

Rare diseases in general practice:

recognising the zebras among the horses

*'When you hear hoofbeats, don't expect to see a Zebra.'*¹

The above adage is especially useful in primary care as many of the conditions we see are common. But it is not so useful when we consider our role in both diagnosing and supporting patients with rare diseases. We must be ready to think again and look out for the horse with stripes.

A rare disease is defined by an incidence of <5 cases per 10 000 population, however the vast majority of the 7000 rare diseases are far less common.² Eighty per cent of rare diseases have a genetic basis,³ and genomic research has led to the determination of new diseases at a rate of five each week.⁴ Despite the vast number of rare diseases, only 100 conditions account for 80% of 'rare patients'.^{2,5} Rare diseases therefore include those that we are familiar with (for example, cystic fibrosis and Guillain-Barré syndrome), and others that may have just a handful of patients worldwide.

Most rare diseases are severely disabling, life limiting and affect children, with 30% of patients not reaching their fifth birthday.⁴ Many patients with rare disease are un/misdiagnosed, particularly those with milder phenotypes presenting at later ages (for example Niemann-Pick disease; Box 1).

Many of the rare 'orphan' diseases are neglected, with a paucity of accurate information, effective treatments or research. Although individually rare, collectively, 1 in 17 persons are affected by a rare disease in their lifetime.⁶

DIAGNOSING RARE DISEASES AND THE ROLE OF PRIMARY CARE

Patients frequently describe a long and protracted 'diagnostic odyssey', taking years, or even decades. These years can be defined by uncertainty, multiple hospital attendances, investigations, misdiagnoses, and inappropriate treatments; with huge emotional cost and wasted time, effort and resources.²

Even in the absence of a disease-specific therapy, a prompt and accurate diagnosis is of huge value. Early diagnosis can put an end to the exhausting diagnostic odyssey and diagnosis validates the individual's symptomatology. It can help inform family planning, especially for inherited paediatric diseases where several children in a family may be affected before diagnosis, it informs

Box 1. Niemann-Pick disease, type C: a highly variable rare disease

Niemann-Pick disease, type C (NPC) is a lysosomal storage disorder, historically considered an aggressive neurodegenerative disease of children, with death typically in their teenage years. There is now much wider recognition that the largest subgroup is undiagnosed, with a less aggressive phenotype, presenting later with insidious onset dementia, ataxia, and frequently, psychosis.

prognosis and importantly, it assists the patient and family in gaining access to social and educational support.

So what role does general practice have in rare disease diagnosis? Where there is suspicion, an accurate three-generation family history may provide clues of an inherited disease. A review of the key features can form the basis of a problem-based search for differential diagnoses utilising web-based resources (for example, www.findzebra.com/; www.omim.org/; www.orpha.net/consor/cgi-bin/index.php; and [phenomizer-orphanet: http://compbio.charite.de/phenomizer_orphanet/](http://phenomizer-orphanet.charite.de/phenomizer_orphanet/)).^{7,8,9}

The differential diagnoses generated will then inform subsequent investigation and referral, advice is normally readily available from clinical genetic departments or, if an inborn error of metabolism is considered, regional specialist metabolic laboratories.

A GP CAN UNIQUELY HELP

Of course it is unrealistic to expect anyone to know all 7000 rare diseases, or for a

GP to make an immediate spot diagnosis the moment a patient walks in. But GPs are in a unique position. We offer whole patient and family care with continuity of clinical record over many years. We are used to managing diagnostic uncertainty, excluding serious pathology and to consider diagnoses that we may only see a handful of times in our career, for example, infectious diseases such as meningococcal sepsis and certain cancers. By keeping an open mind we have the tools and ability to 'join the dots', identify unusual patterns of disease and revisit diagnoses.¹⁰ Asking: 'Is there a more plausible explanation for the patient's problems? Or should we reinvestigate patients with newer advanced diagnostic tests?'

Patients with a rare disease typically seek an empowering and collaborative approach with their clinicians. They and their carers are often 'expert patients', which can challenge the traditional patient-doctor relationship, shifting the usual knowledge asymmetry. By acknowledging each other's mutual skills and expertise an effective and rewarding partnership can be achieved.^{9,11}

CARING FOR PATIENTS WITH RARE DISEASES IN PRIMARY CARE

After a long diagnostic journey, the relief of diagnosis is often short-lived as patients come up against the frustrations associated with orphan diseases: a lack of information, treatments and variability in the level and coordination of care. For some diseases national or regional-specialised centres are in place and make a huge difference, but this may be at the detriment of local

Box 2. The newborn blood spot test

This now includes 9 tests (including 6 inherited metabolic conditions)

- Sickle cell disease
- Cystic Fibrosis
- Congenital hypothyroidism
- Phenylketonuria (PKU)
- Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

Since 2015:

- Maple syrup urine disease (MSUD)
- Isovaleric acidaemia (IVA)
- Glutaric aciduria type 1 (GA1)
- Homocystinuria (HCU)

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knowledge of the patient and their disease. A GP can help fill this void. Through increasing familiarity of the disease and how it impacts the patient and their family we can help navigate and coordinate local hospital specialties’ and other agencies’ involvement.

Simple things can also help. Patients with rare diseases often report frustration that they need to explain their disease to every clinician they meet. Prominently-placed disease summaries, relevant letters and care plans are all easy ways to help ensure familiarity among the health professionals patients may encounter.

Good holistic care for the patient and their family is invaluable for what are often devastating, life-limiting illnesses. It is important to avoid the trap of attributing every ailment to the ‘headline’ disease, overlooking easily-treatable problems. For example, recognising and treating constipation or depression in patients with complex neurological diseases not only has a profound effect on their well-being but even the apparent disease severity.

THE FUTURE OF RARE DISEASES IN PRIMARY CARE

In 2013 the UK Strategy for Rare Disease highlighted the need for better coordination of care, the empowerment of patients, better diagnostics, and earlier disease interventions. It also highlighted the integral, yet difficult role that GPs have, especially in the diagnosis of rare diseases⁶ The UK Rare Disease Forum¹² has recently produced a report assessing the progress made toward the 51 published recommendations. The reports acknowledges the progress made in molecular diagnostics, including the 100 000 genome project, the expansion of the newborn screening programme in 2015 to include 4 more conditions [see Box 2] and a unified registry of rare disease patients, but highlights much work that still needs to be done to achieve the 2020 goal.¹³

“The UK Strategy for Rare Diseases sets out a shared vision for improving the lives of all

those with rare diseases in the UK by 2020.”

IMPLICATIONS OF WIDER AVAILABILITY OF GENOMIC TESTING

GPs are likely to have a greater role in the diagnosis and ongoing management of rare diseases. We must ensure that the electronic record is utilised to its maximum potential, for the benefit of our patients. Computer learning and diagnostic algorithms can aid diagnosis and minimise clinician error, but how do we incorporate this while not hindering the consultation and doctor-patient relationship?

The wider availability of genomic testing poses both challenges as well as opportunities to health services. Do we have the skills to interpret and communicate the findings, especially the uncertainties and the unexpected results? Will we, in primary care, be responsible for conveying this information and if so, how will we do it? Additional rare diseases will continue to be described and common diseases broken into molecularly-defined subtypes, each with targeted therapies. We will need to utilise this knowledge to ensure that the best treatments are given to patients but also at a sustainable cost. Defining what is cost-effective will continue to be a contentious question for society, and a difficult challenge for national commissioners of rare disease services.

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