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Original Research Paper

Dermatology

A STUDY ON RARE KERATINIZATION DISORDERS

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ABSTRACT **Background:** Disorder of Keratinization refers to a broad spectrum of skin disorders when there is abnormal differentiation of the epidermis and appendages with aberrant formation of the cornified envelope. These disorders have been classified on the basis of clinical morphology and presence or absence of extracutaneous manifestations. **Case Series:** We report series of 8 cases of disorders of keratinization which include: Lamellar ichthyosis, Trichothiodystrophy, Darier's disease, Porokeratosis, Progressive symmetrical erythrokeratoderma, Naxos syndrome, Unna thost syndrome and Mal de meleda syndrome. **Discussion And Conclusion:** In many cases, clinical features do not facilitate easy segregation into single distinct and well defined group as many features can co-exist. Advances in genetic technology during the past 10 years have led to an enormous increase in understanding the basic molecular defects responsible for inherited disorders of keratinization. These cases are being reported for their rarity and also to highlight the association of consanguinity in them as genetic counselling can be helpful.

KEYWORDS : keratinization disorders, palmoplantar keratoderma, lamellar ichthyosis, trichothiodystrophy, darier's disease, porokeratosis, naxos syndrome, mal de meleda syndrome, unna thost syndrome, progressive symmetrical erythrokeratoderma

INTRODUCTION

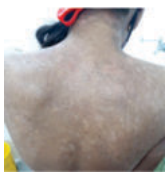
DISORDER OF KERATINIZATION refers to a broad spectrum of skin disorders when there is abnormal differentiation of the epidermis and appendages with aberrant formation of the cornified envelope. These disorders have been classified on the basis of clinical morphology and presence or absence of extracutaneous manifestations. In many cases, clinical features do not facilitate easy segregation into single distinct and well defined group as many features can co-exist. Advances in genetic technology during the past 10 years have led in understanding the basic molecular defects. Diagnostic approach is based on dermatological evaluation, careful family and medical history. Histopathological examination of skin is usually non-specific. Molecular analyses are suggested in cases of inherited disorders.

Case Series

Case No:1 Lamellar Ichthyosis

A 18 years old female patient came with complains of dryness and scaling of skin all over the body since childhood with periodic shedding of scales. History of collodion baby at birth which peeled off after one week. History of winter aggravation present. History of third degree consanguinity is seen in parents. On examination fish like scales noted all over the body. Fixed flexion deformity of middle finger of right hand noted. Nails were thick and ridging noted. Ocular examination showed ectropion and severe dry eyes. Histopathology showed marked hyperkeratosis, hyper granulosis, and moderate acanthosis.

Patient was counselled and started on oral retinoids. Advised topical emollients, eye lubricants and physiotherapy for deformitty.



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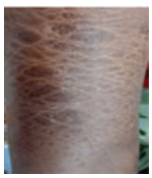

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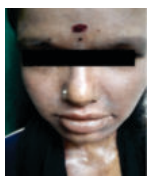

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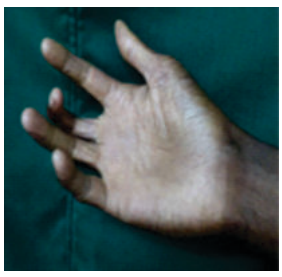

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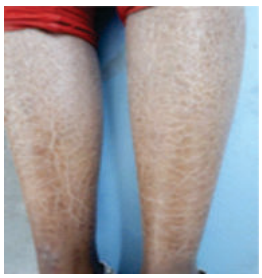

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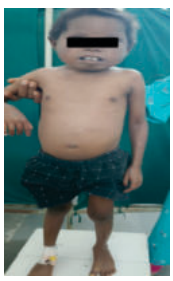
Figure 1(a,b,c,d,e): Lamellar Ichthyosis

Case No: 2 Trichothiodystrophy

A case of 8 years old female child with mother complaining of scaling over entire body since birth with periodic shedding of scales. History of collodion membrane present at birth. History of delay in developmental milestones present. History of failure to gain weight and height noted. On examination scaling and xerosis noted all over the body. Scalp showed scaling with thin and sparse hair. Nails showed longitudinal ridging. On trichoscopy, alternate light and dark bands giving appearance of tiger tail noted.

Genetic testing revealed two copies of pathogenic variant of GTF2H5 gene. Parents were counselled about child condition and advised frequent applications of emollients and photoprotection.



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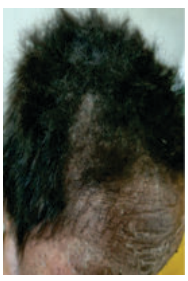

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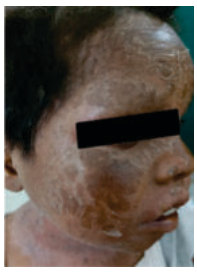


(2c)

(2d)

Figure2(a,b,c,d):Trichothiodystrophy

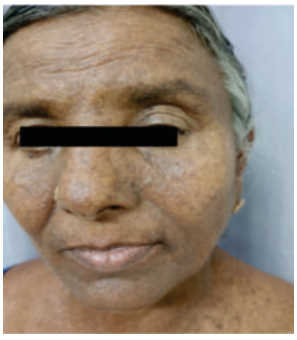
Case No: 3 Darier's Disease

A 40 years old female patient came with complaints of asymptomatic skin lesions all over body since 20 years. History of consanguinity in parents present. History of similar complaints in daughter and son present.

On examination mutliple polysized well defined warty papule and plaques with hypopigmented macules noted all over body, face and scalp. Multiple hyperpigmented papules noted over tongue and labia majora.

Nails showed longitudinal ridging. Histopathology showed hyperkeratosis, acanthosis and papillomatosis. Multiple corps ronds and grains seen in stratum granular and corneum layers .

Patient was started on oral retinoids . Advised sun protection and frequent application of emollients.



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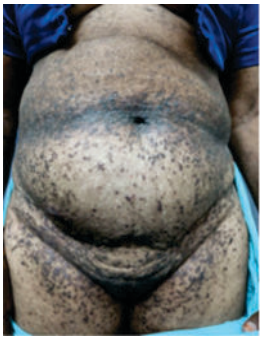

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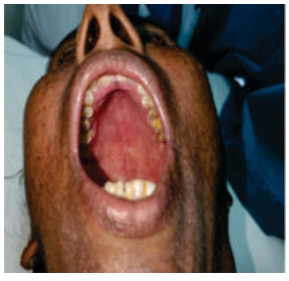

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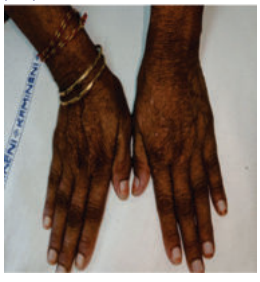


(3d)

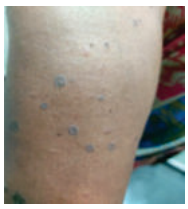
Figure 3(a,b,c,d) :Darier's Disease

Case No: 4 Porokeratosis

A 29 years old female patient complains of asymptomatic dark skin lesions all over the face, neck, both upper extremities since 20 years. Initially lesions started as papules later progressed to annular lesions.

On examination multiple well defined hyperpigmented annular plaques with an elevated border noted over the photoexposed areas. Histopathology (taken from border of lesion) revealed keratin filled invagination, presence of cornoid lamella and absence of granular layer noted.

Patient was started on topical retinoids and advised frequent application of emollients.



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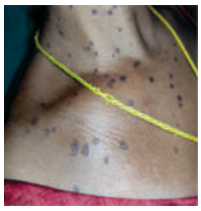

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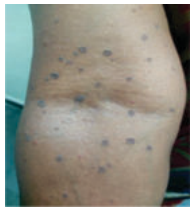


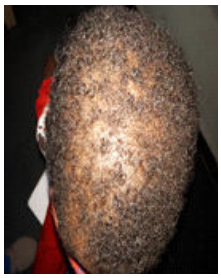
(4c)

Figure 4(a,b,c) :POROKERATOSIS

Case No: 5 Naxos Syndrome

A 10 years old female child presented with thickening of both soles and palms since 3 years. Her mother complains of sparse growth of hair over the scalp since birth. History of hyperhydrosis present . History of consanguinity in parents present. On examination wooly hair over scalp noted . Thickening and hyperkeratotic plaques noted over both palms and soles. ECG and 2D ECHO were normal.

Parents were counselled and started on topical retiniods and kertolytics. Advised salt water soaks & paring and soft cushion foot wear.



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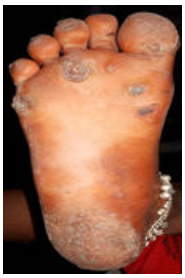

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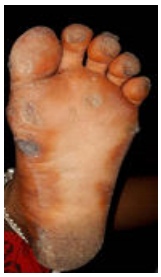
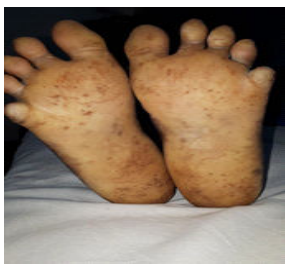


(5c)

Figure 5(a,b,c) : NAXOS SYNDROME

Case No : 6 Mal De Meleda Syndrome

A 25 years old female patient came with complaints of thickening and dark color pigmentation of skin of both hands and feet since 20 years. History of hyperhydrosis and malodour present. History of consanguinity in parents present. On examination transgradient palmoplantar keratoderma with sharp demarcation noted. Palmar creases were lost due to thickening. Fixed flexion deformities of fingers and toes noted. Histopatholgy showed marked hyperkeratosis and acanthosis with perivascular lymphohistiocytic infiltrate. Patient was started on oral retinoids and topical keratolytics. Advised salt water soaks and paring and soft cushion foot wear.



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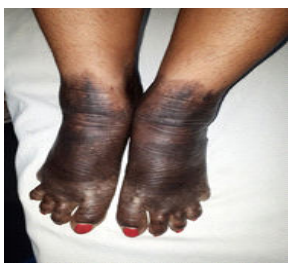

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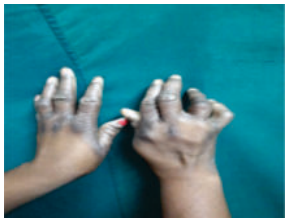
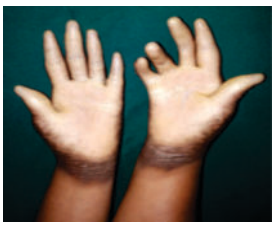




(6c) (6d)

Figure 6(a,b,c,d) : Mal De Meleda Syndrome

Case No :7 Unna Thost Syndrome

A 26 years old male came with complaints of thick scaling over both feet and hands since 3years. History of hyperhidrosis present. No family history of similar complaints. On examination palmoplantar keratoderma with waxy appearance of both soles. Histopathology showed hyperkeratosis, hypergranulosis and moderate acanthosis .

Patient was started on oral retinoids and topical keratolytics. Advised salt water soaks and paring and soft cushion foot wear. (7)

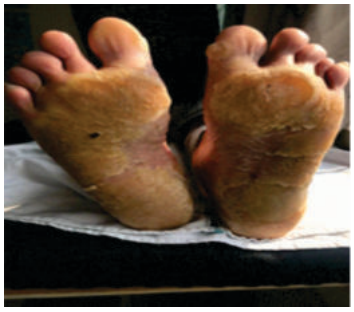
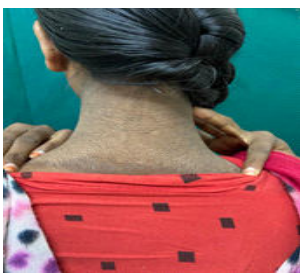


Figure 7: Unna Thost Syndrome

Case No: 8 Progressive Symmetrical Erythrokeratoderma

A 18 years old female patient came with complaints of dark colored skin lesions around neck, both hands and legs which gradually peel off since 5 months. History of winter aggrevation present. No history of parental consanguinity. On examination multiple well defined scaly hyperpigmented plaques noted around the neck, flexural aspect of forearms, posteriors aspect of both legs, both dorsal aspects of both hands. Histopathology showed patchy parakeratosis and hyperkeratosis. Few lymphocytic perivascular infiltrates were found in papillary dermis.

Patient was started on oral retinoids and advised frequent application of emollients.



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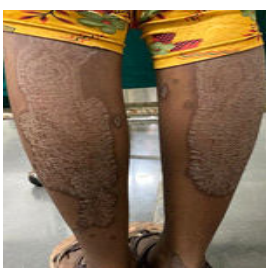

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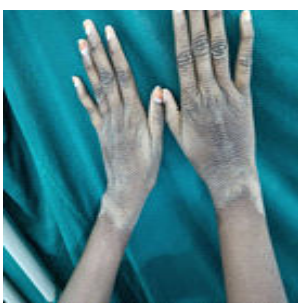

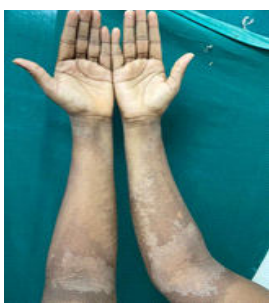

(8c) (8d)

Figure 8(a,b,c,d): Progressive Symmetrical Erythrokeratoderma

DISCUSSION:

Keratinization is a complex process in which the live, nucleated basal cells of the epidermis are gradually transformed into dead, non-nucleated horny cells that from the outermost layer of the epidermis – stratum corneum. Genetics play an important role in the pathway of epidermal differentiation. The defect in genes encoding for cytoskeleton protiens/cornified cell envelope proteins/adhesion molecules result in various keratinization disorders.

Ichthyosiform Disorders:

These are heterogenous group of disorders of cornification characterized by generalized scaling and often areas of thickened skin. Most types are inherited and these usually present at birth or appear in childhood; however some forms are acquired. Scales may vary in size, color, and body site. There may be accompanied by erythema, abnormalities in adnexal structures and palmoplantar keratoderma. They may be associated with systemic findings such as failure to thrive, increased suspectibilty to infection, atopic dermatitis, neurosensory deafness, and neurologic and other disease. Histopathology is usually nonspecific with few notable exceptions. Early genetic testing can aid in diagnosis and anticipation of potential systemic abnormalities. Treatment is usually symptomatic and primarily aimed at reducing hyperkeratosis. topical management consists of emollients, keratolytics, and retinoids. Systemic retinoids may be indicated in severe cases. In our present study 5 cases of ichthyosiform disorder noted.

Table No: 1 – Ichthyosiform Disorder In This Study

ICHTHYOSIFORM DISORDER	GENE MUTATION	MODE OF INHERITANCE
LAMELLAR ICHTHYOSIS	TGM/transglutamina se 1	AUTOSOMAL RECESSIVE
TRICHOTHIODYST ROPHY	TFIIH / TTDN1	AUTOSOMAL RECESSIVE
POROKERATOSIS	POROK2,3,4,5,6,7,8	ACQUIRED
PROGRESSIVE SYMMETRICAL ERYTHROKERATO DERMA	LORICIN	AUTOSOMAL DOMINANT/ AUTOSOMAL RECESSIVE
DARIER'S DISEASE	ATP2A2	AUTOSOMAL DOMINANT

Palmoplantar Keratoderma:

Palmoplantar keratodermas (PPK) are a group of cutaneous disorders characterized by hyperkeratosis of the palms and soles. The majority of the disorders in this group are hereditary, some are part of other dermatosis and few are acquired. Evaluating a patient with PPK should include a through family history, cutaneous examination of mucous membrane, nails and hair, and evaluation for extracutaneous manifestations like cardiac, audiologic, ophthalmologic and dental evaluation. A skin biopsy for histological examination may provide additional diagnostic clues. Genetic analysis is helpful to establish the specific diagnosis, facilitate screening of family members, and enable prenatal diagnosis.

PPK is classified into inherited and acquired. Inherited forms are futher classified into diffuse, focal and punctate. Diffuse PPK can be with or without transgradiens. Focal and punctate can be with or without associated features. In our present study, 3 cases of diffuse PPK reported.

Table No: 2 – Palmoplantar Keratoderma In This Study

PALMOPLANTAR KERATODERMA	GENE MUTATION	TRANSGRADI ENS	INHERITAN CE
NAXOS SYNDROME	PLAKOGLO BIN	NON TRANSGRADI ENS DIFFUSE TYPE	AUTOSOM AL RECESSIVE
MAL DE MELEDA SYNDROME	ARS GENE – SLURP -1	TRANSGRADI ENS DIFFUSE TYPE	AUTOSOM AL RECESSIVE

UNNA THOST SYNDROME	K1/K2	NON TRANSGRADIENS DIFFUSE TYPE	AUTOSOMAL DOMINANT

CONCLUSION

As these are disfiguring conditions which may hinder psychosocial development of an individual. Careful evaluation with early diagnosis and treatment helps in dramatic improvement and prevent further complications. Genetic testing and counselling usually recommended for such inherited conditions. Frequent applications of emollients, photoprotection and physiotherapy for deformities are neccesaary for these conditions.

Statements and Declarations: - Compliance with Ethical Standards

Ethics Approval: -

This is an observational study. The Kamineni Institute of Medical Sciences Research Ethics Committee has approved the ethics clearance for this observational study.

Informed Consent: -

All the patients in this case series gave informed consent for participation in this study and publication of their medical data, including their images and investigations done. Informed consent was obtained from all individual participants included in the study. Informed consent was obtained from legal guardians in cases where the patients were less than 18 years of age. The authors affirm that human research participants provided informed consent for publication of the images in Figures 1 to 8.

Funding: - No Funding was received.

Conflict of Interest: -

The authors declare that they have no conflict of interest.

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