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Tertiary care centres must do more for patients with unknown conditions: Lessons learned from a child

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Cover Page Footnote
We thank the patient and her parents for their detailed editing of the manuscript.

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Personal Narrative

Tertiary care centres must do more for patients with unknown conditions: Lessons learned from a child

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Abstract
Postural Orthostatic Tachycardia Syndrome (POTS) is a debilitating disease with a commonly non-uniform and unspecific presentation that makes diagnosis difficult. A twelve-year-old girl, recently diagnosed with Addison's Disease, was referred to paediatric nephrology for Fludrocortisone-induced nocturnal hypertension. She had fallen off the growth curve for both height and weight from the 50th percentile at birth to below the 5th percentile at presentation. The severity and multitude of her symptoms, including muscle weakness, poor body control, dizziness, light headedness, persistent fatigue, excessive sweating, tachycardia, chronic constipation and recurrent infection hinted at the unusual nature of this case of Addison's. At the time of referral, she had been seen by more than a dozen specialists and subspecialists as well as undergone a number of tests including neurophysiological testing without sufficient explanation. With the help of tilt-table testing, we established the diagnosis of POTS. There is a lack of tested treatment options for POTS, and we established dosing of pyridostigmine in children, based on the emerging literature in adults. While pyridostigmine therapy substantially improved her quality of life, it took another 6 years and referral outside the country, before a final unifying diagnosis was made. Eventually, the patient was diagnosed with Ehlers Danlos Syndrome with associated autonomic dysfunction, including POTS, as well as primary adrenal insufficiency. The parents and the patient experienced considerable stress due to the lack of willingness of many physicians that the family encountered to search for a diagnosis and a treatment.

Keywords
Postural Orthostatic Tachycardia Syndrome (POTS), Ehlers-Danlos-Syndrome, growth retardation, pyridostigmine

Intent of this Essay

"About 8% of Canadians, or 3 million individuals, have a rare disease. Nearly two-thirds of those with rare diseases are children. Canadians have benefitted from public health strategies in diabetes, cancer, heart disease and mental illness whereas the approach to rare diseases has remained fragmented across the country. As a result, Canadian families with rare illnesses face extraordinary challenges, including misdiagnoses, unnecessary surgeries, social isolation, financial hardship, lack of treatment options and early death."[1] (Canadian Organization for Rare Disorders)

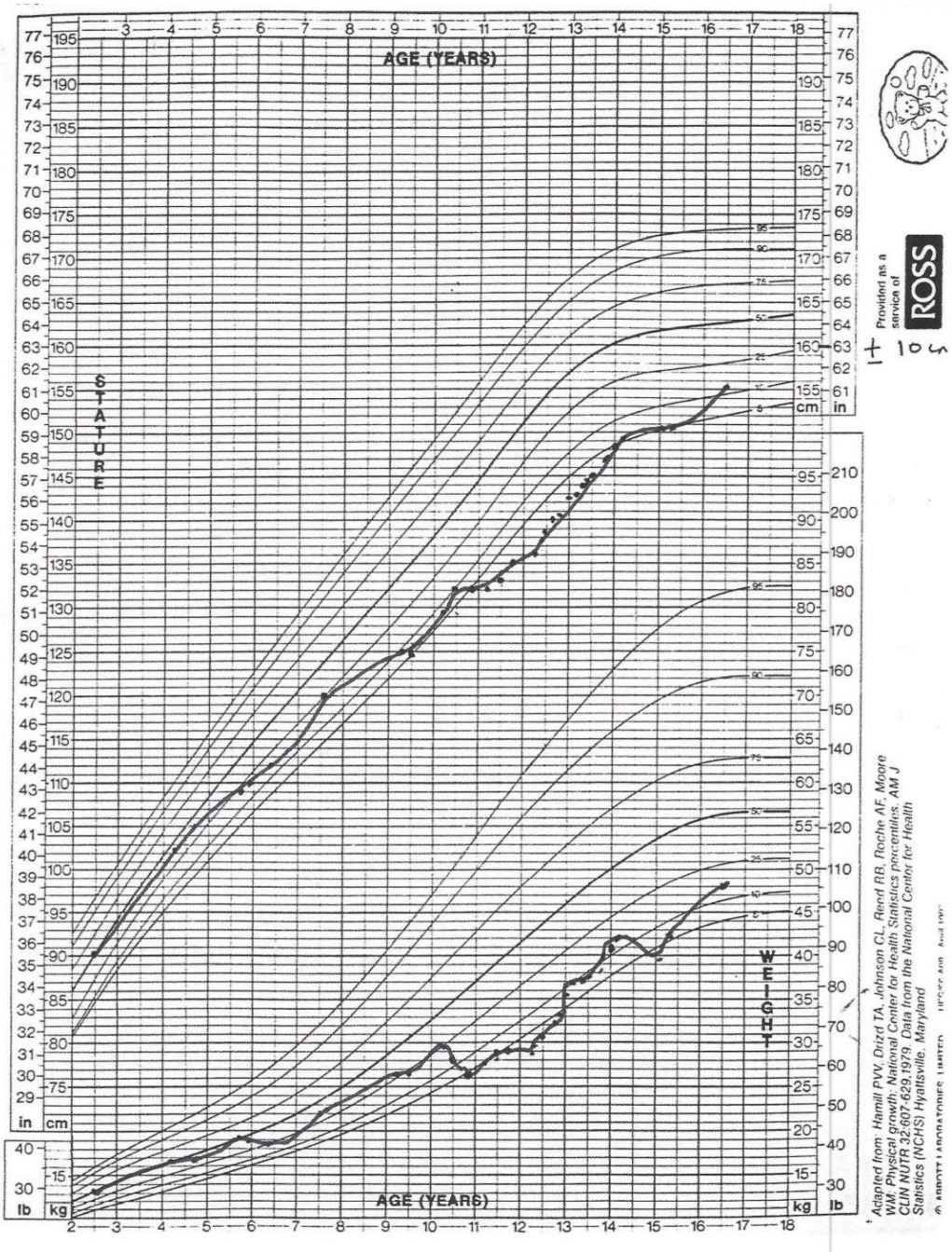
Unfortunately, the experience of pediatric patients with undiagnosed rare diseases remains unfavorable owing to the compartmentalized approach inherent to our subspecialized system. We present a case of complex autonomic dysfunction affecting multiple organ systems and leading to debilitating limitations of day-to-day living that caused an odyssey through the Tertiary Healthcare System and out-of-country referrals before a unifying diagnosis and the best possible treatment was found. The purpose is to showcase in this situation that the diagnostic workup can be improved and years of meandering through the health care system can be avoided.

General Narrative

Our patient is one of the three million individuals in Canada inflicted with the misfortune of having a rare disease. Born with chronic constipation and plagued with recurrent infection and persistent fatigue, the patient and her family started on what would prove to be an exhaustingly long quest for answers. At the time of referral, she had already been seen by more than a dozen specialists and subspecialists as well as undergone a number of tests including neurophysiological testing without a clear diagnosis. As a result of several ER admissions for severe bronchitis and pneumonia she was labeled with incorrect diagnoses. When seen by GI for her chronic constipation, it was suggested she undergo a bowel resection, which her parents fortunately refused. They believed there was a root cause to all of her suffering and were determined to find it.

At twelve years of age, the patient was referred to paediatric nephrology for Fludrocortisone-induced nocturnal hypertension, after having been diagnosed by her second paediatric endocrinologist with Addison's Disease. By age twelve, she had fallen off the growth curve for both height and weight from the 50th percentile at birth to below the 5th percentile (Figure 1). The onset of Addison's Disease was most likely congenital, but diagnosis was delayed due to her lack of hyperpigmentation, though this symptom may only be present in 55% of patients.[2] While this initial diagnosis explained some of her presentation, the severity and multitude of her symptoms, including muscle weakness, poor body control, dizziness, light headedness, persistent

Figure 1. Height and weight of our patient against the reference intervals of the Center of Disease Control (https://www.cdc.gov/growthcharts/clinical_charts.htm). The target height based on the mid-parental height and adjustment for girls was 163 ±10 cm



fatigue, excessive sweating, and tachycardia, as well as joint hypermobility and excessive dorsiflexion of her fingers suggested that this was not a typical case of Addison's Disease. The discordance between the severity of her symptoms and the availability of objective findings characteristic of autonomic dysfunction made for a difficult diagnosis, thus our patient was continually passed from specialist to specialist as each one exhausted the boundaries of their practice.

Eventually, repeated tilt table testing revealed a postural heart rate of up to 200 beats per minute, and the diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS) was assigned; however, it took another 6 years and referrals to Dr. Peter Rowe (Johns Hopkins) and Dr. Blair Grubb (Toledo, both U.S.A), before a final unifying diagnosis was made. Eventually, our patient was diagnosed with Ehlers Danlos Syndrome with associated autonomic dysfunction, including POTS, as well as cortisol deficiency. It is not uncommon for Ehlers Danlos syndrome to be associated with autonomic dysfunction,[3] nor gastrointestinal manifestations.[4] In a recent study, 48.6% of Ehlers Danlos syndrome patients had postural orthostatic tachycardia, 31.4% had orthostatic intolerance and only 20% had normal results.[3] Unfortunately, there are 11 known types of Ehlers Danlos syndrome, and often the classic features of type I (gravis form) are absent. Some authors now consider the association of Ehlers Danlos syndrome and autonomous dysfunction a distinct subtype.[5]

After the diagnosis was made, several treatments including salt supplements, high fluid intake and Fludrocortisone, were tried. Initially, this significantly reduced her symptoms, but they recurred within a matter of months. Additional treatment attempts with both clonidine and Midodrine were abandoned due of severe side effects. The patient's dose of Fludrocortisone was gradually increased, as without it her baseline daytime blood pressure would drop to 70/40 mm Hg (50th percentile for a height of 140 cm 103/60 mm Hg, 5th percentile 85/41 mm Hg).[6]

This eventually led to the development supine/nocturnal hypertension as a side effect of Fludrocortisone, so she started on anti-hypertensives at night. At this point, Pyridostigmine had been investigated for off-label use in adult POTS patients, but no dosing recommendations existed for children and the pharmacokinetics had not been studied. To facilitate the trial of this treatment, we therefore developed a test for pharmacokinetic monitoring using a newly developed semi-automated and specific high-performance liquid chromatography/tandem mass spectrometry assay and established normal pharmacokinetics for children with myasthenia gravis, and then applied the learnings to the patient.[7] A dose of 60 mg resulted in a substantial decrease in the initial tachycardia response to upright tilt that persisted in the plateau phase. To accommodate the rapid metabolism during childhood, the patient received 3 doses over the day with a substantial improvement in the quality of life.

Today, at the age of 28, our patient is unrecognizable from the frail little girl that walked into our office 15 years ago. After completing a Masters and Ph.D. in Physics, she is now working as a Post Doc at a major American university. With the aid of compression stockings and a compression suit, she was able to successfully travel to present her Ph.D. research around the globe. She regularly walks over 2 kilometers per day thanks to physiotherapy and custom orthotics – a huge improvement from the pain that exercise used to cause her.

Reflections/Recommendations Based on Experience

Throughout this process, apart from the suffering of the patient, the family experienced considerable stress due to the lack of willingness of many physicians working within the framework of a fragmented system to search for an appropriate diagnosis that would allow for necessary treatment. The family expressed that "So many of the physicians we met specialized in a small number of conditions and once they ruled those out, were not the least concerned about finding the cause of the patient's problems and treating them. This speaks to each specialist working in their own silo with no overall owner of [our daughter's] file. The worst part [of our experience] is that there is no way to report these kinds of mistakes to the system constructively to ensure that the doctors do not continue to repeat the same mistakes." These remarks illustrate the severity of the disheartening stress endured by the families of paediatric patients with rare and unknown diseases in a system limited by the imposition of stark and specific boundaries of individual specialists.

Unfortunately, this "diagnostic odyssey" that patients and families with rare disorders undergo is actually quite well established in the rare disease literature.[8] A survey of such patients demonstrated that for 25% of participants the time to diagnosis was extensive, ranging from 5-30 years, and during that time, 40% received an incorrect diagnosis, while 50% never received a diagnosis.[8] Recently, several consortia have advocated the idea that earlier institution of whole genome or whole exome sequencing might reduce the odyssey by years.[9]

This patient's positive outcome would have been impossible without this family's perseverance on their long search for answers. Unfortunately, not all families are so resourceful. Autonomic dysfunction is understudied and under-taught, and centers for autonomic dysfunction are only now starting to emerge in Canada, at this point only for adult patients.[10]

Academic health sciences centres are the last frontier for undiagnosed diseases; the last hope for patients that have often been through so much despair. We are fortunate to work in a country where the governments of the provinces acknowledge the need for such research and allow and remunerate for a proportion of scholarly activities to help patients like ours. Thus, it is our duty to our patients to utilize all resources at our disposal for diagnosis and treatment. We must not accept the failure to diagnose patients with rare diseases. Once we have diagnosed, we must not let a lack of tested treatment options resign us to inaction. We must not back away from these challenges, but instead take the time as doctors to search within a much broader framework for the answers our patients need. The rewards for doing so, as this patient has taught us, can be incredible.

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