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Pachyonychia congenita, a paradigm for rare skin disorders

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Samuelov *et al.* Br J Dermatol 2020; **182**:738–746.

Weinberg *et al.* Br J Dermatol 2020; **182**:543–551.

Koren *et al.* Br J Dermatol 2020; **182**:671–677.

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A rare disease, as defined in Europe, affects ≤ 1 in 2000 individuals.[1] These are often chronic and complex, with significant associated morbidity and mortality. Patients frequently face the additional challenges of delayed diagnosis, a lack of local expertise and a paucity of effective treatments.[1] Although individually rare, there are 5000–8000 rare disorders,[2] affecting an estimated 30 million individuals in Europe alone.[1] The global burden is thus significant.

Rare conditions are included in the definition of 'orphan disease' from historically being the 'orphan' of research focus, market interest and public health policy.[1] However, in more recent times, there has been a growing recognition of their impact. Many countries have now adopted strategies specifically aimed at improving care standards,[3] such as the U.K. Strategy for Rare Disease,[2] and legislation passed to incentivize drug development has led to the approval of hundreds of new treatments.[4] Rare disorders have also been included in the remit of important genomic studies, such as the U.K.'s 100 000 Genomes Project and the U.S. National Institutes of Health All of Us project. Progress is being made particularly in genetic characterization but there is a long way to go, with the overwhelming majority of these rare disorders remaining without effective treatment.

Collaboration is recognized as a key element between patients and researchers, different centres and the interactions of diverse healthcare professionals. In this issue of the *BJD*, collaboration is used to report on rare cohorts, providing new insights in larger groups of patients. From national collaboration or centralization, we learn about the impact of epidermolysis bullosa on the quality of life and mental health of 81 children (Soon *et al.*),[5] the genotype–phenotype correlation for autosomal recessive ichthyosis in 146 individuals (Simpson *et al.*)[6] and the use of transmission electron microscopy in 177 individuals with Ehlers–Danlos syndrome (Angwin *et al.*).[7]

For some rare disorders, cohorts will be small, even with national collaboration. Global registries have been proposed as a solution[8] and can create an infrastructure that facilitates education, understanding, research and ultimately outcome improvement.[8] However, there are barriers to their formation and very few exist.[8] This issue of the *BJD* is fortunate to include results from the global registry for pachyonychia congenita (PC): the International Pachyonychia Congenita Research Registry (IPCRR). PC is thought to be a particularly rare skin disease. Its prevalence has been estimated at 0·9 per 1 000 000 individuals,[9] although data from individual countries within the registry suggest that this is an underestimate. From use of this registry, Samuelov *et al.*[9] report on the results of 815 patients with genetically confirmed PC. The authors detail the clinical features of PC by age and genotype, as well as its significant impact on quality of life and mental health. The results offer a valuable insight into the variability and needs of the patient population, as well as excitement about soon overcoming the traditional barriers to investigating rare disorders, such as small cohorts and poor understanding of their natural history.[4]

Evaluative research assessing outcomes that matter the most to patients is important. In the IPCRR, plantar pain had the biggest impact upon quality of life. In their review of pain in hereditary palmoplantar keratodermas, Weinberg *et al.*[10] highlight subepidermal blisters and neuropathic pain as potential drivers of this pain in PC. Although many therapeutic agents have been suggested for this, evidence for these is limited to case reports or series. In this issue, Koren *et al.*[11] report their protocol and a further case series of five patients treated by botulinum toxin injections. Although they suggest a benefit their conclusion is limited by the small sample size and the possibility of a benefit arising from a placebo effect due to the lack of a control arm.

Through identifying large patient cohorts, rare disorder registries may permit comparative studies that more rigorously assess these treatments, utilizing novel trial designs to overcome the challenges unique to rare conditions such as the global dispersion of cases.[4] Registries also encourage interest from academic researchers and pharmaceutical companies.[8] Topical rapamycin, previously reported as beneficial in a 2009 case series,[12] is now undergoing phase II/III evaluation (VALO trial) for three subtypes of PC (PC-KRT6A, PC-KRT6B, and PC-KRT16), sponsored by a pharmaceutical company. More trials for PC are expected to follow, with the IPCRR having the ambition of taking new laboratory discoveries into active studies.

Supporting basic research has been crucial to advances in PC and other rare diseases. Statins were trialled[13] after Zhao *et al.* identified that the only drug-like chemical to significantly reduce *KRT6A* promoter activity in transfected immortalized keratinocytes was a statin-related component.[14] Likewise, the rationale for assessing topical rapamycin was the finding that

functional keratin 6A and 6B mRNAs were found throughout the epidermis, but were only expressed in the palmar and plantar skin – suggesting a potential role for selectively blocking mRNA translation.[12] Funk *et al.*[15] detail several current active avenues of investigation in PC that may provide the inspiration for future studies.

The IPCRR serves as a paradigm for the investigation of rare skin diseases. It has identified a large cohort of patients, described presentation by genotype and age and identified what matters most to patients. Patients continue to enrol in the IPCRR and participation of patients in research is encouraged with the ultimate goal of improving outcomes. It was initiated and funded by the Pachyonychia Congenita Project (www.pachyonychia.org), a patient-driven advocacy group. The Pachyonychia Congenita Project has also funded much of the research in PC, including the aforementioned reports on statins and topical rapamycin,[12,14] and it is an active partner of the VALO trial. The group also provides valuable education and support to affected individuals and families, including opportunities to meet others who are affected, and has been the main driver of advances in PC. Other advocacy groups for rare disorders include DEBRA International and the Ichthyosis Support Group. Together, they have a major role in raising the profile of these rare conditions and ultimately in making positive changes to the lives of patients and their families.

This issue of the *BJD* reflects the growing interest in research in rare skin diseases. Collaborative efforts, including the use of rare disease registries, will continue to drive improvements in patient care. Together with advances in genomics, this will push our ability to understand, diagnose and potentially treat such disorders in the future. After years of neglect, now is a time for optimism.

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