The Spectrum of Genodermatosis in Muslim Majority Population of North India

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ABSTRACT

Introduction: Genetic diseases of the skin or genodermatoses are a group of inherited disorders with a conglomeration of cutaneous and systemic signs and symptoms. Study aimed to document the pattern, describe the diverse clinical presentations and define the magnitude of various genetic dermatological disorders among the patients from Muslim majority population of north India.

Material and Methods: One hundred and twenty eight patients with the clinically proven genetic dermatological disorder reporting to a tertiary care teaching hospital during a period one and a half year from August 2014 to January 2016 were enrolled and epidemiologic and demographic features studied in detail.

Results: Among 128 patients, there were 69 males and 59 females with M: F ratio of 1.17:1. Prevalence of genetic disorders was 0.72 per 100 new cases. The most common group of disorder reported was ichthyosiform disorder in 30 patients followed by genetic blistering disorders (epidermolysis bullosa) in 13. Family history of same disorder was seen in 43/128(33.59%). Parental history of consanguinity was observed in 74/128 (57.8%).

Conclusions: This study is first of its kind from this part of country to document the pattern of genetic dermatological disorders in Muslim majority population. We found a high rate of parental consanguinity, a high percentage of patients with a positive family history, and many siblings affected by these genetic skin diseases.

Keywords: Genodermatosis, Muslim, Consanguinity

INTRODUCTION

Genodermatoses or genetic diseases of the skin are a group of inherited disorders with signs and symptoms of both cutaneous and systemic involvement. Owing to the rarity of the cases and the lack of awareness among patients and treating physicians about these disorders, there is dearth of the relevant data. Moss C[1] in 1991 cataloged 90 genodermatoses but by 2009 the number of known genodermatoses increased to 688 genetic skin diseases.[2] The magnitude and the burden of these diseases is still undefined in India due to the lack of disease specific national registries. Hence, the first step would be to define the magnitude and describe the diverse clinical presentations of these rare dermatoses. There are only case reports or case series of the individual genetic dermatoses reported from India and other parts of world.[3,4,5,6] Due to the paucity of the data pertaining to these diseases, there seems to be the dire need to establish the said databases. With this in mind, the study was undertaken to document the pattern, describe the diverse clinical presentations and define the magnitude of various genetic dermatological disorders among the patients from Muslim majority population of north India. The gathered data can be used to roughly represent the presence of genodermatoses in this part of country and can further help in establishing the national registries.

To the best our knowledge, only two studies from India are available on the pattern of genodermatosis , one in the pediatric age group and one pertaining specifically to the genetic loci of the diseases both with lesser number of patients.[7,8] This study reports the epidemiology and pattern of genodermatosis in the Kashmir valley of North India.

MATERIAL AND METHODS

All the patients with proven genetic and congenital dermatological disorders attending the outpatient department (OPD) of a tertiary care teaching hospital from August 2014 to January 2016 were included in the study. By genodermatosis, we mean diseases transferred from one or both parents to one or more of their children because of the specific abnormalities (mutations) in their genes.[9] Regarding the congenital conditions, we mean structural abnormalities of the skin that exist at, and usually before, birth regardless of their etiology.[9] Only the index cases presenting to the hospital were included, sibs or family members presenting to the OPD later were not included in the total number of patients. An informed verbal consent was obtained from patients and parents in case of children. All ages were included. Their medical records were reviewed and all epidemiologic and demographic data, including sex, marital status, ethnicity, onset of the disease, parental consanguinity, family pedigree, and other associated history, were recorded. Detailed neurological, ophthalmological, cardiological and pediatric examination was carried out wherever relevant. Diagnosis was made on clinical grounds. Relevant investigations as indicated were done for each case. No genetic study was done due to lack of facilities for same. General physical examination and relevant clinical investigations were

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Genetic disorders of keratinisation		No. of patients	Total no.(43)
Ichthyosis	Ichthyosis vulgaris	16	30
	Lamellar ichthyosis	8	
	NBIE*	2	
	BIE**	2	
	X-linked ichthyosis	1	
	Ichthyosis hystrix	1	
Palmoplantar keratoderma	focal	7	10
	diffuse	2	
	With extra cutaneous features	1	
Folliculocentric disorders	Darriers disease	1	3
	KSFD***	1	
	Porokeratosis	1	
* Non bullous ichthyosiform erthroderma, **Bullous ichthyosiform erthroderma, ***Keratosis spinulosa folliculitis decalvans			

Table-1: Genetic disorders of keratinization

S. No.	Familial tumour syndromes Disorders of DNA instability and Piokiloderma-tous disorders.	No. of patients
1	Neurofibromatosis	5
2	Tuberous sclerosis	6
3	Hypomelanosis of Ito	2
4	Cowdens syndrome	1
5	Xeroderma pigmentosum	4
6	Rothmund Thomson syndrome	3
7	Dyskeratosis congenita	1

Table-2: Familial tumour syndromes and Disorders of DNA instability and Piokilodermatous disorders.

S. No	Disorder	No.
1	Porphyria (CEP, EPP)	5 (3,2)
2	Angiokeratoma cor. diff	2
3	Xanthomatosis	1
4	Acrodermatitis enteropathica	2
5	Hereditary angioneurotic edema	2

Table-3: Genetic disorders of metabolism and nutrition

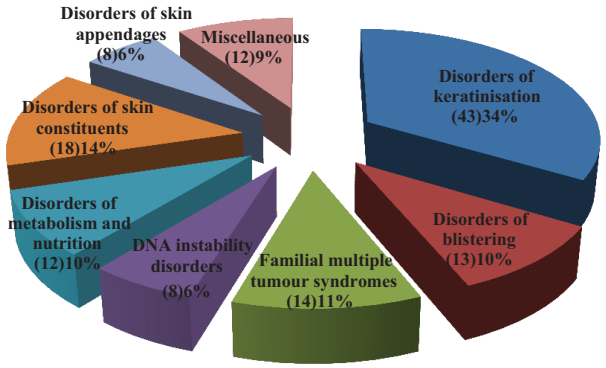

Figure-1: Pie-chart representation of broad group of genetic disorders of skin

done. Classification of the disorders was done by authors themselves following the classification given in the standard text books (Rooks Textbook of dermatology, eighth edition).

STATISTICAL ANALYSIS

The collected data were then entered into a computer and analyzed statistically using descriptive statistics with the help of the SPSS program

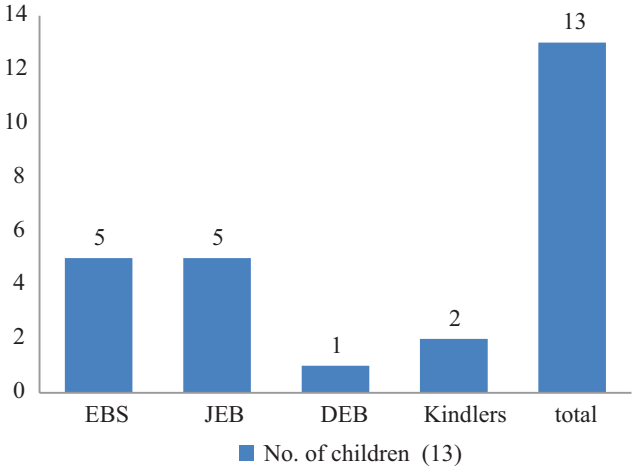

Figure-2: Genetic Blistering disorders

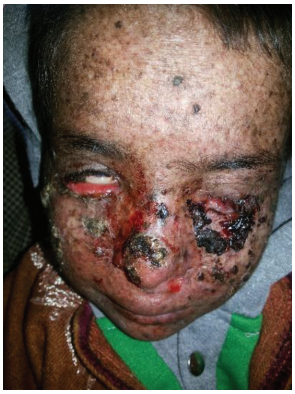

Figure-3: corneal melting with protruding granulomatous mass of eyes with multiple ulcers and keratosis of face in a six year old girl with xeroderma pigmentosum

RESULTS

Total of 128 patients of genetic skin disorders were seen among 17,850 new patients presenting to the outpatient department of dermatology over a period of 18 months giving the prevalence of about 0.72 in our population. There were more males (69/128) than females (59/128) presenting with the genetic skin disease. The age of the patients ranged from new born babies to as old as 40 years with the mean of 12.82 and SD of 9.87. There were more patients from rural areas

S No.	Disorder	No.	Brief notes
1	Elastic tissue (PXE)	4	
2	Collagen (EDS, prolidase def.)	4	2 cases of vascular EDS (positive family history)
3	Histiocytes	4	2 cases of langhans cell histiocytosis, 2 cases of juvenile xanthogranulomas
4	Mast Cells	1	Urticaria pigmentosa
5	Pigment	3	1 case each of Mc-cune albright syndrome, puetz-jeghers syndrome and oculo-cutaneous albinism
6	Nerves	2	Two cases of hereditary sensory motor neuropathy.
	Total	19	

Table-4: Genetic disorders of skin constituents

(91/128, 71.1%) than urban areas (37/128, 28.9%) reporting to the hospital. 43/128 (33.59%) cases had positive history of the same disorder in the first degree family members. A high degree of consanguinity 74/128 (57.8%) was noted in the patients of genetic skin disorders. Figure -1 gives the pie-chart representation of the broad group of genetic disorders of skin seen in our study.

Genetic disorders of keratinisation was the most common group of disorders seen in 43/128 (33.59%) table 1.

Ichthyosis was seen in 30 patients. Most of the patients were males (19/30) and 21/30 had history of consanguinity. Ichthyosis vulgaris was the most common type seen in 16 patients (13 males and 3 females). Associated growth retardation with rickets was seen in three patients of non-bullous ichthyosiform erythroderma (NBIE), bullous ichthyosiform erythroderma (BIE) and lamellar ichthyosis each.

Palmoplanter keratoderma (PPK) were seen in 10 patients. Focal PPKs was the most commonly seen subtype in 6 patients. A family of Mal-de-Maleda was seen with all the sibs affected (index case – 16 year old boy , and three affected sisters). There was history of parental consanguinity with onset since 6 months of age. There was diffuse PPK-yellowish, waxy/ foul smelling with pitted keratolysis of palms and soles. Other important types of PPKs observed were Griethers PPK, Pachyonychia congenita I and Pappilion Leferve syndrome in one each.

Thirteen children with Epidermolysis Bullosa (EB) were seen during this period (figure 2).

Age of the patients with genetic disorders of blistering ranged from new born babies to as old as 14 years of age. One patient of junctional EB had pyloric stenosis and one had developed mitten deformity of hands. Two cases of kindlers syndrome were also seen. One of the child, six year old boy with kindler's syndrome had with an affected elder sister, with both of them having piokiloderma of face and blistering of hands and feet with teeth abnormalities.

All the patients with familial tumour syndromes (Table 2) were > 5 years of age, with more than half of them adults (>18 years); which reflects the tendency to seek medical care only when the major problems like seizures or tumors appear. One patient with neurofibromatosis (NF1) had large plexiform neurofibroma of the left limb with synovial sarcoma of the affected joint. One tuberous sclerosis patient came to seek medical care only when her six year old daughter having history of seizure disorder developed facial angiofibromas. Other tuberous sclerosis patient had angiomyolipoma kidney.

During this period of one and a half year, four patients with xeroderma pigmentosum (XP) came to our OPD (Table 2). Two of the patients had other affected sibs. One was six year old female with elder 10 year old affected brother. Patient had corneal melting with protruding granulomatous mass and ectropion of left eye. There were multiple keratosis on ears, and crusted ulcers over the face (figure 3).

XP de-sanctis type was seen in a seven year old male child with other two affected sibs (all males). Pertinently there was no history of consanguity in this case. All had history of progressive mental deterioration, bilateral sensorineuronal hearing loss and inability to walk or talk as they grew older in addition to the classical signs and symptoms of XP.

Rothmund Thomson syndrome was seen in three patients with one patient having an affected sib, both of whom had piokiloderma face, keratosis over palms and soles , alopecia eyebrows.

Among the patients with genetic disorders of metabolism and nutrition (Table 3), five patients with porphyrias were seen , three of whom had congenital erythropoeitic porphyria (CEP). One patient of CEP with positive history in younger sib also had Lepromatous leprosy with fulminant course and severe eye damage. Symptomatic zinc deficiency was seen in two breast fed infants with features consistent with acrodermatitis enteropathica and showing excellent response to oral zinc supplement.

Nineteen patients were roughly conglomerated into a loose group of genetic disorders of skin constituents (Table 4) with the disorders affecting the cells of different lineages like elastic tissue, collagen disorders, histiocytes, mast cells, pigment cells and nerves etc.

This loose group included 4 patients of pseudoxanthoma elasticum (PXE), 3 patients of ehler danlos syndrome (EDS) and 3 patients of langhan cell histiocytosis. Other diseases in this subgroup included a case each of prolidase deficiency, oculo-cutaneeous albinism, peutzjegers syndrome, Mc-cune Albright syndrome, generalized mastocytosis and two cases of hereditary sensorimotor neuropathy (HSAN). Two of the EDS patients had vascular subtype affecting other sibs and family members with death due to vascular cause in the close family members.

One 18 month old boy with langhans cell histiocytosis presented with severe seborrheic dermatitis and on evaluation had lytic lesions of skull and lung involvement.

In the disorders of skin appendages there were four patients with hair disorders (Hair shaft disorder, Wooly hair syndrome, Monilethrix), two patients with chronic mucocutaneous candidiasis and three patients with ectodermal dysplasias. Among the three patients with ectodermal dysplasias seen during this time period, one 18 year old female with unclassified ectodermal dysplasia had all other sibs (16 female, 12 female) affected with hair , nail, teeth involvement and dyschromia of whole body but had no history of parental consanguinity which reflects the diverse presentation of these group of disorders.

Miscellaneous group of disorders included nevoid syndromes. Congenital nevi were not included, however only when they were a part of the syndrome, they were included in this study like two cases of sturge weber syndrome and a case each of epidermal nevus syndrome, and kleipel taranauy syndrome. ACHSS (4 cases) was included in this study due to the proven genetic basis of the disease.[10]

DISCUSSION

Genetic disorders with skin manifestations often affect other organs as well. From a dermatologists perspective, the genetic disorders may be classified on basis of anatomical involvement, (into disorders of hair, nail) morphological, (papulosquamous, blistering disorders) or pathogenecity (as inherited autoimmune). In this study the diseases were classified as is followed by the standard text books of dermatology. The pattern of dermatological disorders varies from place to place depending upon race, religion, ethnicity and the geographical location. Kashmir province of J&K state is predominantly Muslim majority area and as seen in other Muslim majority populations in the world, consanguineous marriages are more frequently seen here. Also, it is racially different from North India as indicated by pattern of various other dermatological disorders and this pattern of diseases is more synchronous with the Iranian belt.[11]

We observed a vast array of genetic diseases with cutaneous manifestations. In the present study the prevalence of genodermatoses was 0.72 (0.72% of the case load). The exact incidence of these disorders has not been reported in the literature but it is thought that at least 1% of all live births had disorder inherited in a simple Mendelian fashion.[12] The commonest group of disorders was ichthyosis, followed by epidermolysis bullosa which is similar to another study of genodermatosis in pediatric patients.[7] Many of our patients showed a positive family history (33.59%), with one parent, one or more siblings, and/or common one or more relatives with similar dermatoses to the patient. The high prevalence of inherited dermatoses amongst family members may be a result of the traditions that encourage the marriage of relatives, particularly first cousins. In this study, approximately 57.8% of parents were married to the first-degree or second-degree relatives. In 30 patients presenting with ichthyosiform disorders 21 (70%) had parental history of consanguinity. In a study of hereditary ichthyosiform disorders from Saudi Arabia[13] 75% had a positive family history, which is similar to our study. Another study from a south Indian hospital,[14] showed 81.3% of patients had a positive family history, higher than in our study. This high frequency was attributed to the traditional marriage of cousins in both of these ethnic groups. Most of the patients in our study were from a rural background (71.1%) which can be explained as consanguineous marriages are more common in closed rural communities leading to the clustering and higher prevalence of genodermatoses in them. In this study, there was a male preponderance. This male preponderance was also found in a similar other studies.[13,14] In our patients the most common type of ichthyosis was Ichthyosis Vulgaris, accounting for 44.7% of all types. This result is consistent with most published reports in different parts of the world.[14,15,16,17] In some cases of genodermatosis with proven autosomal recessive inheritance like in XP there was no parental consanguinity which suggests other mechanisms of inheritance like point mutations.

As chromosomal mapping/ loci identification is not available in our resource poor setting, we highlight the recognition of the diseases by clinical means alone, confirmed by histopathological examination in some cases.

Another challenge to the genetic/ congenital skin diseases in India is the stigma that leads to the exclusion from various aspects of the daily lives- like school or social gatherings etc. The clinical recognition and the accurate diagnosis help to support the patients and their families with the prognosis and various therapeutic interventions available for same.

Pre-marital genetic counseling would be helpful for all couples with these disorders in families in cases of consanguinity. However there is a lacuna in this field as the formal premarital genetic counseling is not provided here.

Limitations: The lack of genetic testing is the major pitfall of the study which was not done due to non-availability and prohibitive cost in our settings.

What's new?- Recognition of the clinical spectrum of these rare dermatosis helps to raise awareness of their range in high prevalence areas. This rough data can be gathered to establish the regional registries for the genodermatosis which can further contribute to the national registries.

CONCLUSION

To conclude we highlight the importance of recognizing the clinical spectrum of these genetic and congenital skin disorders in developing and relatively resource poor settings such as ours where detailed genetic studies are not available. We have focused on the multi-speciality networking between the various clinicians for accurate diagnosis.

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