Studies on mendelian disorders of cornification

5.3 Valorisation

There are ample reasons to study rare diseases such as the Mendelian disorders of cornification (MEDOC) and the clinical and genetic heterogeneity in MEDOC. First of all, people have them; they are affected by and suffer from MEDOC. Without research on the clinical and pathophysiologic aspects of their disease, it is impossible to deliver appropriate care to these patients. The low prevalence of MEDOC is not an argument to ignore the needs of these patients. Secondly, the study of MEDOC grants us insight in fundamental principles of epidermal functioning. Our knowledge of skin disease is severely limited, mostly because we understand very little about how normal human skin works. By studying the models that nature is offering us, we might attain some comprehension. This understanding may be helpful, in a strict sense, in the development of refined diagnostic strategies and (targeted) therapies for MEDOC. In a broader sense, the extent of the expanding comprehension of epidermal homeostasis may reach as far as areas as the pathophysiology of non-genetic, multifactorial and more common skin diseases such as auto-immune blistering disorders, psoriasis or wound healing. Thirdly, the value of describing clinical and genetic variability lies mainly in the field of patient management: our study provides tools to dermatologists and clinical geneticist that will hopefully improve diagnosis and treatment of MEDOC. Lastly, fundamental research or research without direct apparent benefits for large numbers of individuals is valuable by itself.

The disease burden of MEDOC. MEDOC are rare diseases with few individuals affected in absolute numbers, but the lives of patients are influenced in a profound way. In this regard, MEDOC patients differ from the general dermatological population. Skin diseases are a significant health problem. The disease burden of dermatologic disorders is high in the general population: all skin conditions combined were the fourth leading cause of non-fatal disease burden at the global level[84,85]. However, this is mainly due to the high prevalence of dermatologic disease. The disability rate of most skin diseases is relatively low[84,85]. The opposite is the case for MEDOC. These skin diseases are rare – the reported prevalence for DD is 1:30,000-100,000[86], for EI 1:200,000[87,88] and for MDM <1:1,000,000 (estimated[1]) – but they have a significant impact on health related quality of life (HRQL). Several studies identified a substantial impairment of quality of life in patients with DD[55,89], HHD[89,90] and EI[62-64]. Furthermore, the mean health care related costs associated with congenital ichthyosis, among which EI, is estimated

at $3,192 per annum[62,91]. Up to 30% of these costs is borne out of pocket by patients. Although no cost analysis studies have been performed for DD, HHD and MDM, it can be expected that these costs may be in the same order of magnitude as for ichthyosis. Research efforts and improving knowledge are important steps in optimizing care and treatment to alleviate the burden of patients with MEDOC and reduce health care costs for patients and society.

The advancement of our understanding of the skin. The study of these disorders has provided much insight in epidermal homeostasis. In the past two decades, almost all MEDOC have been linked to defects in various proteins associated with keratinocyte function and differentiation. The prevailing view on epidermal physiology was the "bricks and mortar"-model. Improper functioning of structural proteins due to mutations in their coding genes was thought to impair either the keratinocytes (bricks) or proteins connecting the keratinocytes (mortar). The discovery of defects in genes encoding structural proteins such as keratin 1, causing EI, supported this view. With the discovery of mutations in *ATP2A2*, *ATP2C1* and *SLURP1* as the cause of DD, HHD and Mal de Meleda (MDM) respectively, the "brick and mortar"-model proved to be an insufficient metaphor for epidermal homeostasis[92]. *ATP2A2* and *ATP2C1* encode intracellular calcium pumps and *SLURP1* encodes a protein enhancing the function of an epidermal nicotinic receptor. These proteins are parts of signaling pathways that coordinate cell differentiation and underlie the crucial role of keratinocytes in skin integrity. Research on these pathways revealed complex networks of interacting signal molecules in keratinocytes, and defects of these proteins heavily impair proper epidermal differentiation and function. Patients with MEDOC provide a great opportunity to study the biological consequences of gene mutations affecting epidermal biology in humans. To study a human disease model of MEDOC would otherwise be impossible.

Improvement of patient care. Diagnosis of MEDOC can sometimes be difficult, as we have shown in chapter III and IV for Epidermolytic Ichthyosis (EI), Darier disease (DD) or Hailey-Hailey disease (HHD). Research on MEDOC extends our understanding of the phenotype of these diseases and the disease course. This, in turn, helps physicians in their care for patients with a genodermatosis, which is often difficult. Treatment options are often limited, but almost all patients are helped significantly with a right diagnosis[93,94]. Making the right diagnosis often ends a period of doubt and uncertainty.

The physician therefore must be able to discriminate these rare diseases from more common skin ailments, and should be able to recognize atypical presentation of these diseases.