DEFINING AND COUNTING RARE DISEASES IS NOT STRAIGHTFORWARD.

For more information:

- European Organisation for Rare Diseases (EURORDIS) www.eurordis.org
- National Organization for Rare Disorders (NORD) www.rarediseases.org
- Orphanet database of information on rare diseases and orphan drugs www.orpha.net

Over 6,000 rare diseases affect over 300 million people worldwide. Rare diseases became known as orphan diseases because drug companies were not interested in adopting them to develop treatments. Although people may think of a rare disease as something that happens to someone else, rare diseases can afflict anyone, at any age (1-7).

Firstly, rare diseases are characterised by their low prevalence (less than 1/2,000) and their heterogeneity. They affect both children and adults anywhere in the world. Because rare disease patients are a minority, there is a lack of public awareness; these diseases do not represent a public health priority, and little research is performed (1-7).

Other countries have their own official definitions of a rare disease. In the European Union, a disease is defined as rare when it affects fewer than 1 in 2,000 people. In the United States, a rare disease is defined as a condition that affects fewer than 200,000 people (1-7).

For many disorders, there is a broad diversity of subtypes of the same disease. It is estimated that between 5.000 and 7.000 distinct rare diseases exist today, affecting patients in their physical capabilities, their mental abilities, in their behaviour and sensorial capacities (1-7).

There are many different causes of rare diseases. The majority are thought to be genetic, directly caused by changes in genes or chromosomes. So far what many have failed to realise is that, while patients are few, collectively they represent more than 60 million people in Europe and the US alone (1-7).

The 80% of rare diseases have identified genetic origins, involving one or several genes or chromosomal abnormalities. They can be inherited or derived from de novo gene mutation or from a chromosomal abnormality. They concern between 3% and 4% of births (7-12).

Fifty percent of rare diseases manifest in adulthood. Other rare diseases are caused by infections (bacterial or viral), or allergies, or are due to degenerative, proliferative or teratogenic (chemicals, radiations, etc) causes (7-12).

Many rare diseases, including infections, some rare cancers, and some autoimmune diseases, are not inherited. Moreover, medical research on rare diseases is fast becoming an important source of advances in medical technology and genomics, which could hold the key to future treatments for all diseases (7-12).

For many rare diseases basic knowledge, like cause of the disease, pathophysiology, semiology, natural course of the disease and epidemiological data is limited or worse, missing. Difficulties in obtaining definitive diagnoses contribute, as do limitations in systems for reporting and tracking such diagnoses. Some rare diseases are also caused by a combination of genetic and environmental factors (7-12).

There is also great diversity in the age at which the first symptoms occur. Symptoms of many rare diseases appear at birth or in childhood, including Infantile Spinal Muscular Atrophy, Neurofibromatosis, Osteogenesis Imperfecta, Rett syndrome and most metabolic diseases, such as Hurler, Hunter, Sanfilippo, Mucolipidosis Type II, Krabbe diseases, Chondrodysplasia. In some cases, the first symptoms of the disease, such as Neurofibromatosis, may occur in childhood, but this does not prevent much heavier symptoms to occur at a later stage of life (7-12).

Finding expert help is too frequently a matter of luck rather than a consequence of systematic planning by national health systems. Whilst many diseases cause symptoms in childhood, these symptoms may not translate into a specific rare diagnosis for years. Other rare diseases, such as Huntington disease, Spinocerebellar Ataxias, Charcot Marie Tooth disease, Amyotrophic Lateral Sclerosis, Kaposi's Sarcoma and thyroid cancer, are specific to adulthood (7-12).

Despite differences in their severity and expression, nearly all rare diseases involve a significant reduction in life expectancy. Many rare diseases are complex, degenerative, and chronically debilitating, affecting the person's physical, mental, sensory, and behavioral capacities. However, in some cases, when diagnosed in time and treated correctly, they allow living a normal life (7-12).

Manifestations of rare diseases can occur either at birth or during childhood (Williams and Prader-Willi syndromes and retinoblastoma) or at any phase in adulthood (Huntington disease, Creutzfeldt-Jacob disease, and amyotrophic lateral sclerosis) (7-10).

Moreover, a number of more common rare diseases such as cystic fibrosis and sickle cell disease have known causes and reasonably well understood mechanisms but lack cures, satisfactory treatments, or preventive strategies. Nonetheless, identifying the cause of a condition is usually an important step in building the knowledge base for prevention or effective treatment (7-10).

Treatment of symptoms is the mainstay in many cases. Some rare diseases are now preventable, many are not. Diagnosis is sometimes straightforward but often frustratingly slow. Cures exist for a few conditions but are a distant hope for most (7-10).

Research suggests that genetic factors may affect susceptibility to infectious agents, either increasing susceptibility or having a protective effect. For example, research indicates that sickle cell trait contributes to resistance against malaria. Other genes are likely to affect susceptibility to malaria and leprosy (7-10).

Researchers and policymakers have focused on rare diseases to determine whether they should be awarded different status from that of other diseases, especially in the economic evaluation of related health technologies (9-14).

Medical and scientific knowledge about rare diseases is lacking. While the number of scientific publications about rare diseases continues to increase particularly those identifying new syndromes less than 1,000 diseases benefit from a minimum of scientific knowledge, and these are essentially the "most frequent" amongst rare diseases (9-14).

The acquisition and diffusion of scientific knowledge is the vital basis for identification of diseases, and most importantly, for research into new diagnostic and therapeutic procedures (9-14).

For patients, families and individuals affected by rare diseases, gaining access to services is often extremely difficult. Fragmented knowledge about such diseases, and often limited access to research material, means it is critical that investments in fundamental research go hand in hand with investments in dedicated infrastructure and international networks (9-14).

Finding expert help is too frequently a matter of luck rather than a consequence of systematic planning by national health systems (9-14).

Rare diseases are often life-threatening. They are chronic, progressive, degenerative and disabling. People living with rare diseases face many common challenges, such as delayed or inaccurate diagnosis, difficulty accessing care and lack of knowledge or access to expertise. For the individual sufferer this is a disaster, and for an economy it represents a significant direct and indirect cost (9-14).

Policy makers may also consider epidemiologic information on prevalence and disease burden in combination with scientific, political, economic, ethical, and other factors in making decisions about the allocation of resources for biomedical research. Decisions about research spending, for example, sometimes favor the relatively more common rare conditions such as ovarian cancer, neurofibromatosis, and sickle cell disease, but decision makers also have directed resources to extremely rare diseases, consistent with the value judgments underlying the adoption of special policies to encourage research on rare diseases (9-14).

The prevention of rare diseases may take different approaches. Some preventive strategies are relatively simple but striking in effect, while others are complex and demanding. Some raise ethical questions. The discussion below considers primary and secondary prevention. Tertiary prevention, which involves treatment of evident disease to avoid further progression or suffering or to restore health or function, is considered here as treatment (9-14).

For many patients, diagnosis comes a frustratingly long time after symptoms first become evident. It follows countless tests and visits to different specialists and centers with multiple diagnoses considered and initially or eventually rejected. This kind of diagnostic odyssey for a rare condition is often described in television shows and newspaper stories about diagnostic mysteries (9-14).

Diana Carolina Esguerra Sánchez[1]
María Virginia Pinzón Fernández [2]
Luisa Fernanda Zúñiga-Cerón [3]
Luisa Fernanda Mahecha Virgüez[4]
Jhan Sebastián Saavedra-Torres[5]

About the authors:
1- Medical - Medical Cooperative University of Colombia, Faculty of Medicine, Health Research Group (GIS) - Popayán - Colombia.
2- Bacteriology, Esp. Education, Master's Degree in Public Health, PhD candidate in Medical Anthropology, Full Professor of Universidad del Cauca.
3- Medical student - National University of Colombia, Faculty of Medicine, Laboratory to the Field Corporation (DLC), Health Research Group (GIS) - Popayán - Colombia.
4- Student of Nursing, University of Cauca, Faculty of Health Sciences, Department of Nursing, Health Research Group (GIS) - Popayán - Colombia.
5- Medical student - Universidad del Cauca, Faculty of Health Sciences, Department of Internal Medicine, Laboratorio al Campo Corporation (DLC), Health Research Group (GIS) - Popayán - Colombia.

REFERENCES:

1. Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010. 2, Profile of Rare Diseases.Available from: https://www.ncbi.nlm.nih.gov/books/NBK56184/
2. Johns Hopkins Bloomberg School of Public Health. Fundamentals of Epidemiology. Life Tables. Johns Hopkins Bloomberg School of Public Health website [online], http://ocw.jhsph.edu/courses/FundEpi/PDFs/ Lecture8.pdf (2008).
3. Abbott A. Rare-disease project has global ambitions. Nature 472(7341), 17 (2011).
4. More information about the EurordisCare 2 survey can be found on the following websites: http://www.eurordis.org and http://www.rare-luxembourg2005.org/
5. Julkowska D. *et al* The importance of international collaboration for rare diseases research—a European perspective. Gene Ther. (2017).
6. Christopher P. Austin. Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective. Clin Transl Sci. 2018 Jan; 11(1): 21–27. Published online 2017 Oct 23. doi: 10.1111/cts.12500
7. EURORDIS , *The Voice of 12,000 Patients: Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe* . 2009: EURORDIS-Rare Diseases Europe.
8. Melnikova I. Rare diseases and orphan drugs. Nat. Rev. Drug Discov. 11(4), 267–268 (2012).
9. An NCI working group has defined rare cancers as having an incidence of 40,000 or fewer cases rather than in terms of prevalence (Mikhail, 2005). This specification apparently relates to the specific challenges of clinical research involving populations that include many individuals who have undergone therapies, sometimes multiple therapies.
10. Background Paper on Orphan Diseases for the "WHO Report on Priority Medicines for Europe and the World" – 7 October 2004.
11. "Rare Diseases: understanding this Public Health Priority" - Eurordis, November 2005 – www.eurordis.org
12. Shieppati, A., Henter, J., Daina, E. & Aperia A. Why rare diseases are an important medical and social issue. Lancet 371, 2039–2041 (2008).
13. The European Parliament and the Council of the European Union. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Official J. Eur. Communities L 18/1– L 18/5 (2000).
14. Sara Cannizzo. Rare diseases under different levels of economic analysis: current activities, challenges and perspectives. RMD Open. 2018; 4(Suppl 1): e000794. Published online 2018 Nov 12. doi: 10.1136/rmdopen-2018-000794