

## INVITED ARTICLE

# From amyloidosis to Zellweger syndrome: how can the medical education system include thousands of rare diseases?

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## A disparate bunch

Over 7000 rare diseases have been described in accordance with the European Union definition of a condition that affects fewer than one in 2000 people.<sup>1</sup> An initial browse of Orphanet's Rare Disease Directory reveals a plethora of disparate conditions,<sup>2</sup> which would prove an insurmountable challenge should they all be represented in the medical curriculum. Firstly, their presentation can be incredibly varied; you can be born with a rare disease without any family history, have a long pedigree of rare disease, or acquire one in later life. This makes rare diseases, as a collective, impossible to assign to any particular demographic such as age or gender. Also, while every medical specialty will have its own "common rare disease", many rare diseases fall under a number of specialties and have no place that they can easily call home. Therefore not one specialty can take ownership of all rare conditions and, while some may suggest this is the job of medical genetics, it is estimated that 20% of rare diseases are not considered to have a genetic origin.<sup>3</sup> There are further challenges when teaching about how to spot rare genetic diseases, because one genotype can have drastically different phenotypes caused by processes such as variable penetrance and variable expressivity. That is to say, the same genetic change can manifest differently between individuals, even those in the same family. Given the myriad ways that different people can be affected by different rare diseases, it seems inevitable that there will be inequity in this area of medicine. Medics4RareDiseases (M4RD) is working on an educational approach that aims to equip medical professionals with the tools to think about rare disease as a single area of focus. We believe that basic training on the subject of rare disease with broad messages will help reduce inequity in the medical education system.

## The diagnostic odyssey

Patients rarely describe uniform or standardised pathways to diagnosis. The term "diagnostic odyssey" has been coined to describe the journey to diagnosis that is faced by patients living with a rare disease. The word "odyssey" is not only used to highlight the average 5.6-year wait that people face before diagnosis,<sup>4</sup> but it also conjures up an epic journey with giant-sized obstacles and detours along the way. It is not possible to attend a rare disease event without hearing numerous lived experiences that testify to the reality of the diagnostic odyssey. M4RD is calling for standardised medical education about rare diseases that will enable future clinicians to know when to suspect a rare disease, understand the impact of such conditions and to act as advocates for their patients living with rare diseases.

## Existing inequality in medical education

If you take into account the heterogeneity of rare diseases described in the first paragraph of this article, rare disease medical education feels like a non-starter. In whichever country you carry out your medical studies, you will inevitably have a packed curriculum with every specialisation or interest group competing for your time. Prostate cancer is the most commonly diagnosed cancer in males in England with 41,201 men diagnosed in 2017,<sup>5</sup> however, the charity Orchid is calling for more awareness and improved diagnosis for this common cancer as it is not being diagnosed promptly enough, despite its high incidence.<sup>6</sup> From a utilitarian point of view, should a small patient group expect to be heard when they are also asking for greater awareness of their condition, which only affects a handful of patients in the country? Some may argue that medical students already have enough common conditions, such as prostate cancer, to learn about without tackling rare ones.

Despite the obvious challenges, rare disease education is not entirely absent at medical school, but is also not standardised. The rare diseases that are chosen for inclusion in medical studies can vary significantly. In fact, the rarity of some conditions, such as Cushing's syndrome, may be a surprise to students because of how familiar they are with them, while other rare diseases that are more common may mistakenly be assumed an improbable diagnosis due to lack of inclusion in regular teaching. For example, the Childhood Tumour Trust, a patient organisation supporting those affected by neurofibromatosis type 1 (NF1), reports that NF1 is more common than cystic fibrosis, Duchenne muscular dystrophy and Huntington disease combined.<sup>7</sup> This is something that is unlikely to be common knowledge amongst medical professionals. Without a standardised approach to rare diseases in medical education, it is natural that inequity will arise.

## Rare disease and medical education

How are specific diseases chosen for teaching content? Below are factors that may influence the possible inclusion of a rare disease in formal education.

### PREVALENCE

It may seem like an oxymoron, but there is such a thing as a "common rare disease". In terms of medical education, there are some bread and butter rare diseases that are likely to be universally covered in medical studies based on their prevalence (e.g. cystic fibrosis – a multi-system condition that is caused by disruption of a membrane transport protein called CFTR. It affects more than 10,500 people in the United Kingdom (UK) according to the Cystic Fibrosis Trust).<sup>8</sup>

### MONOGENIC DISEASES TAUGHT DURING GENETICS MODULES

Examples of monogenic disorders include Huntington disease, which is a progressive neurological disorder inherited in an autosomal dominant pattern, and Duchenne muscular dystrophy, an X-linked disorder characterised by progressive muscular degeneration. Both of these diseases have a clear inheritance pattern and are therefore helpful for communicating concepts of inheritance in genetics modules. While genetics modules are an opportune time to teach about rare diseases, we must bear in mind that not all rare diseases are genetic in origin. An example is Guillain-Barré syndrome, which is a rare autoimmune disorder that leads to peripheral neuropathy and is thought to be triggered by an infection. Additionally, those that are genetic are not always inherited (sporadic) and some may be genetic but acquired as in the case of some rare cancers.

### GEOGRAPHICAL LOCATION OF THE MEDICAL SCHOOL

Certain geographical areas have different patient populations and this will impact the likelihood of a medical student seeing different pathologies. Tuberculosis (TB) is typically a pulmonary infection (however, not always restricted to the respiratory system, especially if left untreated) and it is caused by the bacterium *Mycobacterium tuberculosis*. TB rates are currently at an all-time low in the UK with 4655 cases recorded in 2018.<sup>9</sup> This is a rate of 8.3 per 100,000 population and therefore it qualifies as a rare disease. However, certain geographical areas such as Tower Hamlets in East London have a much higher rate (66 cases per 100,000 in 2017) and this will be reflected in the medical education in this region, because students are more likely to come across cases of TB during their clinical placements.<sup>10</sup>

### SPECIALIST CENTRES

According to the “UK Strategy for Rare Diseases”, patients with rare diseases should have access to a specialist centre or “Centres of Excellence”, in order to receive coordinated care for complex conditions.<sup>11</sup> For example, Salford Royal Hospital near Manchester is famous for its Mark Holland Metabolic Unit and is a specialist centre for adult patients with inherited metabolic conditions. It provides services to patients all over the country and some patients have to travel substantial distances to attend appointments. The medical school connected to a specialist centre such as this one will naturally have an artificially high number of patients with a particular rare disease using its services, relative to its local prevalence of that disease. These patients will then be seen by medical students in clinics and on the wards. This creates great opportunities for medical students to learn about specific rare diseases, however, will further contribute to the variability of medical student exposure to different rare diseases.

### LECTURER'S SPECIAL INTEREST

Throughout the UK, there are a huge number of health care professionals and scientists working in rare diseases – whether clinical work or research. Medical students may receive teaching on a rare disease if their lecturer has a special interest in a particular area.

### PATHOGNOMONIC SIGNS FOUND ON CLINICAL EXAMINATION

Infective endocarditis is an acquired rare disease with a high mortality rate. Historically, infective endocarditis was suspected in those with underlying congenital heart disease or a history of rheumatic heart disease. However, these are now relatively uncommon precipitators. Increasingly, age-related valve degeneration, mitral valve prolapse, intravenous drug misuse, and hospitalisation are considered risk factors for this infection.<sup>12</sup> In clinical medical school examinations, it is famous for causing pathognomonic signs called Janeway lesions. These stigmata are painless, erythematous macules found on the plantar and palmar surfaces. A student would be remiss to finish their cardiology Observed Structured Clinical Exam (OSCE) without mentioning that there was “no evidence of Janeway lesions”. This is despite the annual incidence of infective endocarditis being only three to ten cases in 100,000,<sup>12</sup> and Janeway lesions being an uncommon sign of this rare disease.<sup>13</sup>

Infective endocarditis is a potentially life-threatening infection that needs high clinical suspicion in order to treat it effectively, so it is surely a worthy rare disease to include in education. However, many rare diseases could be placed in the same category but are unlikely to be mentioned in a medical school OSCE. Fabry disease is a progressive and systemic, inherited metabolic disorder. It is caused by an enzyme deficiency that results in the abnormal storage of the accumulated substrate, making it one of a group of conditions called lysosomal-storage disorders. Fabry disease can cause visual and hearing impairment, gastrointestinal symptoms, kidney disease, and cutaneous signs. Importantly it can cause myocardial infarction and stroke. Fabry disease is estimated to affect double the number of those affected by infective endocarditis (estimated prevalence is one in 55,000 and newborn screening studies suggest this could be much higher).<sup>14,15</sup> Similar to infective endocarditis, Fabry needs rapid diagnosis in order to start life-saving treatment and to prevent major complications. However, despite the prevalence, severity and treatability of Fabry disease, “no evidence of angiokeratomas suggestive of underlying Fabry disease” is not a phrase that rolls off a medical student's tongue in a cardiology exam.

### MULTIPLE-CHOICE QUESTION-FRIENDLY

Multiple-choice questions (MCQs) are a standard in medical school assessment and represent an effective way to assess understanding about a large volume of varied information. However, they can have the tendency to reduce a subject to very specific details without allowing for nuance, which can mean that variation within a rare disease isn't considered. So while a rare condition may be featured in an MCQ exam, the description learned by students may not be the reality when it comes to clinical practice. For example, the Fragile X Society is highlighting that patients are being dismissed as not having the condition due to a lack of specific facial features, sometimes called “dysmorphic features”.<sup>16</sup> Studies have shown that some characteristic facial features may be absent until after puberty or completely absent.<sup>17</sup> The charity also raises awareness around the fact that Fragile X Syndrome can affect girls as well as boys. Therefore, the following MCQ could be problematic: “A young boy with learning difficulties, challenging and impulsive behaviour is brought in by his mother. Upon examination you notice he has a long, narrow face and prominent ears. What is the most likely diagnosis?”. While this may well be a realistic description of a portion of Fragile X patients it could deter a doctor from thinking of Fragile X Syndrome in a girl without distinguishing facial features but the same behavioural symptoms described.

### Collectively common

It is difficult to establish exactly how rare diseases are covered in UK medical schools because every institution defines its own syllabus and sets its own examinations. Albeit with guidance from the General Medical Council and Medical Schools Council to meet a common standard. Given the examples above, it is fair to assume that all medical students will learn about a number of rare diseases before they graduate and be in a position to diagnose patients with certain diseases. However, the mantra of “common things are common” that is widely used as a diagnostic heuristic through medical practice creates a mental obstacle that can be hard to overcome in clinical practice. It does not take into account that collectively rare diseases are common. Rare Disease UK estimate that 3.5 million people in the UK are living with a rare disease – this is comparable to all women diagnosed with heart and circulatory disease in the UK, according to the British Heart Foundation.<sup>3,18</sup> Therefore, a medical student should expect to see rare-disease patients regularly in their future clinical practice as they would expect to see women with cardiovascular disease.

Worryingly, data that M4RD has been collecting over the last three years strongly suggests that medical students are unaware of the prevalence of rare disease as a whole. Seventy per cent of medical professionals that M4RD has surveyed reported that they were not aware of rare diseases being so common.<sup>19-21</sup> If a doctor practices

with the belief that they will never see a rare disease, this will become a self-fulfilling prophecy and they will be one more obstacle in the diagnostic odyssey. Just because a doctor is not “seeing” rare diseases, it does not necessarily mean they are not there. This is reflected in Shire’s Rare Disease Impact Report, which states that patients will see an average of eight clinicians before receiving a diagnosis.<sup>4</sup> The reality is that a generalist may be unlikely to see any specific rare disease (depending on their patient population, of course) but they should expect to see patients with rare diseases regularly.

**A global issue**

The diagnostic odyssey is not a problem unique to the UK and there are medical student groups across the globe who are also calling for better preparation for managing undiagnosed patients. McGill University in Montreal is home to a Rare Disease Interest Group “RareDIG” and they are “equipping future physicians for the reality of rare disease”.<sup>22</sup> Their “Humans of Rare Disease” project tells the stories of people in Canada who waited years for an accurate diagnosis, and one participant states “I had to leave Montreal after doctors...gave up on finding what I had (they refused to test beyond lupus), with my mental health in shambles and still having no clue what was happening to my body. After nearly dying in late December 2017, I was finally diagnosed with a rare form of vasculitis”.<sup>23</sup>

A student at the University of Auckland, Logan Williams, won the Student Voice Essay Competition 2018 during his fifth year of medical school. His winning essay discussed how the medical education system’s focus on biomedicine, rather than psychosocial and humanistic factors, negatively impacts on the care received by those living with a rare condition.<sup>24</sup> He describes how an outdated disease-based approach, which concentrates on understanding the scientific minutiae of a condition, can leave psychosocial factors as an afterthought in the learning process. In the case of his patient CS with Worster-Drought syndrome, this led to disastrous consequences because his mother was unable to obtain the basic equipment to keep him safe when he was having seizures. The story of CS and his mother illustrates that a physician does not need to know the exact pathophysiology and aetiology of a rare disease in order to make a positive impact on their quality of life and clinical outcomes. It also highlights some of the obstacles faced by many patients and their families: difficulty obtaining equipment; family members as carers; managing complex needs; and adapting the family home. Also, the important role of the “expert patient” or “expert carer” with their “lifetime worth of experience” can be feared by a doctor trained in a traditionally paternalistic field.<sup>24</sup> A disease-based approach in medical education is also an impediment to understanding how to advocate and manage patients with rare diseases because it requires a student to learn about each condition individually. CS and his mother clearly made an impact on Logan and this experience will arguably prepare him better for helping his rare patients in the future than detailed learning about a handful of rare diseases, which will be unlikely to include Worster-Drought syndrome.

As well as Canada and New Zealand, M4RD is aware of medical student activity in rare disease education in a number of other countries: The National Organisation of Rare Disorders in the United States of America has a student chapter; the University of Western Australia involves medical students in the Undiagnosed Disease Program and students are involved in Rare Disease Ghana. In 2004 the French National Plan for Rare Diseases included a details of how rare disease is to be included in undergraduate medical education in partnership with Orphanet. These are just a handful of examples, but it is clear that across the globe there is a sense that we can be doing more for those living with rare diseases from the very beginning of a doctor’s medical studies.

**#DareToThinkRare**

Rare diseases are collectively common and a lack of appreciation of this amongst medical professionals perpetuates the diagnostic odyssey. To combat this problem M4RD is proposing a new approach

to rare diseases in medical education. All medical students should receive fundamental teaching about rare diseases during their studies. Lessons should include broad messages about rare diseases such as the concept of the diagnostic odyssey and how to reduce it; specific challenges faced by those affected by a rare disease; where to find accurate information and support for patients; and crucially, the prevalence and relevance of rare diseases to everyday medical care. While specific diseases and case studies may be used to relay key concepts, the teaching is not designed to focus on any individual rare diseases. This teaching should always be delivered in collaboration with patients, advocates and patient groups, so students hear about the lived experience. M4RD is calling this “Rare Disease 101” and we believe that this will be crucial in reducing the inequality encountered in medical education with regards to rare diseases.

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## Acknowledgements

- > Professor Gareth Baynam, Clinical Geneticist and Program Director, Undiagnosed Diseases Program, Genetic Services of Western Australia and Head of the Western Australian Register of Developmental Anomalies.
- > Dr Gisela Wilcox Consultant in Adult Inherited Metabolic Disorders, Honorary Senior Lecturer at the University of Manchester.