Antisynthetase Syndrome

A Clinical and Research Perspective

Rare Genomics Institute and RareShare

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B5330B-071014
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Based primarily on an Ask the Expert podcast with Dr Fredrick Miller (NIEHS, NIH), Dr Lisa Christopher-Stine (John Hopkins School of Medicine) and Dr Jimmy Lin (RGI/RareShare), on 24 February 2015. We would like to thank the panelists for their participation.

Dr. Fredrick Miller

MD, PhD

Dr Miller is the Chief of the Environmental Autoimmunity Group in the National Institute of Environmental Health Sciences at the NIH in Maryland. Dr Miller's work in the field of autoimmune diseases spans three decades and involves many aspects of the environmental risk factors, epidemiology, immunology, genetics, pathogenesis, evaluation and treatment of immune-mediated diseases. He has focused much of his work on autoimmune muscle diseases. He is leading a number of studies to identify environmental and genetic risk factors for autoimmunity and systemic autoimmune diseases. The focus of his research is on investigations of risk factors for and the pathogenesis of systemic autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and inflammatory muscle diseases (myositis).

Dr. Christopher-Stine is currently co-director of the Johns Hopkins Myositis Center and assistant professor of Medicine and Neurology. Dr. Christopher-Stine's primary research focus is clinical research pertaining to inflammatory myopathies, specifically unique phenotypes, novel therapeutic approaches, and novel disease subsets among patients with inflammatory myopathies. Dr. Christopher-Stine and her team are currently investigating the burden of calcinosis in adult dermatomyositis by patient self-report. Specifically, Dr. Christopher-Stine and her team are undertaking an international effort to determine the most appropriate patient-driven outcome measures in inflammatory myopathies.

Dr. Lisa Christopher-Stine

MD, MPH

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Quick Facts on LGLL

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Antisynthetase syndrome is a rare inflammatory muscle disease with various clinical features.

The most widely-used definition for Antisynthetase syndrome is characterized by the antibodies targeted.

Common antibodies include anti-Jo-1.

Less common antibodies such as anti-KS and anti-HA are not targeted in all patients.

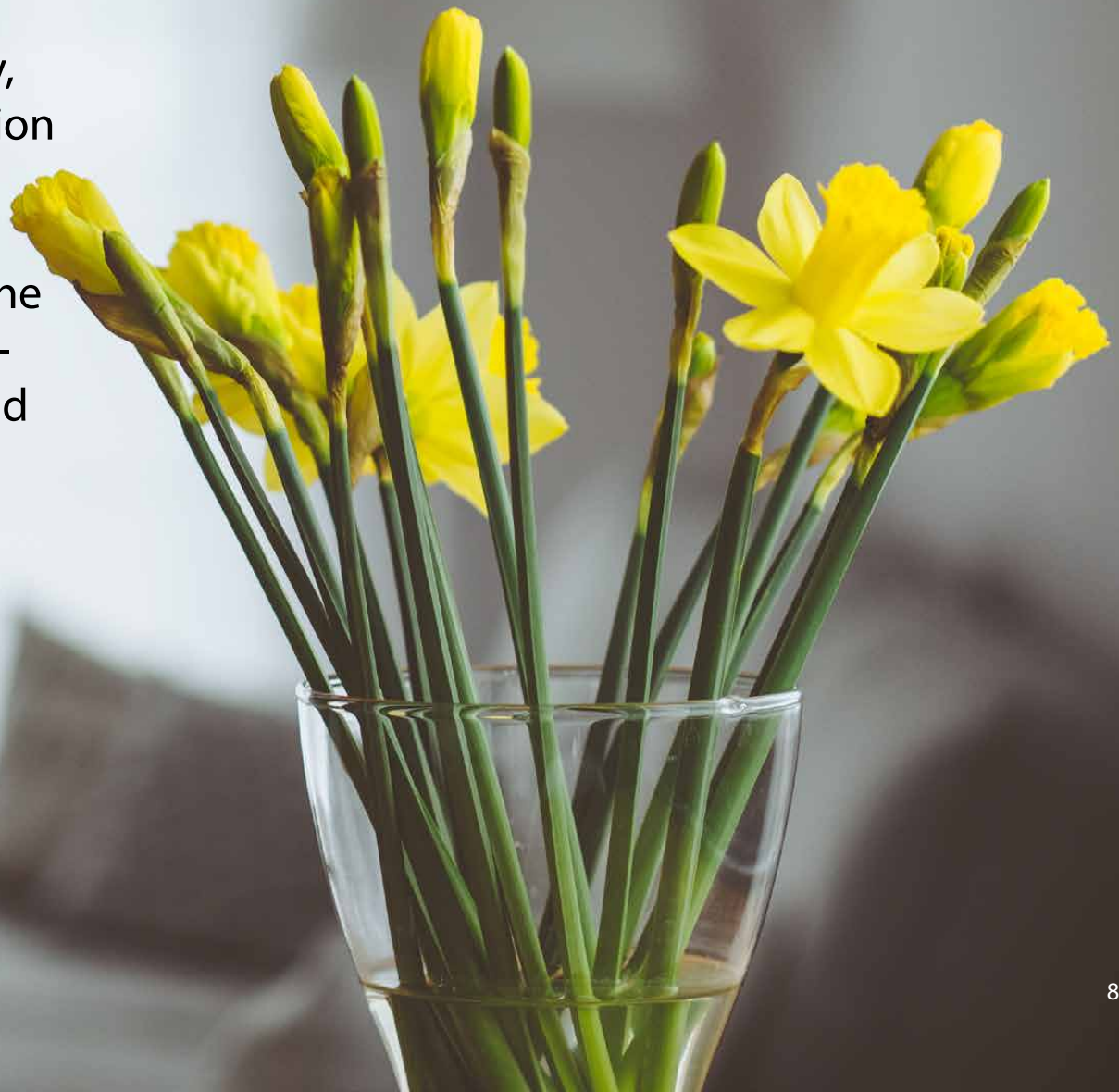
Connection to other conditions

Antisynthetase syndrome (AS) may be connected with other clinical conditions, such as interstitial lung disease and myositis. Mechanic's hands, a condition which consists of cracking and scaling of the fingers, as well as Raynaud's phenomenon, in which the hands can change colors in the cold or with emotional distress, are also conditions that AS patients can express. Not all patients develop these symptoms and conditions at the same time; about a third of patients develop myositis and other symptoms before the lung disease, a third develop all these symptoms at the same time, and another third develop the lung disease before the myositis and other symptoms. The different antibodies targeted may have an effect on the likelihood of developing other symptoms along with the lung disease. For example, AS patients with the attacked Jo-1 antibody tend to have more muscle disease, myositis, mechanic's hands and arthralgias, joint pains or arthritis, and inflammation of the joints.

Relationships between Antisynthetase syndrome and other diseases, such as fibromyalgia, are currently still being studied.

Diagnosis

There are several ways to diagnose Antisynthetase syndrome, including lung or muscle biopsy, CT scan of the chest, lung function tests, electromyography (EMG), and evaluations of swallowing difficulties and aspiration risk. The specific diagnosis procedure depends on the clinical context and the individual patient.



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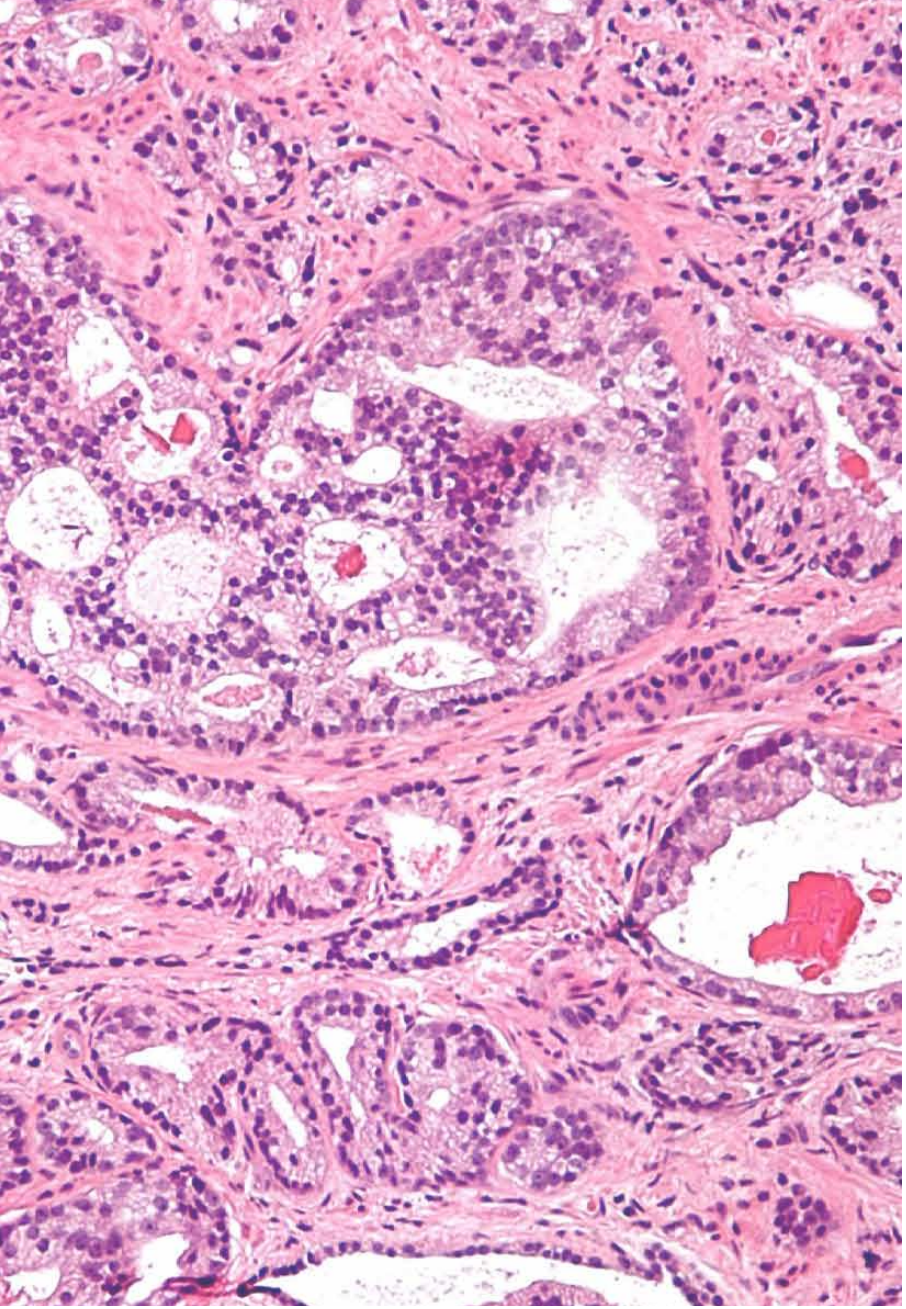
Possible Risk Factors

The causes of Antisynthetase syndrome are unclear, and is currently an area of study. A combination of genetic and environmental risk factors may result in the disease. Smoking may be a risk factor in individuals with certain genetic backgrounds. A major genetic risk factor, particularly in Caucasians, is the HLA-8.1 haplotype. The HLA (human leukocyte antigen) genes are responsible for immune responses to different environmental agents. Other possible risk factors include regular exposure to dust, certain gases, or fumes.

Current Studies

There are various studies being conducted through the NIH. A current study called the **Myo-Risk** study investigates potential risk factors by comparing Antisynthetase patients with other myositis patients and healthy controls. Interested participants can call the recruitment office at 1-800-411-1222.



Common Signs & Symptoms

Signs and symptoms for Antisynthetase syndrome vary over time and depend on the individual. The main symptoms of Antisynthetase syndrome include fever, myositis, polyarthritis, interstitial lung disease, Mechanic's hands, and Raynaud's phenomenon.

Inflammation

One of the chronic symptoms associated with Antisynthetase syndrome is inflammation. Generally, inflammation in myositis syndromes tend to leave damage, scarring or fibrosis involving different organ systems. For example, the skin may be affected in the presence of dermatomyositis, as well as the lungs, muscles, and joints. Thus, early diagnosis is key to controlling your symptoms. Antisynthetase patients may take anti-inflammatory drugs, even during remission, to keep inflammation under control.

Current Treatments

The traditional approach for all myositis syndromes is to start with steroids, but one of the changes in the approach is to be more aggressive early on in the diagnosis. This would mean adding additional medications from the very beginning of the disease. Traditional medications include methotrexate, mycophenolate cyclosporine, tacrolimus and IV Cytoxan, especially when there's lung involvement.

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New Treatments

There are a variety of studies regarding potential treatments for Anti-synthetase syndrome that have demonstrated promising results.

Studies have shown that **rituximab**, an intravenous drug, can be effective in treating myositis and Antisynthetase syndrome. For more information, visit http://www.ncbi.nlm.nih.gov/pubmed/25740830.

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IVIg is another promising therapy which is being studied by Japanese investigators—the intravenous blood product can be added as an adjunctive therapy to other immunosuppressants. For more information, visit http://www.arthritis-research.com/content/15/5/R149.

There has also been success with **tacrolimus**, another immunosuppressant that may treat antisynthetase.

Other novel treatments include **autologous stem cell treatment**. It takes the patient's bone marrow stem cells or the peripheral blood, in essence wiping out the immune system, then returning them back to the body to reset the immuno-stat. This treatment is highly risky and has resulted in death due to infections and other complications. However, there have been a few cases where the patient has gone into remission after the treatment. **Dr. Richard Burt** is conducting an ongoing study about stem cells in myositis at Northwestern University in Chicago.

Dr. Jerry Mendell in Columbus, Ohio is studying the use of gene therapy on a protein called **follistatin** that inhibits the function of a protein called myostatin that tends to block muscle growth in inclusion body myositis. By blocking the inhibitors of muscle growth, muscles can regrow, reform and increase its function in the patients.

For more novel treatments, visit www.-clinicaltrials.gov

Q: Could an AS patient stay in remission indefinitely?

A: There have been Antisynthetase patients that have gone into full remission. There has been reversal and sometimes full remission in patients with severe muscle or lung disease. There are generally two categories in remission: remission on medication and remission without medication, with the former meaning there are no evident clinical symptoms. It requires immunosuppressant medications and sometimes lifelong medications. However, there is the unlikely occasion where patients can get off all immunosuppressants.

Q: What factors could cause a patient to come out of remission?

A: This disease like many others, involves some trauma or insult to the immune system so something as simple as a viral illness, common cold or surgery may trip the immune system and take people out of a remissive state. Another potential factor is the length you were in remission. Often, the longer you are in remission, the longer you are likely to stay in remission. The reality is that autoimmune diseases undulate. You can have the disease quiet for a long time and for unclear reasons, it flares. Patients often blame themselves or try to figure out a trigger, but there is no discernable trigger and it's due to how the disease is patterned.

Muscle Loss

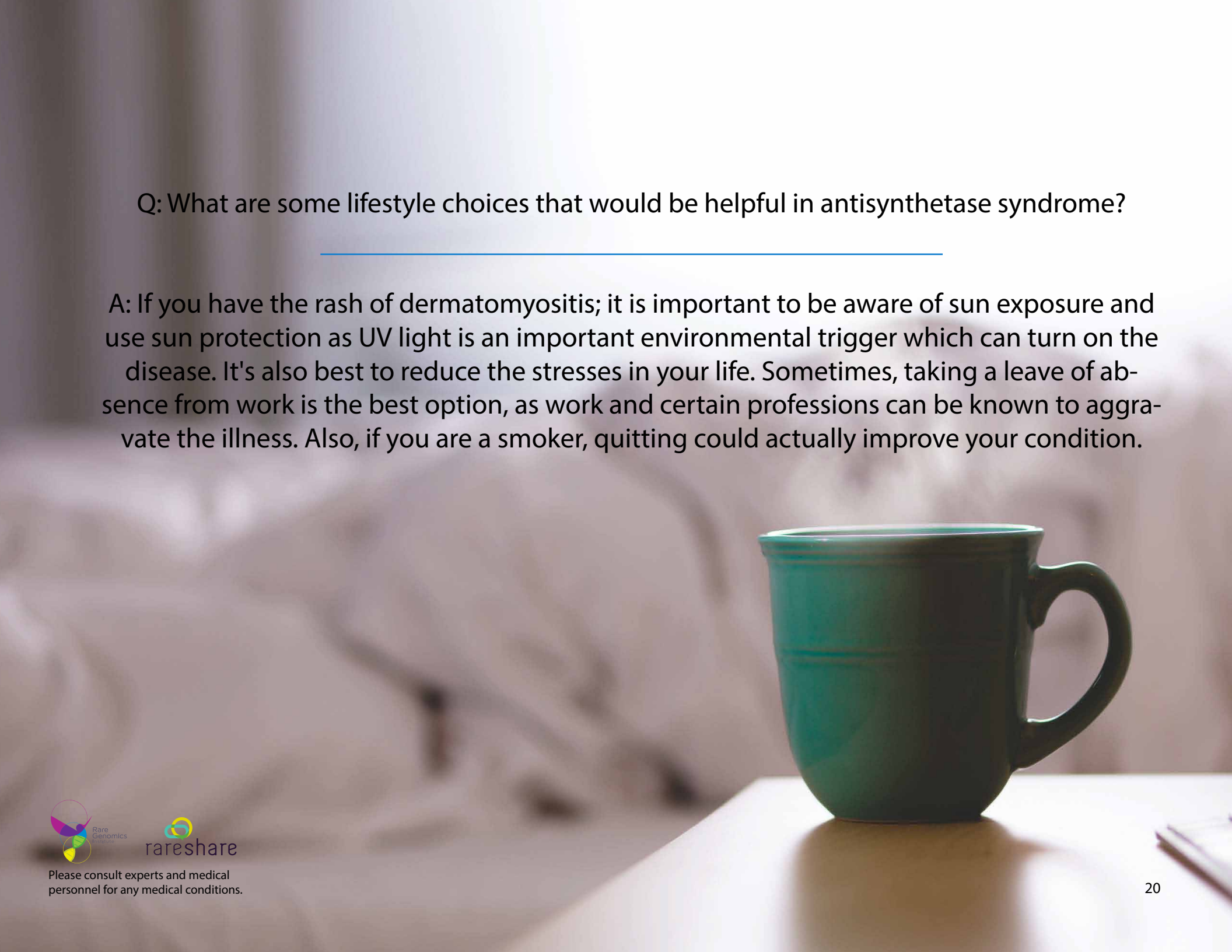
There are two categories of muscle loss. In some cases, the muscles appear to have shrunk as a result of having an atrophic muscle due to inflammation. Sometimes, patients have muscles of normal size with fatty infiltration or fatty replacement. This occurs when a damaged muscle is replaced by fat as a chronic consequence of chronic inflammation. It is the current thinking that muscle cells are terminal when they are dead and dies individually, also called necrosis. When the muscle cell dies, it doesn't regenerate.

Q: How do you help with muscle loss and muscle wasting?

A: Looking from a more macroscopic standpoint, it is possible for patients to increase their muscle bulk again. Some of scientists in Sweden have shown that exercise is absolutely suggested as long as there is no other contradiction or reason a doctor has said not to exercise. It's indicated for this disease, at least after the acute phase, but sometimes it's very difficult to exercise when the patient is first at the onset of the disease. Scientific literature bears out that with time and use, you can build muscle by bulking up muscles that aren't completely dead and also recruiting other healthy muscle to step in.

Q: What are some lifestyle choices that would be helpful in antisynthetase syndrome?

A: If you have the rash of dermatomyositis; it is important to be aware of sun exposure and use sun protection as UV light is an important environmental trigger which can turn on the disease. It's also best to reduce the stresses in your life. Sometimes, taking a leave of absence from work is the best option, as work and certain professions can be known to aggravate the illness. Also, if you are a smoker, quitting could actually improve your condition.



Diet and Lifestyle

In general, get plenty of rest, drink a lot of water and maintain a neutral body weight. Being overweight can cause pain in the joints and place a huge burden on the body (especially for patients with myositis). In order to maintain a healthy weight, it's crucial to exercise and eat well, which entails decreasing your sugar content. In addition, maintain a healthy blood pressure and enhance or develop close personal relationships.

Q: What kind of diet is optimal for antisynthetase patients?

A diet that is low in fat and sugar, such as a Mediterranean type diet is optimal.

Miscellaneous Q&A

Q: What is the change life expectancy for patients with the disease?

A: Several studies in the past have suggested that this syndrome results in a shorter life expectancy than other types of myositis; these studies relate to information collected about 30 years ago when people weren't as good in diagnosing and treating these diseases. There has not been any recent information that has allowed people to expound upon or make the number more accurate.

Q: How may taking medication affect patients with the disease?

A: Medications have potential side effects, such as blocking down the immune system. They can increase the risk of infections and other problems as well, so we have to think about the pros and cons of all the approaches that we take, and do what is beneficial in the long run.

This e-book was written and compiled by the scientific Rare Genomics team at Marc Garneau Collegiate Institute in Toronto, Canada.

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