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Editorial article

Rare diseases in Spain: a look into the future☆

Las enfermedades minoritarias en España: una mirada hacia adelante

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In Europe, rare diseases (RDs) affect less than 5 people per 10,000 inhabitants.[1] There are between 6,000 and 7,000 RDs, so despite their low frequency, they affect 6–8 % of the population, and it is estimated that there are more than 3 million people affected in Spain. Furthermore, most of these diseases are chronically debilitating or life-threatening and due to their low frequency require special efforts to combat them. For all these reasons, RDs represent an important health problem to be addressed. In Spain, notable progress has been made in the management of patients with RDs in recent years. Several specialised units of high scientific level have been set up and have contributed to the dissemination of these diseases, to improve their diagnosis and treatment, as well as to the development of a Strategy on Rare Diseases in the National Health System (NHS).[2–7] Despite this, there are still a number of common challenges to be met and overcome.

Firstly, the dissemination of these diseases and the training of the professionals involved must be improved. In this sense, training on RDs could be included. MM. in the degrees of the different future health professionals (Medicine, Nursing, Psychology, etc.) or during specialized health training, both in medical specialties (as is already the case with the specialty of Internal Medicine), and in Clinical Psychology or Nursing.

Since most RDs have a genetic cause, it is essential to generalize the availability of genetic studies. This is essential to reduce diagnostic delay, which is common in these diseases, and to identify the molecular basis of new RDs, thus harmonizing clinical and molecular diagnosis.[8] NGS (*next-generation sequencing*) panels with the various genes involved according to different groups of RDs (e.g., congenital aortopathy) or *whole exome sequencing* (WES), or *whole genome sequencing* (WGS) are contributing to this. The complexity of these studies and their interpretation confirms the importance of including a clinical geneticist in the care of patients with RDs The official recognition of this professional is a real challenge in Spain, where there is no such accredited specialization. Efforts must also be made to ensure the standardised certification of genetic counsellors, recognition of their professional role and regulation of their competencies, such as genetic counselling, clinical analysis of variants of uncertain significance, parental segregation analysis or providing appropriate information and support to patients and relatives from a genetic perspective.[9,10] The ability to address the accreditation of clinical geneticists and genetic counsellors in Spain will contribute to the optimal utilisation and cost-effectiveness of genetic studies, or going a step further, to the incorporation of functional biological or multi-omics analyses into molecular studies.[5,20] All these developments will also help to address the necessary commitment to respond to patients with undiagnosed RDs.[11] In this sense, we must mention that there is a Programme for undiagnosed RDs in Spain (called *SpainUDP*) within the Rare Diseases Research Institute (IIER) belonging to the Carlos III Health Institute, which aims to offer a genetic diagnosis to these patients through a multidisciplinary clinical approach and using different omics techniques (https://spainudp.isciii.es). Regarding other improvements in diagnosis, the service portfolio of the Neonatal Screening Programme should also be expanded and standardized among the different autonomous communities, in order to improve the early identification and treatment of certain RDs in newborns.

Although they are mostly genetic, not all RDs start in childhood. It is estimated that roughly half of all RDs either start or are diagnosed late in adulthood. This aspect is essential, as it requires the establishment of a high index of suspicion in the adult patient setting, where the Spanish health system is more focused on the prevention and treatment of prevalent diseases, such as cardiovascular diseases. It also involves coordinating paediatric care with adult care and highlights the importance of transitional circuits from paediatric to adult age. An adequate transition is essential for the correct follow-up of these patients, at such a delicate time as adolescence. To overcome these barriers, the transition must be understood as a process that needs to be planned, systematised and standardised, in order to educate patients and families about the disease and to introduce the characteristics of the new healthcare environment.[12] The ïreverse transitionöf children of adult RD patients to paediatric RD units should also be promoted. All this implies the need for health policies that establish stable bridges between Pediatric and adult units. This aspect takes on greater relevance and complexity among those hospitals that exclusively care for paediatric or adult patients.

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Most RDs are systemic, which, together with their low frequency, make their diagnosis and management complex. In order to overcome this complexity, it is imperative that RD units have a multidisciplinary approach. This multidisciplinary approach must be considered in the deepest sense, not only with the incorporation of different medical specialties, but towards interprofessional collaboration, including also other health professionals. In this regard, it is worth highlighting the need for clinical nurses with RD training within the NHS. Their role adds value to the follow-up of these patients, as it has already occurred with other diseases, such as heart failure.[13] The role of the clinical nurse should not be confused with that of the case manager. Their functions improve the quality of medical care, especially by designing both intra- and inter-hospital efficient and flexible care circuits and coordinating complementary examinations and visits with different health professionals. In addition, the diagnosis of a RD has a serious psychological impact, not only for the patient but also for their family.[14] This impact highlights another shared need in the care of patients with RDs in Spain, namely the lack of clinical psychologists forming part of these units. As they are chronic and progressive, RDs often limit patients' functionality and lead to varying degrees of disability or dependence. Therefore, a social worker should also be part of the RD units, someone who is well acquainted with the needs and resources available for these patients. Although it is clear that the possibilities of each hospital in Spain are different in terms of incorporating different professionals, recognition by the management of each centre and by external agencies, such as scientific societies, is essential for the dissemination and consolidation of these units. Moving from multidisciplinary units to solid interprofessional teams, as required by international standards, will contribute to modernizing and adding value to the management of patients with RDs, according to their needs.

The approach to patients with RDs should include referral and follow-up circuits coordinated between the referral unit and the professionals, both from health centres and other hospital centres closer to the patient. It is important that the members of the RD units together with the Family and Community Medicine specialists develop optimal referral protocols between the hospital centre and the health centres dependent on it. This contact will facilitate the appropriate and swift referral of patients suspected of having a rare disease to the appropriate facility and will also improve the joint follow-up of these patients and RD training in health centers.[15] Due to the difficulty of finding professionals with sufficient experience in the various specific RD areas, sharing their knowledge between different centres is a resource to be developed. This implies the implementation of a truly well-developed c̈onsultation telemedicine, which would bring benefits in the clinical assessment of patients with RDs, contributing both to their early diagnosis, as well as to their follow-up and optimal therapeutic decisions without the need for unnecessary patient transfers. This new care practice should be recognised and adapted according to the required material and human resources.

Ensuring access to the European RD networks (ERN, *European Reference Networks*), which so many units deserve in the Spanish territory, will be decisive for their future competitiveness. ERNs are virtual networks of healthcare providers across Europe that facilitate discussion about RDs requiring a highly specialized approach and treatment, and a concentration of knowledge and resources. Access to these networks is regulated by the European Union, but the way to access them is different in different countries. In Spain, access to a ERN is determined by accreditation as a CSUR (reference centre, service or unit of the National Health System). Due to the operational difficulties of these accreditations, it seems imperative to either increase the resources allocated to streamline these accreditations or to officially modify the access to ERNs by means of other criteria defined at state level in accordance with European standards, both in terms of care, training and research. To this end, the current Strategy on Rare Diseases of the NHS should be updated, and it is also recommended to promote a network platform that allows information and knowledge to be shared and to promote research between CSURs and ERNs.[7] In order to standardize care for patients with RDs at a European level, access and reimbursement of so-called orphan drugs in Spain should also be regulated, based on quality-of-life outcomes.[16]

The systemic nature, low frequency and great clinical variability of RDs mean that acquiring sufficient knowledge and experience about them is a complex task, especially in uncommon scenarios. Registries need to be set up to pool the experience of the different RD units in Spain, thus responding to a priority in their management.[17,18] The use of quality registries also makes it possible to reach consensus on diagnostic and therapeutic measures, to provide evidence for clinical guidelines and to generate hypotheses for clinical trials.[17,18] This will require official resources to be devoted to the proper coding of RDs. In addition to ICD-10 coding at national level, it is important to code according to the ORPHANET classification, which is based on the phenotypic, multi-systemic and hierarchical definition of RDs. This would make it possible to unify international diagnostic criteria and benefit from the *big data* provided by the different autonomous communities. The development and implementation of a National Registry of Rare Diseases should also be promoted, a project already initiated by the IIER (https://spainrdr.isciii.es).[7]

Another challenge is to bring basic research closer to clinical groups. Basic research allows, through cellular or animal models, to broaden knowledge of the pathophysiology of RDs and provide new therapeutic targets, either through therapeutic repositioning or with the development of new therapies.[6,19,20] This is the so-called translational medicine aimed at ẗransferringẗhe doubts raised by the patient, to generate new knowledge in the laboratory and return it to the patient.[20] Scientific societies should enhance and facilitate synergies between the two groups to provide this added value to the research conducted in Spain, there are several official organisations, such as the Centre for Biomedical Research on Rare Diseases Network (CIBERER), which could also contribute to this by introducing new groups, thus boosting research on rare diseases in our country. These improvements in research should have an impact on advances in treatment, which is essential in RDs as, despite therapeutic advances, most of them have no specific treatment and are incurable. Thus, translational medicine is a way to move towards personalised and precision medicine, a relevant objective to be achieved in the coming years in the RD context.

RD patient associations also contribute to overcoming all these challenges, highlighting in this sense the role played by the Spanish Federation of Rare Diseases (FEDER). The relationship with patients' associations is essential and, in turn, a key commitment of the different RD units. Channelling aid from private funds or from the pharmaceutical industry through these entities or scientific societies would also contribute to enhancing the transparency of these collaborations. It will also be essential to involve patients and family members in the RD units themselves in order to contribute to the empowerment of patients and their participation in decision-making. The training of ëxpert patientsc̈ontributes to these objectives, as the manifestations and prognosis of patients with RDs are explained by the patients themselves. These patients have a better health concept and are less dependent on hospital care, so the development of Expert Patient Programmes can be considered a cost-effective measure.[14]

The future and advances in the management of patients with RDs will be determined by the ability to address and overcome all these challenges. Following this course, outlined by so many professionals and guided by reference units, together with the support of official bodies, patient associations and scientific societies, the

future of RDs in Spain promises to be productive at the research level, but, above all, outstanding in the care of patients with RDs.

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Conflict of interest

None.

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