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Early Signs & Symptoms of Rheumatoid Arthritis

Announcer:

This is ReachMD. Welcome to Spotlight on: Rheumatic Diseases. This episode titled, “Early Signs & Symptoms of Rheumatoid Arthritis” is sponsored by Lilly. The views and/or opinions expressed are of the medical expert and not necessarily by Eli Lilly & Company.

Here’s your host, Dr Matt Birnholz.

Dr. Birnholz:
Coming to you from the Annual Rheumatology Meeting in Atlanta, Georgia, this is ReachMD, I'm Dr. Matt Birnholz. Joining me today is Dr. Ara Dikranian, a rheumatologist in San Diego, California. Dr. Dikranian has served as Chairman of the San Diego Chapter of the Arthritis Foundation Executive Committee following years of volunteering at previously sponsored free clinics and, more recently, as part of the San Diego County Medical Foundation's Project Access. And today we're going to focus our discussion on the early signs and symptoms of rheumatoid arthritis. Dr. Dikranian, welcome to you.

Dr. Dikranian:
Thank you. I appreciate being here.

Dr. Birnholz:
So, to start, I want to review the progression from preclinical RA to clinical RA, as we traditionally characterize it, sort of an always shifting target, and maybe you can help walk us through how we get from one phase to the next.

Dr. Dikranian:
So, a very topical item to talk about here at ACR because, not just this year but also the previous years, we've had a focus on trying to define preclinical rheumatoid arthritis and then, obviously, the evolution to early RA. I think a lot of this interest has stemmed from the recognition that if you treat rheumatoid arthritis early on, you obviously have better outcomes. So, the definition of preclinical RA, I think, is shifting, as you mentioned, and it stems from somewhere between having risk factors for rheumatoid arthritis and then having an undefined or undifferentiated inflammatory arthritis. Our colleagues at EULAR have actually separated these regions into those who have risk factors, those who have autoimmunity such as the presence of autoantibodies, and then, at some point, have vague symptoms which might suggest inflammatory arthritis, to then the development of inflammatory arthritis and then, obviously, the progression to rheumatoid arthritis as defined by our classification criteria. So, that progression is obviously not known. We don't have a lot of longitudinal studies, but certainly we look at patients who have seropositivity for rheumatoid factor and CCP antibodies and note that those do tend to predict the onset of rheumatoid arthritis by about 50%. If you, on top of that, have genetic factors, risk factors such as smoking or certain environmental factors, and, on top of that, if you add certain factors like arthralgias, then your incidence of developing rheumatoid arthritis becomes even more. So, I think where we are now is there is a recognition of clinically suspect arthralgias. So, people that might have ACPA-positivity or rheumatoid factor positivity, certainly family members who might have rheumatoid arthritis, and, with certain risk factors such as smoking or periodontal disease and others, this clinically suspect arthralgia population is worth looking into in terms of developing rheumatoid arthritis.

Dr. Birnholz:
Right. I definitely want to get to some of that. I'm fascinated by what we were calling this shifting target, this shifting definition, it seems extraordinarily difficult sometimes to be able to work through a diagnosis, if you will, of preclinical RA given how differently it manifests for patients. I came across one statistic saying if and when it becomes known, a patient might have anywhere between a 40 to 70% chance of developing RA within about four years. Has that been your experience?

Dr. Dikranian:
Yeah. So, I think the experience that each of us will have individually, especially in sort of non-academic centers, is really focused on the patients that were referred and we don't have the luxury of that longitudinal follow up to know what the denominator of people who may or may not develop inflammatory arthritis is. But in cohorts where that has been studied, such as through the University of Colorado at Denver, through the Netherlands and certain Scandinavian cohorts, there is a progression of about 20% of people who have these clinically suspect arthralgias with the risk factors and that's over a time course of two to four years. On top of that, we can add certain developing technologies such as diagnostic ultrasounds looking for certain signals. Those studies haven't been very conclusive so, if you take patients with certain symptoms who may have ultrasound findings, those are mixed results, and so I'm not sure that that's been worked out quite yet. But, again, the identification of people that you want to follow closely really depends on this combination of symptoms, and you are absolutely right that identifying these symptoms has been very difficult. There has been a questionnaire developed, again, from our colleagues at EULAR, that looks at about six or seven different symptoms and physical findings that seem to predict who's going to develop arthritis from a cohort of who has just arthralgias. Those seem to be new onset of arthralgias, so within the last year, degree of morning stiffness lasting about 60 minutes, the joint symptoms being focused on the MCP joint seems to be predictive as well, and then, on physical findings, those who have difficulty making a fist and/or who have tenderness over their MCP joints, again, without any detectable synovitis. So, if you have a number of these risk factors, it does have a high sensitivity and specificity about 80 to 90% of predicting inflammatory arthritis.

Dr. Birnholz:
Interesting. But even within that spectrum there are complications, it sounds like, in terms of not everything manifests the way that a rheumatologist would or especially a person in primary care who's looking for the telltale signs of symmetrical joint inflammation, for instance, it doesn't always manifest that way at the preclinical stage.

Dr. Dikranian:
Absolutely not. My background is in psychobiology and this always comes up, is the interplay between the mind and body and the connection that has. So, we know that, obviously, patients who eventually develop rheumatoid arthritis have a genetic predisposition based on the shared epitope and other risk factors, and then we always say there's some stressful event that triggers the onset to inflammatory arthritis. And that stressful event has been hypothesized to be some type of infection or some type of environmental insult, you know, silica has been implicated, certain jobs and occupations have been implicated, but more than that, there's a growing body of evidence that psychological stress has an effect on the onset of rheumatoid arthritis. So, groups have looked at Posttraumatic Stress Disorder, have looked at veterans coming back from wars, and there seems to be an association, a clear association, between the onset of rheumatoid arthritis/inflammatory arthritis following an anxiety or sort of this posttraumatic disorder. In fact, just last month there was a publication that showed that perceived stress, not just a stressful event, is associated with the onset of inflammatory arthritis and that gives us an opportunity to talk about a holistic approach. So, when we mentioned that patients might have improvements by meditation, by well-being, by focusing on health, it's an intriguing concept to think that you might be able to ward off those early stages just by positive feedback.

Dr. Birnholz:
That is fascinating and hopefully our event today won't be contributing to any inflammatory changes.

Dr. Dikranian:
Hopefully not! Hopefully not!

Dr. Birnholz:
So, with all of that said then, why don't we talk through early RA and get a sense of how does early RA actually manifest. What does it look like? Can you walk us through that?

Dr. Dikranian:
Yeah. So, I think, again, this is a heterogeneous definition and there are no criteria on early RA before it gets to that classifiable diagnosable stage. But, in the early stages, people have symptoms so, even before they become patients, they have symptoms such as joint aches and stiffness and, again, this psychological distress whether that's causative or correlative is really not certain, but stiffness certainly is a possibility and involving, especially the small joints of the hands, the inability to make fists, numbness or tingling, or various neurological problems happen in about 20% of patients, and these numbers come from cohorts where people have gone into early arthritis clinics who looked back and saw what are the onset and presenting symptoms. And there seems to be, again, this constellation of stiffness, swelling, and pain which may not necessarily manifest on with objective measures. So, obviously, those are nonspecific symptoms. Many people have those symptoms who don't develop rheumatoid arthritis, so it really becomes a dilemma in a primary care setting to identify who needs a referral to a rheumatologist and who doesn't. So, that's where the interplay of serology comes in, family history comes in, and certain diagnostic modalities like ultrasound may play a role but, obviously, all of that needs to be in the hands of a

rheumatologist and, if there isn't that recognition of early symptoms, then patients aren't going to present until clinically manifest arthritis.

Dr. Birnholz:
Right, and I think you're pointing towards my next question which comes back to the idea of an important point you made, which was the look back to be able to get a sense of the diagnosis. That looking back can often be a very long period and you've talked about this before but can you talk us through why there's such a long delay between the onset of symptoms and the eventual diagnosis? What plays into that?

Dr. Dikranian:
So, I think, rheumatologists well recognize that there are different patterns to the presentation of rheumatoid arthritis. Certain patients will say I remember the exact day that my symptoms started, and others may have more of a vague answer to meandering symptoms that come on over weeks and months. There seems to be different patterns with no different phenotypic variations that we can identify as of yet. So, some patients may have palindromic symptoms that may manifest over weeks and months and many others might have other confounding factors such as osteoarthritis or life changes, hormonal changes during menopause obviously may play a role, so that becomes a little bit difficult to tease out. But, the long delay, I think, is because of basically our stressful lifestyles. Much of that stress manifests as musculoskeletal problems and it is difficult, again, to tease out which of those become important in terms of an inflammatory arthritis and which don't. So, that's where the role of early serology might come into play, inflammatory markers that a primary care physician might check, and/or getting a proper history to see if there is a family history of other risk factors such as smoking and periodontal disease, et cetera, that might trigger that switch to inflammatory arthritis.

Dr. Birnholz:
Yeah, of course. I think you're also leading towards a potential call to action here which is looking for ways in which we can better coordinate care for patients so that we can reduce that time to a diagnosis.

Dr. Dikranian:
Yeah, that's a difficult decision or difficult proposition because, again, there's a lot more benign arthralgias out there and so we really leave it up to people to recognize that aches and pains, especially as people get older, aren't just sort of a normal process of getting older and they need to be brought to attention. Our primary care colleagues need to recognize and try to differentiate inflammatory from non-inflammatory arthritis. Once people get to the rheumatologist, I think we do a pretty good job in terms of identifying early rheumatoid arthritis. Unfortunately, the results from previous attempts at preventing rheumatoid arthritis in at-risk individuals haven't really been born out. So, we know, even as early as about two decades ago, there was a Dutch study looking at treating patients who are at-risk, not because of symptoms, but trying to ward off the diagnosis of rheumatoid arthritis by, for example, giving two dexamethasone injections within six weeks and what that did in these ACPA-positive patients, it reduced their titers but it didn't delay the onset of inflammatory arthritis as compared to placebo. There have been other studies just to see if there's an opportunity there to ward off, and the results have been fairly negative for the most part. Much of that probably has to do with looking at a heterogeneous population as opposed to homogeneous, again, defining that preclinical phase into is the autoantibody positive phase? Is it the early pre-symptomatic phase where patients just have symptoms but no objective findings yet? So, if we can hone in on the specific subgroup there might be an opportunity there to test a various strategy to, again, prevent the onset of inflammatory arthritis.

Dr. Birnholz:
And it also sounds like there's another underlying message here. You said get to the rheumatologist and that is a gap at some points. And even the risk of higher false-positives coming from the primary care side, it sounds like that needs to come down to get patients to the rheumatologist a little bit earlier and be able to shorten that gap in diagnosis.

Dr. Dikranian:
It sure is and this is obviously a worldwide problem that we know there's a rheumatology shortage and some of that just needs to be our own focus on how do we triage patients in terms of who gets in. So, if there are ways to identify patients who are likely to have inflammatory arthritis and give them the benefit of earlier referrals and earlier consultations. This is not just a U.S. problem but around the world where people don't always have the access to rheumatologists that they need. So, you are absolutely right that we need a sort of a composite risk score based on either symptoms, based on serology, or based on other findings that can get patients into the rheumatologist, again, quicker based on those risk factors.

Dr. Birnholz:
Dr. Dikranian, I could keep you here for another hour, but I want to spare you the continued trauma. Dr. Dikranian, I really want to thank you for your time. It's been great talking with you. I hope to speak with you again.

Dr. Dikranian:
Thank you. I appreciate it.

Announcer:
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