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SPECIAL INTEREST GROUP (SIG) GENODERMATOSIS

Editors
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CONTENTS

EXCERPTS FROM LITERATURE

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1. **Clinical profile and mutation analysis of xerodermapigmentosum in Indian patients TamhankarPM, Iyer SV, Ravindran S, Gupta N, KabraM, et al.**

   Ind J Dermatol Venereol Leprol 2015; 8: 16-22.

Introduction: Xerodermapigmentosum (XP) is an autosomal recessive disorder of DNA repair characterized by cutaneous and ocular photosensitivity and an increased risk of developing cutaneous neoplasms.Neurological abnormalities including deafness, spasticity and cognitive impairment may develop in 25% of patients. Nine complementation groups have been described - XPA, ERCC3, XPC, ERCC2, DDB2, ERCC4, ERCC5, ERCC1 and POLH1. Mutations arise most commonly in XPA (25 %), XPC (25 %) orPOLH1 (21%) genes. In addition to XP phenotype, mutations in XP genes may present with phenotypes like: trichothiodystrophy (TTD), Cockayne syndrome with overlap with XP or as cerebro-oculo-facial syndrome (COFS).The exact incidence or the most frequent complementation group in India is not known as there areonly case reports without documentation of mutation analysis from India.The present study carried out mutation analysis for the XPA gene in eight families, for the XPB gene in three of the eight families and forthe XPC gene in four families with XP.

*Subjects and Methods:*Thirteen patients from 10 unrelated families with XP were referred to the ICMR Genetic Research Center, Mumbai for molecular diagnosis from 2011 to 2014. Consanguinity was observed in 6 of the 10 families. Five families each belonged to Maharashtra and Uttar Pradesh. All XP patients showed typical clinical features of cutaneous photosensitivity such as xerosis, poikiloderma and numerous freckles like hyperpigmented macules on sun-exposed skin. Photophobia was present in all patients while 6 patients had keratitis and lid atrophy Neurological involvement was observed

in 6 patients and none had cutaneous malignancy.Mutation analysis by bidirectional Sanger sequencing of all exons and exon-intron boundaries was performed for the XPA gene in all index cases of 9 families, of which 3 families were also tested for mutations in the XPB gene. The XPC gene was analyzed in the 3 index cases of the 9th family and for the index cases of the 6th, 7th and 8th families.

The patients were counseled about photoprotection, physiotherapy was carried out for neurological problems and all families received genetic counseling and education for the possibility of prenatal diagnosis in future pregnancies.

Results: Four distinct mutations (three in exon 3 and one in exon 4) were found in XPA- novel mutation c.378T>G or p.C126W was seen in exon 3. Another novel homozygous mutation c.1243C>T (p.R415X) was found in the XPC gene of 1 family. This patient also showed homozygosity for benign polymorphisms c.1475G>A (p.R492H) and c.1496C>T (p.A499V) in the XPC gene. Another family showed a novel mutation c.1677C>G (p.Y559X) in the XPC gene. Mutation in the XPA gene was found in patients with severe neurological abnormalities. Parents were confirmed as carriers for the same mutations. The mutation c.335_338delTTATinsCATAAGAAA (p.F112SfsX2) was found in 2 unrelated Maharashtrian families showing founder effect on haplotyping. The mutation c.428_429delAG (p.E143GfsX11) in exon 4 of XPA gene was also found in 2 unrelated families from Uttar Pradesh.

Prenatal diagnosis with targeted mutation analysis was done on fetal DNA obtained by chorion villus biopsy in 1 family and the fetus was identified to be carrier for mutation (unaffected).

Discussion: In this study none of the 32 unique point mutations or splice site mutations of XPA and 55 unique XPC mutations listed in the Human Gene Mutation Database or the XP mutation database (describes 128 mutant alleles of the XPA and 54 mutant alleles of the XPC gene) were found. Three of the 4mutations were frameshift- these mutations resulted in premature stop codon, thereby resulting in mRNA instability and the severe phenotype in the study patients. The fourth mutationwas a missense mutation.

Existing data shows that patients with XPA mutations usually have mild to severe neurological abnormalities while patients with mutations in the XPC gene usually do not have neurological abnormalities. Indian patients of XP presenting with neurological symptoms should be screened for mutations in the XPA gene. Rapid molecular diagnosis would aid definitive diagnosis, genetic counseling and prenatal diagnosis.

Comments

The authors present clinical and mutation analysis data of 13 patients with XP. As stated by them, no previous mutation data is available in the 37 Indian families reported till date. They have 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 the patients. 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 carrier state in such high risk communities. Similarly, they could successfully offer prenatal diagnosis to a family. Further, it is significant that in 2 families no mutation was identified in the XPA, B and C gene that was being analyzed. This highlights 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.

2. Threshold levels of 25-hydroxyvitamin D and parathyroid hormone for impaired bone health in children with congenital ichthyosis and type IV and V skin.

Sethuraman G, Sreenivas V, Yenamandra VK, Gupta N, Sharma VK,et al.Br J Dermatol 2015;172: 208-14.

Introduction: Congenital ichthyosis (CI) is characterized by excessive and abnormal scaling. The thick ichthyotic skin acts as a physical sun screen that impairs the photoactivation of 7-dehydrocholesterol leading to vitamin D deficiency and rickets. Literature documents that children with CI are at increased risk of developing vitamin D deficiency and rickets. Serum 25-hydroxyvitamin D [25(OH)D] is considered to be the best indicator of an individual's vitamin D status. Several criteria that have been used to define vitamin D sufficiency include optimal suppression of parathyroid hormone (PTH), calcium absorption

from the gut, bone mineral density and bone markers. Most experts define vitamin D deficiency as serum 25(OH)D < 20 ng mL_1.4 The critical question of what level of serum 25(OH)D is crucial for bone health is debatable Very few studies evaluated the relationship between serum 25(OH)D and PTH, reported that threshold levels of serum 25(OH)D between in healthy children and adolescents in whom the threshold level of vitamin D was 10–15 ng mL_1 define vitamin D deficiency. So far no study has to date evaluated the relationship between vitamin D, PTH and bone health in children with congenital ichthyosis in darker skin types.

Methods: In this cross-sectional study, 119 children with CI and 168 controls were recruited. Serum 25(OH)D, PTH, calcium, phosphate and alkaline phosphatase (ALP) were measured. Radiological screening for rickets was carried out only in children with ichthyosis. Based on the serum 25(OH)D level, vitamin D deficiency was categorized into severe (< 5 ng mL_1), moderate (5–10 ng mL_1) and mild (10–20 ng mL_1).Dietary assessment of calcium and phytate was done in 60 cases (30 each in ichthyosis and controls) through a 24-h recall of food intake. The rickets score was done by using the 10-point radiographic scoring method for rickets. Appropriate statistical evaluation was carried out.

Results: 119 cases of CI and 168 controls (groups1 and 2) were recruited. Autosomal recessive congenital ichthyosis (ARCI) was diagnosed in 56 (47%), Epidermolytic ichthyosis (EI) in 24 (20%) and common ichthyosis (Ichthyosis vulgaris and X-linked recessive ichthyosis) in 35 (29%) cases. Clinical examination revealed one or more skeletal changes suggestive of rickets in 27 (23%) cases; 74 patients gave consent for radiological screening and 31(42%) showed evidence of rickets. Thereby, 47 [41% cases (ARCI, n = 28; EI, n = 13; common type, n = 6)] and none of the controls had evidence of rickets. The dietary intake of dairy calcium was adequate in both the groups. The mean serum 25(OH)D level of the study group was 9_09 _ 6_15 ng mL_1, which was significantly lower than in the control group (11_77 _ 12_52, P = 0_002).

The mean serum PTH level of the cases was 92_53 _ 101_78 pg mL_1, which was significantly higher than in the control group (51_99 _ 45_45 pg mL_1, P < 0_001). Secondary hyperparathyroidism was seen in 28 (75_7%), 14 (34_2%) and 1 (7_7%) cases with severe, moderate and mild vitamin D deficiency, respectively, and this distribution was significantly different from controls [19 (57_6%), 11 (18_0%) and 6 (17_6%), respectively].

Regression analysis of PTH on 25(OH) D showed an average rise in PTH of 37 pg mL_1 for every 1 ng decrease in the 25(OH)D levels (P = 0_02) in cases with 25(OH)D < 8 ng mL_1 in contrast to only a 1_3 pg mL_1 rise in PTH in cases with 25(OH)D≥ 8 ng mL_1 (P = 0_12). Although a similar trend was observed among controls, the rise in PTH was much higher in the ichthyosis group than in controls (P = 0_002). A 25(OH)D level of 8 ng mL_1 was found to be the threshold level for the rise in PTH.

Among cases of ichthyosis, a significant increase in ALP level was observed when the PTH was more than 75 pg mL_1. Regression analysis of ALP on PTH indicated an average increase in ALP level of 2_2 IU for every 1 pg increase in PTH, in cases with PTH ≥ 75 pg mL_1 (P = 0_02).

Of the 107 cases with 25(OH) D and PTH results available, 32 had 25(OH)D≤ 8 ng mL_1 and PTH ≥ 75 pg mL_1. Of these, 18 (56_2%) cases had rickets compared with only seven (22_6%) of the 31 cases with similar 25(OH)D levels but PTH < 75 pg mL_1. Three of the six cases (50%) who had 25(OH)D > 8 ng mL_1 and PTH ≥ 75 pg mL_1 showed evidence of rickets compared with 12 (31_6%) of 38 cases in whom 25(OH)D level was similar but PTH was < 75 pg mL_1. These results indicate that among cases with ichthyosis, 25(OH)D ≤ 8 ng mL_1 in the presence of elevated PTH (≥ 75 pg mL_1) significantly increases the risk for the development of rickets (OR = 2_8; 95% CI: 1_05–7_40; P = 0_04).

Regression analysis of rickets in different subtypes of ichthyosis revealed that both ARCI (OR 4_83; 95% CI 1_74–13_45; P < 0_01) and EI (OR 5_71; 95% CI 1_74–18_79; P < 0_01) are at an increased risk of developing rickets. The mean radiological rickets score also tended to be higher in both ARCI and EI compared with the common type of ichthyosis (2_9 _ 3_5 vs. 0_8 _ 1_4; P = 0_06).

Discussion: Vitamin D deficiency is a major public health concern in Indian children due to lack of adequate sunlight exposure even in a tropical country, poor nutritional status and pigmented skin types. CI is also an important risk factor for vitamin D deficiency and rickets in children. Chronic vitamin D deficiency in these children is associated with secondary hyperparathyroidism which in turn leads to bone resorption and rickets. Increased PTH secretion is one of the earliest signs

of insufficient 25(OH)D. The present study is the first to investigate the relationship between vitamin D, PTH and bone health in children with ichthyosis.

The authors observed a high prevalence of clinical and/ or radiological evidence of rickets in children with CI and hence recommended that treatment with vitamin D and calcium should form an essential part of the management. Serum levels of 25(OH)D≤ 8 ng mL_1 and PTH ≥ 75 pg mL_1 were found to be critical for the development of rickets in children with CI. Both ARCI and EI were associated with a significant increased risk of developing rickets.

Comment

The present study represents the first systematic evaluation of the risk factors for the development of rickets in CI in a large cohort of 119 cases. They provide cut-off values that confer a higher risk and can therefore be used for monitoring the patients. The obtained data has generated a recommendation that treatment with vitamin D and calcium should form an essential part of the management of CI especially in cases of ARCI and EI.

3. Vitamin D Deficiency after Oral Retinoid Therapy for Ichthyosis.

Neema S, Mukherjee S, Vasudevan B, Verma R, Moorchung N, Chatterjee M PediatrDermatol 2015; 32: e151-5.

Introduction: The ichthyoses are a rare set of disorder of keratinization characterized by xerosis, fishlike scales and severe complications in some variants. Mild cases can be managed using emollients and keratolytics and oral retinoids have been proven to be a good therapeutic option in severe ichthyotic disorders. High intake of vitamin A has many adverse effects on bone metabolism. The possibility of such adverse events occurring secondary to initiation of therapy with systemic retinoids in an at-risk population such as children with ichthyotic disorders is possible. The association between rickets and ichthyosis is a known, albeit rare occurrence. The authors report the first report of 2 cases of vitamin D deficiency developing after initiation of oral retinoids.

Case Report: Case 1- A 6-year-old girl, the product of a nonconsanguineous marriage, presented with nonbullousichthyosiformerythroderma (NBIE), pseudo-ainhum in the fingers of both hands. She was of normal weight and height for her age and had achieved normal developmental milestones. After evaluating her hematologic biochemical,and radiologic investigations, which were all normal, she was started on acitretin 25 mg once daily and emollients. Her symptoms gradually improved over 6 weeks after initiation of therapy. Subsequent follow-up examinations, including biochemical profile of liver function tests and lipid profile, were normal. Six months after initiation of acitretin, ichthyosis had improved considerably and mild ainhum was present only in the little fingers. However, her parents noticed knock-knees, and she complained of bone pain. On evaluation she was found to have normal calcium (9.2 mg/dL), high alkaline phosphatase (960 U/L), and low serum 25-hydroxy vitamin D (22 nmol/L) levels. The rest of her renal parameters, hemogram, and liver function tests were normal. Radiographs of the wrists and knees confirmed the diagnosis of rickets. Acitretin was stopped and she was started on vitamin D supplementation and topical emollients and keratolytics were continued.

Case 2-A 2-year-old girl, born of a nonconsanguineous marriage, presented with lamellar ichthyosis. There was no history of collodion membrane at birth. Ectropion of both eyes and hyperkeratosis of the palms and soles were seen. Anthropometry and developmental milestones were normal. She was started on 10 mg of isotretinoin along with emollients and keratolytics and had a gradual response to therapy. Six months after initiation of therapy, her vitamin D levels were found to be 32 nmol/ as compared to a baseline level of 180 nmol/L. She was diagnosed with iatrogenic vitamin D deficiency and oral retinoids were withheld and supplementation with vitamin D was started. At follow-up at 2 months her vitamin D levels returned to normal.

Discussion: Rickets has been a reported complication of congenital ichthyosis. Various contributory factors include limiting sun exposure, inadequate dietary supplementation, abnormal epidermis, with defective synthesis of vitamin D and poor penetration of UV rays and dark skin color. Retinoids are compounds with biologic activity like that of vitamin A. It has been proposed that vitamin A hinders the action of vitamin D. The active metabolites of vitamin A and D, retinoic acid (RA) and 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] regulate geneexpression through nuclear receptors. Further, Vitamin A appears to hamper the intestinal calcium response to vitamin D. Several studies have documented association between chronic high

intake of vitamin A and osteoporosis and the hypercalcemia and highalkaline phosphatase in persons with vitamin A toxicityindicate that vitamin A affects bone. Case reportsin children with hypervitaminosis A have also reported altered skeletal development. Synthetic retinoids have also been reported toalter bone metabolism and increase bone turnover. Receptors for RA are located on osteoblasts andosteoclasts, which indicates that they are directvitamin A targets.

Both of the children presented in this article come from a tropical country and had skin of color, with higher chance ofbeing vitamin D deficient because dark skin synthesizes markedly lessvitamin D on exposure to sunlight and the low dietary intake and also contributes to a higher risk ofvitamin D deficiency in this population. In both patients, there was no evidence of malnutrition orrickets at baseline.

Both cases developedrickets 6 months after initiation of oral retinoids. No previous study has specifically evaluatedthe association between oral retinoid intake and bone status in ichthyosis. It is recommended to start supplementation withvitamin D simultaneously with initiation of oralretinoids to prevent such adverse events.

Comments

This article documents 2 cases of congenital ichthyosis that developed rickets and Vitamin D deficiency after initiation of retinoid therapy. Therefore it suggests the possible role of retinoids in the causation or uncovering of vitamin D deficiency rickets. This has important therapeutic implication wherein in all cases, Vitamin D supplementation may be initiated along with retinoid therapy for ichthyosis.

4. Trichoscopy as a diagnostic tool in trichorrhexis invaginata and Netherton syndrome.

BittencourtMde J, Moure ER, Pies OT, Mendes AD, Deprá MM, Mello AL An Bras Dermatol. 2015; 90:114-6.

Introduction: Netherton syndrome (NS) is a rare autosomal recessive disease characterized by erythroderma, ichthyosis lineariscircumflexa, atopy, growth retardation a hair shaft alteration of trichorrhexisinvaginata(TI) or bamboo hair. TI is pathognomonic of NS and presents itself microscopically as an invagination of the shaft's distal portion to its proximal portion, giving it an appearance of a "ball in a hoop". When there is fracture of hair at the site of the invagination and this type of fractured hair is called "golf tee hair". In recent years trichoscopy has increasingly been used for diagnosing cicatricial and noncicatricialalopecias, inflammatory diseases and scalp hair shaft disorders such as monilethrix, trichorrhexisnodosa, pilitorti, piliannulatiand TI.

Case-A four-year-old boy presented with history of erythroderma since birth, chronic diarrhoea and growth deficit. His motherreported widespread eczematous plaques and had been using topical corticoids, oralantihistamine and zinc regularly, with persistence oflesions and recurrent episodes of exacerbation. He also had brittle andfragile hair. At the dermatological examination short hair, diffuse erythema and scaling(especially over the face) and erythematous scaly plaques over the trunk, abdomen and back of hands were observed. Trichoscopy showedtrichorrhexisinvaginataand golf tee hair and microscopy confirmed characteristic TI changes. Laboratory examinations revealedeosinophilia (14%), thrombocytosis, and elevated Ig E serum levels.

Discussion: Genetic studies identified several mutations in the SPINK5 gene located in chromosome 5q31-32 that codifies serine protease inhibitor LEKTI. Despite advancements in moleculardiagnostics and increasing knowledge about NS the diagnosis remains difficult. Concomitantatopy may lead to errors in diagnosing it as atopic dermatitis. Among NS manifestations,the most specific is hair follicle alterations that may be evaluated in erythrodermic children. Thebasis for the diagnosis remains the visualization of TI under the microscope and thecharacteristic invagination is enough to establish thediagnosis. Eyebrows area good place to visualize this abnormality.Trichoscopy is a quick and non-invasive method that also shows the typical changes of TI. Bythis method it is possible to visualize both hairs typical of bamboo hair as well as golf tee hair.This method also allows diagnosing other hair shaft disorders, such as monilethrix, trichorrhexisnodosa, pilitorti, piliannulati.

Differential diagnosis of small dark nodules in hair axis includes trichorrhexisnodosa,onilethrix and black piedra. The clinical differential diagnoses include Omennsyndrome, generalized seborrheic dermatitis, erythrodermicpsoriasis, staphylococcal

scalded skin syndromeand non-bullous ichthyosiformerythroderma. In this case, trichoscopy visualized both TI and golf tee hair and proved useful in establishingthe correct diagnosis of NS. Therefore, trichoscopy may be a painless, non-invasive diagnostic tool in evaluating erythrodermaand ichthyosis in infants.

Comment

This case report highlights that in the absence of state of the art diagnostic molecular techniques a simple tool-trichoscopy can be used to diagnose Netherton syndrome.

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5. Afamelanotide for ErythropoieticProtoporphyria

Janneke G. Langendonk, ManishaBalwani et al.N Engl J Med 2015; 373:48-59.

Erythropoieticprotoporphyria is a severe photodermatosis that is associated with acute phototoxicity. Patients with this condition have excruciating pain and a markedly reduced quality of life. The authors evaluated the safety and efficacy of an α-melanocyte–stimulating hormone analogue, afamelanotide, to decrease pain and improve quality of life.

Two multicenter, randomized, double-blind, placebo-controlled trials of subcutaneous implants containing 16 mg of afamelanotide were conducted. Patients in the European Union (74 patients) and the United States (94 patients) were randomly assigned, in a 1:1 ratio, to receive a subcutaneous implant containing either afamelanotide or placebo every 60 days (a total of five implants in the European Union study and three in the U.S study). The type and duration of sun exposure, number and severity of phototoxic reactions, and adverse events were recorded over the respective 180-day and 270-day study periods. Quality of life was assessed with the use of validated questionnaires. A subgroup of U.S. patients underwent photoprovocation testing. The primary efficacy end point was the number of hours of direct exposure to sunlight without pain.

In the U.S. study, the duration of pain-free time after 6 months was longer in the afamelanotide group (median, 69.4 hours, vs. 40.8 hours in the placebo group; P=0.04). In the European Union study, the duration of pain-free time after 9 months was also longer in the afamelanotide group than in the placebo group (median, 6.0 hours vs. 0.8 hours; P=0.005), and the number of phototoxic reactions was lower in the theafamelanotide group (77 vs. 146, P=0.04). In both trials, quality of life improved with afamelanotide therapy. Adverse events were mostly mild; serious adverse events were not thought to be related to the study drug.

Comments

Afamelanotide had an acceptable side-effect and adverse-event profile and was associated with an increased duration of sun exposure without pain and improved quality of life in patients with erythropoieticprotoporphyria.

6. Molecular Characterization of NF1 and Neurofibromatosis Type 1 Genotype-Phenotype Correlations in a Chinese Population

Jia Zhang, Hanxing Tong, Xi'an Fuet.al.Scientific reports 5, 09 June 2015

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary disease that is primarily characterized by multiple café au-lait spots (CALs) and skin neurofibromas, which are attributed to defects in the tumor suppressor NF1. Because of the age-dependent presentation of NF1, it is often difficult to make an early clinical diagnosis. Moreover, identifying genetic alterations in NF1 patients represents a complex challenge. Currently, there are no effective detective methods, and no comprehensive NF1 mutation data are available for mainland China. The authors screened 109 Chinese patients from 100

families with NF1-like phenotypes (e.g., CALs, neurofibromas, etc.) using Sanger sequencing, multiplex ligation-dependent probe amplification and cDNA sequencing.

NF1 mutations were identified in 97 individuals, among which 34 intragenic mutations have not previously been reported. Exhaustive mutational analysis detected mutations in 89% (89/100) of the NF1-like probands and 93% (70/75) of subjects fulfilling the National Institutes of Health (NIH) criteria. Findings indicate that individuals who exclusively present with multiple CALs exhibit a high possibility (76%) of having NF1 and show a significantly lower mutation rate ($p = 0.042$) compared with subjects who fulfill the NIH criteria, providing clinicians with the information that subjects only with multiple CALs harbor a considerable possibility (24%) of being attributed to other comparable diseases.

The National Institutes of Health (NIH) criteria for NF1 are generally accepted for making a diagnosis according to clinical information of a patient. These clinical criteria are highly specific and sensitive in adults with NF1. However, only 50% of the pediatric NF1 patients without a family history meet the criteria for diagnosis by the age of 1 year, whereas almost all do so by the age of 8 years, highlighting the importance of molecular diagnosis.

The NF1 gene spans approximately 350 kb of genomic DNA and contains 57 constitutive exons and three alternatively spliced exons. The most common transcript encodes a 2818-amino-acid polypeptide, neurofibromin. One vital functional region, a highly conserved GAP-related domain (GRD) encoded by exons 20–27a, has been identified and well defined.

Mutational analysis of the NF1 gene has been found to be a major challenge because the gene is extremely large, in combination with the presence of pseudogenes, a lack of mutation hotspots and a wide mutation spectrum, ranging from single nucleotide substitutions to large deletions. To date, 2030 different NF1 mutations have been reported and listed in the Human Gene Mutation Database (HGMD). The majority of these mutations lead to truncated forms of neurofibromin, and approximately 25–50% of the mutations are expected to result in RNA splicing abnormalities.

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In total, 89 out of the 100 indexed families harbored pathogenic mutations, consisting of 21 nonsense mutations, 26 frameshift mutations, 15 splicing mutations, 12 missense mutations, 2 in-frame deletions, 1 indel, 11 microdeletions and 1 single-exon deletion. Thirty-four intragenic mutations were novel . The mutations were evenly distributed along the NF1 coding sequence at first glance. However, after being weighted by exon size, exon 15 was found to show a remarkably high mutation frequency .

In this study, the patients with anemic nevus ($n = 4$), juvenile xanthogranulomas ($n = 1$) or hemangiomas ($n = 1$) all had a confirmed molecular diagnosis of NF1, suggesting that these cutaneous signs bear potential diagnostic value, as previously reviewed.

Compared with the findings of Lee et al., the proportion of mutation types and clinical features were similar, with the exception of Lisch nodules (65.4% versus 4.4%). Mutations c.574C>T, c.1318C>T, c.3826C>T and c.7486C>T are shared in both studies, but they are also common in other studies . This study adds to the notion that there are no obvious mutation hotspots in NF1, and we were unable to find any novel clear relationships between the type and locus of mutations and distinct clinical features. Phenotypic differences in NF1 patients are more likely to be caused by mechanisms such as "a second hit", modifying genes that are unlinked to the NF1 locus, epigenetic alterations or other environmental factors.

Comments

The present study represents the first large genetic study of NF1 patients in mainland China. The aim of the present study is to characterize a wide spectrum of NF1 mutations and elucidate genotype–phenotype correlations through integrated mutational screening and clinical data collection. The obtained data should consequently provide a simple and effective strategy

for early diagnosis and genetic counseling. However, this exhaustive mutational screening method can still serve as a cost-effective diagnostic strategy with high sensitivity in the setting of Chinese patients suspected of NF1, but without adequate clinical features corresponding to the NIH diagnostic criteria.

7. Aplasia Cutis Congenita with "Vanishing Twin"

Enrico Valerio, MargheritaFantinato, Irene Giovannini. May 2015 Vol 166, Issue 5, Pages 1316

A monochorialbiamniotic pregnancy was obtained with intracytoplasmic sperm injection procedure; at 13 weeks, in utero death of 1 twin occurred with complete fetus reabsorption. Normal fetal growth was observed in the other twin, who was delivered vaginally at 39 weeks of gestation. At birth, symmetrical extensive areas with absent skin were noted at flanks bilaterally; similarly, cranial vertex presented with an extensive area of disepithelization with absence of the underlying bony plate. The clinical picture was consistent with aplasia cutis congenita (ACC). The baby received prophylactic antibiotic treatment with oral amoxicillin-clavulanate till lesion re-epithelialization, which was completed in 10 days' time along with bony plate restoration . A cerebral magnetic resonance scan, as well as cardiac and abdomen ultrasound turned out normal.

ACC is characterized by congenital absence of skin tissue at birth. This occurs most commonly on the scalp, but can also affect any portion of the body, such as trunk and limbs; this last condition is referred to as Adams–Oliver syndrome. ACC with involvement of multiple districts is often linked with intrauterine death of a second twin, progressively pressed flat between the living twin and the uterine wall and consisting at birth with a fetuspapyraceus. Incidence of such condition is 1:12 000 in live births In some cases, the dead twin completely reabsorbs in utero (as in the presented case), leading to the term "vanishing twin."

The pathophysiology of ACC associated with fetuspapyraceus/vanishing twin is still unknown; one opinion is that the in utero dead twin may release thromboplastic material, which is spread through the vascular anastomosis of the fetus, eventually giving rise to disseminated intravascular coagulation in the surviving twin leading to altered skin development, Also, ischemia may attract other organs and systems apart from skin, leading to possibly accompanying congenital defects such as duodenal, ilial, and/or biliary atresia with intestinal infarction, cortical renal necrosis, among others.

Comments

Treatment of ACC should be conservative since spontaneous re-epithelialization and re-ossification of the scalp occur, in time, in most patients. Careful monitoring for cerebral damage and/or infections during the healing period of the lesions must be maintained.

8. Melanoma in xerodermapigmentosum type C children: Overrepresentation of desmoplastic type?

Stéphanie Leclerc-Mercier ,Christine Bodemer, Benoit Michel, NademSoufir, Eva Bourdon-Lanoy, AnnonciadeFrassatti-Biaggi et.al.June 2015,Volume 72, Issue 6, Pages e173–e176

Xerodermapigmentosum (XP) is a disorder of DNA repair that affects the skin, eyes, and central nervous system. It is caused by a genetic defect involving the nucleotide excision repair pathway. In the most common form, type C (XP-C), dermatologic manifestations are mostly due to cellular hypersensitivity to ultraviolet radiation and begin as photosensitivity in early infancy with later progression to tumor development.

The risk of melanoma in XP is approximately 2000-fold higher than in the general population, with a median age of initial diagnosis during early adulthood . In a previous multicenter study, the authors reported 10 melanomas found in 31 patients with XP-C, 3 of which were desmoplastic. To further study this condition, they retrospectively reviewed 208 tumor samples from 13 pediatric XP-C patients followed up at their national referral center from 1993 to 2013. Three independent dermatopathologists reviewed all melanocytic lesions. Eleven melanomas were identified in 6 molecularly proven XP-C patients. All tumors were desmoplastic melanomas (DMs) defined as invasive spindle cell tumors showing strong S100 protein positivity and exceptional or absent HMB45 and MelanA staining on immunohistochemistry with at least 1 of the following features: asymmetry, irregular and infiltrative silhouette, absent maturation, paucicellularity, collagen fibrosis, overlying in-

traepidermal atypical melanocytic proliferation/melanoma in situ, or lymphocytic aggregates within the tumor .

The 11 DMs were described as small, pink or dark-brown plaques or papules, and were all located within sun-exposed areas (8 head and neck, 3 limbs). Lesion size ranged from 0.2 to 1.5 cm in diameter, and the median age at diagnosis was 11.5 years . All tumors were surgically removed. Restricted margins (2 mm) were used on the face. No patient underwent sentinel lymph node biopsy. A cutaneous metastasis occurred on the scalp in 1 case 8 years after excision. Two patients died of unrelated causes.

DM typically affects the head, neck, and extremities, and while local recurrences are frequent, metastases to regional lymph nodes are rare. The incidence of DM is 2.4 per million. Clinical diagnosis is complicated by the absence of the classic clinical features of melanoma in some DM cases. DM immunostaining can be negative for common melanoma markers. Furthermore, unique DM histology, including low tumor density, absence of significant cytologicatypia, absence of mitotic figures and presence of nonpigmented cells may lead to misdiagnosis and underestimation of the prevalence of DM in XP-C. Consequently, spindle cell proliferations, especially if there is melanocytic lentiginous hyperplasia of the overlying epidermis, must be carefully examined in all XP-C patients. Additional sections and immunohistochemistry are mandatory.

Comments

In their small cohort, outcomes suggest that reducing the excisional margin size for XP-C patients with facial pure DM may be safe and allows for improved cosmetic results. Furthermore, sentinel lymph node biopsy may not be necessary for these patients.

The occurrence of DM in XP-C underlines the central role of ultraviolet radiation exposure and cellular microenvironment in carcinogenesis in patients with XP. Polymorphisms within the XPC gene could explain the late occurrence of DM in non-XP-C patients

ICTHYOSIS UPDATE

Dr Meghana Phiske

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Definition: Icthyosis is a large group of cutaneous disorders characterized by abnormal epidermal differentiation presenting with localized/ generalized scaling and can be associated with additional cutaneous and/or systemic manifestations.[1]

Classification: Icthyosis is broadly divided as non-syndromic and syndromicichthyoses. The term autosomal recessive congenital ichthyosis (ARCI) includes harlequin icthyosis(HI), lamellar ichthyosis(LI) and congenital ichthyosiformerythroderma (CIE). Ichthyoses due to keratin mutations are referred to as keratinopathic ichthyosis (KPI) and include epidermolytic ichthyosis (EI) and superficial epidermolytic ichthyosis (SEI).[2]

Major subgroups: Syndromic form; Nonsyndromic form

Keratinopathic ichthyosis (caused by keratin mutations): Epidermolytic ichthyosis; Superficial epidermolytic ichthyosis; Ichthyosis Curth-Macklin

Autosomal recessive congenital ichthyosis: Harlequin ichthyosis; Lamellarichthyosis; Congenital ichthyosiformerythroderma

Pleomorphic ichthyosis: Self-improving collodionichthyosis; Ichthyosis prematurity syndrome; Rarer forms characterized by a phenotypic shift in early childhood

Classification based on presentations of icthyosis: Colloidion membrane; Lamellar icthyosis; Self healingcollodion baby; Neonatal Gauchers's disease; KID syndrome (occasionally); Netherton syndrome (occasionally); Sjogren-Larsson syndrome (rarely); Neutral lipid storage disease (rarely); Massive constrictive scales; Harlequin icthyosis; Erythroderma; Netherton's syndrome; KID syndrome; Scaling, hperkeratosis or exaggerated neonatal desquamation; Recessive X linked icthyosis; Sjogren-Larsson syndrome; Neutral lipid storage disease; Erosions/blisters with/without erythema and hyperkeratosis; Epidermolytic hyperkeratosis; Annular epidermolytic ichthyosis; Excessive 'vernix'; KID syndrome; Harlequin icthyosis; Normal skin; Refsum's disease; Neutral lipid storage disease; Icthyosis vulgaris; Recessive X linked icthyosis; Netherton's syndrome

Etiopathogenesis: In all types of icthyosis the permeability barrier abnormality could be due to

1. Abnormalities in the supramolecular organization, synthesis, and/or secretion of the extracellular lamellar bi-layers.
2. Metabolite accumulation or pathway product deficiency, or both leading to alteration in the lipid content and distribution causing stratum corneum architecture disruption.[3]

Genes responsible for icthyosis: The genes in which causative mutations have been identified include

Transglutaminase 1(TGM1) (account for 50%–60% ARCI and 90% of LI).

ALOX12B, ALOXE3, ABCA12

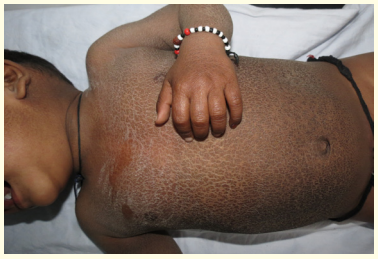
NIPAL4 (ichthyin)

CYP4F22, LIP

Clinical types[1,4,5,6,7,8,9,10]

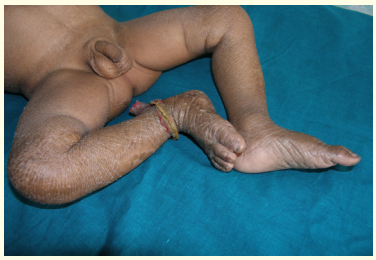
Icthyosis vulgaris: It is an autosomal dominant disorder presenting between 3 and 12 months of age and characterized by fine scales that appear pasted over the body. The extensor surface of the extremities are involved. Scales are more coarse on the lower extremities.Associated findings include accentuated skin markings and hyperkeratosis on palms, keratosis pilaris and atopy.

X-Linked Ichthyosis (XLI): In X-linked ichthyosis (steroid sulfatase deficiency/ recessive X-linked ichthyosis) the affected male infants at birth show pink or red skin and peeling of large, translucent scales which darken with age and have decreased tendency to desquamate. The scaling is generalized, but the lateral face, axillae and neck always remain involved. Darker color of the scale, more 'centripetal' distribution and sparing of palms and soles, points to a clinical diagnosis of XLI. Affected males have an increased risk of cryptorchidism and corneal opacities (usually not present in infants but diagnostic when present).



Recently around 40% of XLI patients have demonstrated cognitive behavioral abnormalities, such as attention-deficit disorder due to altered sterol metabolism in the central nervous system.Steroid sulfatase is deficient in the placenta, resulting in low maternal urinary estrogen secretion and low amniotic fluid estrogen, leading to insufficient cervical dilation and subsequent prolonged or difficult labor.

Lamellar ichthyosis (LI) and congentialicthyosiformerythroderma (CIE): Both conditions may be indistinguishable at birth, as both have collodion membrane, ectropion, eclabium beaked, curved nails, crumpled ears, palmoplantarkeratoderma, decreased sweating with heat intolerance, scarring alopeciaand a normal life span. LI remains severe throughout life but CIE may improve at puberty.Both develop into distinct phenotypes after infancy, LI presenting as brown, plate-like scale on a non-erythematous base and persistent ectropion while CIE presents with generalized erythroderma with fine, white scaling. Other manifestations of LI include corneal opacity, photophobia, and abnormal



deciduous and permanent teeth.

Autosomal Recessive Congenital Ichthyosis (ARCI): The clinical presentation of ARCI may range from HI to LI and nonbullous congenital ichthyosiformerythroderma (NCIE). Epidermal scaling is the clinical hallmark of ARCI but patients may also have a collodion membrane at birth, ectropion, eclabium, alopecia, palmoplantarkeratoderma, hypohidrosis, and/or variable erythema.

Collodion baby: It is a common presentation of several congenital ichthyoses, including lamellar ichthyosis , congenital ichthyosiformerythroderma and self-healing collodion baby. As compared to HI it is less severe but has significant morbidity and mortality . These patients are born prematurely and at birth they are encased in a yellow, shiny, taut, cellophane/ parchment like membrane, which around the eyes and mouth leads to ectropion andeclabium . After birth, the membrane becomes dry and fissured, shedding within the first weeks of life (2 weeks to 3 months) at which point clinical manifestations of the underlying disease start developing.

Harlequin Ichthyosis (HI): These Infants are born prematurely and at birth are encased in a markedly thickened, armor-like hard stratum corneum. Soon after birth this casing cracks, resulting in deep transverse and longitudinal fissures separating thick, yellow, geometric plates of skin.Other features include ectropion, eclabium, flattened and rudimentarynose and ears, edematous hands/ feet, which are enveloped in a mitten-like casing, constricting bands over extremities.These infants more prone to sepsis, dehydration, and impaired thermoregulation. Milder phenotype similar to a collodion baby or presentation with whitish-yellow thickened scale (vernix-like) are also seen.

Epidermolytic Ichthyosis (EI): At birth EI presents with blistering and areas of denuded skin which decreases and later hyperkeratosis becomes the prominent, making the skin prone to tearing secondary to traction. Six clinical phenotypes are described with variable scaling and extent of involvement.

Ichthyosis hystrix: Ichthyosis hystrix presents with massive spiky or verrucous hyperkeratosis, erythema without blistering, mainly on extensor aspect of arms and legs and palmoplantarkeratoderma severe enough to cause contracture, fissuring, nail dystrophy, or functional disability. Scaling may improve or stabilizes with age.

Three types are known

Lambert type: Patients are alright at birth but develop dark warty scaling at the age of 7 weeks or later and face.

Bäfverstedt type: There is ichthyosis with hystrix scaling on the face along with palmoplantarkertoderma.

Ichthyosis hystrix of Curth-Macklin type: Presents with severe palmoplantarkeratoderma, porcupine spine or symmetrical hystrix with dull brown scaling seen over extensor aspect of limb, and trunk.

Rheydt type: Connexin 26 defect causing hystrix-like ichthyosis deafness (HID) syndrome is a variant of ichthyosis hystrix which is also known as Rheydt type.

Multiple sulfatase deficiency: The scaling is milder than X linked icthyosis. Other features include developmental delay, coarse facial features and spastic quadriparesis.

Netherton Syndrome: Presentation is shortly after birth with erythroderma, and peeling. Other findings include hair shaft abnormalities (trichorrhexisinvaginata) and elevated IgE levels.

Keratitis-Ichthyosis–Deafness Syndrome (KID syndrome): Cutaneous manifestation range from discrete erythematous plaques to mild, generalized hyperkeratosis. Other findings are sensorineural hearing loss, vascularizing keratitis, sparse or absent scalp hair / eyebrows/ eyelashes, deformed or normal nails and defective teeth.

CHILD syndrome: It presents with circumscribed linear plaques surmounted by prominent wax like scales in a unilateral distribution.

Sjögren-Larsson syndrome and Neutral lipid storage disease with ichthyosis(NLSDI): Both disorders present with ichthyosis and neurologic features (severe in Sjogren Larsson).

Ichthyosis with confetti: Ichthyosis with confetti, is a rare form of ichthyosis characterized by severe erythroderma in which healthy spots gradually develop since childhood.It is caused by mutations in keratin 10.

Investigations for icthyosis[4,5,11]

The following tests can be used to diagnose icthyosis

1. Ichthyosis vulgaris: Skin biopsy (if needed)
2. XLI: Measurement of substrate accumulation in skin (cholesterol sulfate) or blood (cholesterol sulfate or other sulfated steroid hormones) and the assay of SSase activity in epidermis, cultured fibroblasts, or leukocytes. Fluorescence in situ hybridization (FISH) analysis for detecting carrier state.Placental sulfatase deficiency syndrome (PSD) detected by low maternal urinary and blood estriol levels (during second trimester) .
3. LI: A prenatal biopsy performed at 20 weeks shows early thickening of outer skin layer .It is used to test transglutaminase activity, which is a reliable marker for LI.
4. CIE: No laboratory test indicated.
5. HI: Ultrasonography
6. ARCI: Skin biopsy
7. EI: Skin biopsy and keratin gene studies
8. CHILD syndrome: Radiographic studies
9. KID syndrome: Skin biopsy (if necessary).
10. Netherton's syndrome: Hair shaft examination
11. Neutral lipid storage disease: Skin biopsy (frozen) and blood smear for vacuoles
12. Sjögren-Larsson syndrome: Assay of FAO activity.
13. Other methods: Chorionic villus sampling, fetal skin biopsy and preimplantation testing.
14. Genetic testing: For uncertain diagnosis or for confirmation of suspected diagnosis.

Complications[1,12,13]

Highest risk for complications occurs in infants with harlequin ichthyosis, collodion babies, epidermolytic ichthyosis and Netherton syndrome and include

1. Prematurity
2. Impaired barrier function causing morbidity and mortality.
3. Increased transepidermal water and heat loss causing hypernatremic dehydration
4. Electrolyte imbalance
5. Disrupted thermoregulation

6. Calorie malnutrition.
7. Fissuring and denudation leading to skin infections and sepsis.
8. Complications due to impaired flexibility (seen with Collodion babies or HI)
   a. immobilization resulting in impaired ventilation
   b. hypoxia and restrictive lung movement with subsequent risk of pneumonia
   c. difficulty in sucking or feeding.
   d. contractures and compartment syndrome.
9. Constricting bands leading to peripheral edema and ischemia.
10. Exposure keratitis.

Management [1,5,7,12,13,14,15]

Principles of management:

Primary-Improvement of barrier function

Secondary- Treatment of consequences of impaired function of skin like dehydration, malnutrition, or infection

Admission: Admission to the neonatal intensive care unit is required for infants presenting with collodion membrane, HI, erythroderma, or widespread blisters.

Environment management

1. Placement in humidified incubator.
2. Providing temperature-controlled environment via an isolette

Lubrication:

1. Liberal applications of bland emollients such as petrolatum-based products.Lubricating agents may be in form of lotions, creams, oils and ointment.
2. Removal of thick scale by keratolytic agents like urea, salicylic acid and alpha hydroxy acids facilitates desquamation.
3. For mild scaling topical keratolytic agents such as salicylic acid, urea, propylene glycol and agents with α-hydroxy acid (lactic acid, glycolic acid, etc)

Bathing: Daily bathing with only water or mild cleanser. Humidification with long baths (hydrates and facilitate scale removal by abrasives). Lubrication with bath oils or after bathing to wet skin (helps prolong skin hydration and flexibility).

Correction of dehydration, electrolyte Imbalance and increased metabolic demand: Close monitoring of urinary output, weight and electrolytes and treatment with intravenous hydration. Nutritional consultation to manage the caloric requirements.

Infection management:

a. To send blood culture if the infant is temperature and/or thermodynamically instable, lethargic, irritable and feeding poorly.

b. To send wound swabs in cases of purulent discharge or extensive erosions and treat identified infections aggressively.

c. Topicalmupirocin for isolated cutaneous fissures and erosions

d. To use prophylactic antibiotics for widespread fissuring or denudation

Care of fragile skin:

a. Gentle and careful handling.

b. To avoid conventional adhesives and use gauze or self adherent material to secure intravenous lines and tubes.

Management of pain: Use of acetaminophen, non-steroidal anti-inflammatory medications or narcotics for pain control.

Treatment of impaired flexibility: Liberal application of emollients to improve pliability. Surgical assistance for management of compartment syndrome and release of contractures/ constricting bands of skin

Other aspects of management:

a. A complete medical assessment

b. Detailed ophthalmological examination.

c. Attention to psychological and emotional status of the infants

d. Early referral to support groups through the Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.)

Treatment of ocular Complications:

a. Hourly lubrication with artificial tears or ocular lubricant to treat exposure keratitis.

b. Topical antibiotics for conjunctivitis or corneal abscess.

c. Surgical intervention

Care for xerostomia:

a. Check thesalivary flow

b. Frequent sipping of water

c. Unnecessary manipulation of perioral skin during procedures to be avoided.

d. Reduction in dose of local anaesthetic agents during dental treatment for patients on retinoids.

Retinoids

Systemic retinoids provide phenotypic improvement in all icthyosis except in Netherton syndrome. Improvement occurs within weeks to a month, but on stopping retinoids the scaling recurs.

Benefits of retinoids:

1. Retionids may increase the ability to sweat thus benefiting those who fatigue easily because of overheating secondary to absent sweating.

2. They can ameliorate ectropion or pseudoainhum.

3. They have generalized keratolytic effect, abruptly leading to extensive shedding or peeling of scale.
4. In erythrodermic variant they produce marked response in palmoplantar hyperkeratosis.
5. In cases of HI, retinoids help relieve the constricting scales which can lead to necrosis of distal digits. Also the thoracic constriction by thick scale can impede breathing and this be reduced by retinoid therapy.
6. Retinoids improve skin appearance and function
7. By reducing hyperkeratosis, retinoids can reduce the frequency of skin infection.
8. Retinoids help to accelerate shedding of the thick scale.

Dose of retinoids: The main aim of choosing a dose is to find the lowest acceptable dose. Most patients do not require more than 1 mg/kg of isotretinoin or 0.5 mg/kg of acitretin. Since systemic retinoid therapy is likely to be used long-term, the dose should be kept as low as is practical, to allow retinoid-free periods (retinoid holidays) and to encourage the use of topical therapy to reduce the dose of retinoids.

Oral liarozole

Inhibitors of cytochrome P450 (CYP) 26, the rate-limiting enzyme in the catabolism of retinoic acid, have been developed as RAMBAs. Liarozole (0.1 g/day) is an effective treatment for ichthyosis. Liarozole 5% cream is effective in ARCI and is well tolerated.

Miscellaneous management:

1. Harlequin ichthyosis may be treatable with topical glucosylceramide
2. Tazarotene, a more selective topical retinoid, works via binding of retinoic acid receptors in the skin. Because topical tazarotene lead to a less cohesive and thinner stratum corneum, it can be potential effective treatment and alternative to surgical intervention for ectropion. It has been used successfully in the treatment of congenital ichthyosis .
3. Ammonium lactate (AL) is lactic acid (an alpha-hydroxy acid) buffered with ammonium hydroxide to provide a pH of 4.4 to 5.5. Apart from its role as a humectants, it stimulates ceramide biosynthesis, thus treating the mortar component by enhancing the intercellular lipid bilayer. AL 2 to 10% solution increases dermal glycosaminoglycan while AL 12% lotion exhibits a slower relapse of xerotic skin changes.
3. A combination-therapy with a physiological lipid-based barrier repair topical emulsion and ammonium lactate 12% lotion applied topically is found to be effective, as it addresses the concept of corneocytes and the intercellular lipid bilayer.
4. Application of complete physiological lipid mixtures containing ceramides, cholesterol, and fatty acids in the proper ratio facilitates the barrier recovery mechanism. Physiological lipid mixtures, such as Ec cream, traverse the epidermis and the individual lipid components may be incorporated into lamellar bodies at the granular layer after application. Ec cream is a ceramide dominant barrier repair cream containing all three key lipids (ceramide, cholesterol, free fatty acids) in an optimized 3:1:1 molar ratio, thereby increasing the lipid bilayer and ultimately treating the mortar component of the barrier.
5. N-acetylcysteine (NAC) is a non-toxic, hypoallergenic amino acid derivative that has been used systemically as a mucolytic, an antioxidant, a nephroprotective agent and an antidote of acetaminophen toxicity.NAC inhibits keratinocyte and fibroblast proliferation and has lesser side effects. Hence it is likely to be a safe, non-toxic therapy.
6. Topical enzyme replacement therapy has emerged as a promising alternative.

Recent advances[16,17,18]

For genetic diagnosis, obtaining mRNA from hair follicle epithelial cells, which are analogous to keratinocytes in the interfollicular epidermis, is a minimally invasive method in patients with ARCI.

For definitive diagnosis and the exclusion of other disorders like LI electron microscopy can be done which shows abnormal or absent lamellar granules and a heavy accumulation of lipid droplets in the keratinocytes.

Identification of the gene underlying HI has enabled DNA-based prenatal diagnosis at the earlier stages of pregnancy with low risk.

Trichoscopy has proved to be useful in establishing the correct diagnosis of NS (shows presence of bamboo hair and golf tee hair). Thus it can painless, non-invasive diagnostic tool, precise in evaluating erythroderma and ichthyosis.

Management

Principles of management

Primary

Improvement of barrier function

1. Environment management
2. Lubrication Applications of bland emollients
3. Bathing:
   Daily bathing with only water or mild cleanser
4. Care of fragile skin
   Gentle and careful handling

Secondary

Treatment of consequences of impaired function

1. Correction of dehydration, electrolyte imbalance
   Placement in humidified incubatorTreatment with intravenous hydration.
2. Nutritional consultation
3. Infection management Topical/oral/prophylactic antibiotics Removal of thick scale by keratolytic agents

Specific management

Oral

- Systemic retinoids → For all icthyosis
- Oral liarozole → Autosomal recessive congenital icthyosis

Topical

- Emollients
- Tazarotene

Management of complications

- Ocular complications → Lubrication Antibiotics Surgery
- Xerostomia → Frequent sipping of water
- Impaired flexibility → Surgery
- Psychological aspect → Referral to support group

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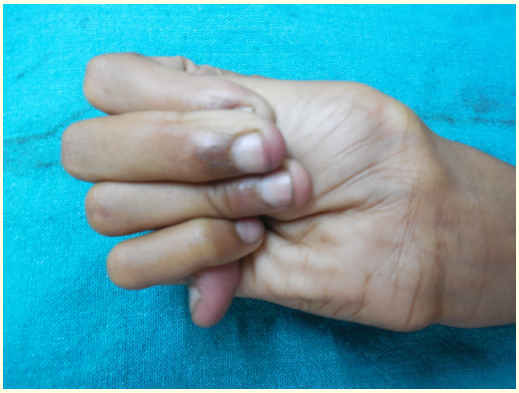
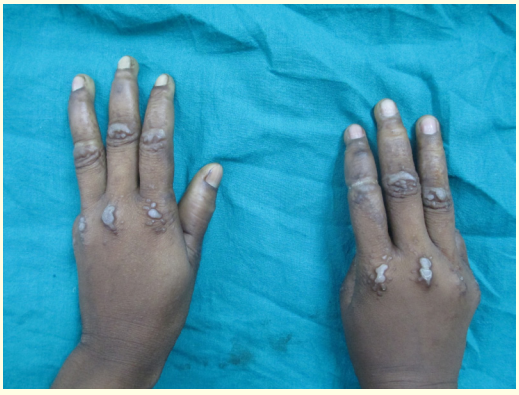
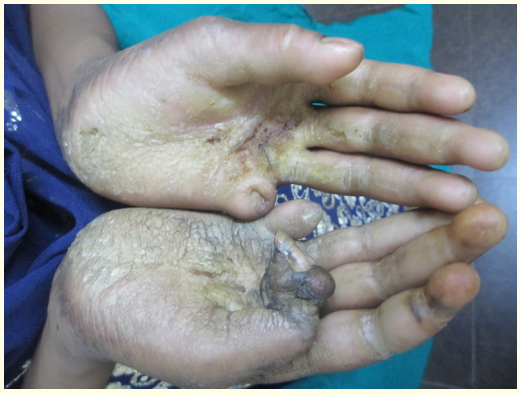
QUIZ FOR NEWSLETTER

1. In which genetic condition you find Steinberg's sign?



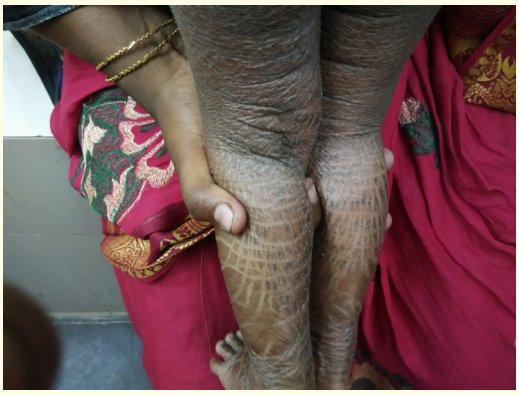
2. A 17 year old presented as diffuse palmo plantar keratderma since 2 years of age. She has pseudo-ainhum and keratosis and on the knuckles. She did not have much ichthyotic changes but in audiometry she showed partial sensori-neural deafness. Which gene protein of her is affected?



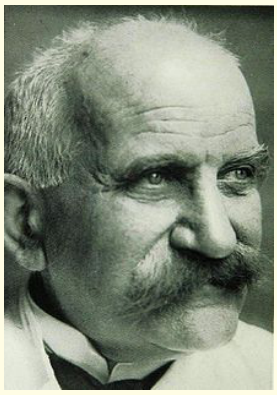


3. The two sibling shown below are born out of consanguineous marriage. Which molecular pathway is possibly affected in these kids?

4. A 2-year-old born out of consanguineous marriage, had history of collodian membrane. He had large, thick, plate-like brown scalesin generalized distribution; no eryhtroderma and ectropion. Which disease it is?



5. A one-year-old kid was diagnosed as Congenital Ichthyosis and Retinitis Pigmentosa. Which metabolic pathway is possibly involved?
6. What is DEBRA international?
7. What does "Harlequin" refers to?
8. Who is this famous scientist?



9. Which disease RICCARDI classification was proposed to?
10. Which gene-protein is involved in Kindler syndrome?

Answers

1. Steinberg's signor the thumb sign is seen in Marfan syndrome.In this condition, when the thumb is held across the palm of the same hand, it projects well beyond the ulnar surface of the hand.Another sign which is elicited in MarfanSyndrome is wrist sign or Walker's sign which shows appreciable overlap of the thumb and fifth finger when the wrist is gripped with the opposite hand.
2. She has mutilating keratoderma of Vohwinkel syndrome possibly due to Connexin 26 defect.
3. Nuclear Excision Repair Pathway.
4. Lamellar Ichthyosis
5. Phytanic acid (Refsum Disease)
6. DEBRA (Dystrophic Epidermolysis Bullosa Research Association) International is the worldwide alliance of Epidermolysis Bullosa (EB) patient support groups, working in over 40 countries
7. "Harlequin" refers to the resemblance of the facial features and diamond-shaped scales in affected neonates to a mute character in traditional pantomime, typically masked and dressed in a diamond-patterned costume
8. Josef Jadassohn, a German Dermatologists. Many conditions including a type of ectodermal dysplasia called Jadassohn-Lewandowsky syndrome were named after him.
9. In 1982 , Neuroibromatosis was classified by RICCARDI in 8 subtypes.
10. Kindlin 1