occur more frequently in women. And globally, prevalence ranges from about three to 34 cases per 100,000 people, based on data collected from patient cohorts between 2009 and 2015.[2]

Dr. McDonough:
Now, as I understand it, the classification of these diseases are still evolving, but how is IIM currently categorized in clinical practice?

Dr. Paik:
Yeah, you're absolutely right; the classification of IIM or myositis continues to evolve as we really learn more.[3,4] And that said, in clinical practice today, we typically recognize several key subtypes, each with its own distinct clinical features.[3] And what really unites all of these is immune-mediated inflammation affecting skeletal muscle.[1] And these major subtypes include dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, inclusion body myositis, and overlap myositis.[2,3]

Historically, polymyositis was also considered a subtype, but more recently, it's viewed as a diagnosis of exclusion. And no specific auto-antibody is associated with Polymyositis. Polymyositis is now considered when the muscle biopsy shows a specific CD8-positive T cell–mediated endomysial infiltrate in the absence of other subtype-defining features.[2,3]

Among all subtypes, dermatomyositis is the most common as it accounts for about one-third of cases. That's followed by immune-mediated necrotizing myopathy, which makes up roughly 20 percent of cases.[5]

Dr. McDonough:
So then let's talk about what's driving these diseases. What do we currently understand about the pathogenesis of IIM?

Dr. Paik:
That's a great question, and one we're still learning a lot about. The potential contributors for IIM aren't fully defined, but the current understanding points to a multifactorial process which includes genetic susceptibility, environmental exposures, and immune dysregulation.[2,5,6] Adding another layer, these factors are potentially initiated or amplified by things like infections and medications, such as statins and immune checkpoint inhibitors. Some IIM subtypes are also associated with a greater risk of malignancy compared to the general population.[2,6]

Dr. McDonough:
So how does the immune response lead to the onset of inflammation and tissue damage once these triggers are in play?

Dr. Paik:
When it comes to immune pathways, we see evidence of both innate and adaptive mechanisms at play[5,7] and most notably, the activity of IgG autoantibodies are increasingly recognized as central drivers of disease.[2,6,8,9]

For example, we see that specific myositis-associated autoantibodies link to distinct clinical features, and there's evidence that higher serum autoantibody levels correlate with greater disease activity. And these associations support the idea that these autoantibodies play a key role in disease pathogenesis.[10]

In IIM subtypes like dermatomyositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome, these IgG autoantibodies are thought to contribute to disease through several pathways.[8,9] For example, they may activate type I interferon signaling, disrupt normal myofiber function, and engage the classical complement cascade.[5,8,11-13]

Building on that, what's key is that these autoantibodies aren't just circulating, but have been shown to be internalized into muscle cells where they may interfere with the function of their target protein.[6,14] That intracellular disruption may lead to muscle cell toxicity with muscle fiber damage, necrosis, or impaired regeneration.[1,14]

We're still learning about how these IgG autoantibodies are active participants in the pathogenesis of IIM disease. And while we hope to discover the full scope of their role, IgG autoantibodies are already becoming central to how we diagnose and classify these diseases in practice.[4,8]

Dr. McDonough:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Brian McDonough, and today I'm speaking with Dr. Julie Paik about IIM and the role of IgG autoantibodies in subtype pathogenesis and diagnosis.

So if we continue diving into that idea, Dr. Paik, how are IgG autoantibodies used clinically to help diagnose and differentiate the subtypes of IIM?

Dr. Paik:
That's actually been a major advance in the field. The discovery of these IgG autoantibodies has changed how we diagnose and classify IIM.[2,4]

They can be categorized into two groups: myositis-specific autoantibodies, or MSAs, and myositis-associated autoantibodies, or MAAs.[2,4]

Let's begin with MSAs. In clinical practice, we typically rely on a combination of information to help determine which subtype of IIM a patient has—things like the patient's clinical presentation, muscle biopsy and electromyography findings, along with laboratory testing.[2,4]

Now, what makes MSAs particularly useful is that they're found almost exclusively in patients with IIM and they're strongly linked with specific clinical phenotypes.[2,4] It's also extremely rare for a patient to have more than one MSA.[15] So, when we identify an MSA, it can really help clarify the diagnosis of a particular IIM subtype.[2,4]

And identifying the specific autoantibody can also provide insight into how the disease might behave over time, such as which organs

may become involved.[2,4]

Dr. McDonough:
So MSAs can help distinguish subtypes and help us better understand the disease course for an IIM subtype—are they detectable in all patients?

Dr. Paik:
So, you bring up an important point. MSAs are present in up to 60 percent of patients with IIM.[2] But not every patient with IIM has a detectable MSA, and so a portion are considered seronegative. For example, in one study of patients with immune-mediated necrotizing myopathy, 34 percent were seronegative.[16]

And interestingly, some of these patients showed unique features, like more extensive extramuscular involvement that couldn't be attributed to another connective tissue disease.[1,16] It's thought that some of these individuals who are seronegative may have yet-undiscovered autoantibodies.[17] So while the absence of a known MSA may not rule out the diagnosis, it could make the diagnostic workup more nuanced.[16]

Dr. McDonough:
Now, you also mentioned myositis-associated autoantibodies, or MAAs. How do they differ from MSAs, and what role do they play clinically?

Dr. Paik:
So MAAs are less specific to IIM than MSAs, as they're often seen in a range of other systemic autoimmune diseases like systemic sclerosis or scleroderma, lupus, mixed connective tissue disease, and Sjögren's syndrome. And that said, MAAs can still offer valuable clinical information.[18,19]

While it's extremely rare for a patient to have more than one MSA, MAAs may co-occur with MSAs. And in these cases, MAAs, or myositis-associated autoantibodies, can help identify disease overlap or offer prognostic value for certain complications. So while they don't typically define a myositis subtype the way MSAs, or myositis-specific autoantibodies, do, they can provide important context.[2,15,18]

For example, anti-Ro52 is one of the more frequently encountered MAAs, and it's often found in patients with antisynthetase syndrome. And its presence has been associated with more severe ILD, or interstitial lung disease, and poorer outcomes, so it may carry prognostic value, even if it's not specific to IIM.[15]

Other myositis-associated autoantibodies, or MAAs include anti-PM-Scl, anti-Ku, anti-U1RNP, and anti-U3RNP. These are often seen in overlap syndromes, where features of myositis coexist with another connective tissue disease.[2,15] So even though MAAs don't define an IIM subtype on their own, they may help paint a fuller picture of disease complexity.

Dr. McDonough:
And looking ahead, where do you see the field moving as we continue to deepen our understanding of IgG autoantibodies?

Dr. Paik:
Well, I noted earlier that these antibodies, you know, are now known to be internalized into muscle cells where they can contribute to inflammation, necrosis, and impaired regeneration.[6,14] As a result, they're increasingly being studied as therapeutic targets for IIM disease. And, I see potential in modulating or blocking the intracellular effects of these pathogenic IgG autoantibodies.[8]

So while there's a lot to uncover, it really appears that we're entering a new phase of precision medicine in IIM—one that's rooted in serologic profiling, but also increasingly focused on targeted immune modulation.[3,8]

Dr. McDonough:
As we wrap up our discussion today, Dr. Paik, what are your key takeaways on IIM?

Dr. Paik:
I think the biggest takeaway is that our understanding of IIM has grown significantly, both in terms of how we classify these diseases and how we think about what's driving them at a mechanistic level. And with recent advances in understanding their intracellular activity, IgG autoantibodies have emerged as potentially key players in disease pathogenesis.[1,2,4,6,8,9,14]

As a result, identifying the autoantibody profile, in particular an MSA, can add critical depth to how we approach IIM—from how we distinguish between subtypes to how we anticipate disease course in clinical practice.[1,2,4,15,16] And so ultimately, our evolving

understanding may help us make more informed decisions for our patients in the clinic.

Dr. McDonough:
That's a great takeaway from today's program. And I want to thank my guest, Dr. Julie Paik, for helping us better understand the role of IgG autoantibodies in autoimmune IM. Dr. Paik, it was great to have you with us today.

Dr. Paik:
Thanks for having me.

Announcer:
This medical industry feature was sponsored by Argenx. If you missed any part of this discussion or to find others in this series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge.

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