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ABSTRACT

Paradoxically, rare diseases are common, collectively affecting 6–10% of the population and have a huge impact on patients and families, health services, clinicians and the wider community. Accurate data are required to inform clinical practice, government policy and health service planning. We recommend a national approach, similar to that adopted in the USA and Europe, to support research and promote advocacy and equitable access to services for children with rare diseases.

By definition, rare diseases have a low prevalence. In Europe a rare disease is defined as one with a prevalence of less than 1/2000, in the USA as one that affects less than 200 000 people, and in Australia as one with a rate of 1/10 000.[1–3] There are about 8000 rare diseases, which collectively affect approximately 6–10% of the population.[1–3] This equates to 30 million people in Europe, 25 million in the USA and 1.2 million Australians.[1–3] Comparatively, diabetes affects an estimated 20.8 million people in the USA and 1.4 million in Australia.[4 5] It is increasingly acknowledged that low prevalence does not equal low impact, yet epidemiological and scientific data are lacking for many rare diseases.[2 3] Rare diseases often begin in childhood, continue throughout life, are disabling or life threatening, and are difficult to diagnose. Most have no cure, yet few publications describe their impacts on individuals, health professionals, health services and the community. We chose fetal alcohol syndrome (FAS) and Rett syndrome to demonstrate impacts because published data are available, and both cause physical, neurological, intellectual and behavioural problems, which are the components of many rare diseases, regardless of aetiology. We also reviewed the literature to address the following:

- What are the impacts of rare diseases on patients, families, caregivers and the community?
- What are the impacts of rare diseases on clinicians and health services?
- How have governments responded to the need for health services, research and policies relating to rare diseases?

METHODS

We searched Medline (via CIAP) from January 2000 to May 2008, for articles in English using the MeSH terms:

- Rare diseases (economics/epidemiology/psychology): 95 titles were found; 14 relevant papers were reviewed.
- Rett syndrome (economics/epidemiology/psychology/complications): 145 titles were found; two full papers were reviewed.
- Fetal alcohol syndrome (economics/epidemiology/psychology/complications): 227 titles were found and five full papers were reviewed.

The Cochrane Library (www.cochrane.org) was searched using the MeSH terms: rare diseases, Rett syndrome and fetal alcohol syndrome (title, abstract or keyword). No systematic reviews were found; there were 10 clinical trials for Rett syndrome, 12 for FAS and two for rare diseases, but none was relevant to our study. The internet was searched (www.google.com.au) using the same terms and 15 documents were reviewed from 10 relevant sites.

Articles and documents were reviewed only if they contained information on the impacts of rare diseases on families, clinicians, health services and policy.

RESULTS AND DISCUSSION

What are the impacts of rare diseases on patients, families, caregivers and the community?

Families and carers of children with rare diseases experience significant psychological stress due to social isolation, unemployment, diagnostic delays, uncertainty about the future, lack of information and difficulty accessing appropriate health care.[1 6–8] Access to appropriate health services has been described as a "post code lottery".[8] In the USA, 6% of people with rare diseases had to move home, and almost half had to travel more than 50 miles to access appropriate medical services.[1] In Europe, a quarter of patients with rare diseases had to travel to a different region and 2% to a different country for diagnosis,[6] and 26% of patients found it difficult or impossible to access medical services.[8] In Australia, a population-based longitudinal study of Rett syndrome highlighted difficulties in accessing services, lack of services and a shortage of appropriately trained therapists.[9] Transition from paediatric health services to the adult health setting is also recognised as a significant problem for girls affected by Rett syndrome.[9]

The social impacts for patients with rare diseases include isolation, stigmatisation, discrimination, and reduced educational and employment opportunities. At least half of all rare diseases have their onset in childhood and for many children schooling is disrupted or impossible.[1 2 9 10] Parents of girls with Rett syndrome report difficulties accessing appropriate education.[9 11] Similarly, children with FAS experience learning difficulties and two thirds require remedial education.[12] Delays in diagnosing FAS hinder opportunities for early educational interventions and increase the risk of future adverse outcomes such as imprisonment and long-term unemployment.[13 14] Estimates from the USA suggest FAS costs US$3.6 billion annually, and the lifetime cost per individual is estimated at

US$2.9 million.[15] There are no cost estimates for schooling children with disabilities resulting from rare diseases, but based on 1999–2000 USA school-year data, the cost of educating the average student with disabilities was almost double that required to educate a student without special needs.[16] A recent French study of children with disabilities showed that in 26% the disability was attributed to a rare disease.[17]

Families affected by a rare disease are under-supported, over-burdened and experience financial hardship.[1 6 9 11] There are few estimates of the costs to families of raising a child with a rare disease, although the cost of raising a child with a disability is significantly higher than for a non-disabled child.[18] Costs include specialised medical, allied health and educational services, specialised equipment, travel, and partial or total loss of income for the primary caregiver. In Australia, almost one third of mothers of girls with Rett syndrome reported loss of income from paid employment due to the need to care for their daughter.[9 11] Mothers also had significantly lower than average physical and mental well-being scores.[9 11] Families frequently access, and contribute financially to, respite or full time residential care for their children, which has economic implications for families and communities.[6 9–11] Services for FAS are costly and disruptive to families: more than two thirds of children with FAS live in foster or residential care and more than a third of affected adolescents are hospitalised for psychiatric or drug and alcohol treatment.[12–14] The quality of life for siblings of children with rare diseases also suffers.[11 19]

Although many rare diseases are incurable, parents value a definitive diagnosis (box 1). It allows parents to explain what is wrong with their child and to plan for ongoing care for the child and for future pregnancy.[20] Having a diagnosis alleviates some of the stress and powerlessness associated with not knowing.[7 20–22]

The internet is increasingly used as a source of information and support by families affected by rare diseases.[23–25] In Europe, the UK, the USA, Canada and New Zealand, web portals provide access to family support groups such as "Contact a Family" in the UK.[24] The Rare Disease Patient Solidarity Project of the European Organisation for Rare Diseases (EURORDIS) provides information on services for respite and social integration and telephone help lines, and conducts social research to determine the collective needs of people with rare diseases in Europe.[25] In Australia, the Association for the Wellbeing of Children in Healthcare (www.awch.org.au) and the Association of Genetic Support of Australasia Inc (http://www.agsa-geneticsupport.org.au/) provide lists of support groups and the SMILE Foundation supports rare disease research (www.smilefoundation.com.au). Families affected by rare diseases need accurate, locally relevant information, advocates and opportunities to interact with other families. National rare diseases support websites are still required in many countries.

What are the impacts of rare diseases on clinicians and health services?

Rare diseases pose a challenge to clinicians working in primary, secondary and tertiary health care settings.[3 6–8] For many rare diseases standardised diagnostic criteria do not exist, resulting in multiple, often avoidable investigations.[6 7 26–28] Diagnostic delays are common: a third of USA patients remained undiagnosed for more than a year,[1] and a quarter of European patients waited between 5 and 30 years for a definitive diagnosis.[6] In Australia, a diagnosis of Rett syndrome is frequently delayed, sometimes for years.[9] Only 19% of Australian paediatricians knew the diagnostic criteria for FAS and 70% were concerned that making a diagnosis would stigmatise the child.[26] Once a diagnosis is reached, clinicians are challenged by a lack of management guidelines, referral pathways and services for their patients.[26–29] Difficulties with diagnosis and management often stem from lack of knowledge, lack of evidence-based information or difficulty accessing information.[3 9 12 26–29] Because there are approximately 8000 rare diseases, it is unrealistic to provide training for health professionals on every disease. Nevertheless, primary care clinicians and paediatricians believe there is insufficient awareness about rare diseases and want access to evidence-based information for themselves and their patients about diagnosis, management and specialised referral clinics.[3 7 9 12 29]

There is scant information about clinicians' use of the internet to obtain information about rare diseases.[28 30] In a random sample of New Zealand general practitioners, 48.6% had sought clinical information from the internet, predominantly about rare diseases.[28] EURORDIS, the National Organisation for Rare Diseases (NORD) and the Office of Rare Diseases (National Institutes of Health, USA) maintain databases on over 5000 rare diseases and promote the latest research.[31–33] Orphanet provides free access in six languages and a "search by clinical signs" facility to aid diagnosis.[34] These web portals provide links to relevant clinics, registries and support groups. Although they can be accessed from anywhere in the world, they are most useful to families and health professionals if they provide local information about educational opportunities, referral services and patient support groups.[3]

The frequent use by people with rare diseases of multiple health professionals and their need for specialised services, investigations, equipment, therapies and orphan drugs, significantly impacts on health expenditure.[1–3 9 35 36] For example, girls with Rett syndrome are often severely disabled and functionally dependent due to problems with development, mobility, epilepsy, scoliosis and other orthopaedic conditions, feeding, constipation, gastro-oesophageal reflux and sleeping.[9 29] Each year a girl with Rett syndrome attends an average of nine medical appointments, one third require hospital admission,

Box 1 Parent comments about the importance of a diagnosis

- "Obtaining the correct diagnosis has had significant implications for us… We were able to understand and accept Rett syndrome… We are finally able to explain to others, when they ask, what is wrong and to foster more realistic expectations of our child's future including planning ahead for equipment and schooling and also to further extend our family."[20]
- Comments after a child who had been dead for 14 years was diagnosed with Rett syndrome by analysis of DNA from a baby tooth: "It's healing… It was this huge relief when they told us… I spent all my time when she was alive looking for an answer".[21]
- Parent of a child with a rare disease, as yet undiagnosed: "I had to find the right doctors and to be insistent but not obstinate. On the one hand, I had to save Mathilda from unnecessary diagnostic tests, often saying 'no' and 'why?'. On the other hand, I had to ensure that she received everything she needed".[7]
- From the birth mother of a child subsequently diagnosed with FAS: "I need to do something for him, but I don't know what to do next. I need a diagnosis so that I can help him manage".[22]

and over two thirds attend regular therapy sessions.[9 11 29] Similarly, FAS results in physical, behavioural and learning disabilities with lifelong implications; in the USA the medical costs alone of FAS are estimated at US$2.8 billion annually.[36]

Several EU countries have established integrated health services to provide family counselling, respite, referral services, educational resources and information on the latest research into treatments for rare diseases.[34] For example, the Agrenska Centre in Sweden provides integrated services to children with over 140 rare diseases.[37] Average health care costs per child using the Agrenska program are approximately one third of those for similarly affected children accessing non-integrated disability programs.[37] In many countries there are few specialised diagnostic and management services for rare diseases, including FAS[38] and Rett syndrome.[9]

How have governments responded with regard to health services, research and policies relating specifically to rare diseases?

Governments initially responded to the burden of rare disease by introducing "orphan" drugs legislation. The USA Orphan Drug Act (1993) supported pharmaceutical companies to develop new drugs for rare diseases.[35] Similar policies were implemented in Singapore (1991), Japan (1993), Australia (1998) and the European Union (2000). In 2005, orphan drugs gained international attention when the WHO Expert Committee on the Selection and Use of Essential Medicines recognised the need to add orphan drugs to the Model List of Essential Medicines.[39] The wider community also benefited, because many important drugs with wide application, such as erythropoietin and infliximab, started life as orphan drugs.[34 40 41] However, the high cost of developing and providing orphan drugs poses significant challenges for governments.[39–42]

In 2002 the USA passed the Rare Diseases Act and established the Office of Rare Diseases within the National Institutes of Health to promote research, stating[32]:

> Because of the small number of affected patients in any one location, rare disease research requires collaboration of scientists from multiple disciplines and the capacity to share access to geographically distributed national research resources and patient populations. Knowledge about rare diseases may offer leads for scientific advancement in other rare diseases and in more common diseases.

The introduction of rare disease policy resulted largely from lobbying by patient advocacy groups such as NORD and EURORDIS.[31 33] Similar umbrella organisations have been established in Canada (CORD) and New Zealand (NZORD)[3] and both are advocating for national government plans to address rare diseases. On February 29th 2008, EURORDIS, in partnership with national rare disease alliances, held the first European Rare Disease Day, which culminated in a public hearing on rare diseases at the European Parliament in Brussels.[43] Many countries outside Europe also joined Rare Diseases Day.[43]

Rare diseases are under-researched, resulting in a lack of evidence for translation into clinical practice and health and social policy. This gap is increasingly addressed by clinicians through the establishment of research networks and registries, including the British Paediatric Orphan Lung Disease registry,[44] the UK Obstetric Surveillance System,[45] and the InterRett database.[46] The Rare Diseases Clinical Research Network[35] and Orphanet[34] facilitate the development of registries, national centres of reference and research networks. Given the complexity of rare diseases, inter-institutional and international research collaboration is needed, both to recruit sufficient numbers of cases and share highly specific expertise that is unlikely to exist within a single institution. In the USA, the National Institutes of Health recently launched the Undiagnosed Diseases Program, which brings together experts from a number of eminent institutions and is accessible to patients with longstanding undiagnosed diseases and their doctors.[47]

Paediatric surveillance units (PSUs), established and supported by paediatricians, are a valuable source of prospective national data on the epidemiology, management and outcomes of rare childhood conditions but struggle with underfunding.[48] For most conditions studied, PSUs provide the only national data, which inform clinical and public health policy, stimulate further research and enable establishment of cohorts of patients for intervention and longitudinal studies.[48]

Many countries including the USA, France, Greece, Spain, Italy, Portugal and Romania, have specific national policies and plans that include support for research into rare diseases.[2 3 49–51] The USA and at least nine EU countries have allocated specific funding for rare diseases research; for example, Italy has allocated €8.3 million per annum for basic and clinical research and clinical trials.[49] The French National Rare Diseases Plan was the first to provide multiple strategies to address the complex impacts of rare diseases (box 2).[51] The European Union Task Force on Rare Diseases is currently calling on all EU countries to adopt similar coordinated national plans.[50] In Australia, family physicians, paediatricians and researchers have called for a coordinated response to the burden of rare diseases.[52]

CONCLUSIONS

The low prevalence of rare diseases belies their social and economic impact, which extends beyond affected individuals. Economic impacts are associated with provision of specialised health and educational services, loss of income for caregivers and loss of productivity for society. In addition, health departments are challenged by the costs of specialised services and orphan drugs. However, few estimates have been published of the economic burden to society from rare diseases, individually or collectively. Economic analysis should be a priority to inform health service planning and resources.

Many governments recognise the need to support research that provides information on the epidemiology, aetiology and management of rare diseases and will inform clinical guidelines and health policy. Our review indicates the EU and USA have responded to the burden of rare diseases by allocating research funds and developing coordinated national plans aimed at improving quality

Box 2 French National Rare Diseases Plan 2005–2008[51]

Ten strategies to ensure "equity in the access to diagnosis, to treatment and to provision of care" for people with rare diseases:

- Increase knowledge of the epidemiology of rare diseases
- Recognise the specificity of rare diseases
- Develop information for patients, health professionals and the general public concerning rare diseases
- Train health professionals to better identify rare diseases
- Organise screening and access to diagnostic tests
- Improve access to treatment and the quality of patient care
- Continue efforts in favour of orphan drugs
- Respond to the specific accompaniment needs of people suffering from rare diseases
- Promote research on rare diseases
- Develop national and European partnerships.

of life for affected individuals. National plans provide important roadmaps to address common issues faced by people with rare diseases. However, decisions cannot be based on economics alone, and must be considered within the context of evidence from medical research and ethical and moral principles.

Patient organisations, including CORD and NZORD, are currently calling for coordinated government plans to address the impacts of rare diseases. In many countries, there remains an urgent need for a national plan and patient-focussed organisations to advocate on behalf of families. Priority funding for research into the health, social and economic burdens of rare diseases and the needs of affected individuals is required to provide an evidence base to support public health policy. Paediatricians have an important role in advocating for this neglected group of children.

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