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Genodermatoses Picture: Difficulties Faced And Way Forward in Nepal

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ABSTRACT

Genodermatoses are group of genetic disorders that present with cutaneous manifestations. The exact prevalence on many of these conditions are unknown due to its rarity, need of specialized tests for diagnosis and lack of proper reporting system. Most of the patients are faced with life-long disability and associated stigma. There is a need for specialized centers for proper diagnosis of these conditions and a very elaborated yet simple reporting system in Nepal. These rare conditions should be kept in priority by the government in align with the sustainable development goals to ensure healthy-lives and promote well-being for all. A wider engagement of patient-led support groups might be useful in providing necessary information on the disease to the general population and alleviate the stigma associated with these diseases.

Keywords: Epidermolysis bullosa; genodermatoses; rare diseases; Nepal

INTRODUCTION

Genodermatoses are a group of inherited group of systemic disorders which presents with cutaneous manifestations. They are classified according to the mutation present namely: chromosomal, single gene or polygenetic. The majority of the genodermatoses present with significant morbidity and mortality. Recently, number of genodermatoses are increasing in number as the molecular testing has become more sophisticated.[1]

Genodermatoses can be classified in various ways. A revised and simplified classification of genodermatoses adapted from Irvine and McLean is presented below.

CLASSIFICATION OF GENODERMATOSES[1,2]

Epidermolysis Bullosa EB	EB simplex
	Junctional EB
	Dystrophic EB
	Kindler syndrome
Disorders of keratinization	Ichthyoses (syndromic and non-syndromic)
	Palmoplantar keratodermas (diffuse, focal, and punctate)
	Follicular keratoses (Darier's disease)
	Erythrokeratodermas
Disorders with abnormal pigmentation	Albinism Piebaldism
	Waardenburg syndrome
Disorders associated with malignancy	DNA repair disorders (Xeroderma pigmentosa, Cockayne syndrome)
	Familial cancer syndromes (Muir-Torre syndrome, Gardner syndrome)
	Epidermodysplasia verruciformis
Disorders of ectodermal appendages	Ectodermal dysplasia syndromes
	Hypotrichosis syndromes
	Nail-patella-elbow syndrome
Connective tissue defects	Cutis laxa
	Ehlers-Danlos syndrome
	Pseudoxanthoma elasticum
	Fabry disease
	Marfan syndrome
Vascular and lymphatic disorders	Osler-Weber-Rendu syndrome
Metabolic disorders	Porphyrias
	Acrodermatitis enteropathica
Primary immuno-deficiency disorders	Wiskott-Aldrich syndrome
	Omenn syndrome
	Hyper-IgE syndromes

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Miscellaneous disorders	Werner syndrome
	Bloom syndrome
	Rothmund Thompson syndrome
	Lipid proteinosis
	Hereditary angioedema

New technologies are changing the way we diagnose and treat genodermatoses. Many of the genodermatoses are associated with malignancy which gravely affect its prognosis. Therefore, early diagnosis is crucial for an early malignancy surveillance.[3] Newer laboratory discoveries for exact diagnosis of these diseases are being discovered at a very rapid pace with the improved knowledge of human genome analysis. These new genetic discoveries are well-documented on different online portals. Online Mendelian Inheritance of Men (OMIM) is one such extensive database where disease categorization and clinical characteristics are mentioned in detail.[4]

The diagnosis for genodermatoses still remains a huge challenge despite the improvement in genetic diagnosis. However, following some of the undermentioned points might be useful in reaching to a proper diagnosis which includes recognition of the "red flags" or "tell-tale" signs of a particular disease; obtaining a complete medical history and detailed physical examination including appendages and extracutaneous features; specific sophisticated laboratory testing and finally having a genotype-phenotype correlation. In cases where the results are inconclusive, those samples should be preserved for more extensive advanced examination at a later time.[1]

More recently, advances in treatments of these conditions are emerging whereas the previous treatment was limited to management of symptoms only.[5] Furthermore developments of orphan drugs and even vaccines that are intended to prevent, treat, or at times diagnose rare disease are an exciting frontier. However, even though orphan drugs are the critical for reducing morbidity and mortality of rare diseases, there is a paucity of their availability in low income countries like Nepal.[6] There is also a lack of established regulations, legislations and policies for the use, research and development of such orphan drugs in the country.

Summarily, an early diagnosis of genodermatoses allows vigilant surveillance and preemptive treatment, which can dramatically impact the increased risks of morbidity and mortality of affected patients. The improvement in an accurate genetic diagnostic testing now allows for an early identification of asymptomatic yet at risk family members so that monitoring can be initiated as early as possible.[3] Prenatal diagnosis has been made easier with the newer DNA-based prenatal diagnostic modalities with newer non-invasive methods. Any national plans on the genodermatoses should consider on its burden and its socio-economic impact from these diseases.

INCIDENCE AND BURDEN OF GENODERMATOSES

There is a lack of published data on the exact burden of any genodermatoses in Nepal. Lack of proper laboratory diagnosis, and recording and reporting of the genodermatoses are the main reason for this failure. Even tertiary level medical institutes and the central laboratory of the country still lack the diagnostics facilities necessary to make the diagnosis of genodermatoses. Moreover, without a proper diagnosis there cannot be any population based studies on the disease burden.

There are few studies which have mentioned on the incidence of certain genodermatoses in a hospital set-up in Nepal, but most of these are still lacking a proper genotypic diagnosis.[7-10] The prevalence of genodermatoses diagnosed clinically in few hospital based studies from Nepal was found to range from 0.08%[7] to 1.1%.[8]

A large cohort mutational study conducted in India over a three-year period (2011-2013) identified a relative genodermatoses incidence of 0.67% with ichthyosis being the most common.[4,11,12]

IMPACT ON QUALITY OF LIFE IN PATIENT WITH GENODERMATOSES

The Quality of life (QoL) refers to an individual's sense of overall well-being encompassing physical, psychological, emotional, social, and spiritual dimensions. There is a significant impact on the QoL in patient living or diagnosed with genodermatoses. Although, genodermatoses have a propensity towards a significant negative QOL, the conditions do not necessarily mean a poor QoL in all. Therefore, management in these patients should not only focus on the cutaneous manifestation but holistically include psychological well-being, coping and illness perception This is particularly so for specific conditions such as ichthyosis[13] and EB, an inherited[14,15] group of disorders characterized by blistering of the skin following friction or mechanical trauma. EB has a clinical and socioeconomic impact on patients Patient with genodermatoses are even faced with multiple problems with education, work place discrimination and disability preventing certain work. Similarly, there is a

significant stress even in the family members or care taker in these disease.[14]

ECONOMIC AND PSYCHOLOGICAL BURDEN OF THE DISEASE TO FAMILY

Nepal is a low-income country with a per capita gross domestic product of $21.13 billion and a gross national income per capita of $730 as of 2016. The household expenditure on health care is only about 5.5% of the total household expenditure.[17,18] In addition to limited financial resources including medical insurances, illiteracy and belief in traditional healing techniques among Nepalese further limit their health-seeking behavior. In India, more than 1 billion population are burdened with rare genodermatoses and so remains the possibility in Nepal with similar diverse ethnic population.[19] The diagnosis and treatment of these rare genodermatoses are extremely expensive. Therefore, there is a significant economic burden attributable to the high direct cost to the families. In a country where the medical expensive is mostly out-of-pocket, the problem would be even worse.

We should find ways a low-income country like Nepal can improve diagnosis and livelihood of patients living with genodermatoses.

PROVIDING DIAGNOSTIC FACILITIES IN A SPECIALIZED CENTER – A POSSIBLE SOLUTION

The rarity of these diseases with prevalence of less than 1% makes the allocation of a specialized center for the treatment and management of these disease a natural solution . A single center set-up will be beneficial both to the patient and the government as this can be done with less government expenditure. This center can in turn can act as a training centers to other health care professionals dealing with genodermatoses.

Nepal has few specialized centers for the treatment of malignancy, trauma and orthopedic surgeries, but there is no allocation of even a single center for the treatment of genodermatoses.

The only central public laboratory of the country also lacks facilities for special genetic studies required for diagnosing genodermatoses. In absence of such facilities inside the country, a collaboration with expert centers to perform special tests can be initiated. Cancer care has improved significantly with international collaboration in the recent years. Such collaboration seems to be of utmost need for improvement of both diagnostics and patient care in genodermatoses.

CREATING A GENODERMATOSES REGISTRY

The field of genetics in dermatology has progressed at an astonishing rate. However, most research works in genetics relating to genodermatoses has been confined to the western population. Very few reports, if any, have been published from Indian studies. A first step may be to develop a registry to link most of these cases providing a full description of the clinical phenotype.[20] Nepalhas initiated the maintenance of a registry of cases in certain specialty including malignancy.[21] We would need to attempt genetic analysis of these conditions thereby detecting any novel mutations in known and unknown genes different from the western population.

INCLUSION OF GENODERMATOSES IN THE GOVERNMENT TREATMENT BENEFICIARIES

The government of Nepal provides a financial subsidies of almost $900 one-time to Nepalese diagnosed with specific enlisted rare disease but not to all genodermatoses. Even though the subsidy is insufficient to pay for cost of care, it still provides some relief to the patients and family since majority of the health care expenditure is out-of-pocket for patients. An inclusion will also be useful in estimating a disease burden since all of the recipients will be recorded centrally.

CREATE AWARENESS OF THE DISEASE

Awareness on the genodermatoses is typically lacking not only in the general people but even among the medical professionals. A massive public private partnership is required to create awareness of the disease so that there would be an increase in the health seeking behavior in patients. This will in turn decrease the discrimination prevalent in the society towards these diseases.

ESTABLISH PATIENT SUPPORT GROUP

There are several patient support groups for different genodermatoses including Dystrophic Epidermolysis Bullosa Research Agency (DEBRA) for EB patients. The psychological, educational and financial support offered by these groups decrease the stress among patients and families. Creating such groups in Nepal will also promote sharing knowledge, sorrows and ideas among themselves and deplete the misunderstanding about the disease. This might be useful to make necessary legislative changes which are needed at present for betterment of these patients and their inclusion and better opportunities.

CONCLUSIONS

Genodermatoses remains largely undiagnosed in Nepal. There is an urgent need from the government to recognize these rare conditions which are associated with significant morbidity and mortality. To improve the care of patients with these conditions, a public health awareness through education and information dissemination preferably by the government and patient centered organization seems beneficial. Similarly, facilities to diagnose the disease at a very low or free of cost and to allocate center for international collaboration to provide better management and treatment of these rare genetic conditions would be extremely beneficial both for the patient and health care provider.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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