A powerful team: The family physician advocating for patients with a rare disease

Tracy Dudding-Byth

CPD

Background

Rare diseases are characteristically difficult to diagnose and for the majority, there are no effective treatments or evidence-based management guidelines. Although it is unrealistic to expect family physicians to recognise the wide clinical spectrum of rare diseases, their longitudinal and holistic approach to medicine place them in a unique position to consider the possibility of a rare disease.

Objectives

This article outlines the challenges faced by the rare disease community, and the role of the primary care physician to advocate for answers as their patients transition through the healthcare system.

Discussion

The road to the diagnosis of a rare disease can test the doctor–patient relationship. Patients often struggle for answers and family physicians are stymied by a lack of information. At the same time, the availability of cyber-based health information and online rare-disease patient groups has led to the emergence of the 'expert' patient, who seeks a collaborative and empowering relationship with their physician. Following diagnosis, the family physician plays a crucial part in providing continuity of care, advocating access to expert healthcare, coordinating complex management and becoming a source of psychological support.

Rare disease

A rare disease is defined as a condition with a prevalence of less than one per 2000.[1,2] Although accurate epidemiological data are limited due to lack of disease registries and disease specific classification codes, an estimated 75% of the 6000–7000 rare conditions have a prevalence of 0.1–10 person per 100,000.[3] However, low prevalence does not equate to low burden of illness. Rare diseases frequently begin in childhood and can be chronically disabling or life-threatening.[4] These diseases are characteristically difficult to diagnose, and the majority have no effective treatment or evidence-based management guidelines. The emotional, psychosocial and financial impact of rare diseases on the patient and their carers is further compounded by a lack of experience among healthcare providers, limited information and a sense of isolation.[1,2,4] Having been neglected for many years by researchers and health policy makers, these conditions are also known as orphan diseases.

The diagnostic odyssey

It is the low prevalence of these diseases that leads to the diagnostic odyssey or 'medical merry-go round' – a lengthy and often costly journey towards a diagnosis. A delayed diagnosis (5–30 years) is reported in 25–40% of cases,[2,4] and 40% are initially given an incorrect diagnosis.[4] This is a time of uncertainty, anxiety and isolation as individuals are left without an explanation, clear prognosis or management plan. Parents of a child with an undiagnosed rare condition may go on to have a second child with the same condition before a diagnosis has been made in their first child. In addition, a delayed diagnosis of treatable rare diseases can lead to severe irreversible and life-threatening consequences.[4]

The value of a diagnosis cannot be underestimated, even in the absence of an effective treatment. A diagnosis provides an explanation, validates an individual's symptomology, informs prognosis and management, and can restore reproductive confidence for parents of a child with a rare disease. The inherent rarity of rare diseases means it is simply not possible for primary care physicians and medical specialists (including clinical geneticists) to have clinical exposure to all rare diseases, let alone have the experience to recognise the wide clinical spectrum of each of these conditions.

Eighty per cent of rare diseases have a genetic basis,[3] with variable ages at presentation and disease progression. Initial symptoms may be attributable to a more common condition but, often, it becomes apparent over time that the evolution of symptoms is not explained by the original diagnosis. Rare genetic conditions often affect multiple organ systems and can present with several seemingly unrelated problems. Without a diagnosis, individuals lack a narrative to explain their symptoms and have to defend their right to access healthcare and support. This lack of a unifying diagnosis often leaves the doctor and patient feeling frustrated and helpless, and has the potential to adversely affect the doctor–patient relationship.[5]

The family physician and rare disease diagnosis

It is generally unrealistic to expect a rare disease diagnosis to be made during an initial primary care consultation. However, the comprehensive whole-patient care provided by family physicians makes them ideally placed to recognise the evolution of an unusual pattern of seemingly unrelated problems. There are several strategies to minimise cognitive errors in the diagnostic process.[6] When a patient's symptoms, signs or investigation results are atypical and not explained by an initial provisional diagnosis, clinicians are encouraged to routinely ask if there might be an alternative diagnosis.[6]

A three-generation family history will often provide clues to an inherited rare disease. As it is not possible to immediately recognise all rare diseases, the diagnosis of these conditions requires a problem-based, first principle approach using web-based resources (*Table 1*). A family physician faced with a combination of features can type keywords into OMIM (Online Mendelian Inheritance in Man), Phenomizer, PubMed, Orphanet or Google to generate a list of differential diagnoses. Start a keyword search with the two most concrete features and use a combination of different web-based resources (*Table 2*).

Increased access to the internet means patients will often independently access these web-based resources and present to a doctor with a list of rare disease diagnoses they believe could explain their symptoms.[7–9] This shift in the traditional doctor–patient interaction is commonly encountered in the area of rare diseases,[7] and primary care physicians in the UK are encouraged to engage patients in the diagnostic phase, with the clinician acting as a 'well-informed' facilitator.[10] Differential diagnoses will inform subsequent investigations or appropriate referral.

The referral may be to a paediatrician, sub-specialty physician or a clinical geneticist depending on the differential diagnoses. On-call clinical geneticists and genetic counsellors, from regional clinical genetic services throughout Australia, can provide guidance and expert advice to family physicians on a range of issues including disease information, diagnostic approaches and appropriate referrals (www.genetics.edu.au/Genetics-Services). Clinical geneticists are trained in the diagnosis and management of rare paediatric and adult genetic diseases, and one could argue that clinical geneticists should be able to recognise and diagnose rare conditions with a prevalence of at least one in 100,000.[11] When a diagnosis is not immediately obvious, a problem-based approach using dysmorphology databases, literature review, web-based resources and email consultations with national or international experts is often required. Regional genetic services also provide genetic counselling. In addition to providing understandable information about the implications of a genetic diagnosis, genetic counselling is a communication process that supports individuals or families to make useful decisions in light of their unique experiences, and family, social, religious and cultural backgrounds.[12]

Family physicians' care of patients with rare diseases

Although diagnosis of a rare disease may be a welcome relief after years of searching for an explanation, it is also often a time of grief and isolation. Individuals with a newly diagnosed rare disease, or their parents/carers, will be seeking updated and reliable information about conditions for which the majority of health professionals have no or limited experience.

The vast majority of rare genetic conditions have no curable treatment. Ultra-rare diseases lack management guidelines and information on natural history and prognosis.[13] Multi-system involvement can require complex care by a number of separate sub-specialist clinicians. Family physicians know their patient's story and play a key role in coordinating and advocating for accessible, ongoing care. Locating accurate information, physician expertise and reference centres of expertise is the first challenge. There are a number of accurate and comprehensive websites dedicated to rare diseases, which provide clinical information, best-practice guidelines and links to patient support groups (*Table 3*). Genetic Alliance Australia facilitates support for individuals affected directly or indirectly by a genetic condition (www.geneticalliance.org.au). Rare Voices Australia, a national advocacy organisation provides online links to a broad range of national and international rare disease organisations and online portals (www.rarevoices.org.au). The majority of patients with rare diseases seek their own information. Web-based patient groups and Facebook groups allow individuals to make contact

with other similarly affected individuals globally.[14] Patients will often successfully locate expert physicians and research centres. Patient-sourced information, combined with limited medical expertise and published best-practice guidelines, can challenge the traditional doctor–patient encounter; however, it is particularly important for the family physician to acknowledge and respect the patient's role in ongoing management decisions.[7]

Individuals with a rare disease and their families report significant financial and psychological burden.[2,4] It is not uncommon for parents to cease regular employment to care for a disabled child. Mothers of children with chronic illness describe 'living grief' as they face the recurring disparity between expectations for their child and the challenges their child now faces.[15] As doctors, we may not have all the answers, but it is the long-term, trusting, supportive and family-oriented

Table 1. Web-based resources for searching key features

Online Mendelian Inheritance in Man (OMIM), www.omim.org	The OMIM database is a comprehensive, authoritative compendium of human genes and genetic phenotypes housed within the US National Center for Biotechnology Information (NCBI).
Phenomizer, http://compbio.charite.de/phenomizer/phenomizer.html	An open access, web-based tool that assists in finding the correct clinical diagnosis by exploiting the semantic structure of the Human Phenotype Ontology. The Phenomizer-A tutorial is available on YouTube (www.youtube.com/watch?v=4EObfZbMQ3U)
Orphanet, www.orpha.net	Orphanet has a search by sign service.
Pubmed, www.ncbi.nlm.nih.gov/pubmed	Search keywords.
Google, www.google.com	Search keywords.

Table 2. Examples of searching keywords

Keywords	Resources	Possible diagnosis
Pneumothorax AND Family history of renal cancer	MIM/Pubmed/Google/Phenomizer	Birt-Hogg-Dube syndrome (OMIM 135150)
Painful AND Fat	Google	Lipedema (OMIM 61403) Adiposis Dolorosa (OMIM 103200)
Joint pain AND Abdominal pain	OMIM	Fabry disease (OMIM 301500)
Large head (macrocephaly) AND Café au lait spots	OMIM/Google/Pubmed/Phenomizer	Neurofibromatosis Type 1 (NF1, OMIM 162200)
Toe walking AND Weakness	OMIM/Pubmed/Google	Muscular dystrophy
Joint subluxation AND Joint pain	OMIM	Ehlers-Danlos syndrome, Type III (OMIM130020)
Deafness AND Diabetes AND Seizures	OMIM/Pubmed/Google/Phenomizer	MELAS (OMIM 540000)
Chronic AND Cholestasis	OMIM	Progressive Familial intrahepatic cholestasis (OMIM 211600)

OMIM, Online Mendelian Inheritance in Man

relationship at the heart of primary care that can make these patients' journies a little easier.[16]

Individuals who remain undiagnosed

Rapid advances are being made in the field of clinical genetics. The molecular karyotype (microarray-based comparative genomic hybridisation), which allows the detection of sub-microscopic chromosomal deletions or duplications, has a diagnostic yield in children with an intellectual disability of 15–20%.[17] Over the past 5 years, high-throughput, genetic sequencing (next-generation sequencing) has seen the emergence of whole exome sequencing (referred to as clinical exome sequencing for diagnostic purposes). In contrast to single-gene testing, this technology allows parallel sequencing of a large number of genes known to be associated with a particular phenotype (clinical presentation). Future availability of an intellectual disability clinical exome, which allows rapid and simultaneous testing of all the known intellectual disability genes, has a diagnostic yield of about 25%.[18] A similar diagnostic rate is reported for a range of early-onset and adult-onset neurological disorders.[19] Despite advancing technology, however, the majority of children with a suspected genetic form of intellectual disability do not have a molecular diagnosis. A large proportion of adults and children in the National Institutes of Health (NIH) Undiagnosed Diseases Program are without a diagnosis despite numerous investigations and years of searching.[20]

Doctors may feel they are unable to meet the needs of patients with unexplained symptoms, and patients may lack legitimacy in seeking help. These patients are at risk of losing faith and disengaging from their doctor. However, without a diagnosis these patients can require increased levels of emotional support and advocacy to access necessary healthcare, social and financial services. Even without a diagnosis, the family physician continues to play a vital role in providing ongoing holistic healthcare for this group of patients.

Clinical geneticists frequently address the uncertainty faced by individuals with an undiagnosed condition, or their parents/carers. As clinical genetics is a rapidly changing area of medicine, we always encourage patients to be reviewed every 3–5 years because emerging technology makes a diagnosis quite possible over time.

National advocacy

Given that an estimated 6–8% of Australians live with a rare disease,[21] unity became the foundation stone for Rare Voices Australia, a national not-for-profit advocacy organisation established in 2012. Rare Voices Australia provides a strong, united voice advocating on a state and federal level for a National Rare Disease Strategy. The organisation works with governments, researchers, clinicians and industry to promote diagnosis, coordinated care and access to treatment and research for all rare diseases in Australia.

Table 3. Web-based resources for reliable information

National Health and Medical Research Council (NHMRC), www.nhmrc.gov.au/health-topics/genetics-and-human-health	A central repository for human genetic resources and information developed by NHMRC.
Genetics Alliance Australia, www.geneticalliance.org.au	Facilitates support for individuals affected directly or indirectly by a genetic condition.
NSW Centre for Genetic Education, www.genetics.edu.au	Focused on providing genetic education and resources for health professionals. Provides a link to Australian genetic counselling services.
Rare Voices Australia, www.rarevoices.org.au	Australian rare disease information portal linking patients and health professionals to national and international resources. Provides links to specialised social services.
Genetic Home Reference, www.ghr.nlm.nih.gov	Consumer-friendly information about human genetics from the National Library of Medicine. Provides links to recent literature, comprehensive clinical summaries (GeneReviews), US clinical trials and patient support groups.
Orphanet, www.orpha.net	European website providing information about rare diseases, orphan drugs and support groups.
GeneReviews, www.ncbi.nlm.nih.gov/books/NBK1116	Expert-authored, peer-reviewed disease descriptions focused on clinically relevant and medically actionable information on the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.
US Office of Rare diseases, www.rarediseases.info.nih.gov	Provides links to rare disease information and patient groups.
Unique, www.rarechrom.org	Support and information for families of children with rare chromosomal disorders.

Case

LW, a woman aged 40 years, presented with a 2-year history of fatigue and generalised, poorly localised pain, which she described as a dull, heavy feeling affecting all her limbs and becoming worse with movement. The pain was relieved by daily paracetamol. Her sleep pattern was disturbed and her mood was flat. A diagnosis of depression was made and she was commenced on a low dose of escitalopram, which provided some improvement. She presented again 18 months later because of concern about worsening cognitive function, which she described as 'living in a fog'. This was interfering with her ability to function as an editor, and she requested a referral to a neurologist. A neurocognitive assessment reported some mild difficulties with memory, word-finding and understanding complex problems. However, her neurological evaluation and cerebral magnetic resonance imaging (MRI) was normal. Assessment by a psychiatrist was recommended. LW moved interstate and presented with chronic fatigue and generalised body ache to a new doctor. An immunology consultation was arranged, but her symptoms remained unexplained.

Over the next 3 years, new symptoms emerged for which no clear medical explanation was found. These symptoms included abdominal cramps, palpitations, dizziness and urinary frequency. Her affect remained flat and she apologised for being 'so much trouble'. At the age of 45 years, she presented to her family doctor with written information about a condition called Ehlers-Danlos syndrome, hypermobility type (EDS-HT). She explained that her joints were extremely hypermobile as a child and she had the ability to lift her legs up over her head. She also had a history of recurrent joint subluxations, which were managed by her chiropractor. Referral to her regional genetics department confirmed a clinical diagnosis of EDS-HT.

LW has since been linked with other individuals with EDS-HT through support groups and Facebook, and has become an expert on this rare condition. She is now being investigated for associated orthostatic hypotension and sleep-disordered breathing. Her family doctor is coordinating her rehabilitation and pain management. Despite her disability, it is validating for LW to have a diagnosis that accounts for all her seemingly unrelated features.

Author

Tracy Dudding-Byth BMed, FRACP, PhD, Consultant Clinical Geneticist, Hunter Genetics & NSW Genetics of Learning Disability (GoLD) Service, Hunter New England Health, Newcastle, and conjoint senior lecturer, The University of Newcastle, NSW, and co-founding director of Rare Voices Australia. Tracy.dudding@hnehealth.nsw.gov.au

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correspondence **afp@racgp.org.au**