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## Rare and undiagnosed: Daunting challenges for patients, doctors, and researchers alike

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### Abstract

This personal narrative identifies several challenges for patients, doctors, and researchers posed by rare illnesses and difficult to diagnose/long-term undiagnosed patients. In it, I describe several observations on my experiences as a long-time undiagnosed patient and now as one with multiple rare conditions. Rare conditions are all too often missed in diagnosis or dismissed, and treatment is often significantly delayed, such as it was in my case for nearly two years. Adding rare symptoms into the mix makes the challenges of diagnosis and treatment even greater, and I had some extremely rare symptoms. The only way I was able to identify my symptoms as being associated with my suspected diagnosis was by researching assiduously until I finally found a one-off case study describing two women with the same symptoms and with a diagnosis akin to the one my doctor was considering for me. I was able to rely on this case study; but when we consider that many medical practitioners, even medical specialists, don't submit research papers for publication, it is clear there are holes in the reporting system when it comes to rare conditions. My neurologist, for example, does not publish, and so my case study is not in the medical literature. There need to be outlets for posting of such anomalies as I experienced if rare illnesses and rare conditions are to be fully documented in the literature.

### Keywords

Patient experience, patient-centered care, quality of life, continuum of care, undiagnosed illnesses, rare illnesses, Loeys-Dietz Syndrome, cerebrospinal fluid leaks, system change, medical research

### Background

Rare illnesses and undiagnosed illnesses are closely intertwined challenges faced by patients and by the medical community. Many times, undiagnosed illnesses remain undiagnosed for longer than they should because of the rareness of the underlying disorder and the accompanying lack of knowledge in the medical community. No one can know all potential symptoms of all rare illnesses—with apologies to Dr. Gregory House. Additionally, the symptoms themselves may not be among the mainstream of symptoms associated with a particular rare illness—in other words, the symptoms themselves may be rare. Rare symptoms of a rare illness—a difficult combo to face.

As a patient having lived through an extended period of being undiagnosed (technically my entire life up to age 57) and now dealing with the way that the medical system grapples with my rare diagnoses, I have been able to make some observations on the system and on how doctors and researchers can adjust their practice to meet these challenges. As a researcher, though not a medical researcher, I have been able to note some of the reasons why doctors may not respond appropriately to a rare or undiagnosed illness, even when basing their practice on the prevailing literature. Drawing these two perspectives

together, I make what I hope are useful suggestions for practitioners and for researchers alike.

### A sudden injury from an innocent, everyday movement

One day a few months ago, while sitting on my bed, I realized my cell phone was just behind me on the bed. Reaching for my cell phone the way I did should not usually have landed a devastating blow to my shoulder. But this reach did. A grade 3/high grade tear of the supraspinatus tendon. Over .6 mm both long and wide at .9 mm by 1 cm, it ranks as grade 3, the highest grade according to a common measure, the Ellman scale<sup>1</sup> and at over 50% torn through the tendon, it was labelled “high grade” on my ultrasound report. I heard a loud pop at the time I made the movement and felt a shearing pain in my shoulder and throughout my arm that I despair will not be easy to remedy in the long term. “Here I am,” thought I, “suffering with COVID-induced pneumonia, a transient peripheral vision loss, and a series of urethral infections—now this.” Whatever *this* was.

Since that incident, which still causes me considerable pain and for which I have begun physiotherapy, but may have to consider surgery, I have needed to read about my condition in greater depth to understand how this could

happen to me. My condition being Loeys-Dietz Syndrome (LDS), that is, the diagnosis that I gained in the past couple years. In doing more research on it since my reaching incident, I've come upon people in the hypermobility disorders chat rooms who have described similar experiences, such as tearing a tendon when simply making their bed or having to have surgery after stumbling slightly and reaching out to stabilize themselves. The medical literature explains that, as we age, those of us who have LDS and similar hypermobility conditions end up with greater brittleness of the connective tissue, such as tendons, after a lifetime of stretchiness.<sup>2</sup> Where others might experience a strain or a sprain, or not have any issue at all, we are more likely to dislocate a joint or tear a tendon. A doctor at the emergency department, however, dismissed the likelihood of a tear in my case because of the nature of the incident and because he doubted that tears could come from such actions—strains or sprains were much more likely. He gave this diagnosis despite the depth of the pain in my shoulder and the limitations of movement I had lived with for three months before I finally went to the emergency department when the pain suddenly got considerably worse.

### **A surprising approach from my general practitioner**

When I eventually saw my general practitioner for the pain in my shoulder, she did two unusual things. She told me not to do physiotherapy until we got some tests done and were sure what we were dealing with. And she sent me for an ultrasound, even though an x-ray showed nothing unusual. Why is this so remarkable? Well, remember, all I had done was reach back a little behind me. I had not picked up anything, just reached, when the popping noise and searing pain ensued. What my GP did was tailor her usual response to my rare illness. Now I don't expect my GP to research my condition and know all the medical literature on it. Most doctors I encounter have never even heard of LDS. But she has understood the key elements of my disorder and has been willing to use caution where usual practice would not bother with additional tests or precautions. In the end, my little reaching incident turned out to be fairly severe, as tendon injuries go, so she was right in her approach. In addition to the complex, high grade tear, my ultrasound also showed a spate of issues typical of hypermobility illnesses – calcifications in the subscapularis tendon, a thickened bursa, and tendinosis in the infraspinatus tendon.

It is not surprising that most doctors would not recognise my diagnosis. LDS is a relatively recently described (2005), very rare condition, similar to some types of Ehlers-Danlos Syndrome or Marfans, both hypermobility conditions, but LDS also tends to be associated with aortic and vascular weaknesses and tortuosity.<sup>3</sup> In keeping with my diagnosis, I have developed in recent years an aortic

aneurism and tests have shown vascular tortuosity (twisted arteries), along with the hypermobility and other signs of LDS.

The above incident, tearing a tendon while reaching, just adds to all the other connective tissue-related issues I have experienced over the course of my life, while not knowing why these happened to me. In another edition of this same journal,<sup>4</sup> I have published an account of my journey through the tormenting uncertainty of being undiagnosed, despite debilitating symptoms. In the end, the cerebrospinal fluid (CSF) leak that I was diagnosed with responded to treatment. The Epidural Blood Patch (EBP) that I underwent allowed me to return to most of my daily activities, including, eventually, a very hectic job. This CSF leak was due to a weakness/hole in the dura mater, one of the tissues that apparently can be affected by connective tissue disorders.<sup>5</sup>

I have had a wide variety of connective tissue problems throughout my life, starting with a strangulated inguinal hernia at the age of five and including such issues as a recurrent urethral stricture, repaired several times by surgery, and a hip replacement after a seemingly innocent fall on an icy sidewalk that caused a severely torn labrum, described in the MRI report as “severely shredded.” A fuller list of medical conditions I have had—related to connective tissue issues or not—would include a sliding hiatus hernia, the previously mentioned aortic aneurism, flat feet and plantar fasciitis, costochondritis, environmental allergies, myopia, peripheral neuropathy, shin splints, slow-to-heal scars, breathing problems, recurrent bronchitis and pneumonia, crepitus, a tectal lipoma, pre-cancerous skin lesions, generalized staphylococcus aureus infections, hypermobile joints, osteoarthritis in most of my joints, Monoclonal Gammopathy of Unknown Significance (MGUS), temporomandibular joint issues, Irritable Bowel Syndrome, essential tremor, sleep apnea, and mitral valve prolapse. And, of course, there's the tendon tear and the CSF leak to boot. Some of these conditions have been documented in the literature as being “associated with” connective tissue disorders. It will be a while until causal associations attributable specifically to Loeys-Dietz will be fully documented. Even many of the conditions that, hypothetically, would lend themselves to association with connective tissue disorders, may not have been adequately documented as such at this time. For example, the prevalence of a urethral stricture does not seem to have been documented in relation to connective tissue illnesses, despite the urethra having a significant sheath of connective tissue as part of its make up.

This lack of documentation of the associations between rare diagnoses and various conditions needs to be rectified in the coming years. The best place to start would seem to be to continue researching conditions that may be

associated with connective tissues, but the list of connective tissues in the body is extensive, as it covers even cartilage, bone, and blood, among many other tissues in the body.

One of the challenges that the patient with rare illnesses has to face is that many conditions are considered “benign” even though there are documented cases of not-so-benign symptoms. For example, I have an observable brain “tumour” called a benign tectal lipoma. It is not cancerous, so benign in that sense, but 20% of these tectal lipomas cause symptoms that can be challenging or even serious, such as seizures.<sup>6</sup> Yet, the neurologist who first observed my lipoma dismissed it and did not even share with me its existence. I read about it on a subsequent MRI report, some 10 years later, at a time when I was dealing with some serious conditions and was looking for a reason for a spate of debilitating symptoms. My MGUS is also dismissed as benign, although, again, 20% of cases can exhibit symptoms, including peripheral neuropathy,<sup>7</sup> which I do experience, and which is dismissed as of unknown origin in my case. Documenting fully the association of uncommon symptoms with medical conditions is an important first step to ensuring that doctors dealing with rare conditions can understand what may be going on with these patients.

### **The importance of publishing anomalous case study reports in medical journals**

It is also for this reason that researchers/practitioners need to continue to document one-off cases and anomalies, particularly unusual symptoms. This kind of reporting in the literature provided me and my neurologist with valuable information at a crucial time in my search for a diagnosis a few years ago. While my family and I were struggling with my undiagnosed dark night of the soul that was a CSF leak, I did as much research as I could. Barely able to sit up most of the time and only gaining some relief by lying flat on my back, classic symptoms of a CSF Leak, I researched mostly by scrolling through medical literature on my phone. When I would find interesting literature, usually about rare disorders that exhibited my symptoms, or at least some of them, I would spend whatever time my leak would spare me to read parts of these studies.

At one point, having through a remarkable stroke of luck discovered the concept of Spontaneous Intracranial Hypotension, which is related to CSF leaks, I was referred to a neurologist who had dealt with CSF leaks before. He was willing to treat me as having a leak but expected he might get pushback from others in the medical profession because of my strange set of symptoms, many of which were not typical of CSF leaks. As part of my suite of symptoms during this time, I experienced the following: severe orthostatic headaches, neck and intrascapular pain, tinnitus, nausea, vomiting, dysphagia, stuttering, slurring,

photophobia, fatigue, motor and vocal tics, mental slowness, searching for words, numbness in the right cheek, balance problems causing falls, and phonophobia. I managed, through assiduous research, to find literature that showed the association between leakers and nearly all of my conditions. However, the vocal and motor tics were a particular anomaly that evaded my research for the longest time. Finally, one day, as I lay on the couch researching on my phone, I called out to my wife. What I had found was a report of two women in Italy—just two women—a one-off report in the medical literature of two women with a CSF leak who exhibited exactly the vocal and motor tics I had been plagued with for so many months.<sup>8</sup>

The connection became real in that moment. Finding this report helped to solidify the course of my treatment; it meant in particular that I was able to bring some medical literature when I would go for more tests and use it when I was greeted by a medical professional skeptical of my having a CSF leak. It was extremely useful when I went for my ultimate—and ultimately successful—treatment, the EBP mentioned above. The interventional anaesthesiologist who was to perform the procedure began with a skeptical and dissuasive speech about why the procedure was probably not warranted in my case, but after reviewing my neurologist’s notes, which included the literature references, he relented and performed what I can only describe as a miraculous cure. My symptoms disappeared, instantly. Only one of the symptoms, tinnitus, has since returned. I had awoken, as I described in my other article,<sup>4</sup> from a true nightmare of uncertainty and pain.

The role that these one-off reports (case studies) in the medical literature can play is life changing. The researcher and the practitioner alike need to remember that, as you deal with rare illnesses, you may also be dealing with rare symptoms and anomalous situations. My neurologist was a practitioner, but not a publishing researcher. As a result, my anomalous symptoms went undocumented. There has been no published case study of my rare symptoms. How many other leakers with motor and vocal tics have gone unwritten about? One documented case may represent many more undocumented ones.

Sometimes, in research, exceptional cases can be truly instructive. Oliver Sacks made a literary career of writing about the anomalies.<sup>9</sup> Note that all the physiological changes attributable to CSF leaks have barely begun to be mapped in the literature. Knowing that some cases can involve rather significant vocal and motor tics could help to complete the mapping of how CSF leaks, and in particular the brain slump that often accompanies it,<sup>10</sup> can affect the brain. After my EBP “cure,” I needed to undergo a ten-week program in work hardening/brain retraining, attesting to the extent that this condition can impact brain function. It was a struggle to return to work,

but now I am back fully and consider myself a valued part of a highly contributing group in a high paced operational environment. And I am loving every minute of my extremely challenging and fast-paced workdays.

## Conclusion

In all this, I consider myself extremely lucky. My family has been supportive and with their support I have been able to cultivate a positive outlook even through the worst of times. My family, my friends, and my doctors have had patience and have adjusted their usual approaches to my particular rare illness. But so many people with undiagnosed illnesses continue to suffer, much longer than I did, or without any answer through their entire life. I cannot imagine the pain and uncertainty they endure. And so many people with rare illnesses do not receive the accommodations in their treatment that they so desperately need. They do not receive the precautions added to their treatment plan, the extra tests to ensure we know that, however improbable when considered from a usual diagnostic perspective, the worst has not happened. And they do not receive a willingness on the part of their doctors to push for treatment when it is not supported by the predominance of evidence in the literature.

As one of the building blocks of a better approach to undiagnosed patients, research in the area of rare illnesses needs to be tailored to the exception, the anomaly. It needs to include the one-off case study. I am encouraged that networks focusing on rare diseases have been set up in such a way as to exchange information/solicit potential diagnoses from doctors.<sup>11</sup> This process could be supplemented with surveys of non-publishing medical practitioners who work in particular fields, such as neurology, soliciting atypical symptoms observed in patients who have been shown to have rare illnesses. Large, random, double-blind studies may be the gold standard for research in general, but describing the one-offs, the anomalies, needs to be standard in rare illness research reporting.

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