Editorial

Current status of genodermatoses: An Indian perspective

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Genodermatoses or genetic diseases of the skin are a group of inherited disorders with a conglomeration of cutaneous and systemic signs and symptoms. The rarity of the conditions and lack of awareness are major obstacles in the management and the planning of research in this specialty. This is especially relevant in the context of developing countries where multi-specialty networking or multi-centre collaboration may not be feasible. The pertinent issue is how to tackle a problem where the magnitude is undefined. The first step, therefore, is setting up disease-specific national registries with detailed phenotypic inputs for confirmation of accurate diagnosis. The relevance of this is obvious in the series of articles published by Fine *et al.* that reported the data of 3280 patients registered in the National Epidermolysis Bullosa (EB) registry of United States during the period 1986–2002 for the risk of childhood death and development of renal complications.[1,2] The information from this large series could help in formulation of disease and complication-specific guidelines. In contrast, no such registry has been initiated in a country like India with only case reports or case series of various genodermatoses being reported in literature.[3] In addition to the magnitude, there is dearth of data pertaining to the clinical presentation in our patients. This is a cause of concern because phenotypic heterogeneity is known in these syndromes and there is a need for country-specific management guidelines which are currently lacking. The study "Analysis of twenty pediatric cases of tuberous sclerosis complex – are we doing enough?" that appears in this issue is an attempt to generate data on the phenotypic presentation and systemic involvement in patients of tuberous sclerosis complex (TSC). The major strength of this study is that it is an example of the importance of multi-disciplinary approach to management of a genodermatosis with the involvement of dermatologist, pediatrician, and neurologist. The authors found that their patients had a higher retinal involvement (40%) than previous Western studies and a high incidence of mental deficit, epilepsy, and cortical tubers (30% each).[4] This calls for multi-centric Indian studies of a larger cohort to confirm these findings and generate protocols for the management of tuberous sclerosis complex. The main drawback of the study is the lack of genetic testing, which as the authors themselves state, has been included as a definitive diagnostic criterion in the 2012 revised guidelines.[4]

There is now better understanding of the genetic bases of genodermatoses with tremendous progress in their molecular diagnosis. The knowledge of genetic mutations facilitates the determination of gene function and correlation of the genotype with phenotype. The latter is especially relevant for prognosis and to make informed management decisions. Mutation analysis permits the offering of appropriate genetic counseling and makes DNA-based prenatal diagnosis feasible in high risk families.[5] The process was initiated in 1987 with the discovery of the deletion defect in the steroid sulfatase gene resulting in X-linked recessive ichthyosis. With the completion of the human gene project in 2003, we now have a mutation and single nucleotide polymorphism database of the majority of single gene inherited

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skin disorders.[6] However, most research has been confined to the Western population with very few reports providing mutation analysis from India[3] and there is paucity of data about novel mutations that may characterize the phenotypic presentation of a particular syndrome in our context. This highlights the importance of the study by Tamhanker *et al*. The authors present clinical and mutation analysis data of 13 patients with xeroderma pigmentation (XP). As stated by them, no previous mutation data is available in the 37 Indian families reported till date. They detected frame shift mutation resulting in stop codon formation in the XPA gene of patients with severe neurological abnormalities and a novel mutation in the XPC gene. This obviously facilitates the prognostication of patients.[7] They also found founder mutation in two unrelated families, which is very likely given the socio-epidemiological characteristics of the Indian population. The identification of the mutation can facilitate the screening for a carrier state in such high risk communities. Similarly, they could successfully offer prenatal diagnosis to a family. Further, it is significant that in two families no mutation was identified in the XPA, B, and C gene that was being analyzed.[7] This emphasizes the need to analyze the other complementation groups and the difficulties inherent to any initial attempts at generating mutation analysis data in the Indian context.

Perhaps the greatest advantage of the advances made in genotyping is the development of somatic gene therapy; for example, gene replacement therapy for autosomal recessive epidermolysis bullosa.[5] If novel mutations indigenous to our population are found, they will clearly have a role in gene therapy for our patients. Further, molecular diagnosis provides an option to offer treatment for the "incurable" genodermatoses. A novel approach, for example, is one of suppression therapy for genetic diseases resulting from mutations producing premature stop codons. Aminoglycosides can induce read through of these stop codons and positive outcomes have been obtained in *in vitro* models for ataxia-telangiectasia and phase-III clinical trials are under way for cystic fibrosis.[8] The use of mammalian target of rapamycin (mTOR) inhibitor rapamycin for subependymal giant cell astrocytoma of tuberous sclerosis complex is also attributable to the clues given by the knowledge of the function of proteins produced by *TSC1* and *TSC2* gene.[9] Lastly, another fascinating aspect is that elucidation of the molecular basis and genotypic phenotypic correlation has provided insights into the causation and the development of targeted therapeutic options for some of the more common acquired skin diseases.[5]

The main pitfall is the limited access patients and clinicians have to diagnostic tests for these devastating diseases. Many of the new assays are being carried out in research laboratories and are thus inaccessible.[5] The costs of commercial diagnostic laboratories are prohibitive. Further, the lack of clinician training in diagnosis and absence of a database of mutations in the Indian population may make the assay undertaken unreliable or costly.

It is imperative to remember that a lot still needs to be done; the genes responsible for some genodermatoses remain unidentified and the pathomechanisms of some needs elucidation. Several genodermatoses have a multi-system involvement resulting in severe morbidity and mortality that necessitates more focus on this specialty. Each country should have a national database facilitating screening, diagnosis, and management of patients. The professional physician bodies should encourage formation of self-help groups to cope with debilitating disease and improve the quality of life of the patients. Greater collaboration should be initiated between centers to recruit a larger cohort of patients and obtain more meaningful results. The use of alternative methods of diagnosis may also be warranted. A recent Indian study that recruited 86 patients of epidermolysis bullosa diagnosed by immunofluorescence mapping illustrates the importance of this initiative.[10] Lastly genodermatoses are amenable to teledermatology and international collaboration with well established international laboratories. The details of the latter are available, for example, from the following website: GeneTests (http://www.ncbi.nlm.nih.gov/sites/genetests/) and the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/)/.[6]

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