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An Invisible Epidemic: The Significance, Challenges, and Science of Autoimmune Neuropathy

Anna Harrison

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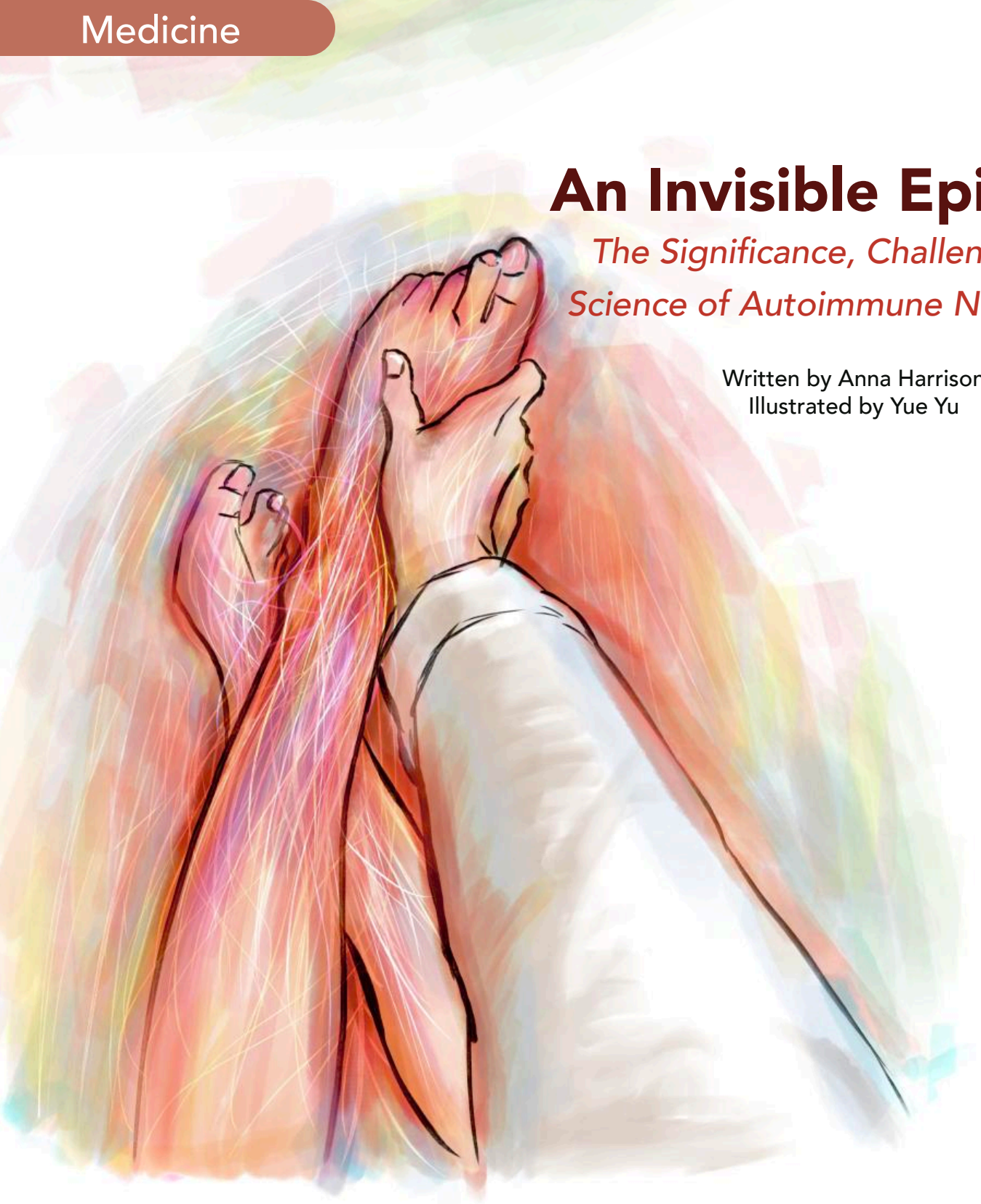
The Significance, Challenges, and Science of Autoimmune Neuropathy

Written by Anna Harrison
Illustrated by Yue Yu



Autoimmune neuropathies are a class of disorders that encompass a variety of conditions where an individual's immune system attacks the peripheral nervous system. Often responsible for the propagation of chronic symptoms including fatigue, nausea, and chronic pain, autoimmune neuropathy is an increasingly important area of research. Despite the pressing need for further research on this topic, scientific knowledge on this class of disorders remains largely unknown. A few disorders have known initial triggers and modes of pathogenesis that have been well-defined but most remain a mystery. As a result of this void in autoimmune neuropathy research, public awareness is lacking, pharmaceutical development is stunted, and patients are left in vulnerable positions with few treatment options and very little information about their conditions or, for that matter, validation of their pain.

It is extremely common for neuropathy to occur on small nerve fibers, part of the sensory and autonomic nervous system. In fact, a recent meta-analysis study concluded that small-fiber neuropathy underlies about half of the illnesses labeled as fibromyalgia, which affects 2-5% of the global population. While certain large-

fiber neuropathies such as chronic inflammatory demyelinating polyneuropathy can cause permanent damage, small-nerve fibers regenerate throughout life, so patients who receive proper care have a high likelihood of recovering completely. Symptoms can include reduced tactile sensation, hypersensitivity to tactile stimuli, poor balance (sensory ataxia), burning sensations, abnormal blood pressure and heart rate, and gastrointestinal dysfunction. In fact, neuropathy is the underlying cause of many cases of irritable bowel syndrome.

This article will review the current research methods utilized in studying autoimmune neuropathy and the barriers that researchers face in understanding the pathology of this class of disorders and creating safer treatment alternatives.

Neuropathy is the damage or death of nerves in the peripheral nervous system which includes nerves outside of the brain and spinal cord. Two main types of peripheral neurons include motor neurons that are in charge of movement and sensory neurons which sense and communicate stimuli and regulate bodily functions. Autoimmune neuropathy begins with a number of different initial inflammatory triggers such as diabetes, injury, infection, toxin exposure, or molecular mimicry. Molecular mimicry, or the overlap in reactivity between a foreign epitope and self-tissue, has been implicated in some autoimmune neuropathies, particularly from human papillomavirus. Regardless of the trigger, an unknown neuroinflammatory mechanism is activated where the immune cells mount an attack on part of the nerve fibers. Researchers are interested in understanding this unknown mechanism since it is a crucial piece needed to develop better diagnostics and treatments for autoimmune neuropathies.

One way in which scientists examine this unknown mechanism is through the use of model organisms. Rodent models are often used to study immune modulated pain or neuropathic conditions because of the ability to transfer disease through passive transfer, a technique in which a patient's immune components are transferred to a rodent in order to further study the specific disease. For example, researchers like Anne Louise Oaklander at Massachusetts General Hospital are able to study suspected autoimmune small-fiber neuropathy in rodent models. A sample containing a small-fiber neuropathy patient's immune components is passively transferred to mice or rats through a series of intraperitoneal injections. The goal of this passive transfer is to give healthy mice the autoreactive cells or other components that propagate the disease. Some researchers use serum, which includes all immune cells, proteins, hormones, and other non-red blood cell blood components while others use plasma, which is serum with the addition of an anticoagulant. Most commonly, however, immunoglobulin G antibodies are extracted from the serum and used for passive transfer to demonstrate the role of autoantibodies in pathogenesis.

Antibodies are proteins secreted by B-lymphocytes that bind to foreign targets and mark them for degradation by the immune system. When antibodies become autoreactive, they bind to our tissue and mark them for destruction by the immune system. Immunoglobulin G antibodies account for about 75% of all circulating antibodies. While there are a number of differences between human and mouse immune systems and care must be taken in performing these procedures, successful transfer of immunoglobulin G has been demonstrated.

A number of different assays are used to detect the sensitive changes that occur in small fiber neuropathy. The most common of which are behavioral tests that measure responses to physical stimuli to determine the threshold at which the rodents feel pain. When neuropathy is present, this threshold will either significantly increase (hypersensitive) or decrease (hyposensitive). The Hargreaves test and cold-water tail-flick are common methods to assess thermal pain. The Von Frey test is a classic measure of tactile stimuli used to calculate the mechanical withdrawal threshold via a range of blunt forces applied to the rodent's paw.

While these behavioral tests have been performed successfully hundreds of times and provide valuable insights in many painful conditions, as biotechnology advances the utility and robustness of the assays are called into question. A closer look at the literature shows a significant amount of variability in the data. Furthermore, assays often fail to reach statistical significance even when post-mortem pathological studies prove the presence of disease. For example, Dawes et. al demonstrate the presence of autoantibodies in a hypersensitive neuropathic pain model through immunohistochemistry, yet many of their behavioral pain assays lack statistically significant results. Several studies have been published demonstrating the vulnerability of mice to changes in their pain thresholds from a number of variables including things as simple as the color of the researcher's shirt.

Alternatives to behavioral assessments for pain or sensory neuropathy include electrocardiograms and electrophysiology studies to quantify changes in heart rate as well as transit studies to assess GI motility (both commonly affected by an autonomic neuropathy). Rodent plasma can also be analyzed for the levels of various inflammatory markers, and immunohistochemistry can be conducted to stain tissues with nerve damage. Recently, a study on acute painful neuropathy labeled patients' own antibodies and used them to immunostain small and larger fiber tissue to see if there was a response. Nerve density readings can also be done and are currently the standard objective clinical diagnostic measure of small fiber neuropathy.

While researchers are working diligently to create new methods to assess pain, challenges arise due to the high number of sub-categories and variable clinical presentations of autoimmune neuropathies. While they have clear pathologic distinctions, it becomes difficult to talk about these conditions when few doctors and researchers are familiar with the different variations of autoimmune neuropathy and the symptoms it can cause beyond the classic distal nerve pain and erythromelalgia.

Another barrier to studying autoimmune neuropathy is the specific population impacted. Individuals experiencing chronic pain, fatigue, and fibromyalgia are more likely to be female and/or reliant on pain medications like opioids. While searching for a solution to an unrelenting pain, far too often patients are denounced and labeled as hysterical or chronic complainers. Without the proper scientific evidence and the gender and social hierarchy present in medicine, the medical community has failed to acknowledge or provide for these patients, which perpetuates the challenge of research funding. Empowering this population of patients, bringing this issue to the attention of doctors, and changing the chronic-condition dialogue could be the first step towards forging change in this field.

Despite the tremendous national burden of chronic pain, fatigue, and fibromyalgia, funding for these autoimmune neuropathy disorders still remains low, and research for a new-generation global problem appears to be stuck in past generations. Increasing public awareness about autoimmune neuropathies and challenging the misogynistic dialogue about "chronic complainers" could be the first step in forging the way for advancements in autoimmune neuropathy research. • • •