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CONTINUING MEDICAL EDUCATION

SKIN IN METABOLIC DISORDERS OF CHILDREN

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Diseases related to metabolic dysfunctions are associated with a heterogenous assortment of manifestations in the skin; some of which are minor, others major. These disorders are caused by a wide variety of factors many of which are genetically determined with defects of enzyme regulation as the prime abnormality. The absence of activity of a specific enzyme may cause one or several defects.

Metabolic diseases may manifest for the first time at any age. This article reviews the metabolic disorders with skin changes which appear in infancy or childhood. Such disorders relate to the metabolism of carbohydrates, lipids, proteins, aminoacids, pigment and minerals. The therapeutic aspects of the disorders are not discussed.

Disorders of carbohydrate metabolism

Diabetes mellitus (DM): Diabetes mellitus is a common metabolic disorder in pediatric practice. It is a disorder of energy metabolism which results from absolute or functional defect of insulin. Insulin deficiency leads to impairment of glucose transport, a defect in the synthesis and storage of lipids and decrease in the synthesis of protein.

Unlike in the adult disease, there are no cutaneous markers of DM in children; the symptom complex of childhood diabetes being polyuria, polydypsia, polyphagia, weight loss, fatigue and irritability.[1] The diabetic new-born is a large baby, often an over-grown premature infant. Macrosomia and odema characterise this infant.

The most frequent (55%) skin problem in a diabetic child is infection, and majority of the infections are pyogenic. This complication of DM is adequately handled by the pediatrician and the role of a dermatologist in handling a diabetic child is insignificant. Among 30 diabetic children admitted to the pediatric unit of the Christian Medical College Hospital, Vellore, during a 10 year period, 9 had skin lesions, 5 of them being pyogenic infections; carbuncle 1, furuncles 2, impetigo 2. All the five had ketoacidosis, probably precipitated by the infection.

Disorders of lipid metabolism

These disorders can be classified into 4 main groups; hyperlipidemias, dyslipidemias, hypolipidemias and lipoidoses.

I. Hyperlipidemia (hyperlipoproteinemia)

The term hyperlipoproteinemia denotes an increase in the level of one or more serum lipoproteins (LPs). LPs are composed of lipids bound to the protein in the form of a large molecular complex with varying amounts of cholesterol, triglycerides and phospholipids. LPs differ in their densities and electrostatic charges. Therefore these can be fractionated either by ultracentrifugation or paper electrophoresis. In the order of increasing electrophoretic mobilities, four LP fractions are recognised; chylomicrons, betalipoprotein, prebetalipoprotein and alpha lipoprotein.

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Based on their pattern of distribution 6 LP profiles are delineated and these are designated by the Roman numerals I, IIA, IIB, III, IV and V.[2]

Hyperlipidemias may be primary or secondary. Primary hyperlipidemias are rare disorders involving an inborn error of metabolism.

Type I hyperlipoproteinemia (HLP). Burger-Grutz syndrome is the familial form of type I HLP. This is a rare autosomal recessive disease with marked hyperchylomicronemia. Deficiency of lipoprotein lipase is the biochemical abnormality. This enzyme facilitates removal of triglycerides at the capillary endothelial wall. Symptoms may develop by the age of 10 years. Children complain of recurrent abdominal pain due to pancreatitis especially after a fatty food intake. Eruptive xanthomas also occur in childhood. In later years, hepato-splenomegaly develops. Post-prandial plasma is turbid. Serum triglycerides are high. Fat free diet for 4-5 days will allay symptoms. There is no accelerated vascular disease.

Type IIA hyperlipoproteinemia. This is also known as hyperbeta lipoproteinemia. Betalipoprotein levels are raised. Familial type IIA HLP is an autosomal dominant disease. Homozygotes have severe form of the disorder. There is paucity and dysfunction of receptors for this low density lipoprotein. In addition there may be increased production of beta lipoprotein. Xanthomas and premature atherosclerosis are the main features. In homozygotes symptoms start in childhood which become florid by around the twentieth year. In heterozygotes these manifestations are of milder degree.

Type IIB HLP. This has essentially similar clinical features to type IIA disease. Biochemically, along with hyperbetalipoproteinemia there is an increase in the concentration of prebeta lipoprotein also.

Types III, IV & V HLPs appear after childhood and hence are not discussed.

Xanthomas are the tell-tale signs of hyperlipidemias. On the basis of their morphology and distribution pattern, xanthomas are classified as xanthoma tendinosum, X. tuberosum, X. eruptivum, X. striata palmaris, X. plana and xanthelasma (plane xanthoma on eyelids). Although the type of xanthoma is not specific for any type of LP profile, certain relationships between the two exist as shown in table I.

Tendon xanthomas are characteristic of high serum cholesterol level. Therefore tendon xanthomata are seen often in betalipoproteinemia. Eruptive xanthomas are characteristic of high serum triglyceride level. X.tuberosum and plane xanthomas occur with increased serum cholesterol or triglycerides. In

Table I. Types of xanthomas in relation to the type of LP profile.[3]

LP profile	Bio-chemical features	The clinical type of xanthoma					
		Tendon	Tuberous	Eruptive	Plane	Striata palmaris	Xanthelasma
I	C′T′	—	—	+++	—	—	—
IIA	C′	+++	++	—	++	—	++
IIB	C′T′	+	++	++	—	—	—
III	C′T′	++	+++	+++	+++	+++	++
IV	T′	—	++	+++	—	—	—
V	C′T′	—	—	+++	—	—	—

C (Cholesterol), T (Triglycerides), ′ (Increased).

75% of xanthelasma, there is normolipidemia.

Secondary hyperlipidemias are seen in insulin dependent DM, nephrotic syndrome, chronic pancreatitis, hypothyroidism, obstructive biliary disease, lipid storage disorders and paraproteinemias.

II. Dyslipidemias

Two rare dyslipidemic conditions are known.

Cerebro-tendinous xanthomatoses (CTX) Syn. Cholestanalosis. CTX is a rare disease which is recessively inherited. The biochemical abnormality is accumulation of cholestanol which is normally synthesized from cholesterol. Two of the most common findings in this disease are indicated in the name, namely presence of tendinous xanthomas and CNS xanthomas.[3] In addition are seen cataract, dementia, cerebellar signs, palsies due to spinal cord lesions, bone granulomata etc.

Beta sitosterolemia. This is another rare disease characterised by an abnormally increased capacity to absorb plant sterols which in turn can be demonstrated in the plasma and the xanthomata by chromatography. Tendon and tuberous xanthomata are seen in the absence of hyperlipidemia.

III. Hypolipidemias

This rare group of disorders occurs due to a genetic defect in the synthesis of apoproteins. Apoproteins are specific globulins which combine with cholesterol, triglycerides and phospholipids to form the macro-molecules of lipoproteins. The diseases of this group are (1) *a-beta-lipoproteinemia,* an autosomal recessively inherited disorder, with complete absence of low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons, (2) *Hypo-beta-lipoproteinemia* with dominant inheritance and abnormally low levels of LDL and VLDL, and (3) *hypo-alpha-lipoproteinemia* or *(Tangier disease)* of recessive inheritance with absence of high density lipoprotein (HDL). The alpha LP deficiency results in storage of cholesteryl esters leading to peculiar orange discolouration of tonsils, pharynx and rectal mucosa. One instance of skin papules of acneform nature, reddish brown in colour on trunk and proximal part of extremities in an adult has been described in Tangier disease.[4] In a-beta- and hypo-beta-lipoproteinemia, the manifestations are non-dermatological; being severe malabsorption from early childhood, neurological manifestations and presence of acanthocytes in peripheral blood.

IV. Lipoidoses (Lipid storage diseases)

These constitute a group of inborn disorders of metabolism characterised by accumulation and storage of complex lipids. The basic defect in these diseases lies in the absence or hyperfunction of specific catabolic enzymes located in cytoplasmic organelles or lysosomes.

Among the several lipoidoses, skin changes of a distinct nature are seen only in the condition angiokeratoma corporis diffusum, also known as Fabry's disease, or ceramide-trihexosidosis.

Fabry's disease. This is a hereditary sex-linked disorder due to deficiency of the enzyme ceramide-galactosidase resulting in accumulation of the glycolipid galactosyl-galactosyl-glycosyl-ceramide as the major abnormality. Two other glycolipids also accumulate, namely galactosyl ceramide and hexoglycosyl ceramide. The enzyme defect is on the X-chromosome. Therefore females with one normal X-chromosome have an intermediate level of ceramide trihexosidase activity. Lipid accumulation in endothelial cells, smooth muscles like cardiac muscle, neurons, renal epithelium, histiocytes etc determine the

symptom-complex of the affected individual.

The earliest sign consists of small ectasia of superficial dermal vessels followed by thickening of the overlying epidermis giving rise to the angiokeratoma lesions. The first telangiectatic lesions which appear in childhood being very small, may be overlooked. By the age of 8-10 years lesions become more prominent. Due to ectasia there is extensive varicosity of the vessels. These are commonest on the limbs and scrotal skin. Prognosis is poor because of eventual renal failure which may occur in the second or third decade. The protracted clinical course of Fabry's disease is in contrast to the rapid deterioration of other lipoidoses like Gaucher's disease. This may be related to the greater solubility of ceramide-trihexoside and hence its slower rate of deposition than glucocerebroside which is deposited in Gaucher's disease.

Niemann-Pick disease. Basic defect in this disease is the deficiency of lysosomal enzyme sphingomyelinase. Skin changes are minimal. Skin appears waxy with ill defined yellowish-brown pigmentation of the exposed areas. Major findings are related to the reticulo-endothelial system. An apparently normal infant begins to lose weight about the 2nd or 3rd month of life. Abdomen becomes protuberant with hepato-splenomegaly. Bone marrow, lymph nodes, lungs and CNS symptoms also manifest.

Gaucher's disease. In children this condition produces no skin changes, although in the adult there is pigmentation. The disease is the commonest among the lipoidoses resulting from deficiency of the lysosomal enzyme glucocerebrosidase causing accumulation of a gluco-cerebroside in tissues of the reticulo-endothelial system and the neurons.

Refsum's disease. This familial disease is caused by deficiency of phytanic oxidase. Consequent to this, phytanic acid from dietary phytol accumulates in the plasma and tissues. Dry ichthyotic skin is present with ataxic neuropathy, anosmia, retinitis pigmentosa and skeletal abnormalities. Low phytol intake is the treatment.

Farber's lipogranulomatois (ceramidase deficiency). Described first in 1952, Farber's lipogranulomatosis is an unusual syndrome in which histiocytic granulomas are found, but in which there is an additional inborn error of metabolism. Disease is characterised by presence of peculiar subcutaneous masses over wrists and ankles.[5] Pebbly texture of the skin has been reported in one case. The subcutaneous masses are also seen in tendon sheaths, synovia and viscera. The foam cell granulomas show accumulation of ceramide and specific deficiency of tissue acid ceramidase levels. In the central nervous system the neurons of the grey matter and retina are distended in a fashion characteristic of inborn error of metabolism. Borderline mental retardation is common.

Disorders of purine and pyrimidine metabolism

Gout is the best known of the diseases related to abnormal purine metabolism. The typical gouty patient however is an adult.

Lesch-Nyhan disease. This a rare condition, closely related to gout. It is characterised by the deficiency of an enzyme of purine metabolism, hypoxanthine-guanine-phosphoribosyl transferase (HPRT). There is a severe degree of excessive uric acid production in this condition with a wide range of clinical expression. The less severe form of the disease with partial deficiency of HPRT presents with gouty arthritis and tophi in late childhood and adolescence.[6] Renal calculi is another common problem. In the most severe form, neurological symptoms predominate showing choreo-athetosis, spasticity, mental retardation

and compulsive self-mutilation. Susceptibility to bacterial infections with development of furuncles and paronychia have been noted.[7]

Xeroderma pigmentosum. This is a rare recessively inherited heterogenous disorder, the hall mark of which is pigmentary changes with associated photosensitivity. It is also characterised by high rate of sun-induced malignancies of the exposed skin areas and defective repair of UV-induced DNA changes. Pigmentary abnormalities are those of macular hyperpigmentation and depigmentation most prominent on sun-exposed parts. Pigmentation is of variable intensity from light brown to black. Pigmented macules may be seen on palms, soles and mucous membranes. Atrophy, dryness, fine scaling and telangiectasia are other features. Benign and malignant tumours of the skin are invariably seen by late childhood or adolescence. Keratoses, warty papillomas, keratoacanthomas, fibromas, neurofibromas, angiofibromas, angiomyomas are all seen as the benign tumours. Malignant ones are basal cell carcinoma, squamous cell carcinoma and malignant melanoma.

Secondaries are common and death generally occurs before adulthood. Non-cutaneous neoplasms are infrequent and include some rare brain tumours. XP subgroups can be defined by complementation analysis.[8] There is wide variation in the expressivity of the different subgroups; however, the clinical and biochemical features are relatively constant within each complementation group which have been analysed according to subgroups A-I and variants. At least eight different enzymes have been recognised to be responsible for the defective DNA repair and replication.

Errors of aminoacid metabolism

Metabolic errors related to some aminoacids have distinct clinical features and specific biochemical abnormalities. Three such diseases are alkaptonuria, Hartnup disease and tyrosinemia type II.

Alkaptonuria. Phenyl alanine and tyrosine normally undergo oxidative degradation to acetoacetic acid. Homogentisic acid (HGA) is a molecule with an aromatic ring in the series of this pathway. Deficiency of the enzyme HGA oxidase prevents cleavage of this ring causing accumulation of HGA which in turn is responsible for the following sequence of signs and symptoms.

a. Alkaptonuria. 'Alkaptos' denotes a substance with great avidity for oxygen at an alkaline pH. Term alkaptonuria refers to a brownish discoloration of the urine when it is allowed to stand. Consequently, mothers notice brown stain on the napkins of affected infants.

b. Pigmentation. Bluish black discoloration of the sclera, pinna, cartilages, skin of palms and soles, tendons and other mucosae, occurs primarily due to the formation of ochronotic pigment granules in the dermis and sweat glands. Intrinsic pigmentation of the skin is less prominent. Pigment also occurs in tympanic membrane, heart valves, larynx etc.

c. Ochronotic arthropathy. The arthropathy usually affects the spine, knees, shoulders, hips etc. Clinical features are those of osteoarthritis which occurs in relatively young individuals. The accumulated HGA inhibits the enzyme lysyl hydroxylase as a result of which structural integrity of collagen is reduced, leading to the degenerative ochronotic arthropathy.

Hartnup disease. This is a rare autosomal recessive metabolic disorder showing characteristic renal aminoaciduria with excess indicanuria. A definite malabsorption of tryptophan and other aminoacids such as alanine, serine, leucine and phenyl alanine occurs due to failure of transport across the jejunal mucosa. Tryptophan deficiency leads to

deficiency of nicotinic acid which in turn produces signs and symptoms of pellagra. The pellagral dermatitis precedes the neurological manifestations of cerebellar ataxia manifesting between third to ninth years. Early diagnosis is of value because of the curative effect of nicotinamide which controls both skin and CNS disturbances.

Tyrosinemia type II (Richner-Hanhart syndrome). This autosomal recessively inherited disorder results from deficiency of a hepatic enzyme tyrosine aminotransferase (TAT), responsible for transamination of tyrosine. Consequently tyrosine and tyrosine metabolites increase in blood and urine respectively. There is accumulation of tyrosine crystals in the cells, consequent lysosomal activation, lysosomal rupture and release of lysosomal enzymes which induces polymorphonuclear infiltration owing to presence of chemotactic factors. Manifestations of the disorder start in infancy or childhood as (a) inflammatory palmoplantar keratoderma and (b) inflammatory eye lesions. Skin lesions are painful, non-pruritic and frequently associated with hyperhidrosis. Eye lesions appear before skin lesions and may cause eventual scarring. Rarely mental retardation is present. Low tyrosine, low phenyl alanine diet can resolve skin and eye lesions.

Familial goitre. This is a rare disorder of autosomal recessive inheritance with absent or defective enzymes for organification and deiodination. It is possible to classify the disorder according to the various identifiable biochemical lesions; but the net effect is the same. The decreased secretion of thyroid hormone consequent to the biochemical defects leads to enhanced secretion of thyrotropin producing goitre with or without hypothyroidism. In the hypothyroidic patient, skin is dry, scaly and ichthyotic.[9] Sweat and sebum production are reduced. The hair is also dry and may be sparse. Mucin deposition in the skin is responsible for the characteristic cretinoid facies In severe cases, mucin deposition in the skin is seen as papules or plaques.

Prolidase deficiency (Hyperimidopeptiduria). About 20 individuals with this condition have been reported in the world literature. Prolidase is an enzyme that splits the dipeptides with proline or hydroxy proline. Skin is the primary target organ showing recurrent ulcers in the lower extremities. Rare skin manifestations include telangiectasias, scaly erythematous maculo-papular lesions, premature greying of hair, photosensitivity etc.[10]

Other aminoacidopathies

Albinism.
Phenylketonuria.
Oat-house disease.
Argininosuccinic aciduria.
Orotic aciduria.

These disorders of aminoacid metabolism have manifestations on the skin and hair. The skin shows pigment dilution, eczemas and malar flush. The hair shows pigment dilution, fragility and sparseness. In general, aminoacids responsible for normal melanin formation when deficient, cause decreased pigmentation and sulphur containing aminoacids necessary for formation of hard keratin like hair when deficient, cause fragility and structural abnormalities.

The most common among the above mentioned diseases encountered in dermatological practice is albinism.

Albinism. The term albinism restricts itself to a recessively inherited condition with universal hypomelanosis limited to the eye and skin referred to as oculo-cutaneous albinism (OCA) or to the eye alone refered to as ocular albinism. There are ten types of OCA; tyrosinase negative, tyrosinase positive, yellow mutant, Hermansky-Pudlak syndrome (HPS),

Cross-Mckusick-Breen syndrome, Chediak-Higashi syndrome (CHS), brown albinism, autosomal dominant albinism, rufours albinism and BADS (black-locks albinism, deafness of sensori-neural type) syndrome.[11] In tyrosinase negative OCA there is inability to synthesize tyrosinase, whereas in tyrosinase positive albinism, the nature of defect is not known. Hermansky-Pudlak syndrome and Chediak-Higashi syndrome are distinctive in that in addition to features common to other forms of albinism, they show hematologic abnormalities. In HPS the hemorrhagic diathesis is secondary to a defect in the storage and release of adenine nucleotides by the platelets.[12] In CHS, melanocytes are normal in size and number and contain fully melanised stage IV melanosomes. However, most of the melanosomes are large and pass with difficulty into keratinocytes. In CHS, leucocytes as well as internal organs, skin and mucous membranes contain a few azurophilic granules. The mechanism of formation of these granules is not known, but these are responsible for the symptomatology with which the patients present at various ages. These are recurrent infections, convulsions and neuropathy, anemia, thrombocytopenia, neutropenia and lymphoreticular malignancy.

Disorders of pigment metabolism

Porphyrias. The porphyrias constitute a group of diseases representing inborn errors of metabolism affecting the pathway of heme synthesis. Deficiency of the various enzymes which normally take part in the formation of heme results in accumulation of intermediary products such as porphobilinogen, uroporphyrin, protoporphyrins and coproporphyrins. These can be detected in the skin, bone marrow, liver and other tissues as well as in blood, urine and stools. The nature of the porphyrin detected in any tissue depends upon the type of enzyme deficiency.

The prophyrias are classified as (a) erythropoietic and (b) hepatic, indicating the source of the abnormal porphyrins which are responsible for the clinical symptomatology. The erythropoietic porphyrias are (1) congenital erythropoietic porphyria (CEP), and (2) erythropoietic protoporphyria (EPP). The hepatic porphyrias are (1) acute intermittent porphyria (AIP), (2) variegate porphyria (VP) or mixed porphyria, (3) porphyria cutanea tarda (PCT) and (4) hereditary coproporphyria (HCP).[13]

CEP is an autosomal recessive trait whereas all other porphyrias are of dominant inheritance.

All the porphyrias except AIP have skin manifestations of photosensitivity with oedema, erythema, blistering and ulcers as acute features; pigmentation, fragility of skin, hypertrichosis, weather-beaten and sclerodermoid appearance with scarring and mutilation as late features. The photosensitivity is consequent of the damage to the cell membrane and cell constituents which is brought about by the uro, proto or copro porphyrins in the skin which absorb the SORBET band. In AIP, porphobilinogen is the accumulated intermediary product and this has no photosensitising properties. Hence the absence of skin manifestation in AIP. In AIP, manifestations are predominantly neurological because of the toxic damage to the neurons and peripheral nerves by the porphobilinogen.

AIP, because of absent skin changes and PCT and VP, because their manifestations appear only in the adult age, will not be further discussed.

Congenital erythropoietic porphyria. In CEP, in addition to skin changes of acute and chronic photosensitivity already described, there is erythrodontia, hemolytic anemia due to the shortened RBC life-span, splenomegaly and pink red urine. The teeth, bone marrow and urine fluoresce red under ultraviolet light. Biochemical defect is deficiency of uroporphyrinogen-co-synthetase which allows

accumulation of uroporphyrin.

Erythropoietic protoporphyria. EPP appears in early childhood or after adolescence. Generally EPP runs a course milder than CEP since protoporphyrins are less photosensitive than uroporphyrins. Cholelithiasis and terminal hepatic failure occur in a small group of patients. RBCs and bone marrow fluoresce intensely red. Biochemical defect is deficiency of ferrochelatase in RBCs and fibroblasts. Protoporphyrins are present in RBCs and excreted in stools.

Hereditary coproporphyria. This appears at any age. The disease can be asymptomatic. Photosensitivity occurs only in some patients and they may show a blistering skin. In HCP there may occur acute attacks as in AIP or VP. As in AIP acute attacks are precipitated by drugs. Marked elevation of fecal porphyrins can be detected and during acute attacks urinary and fecal coproporphyrins are elevated. Deficiency of coproporphyrinogen oxidase in lymphocytes and fibroblasts is the biochemical abnormality.

Acatalasemia. Erythrocyte catalase deficiency was first described by Takahara in 1946. It is inherited as a recessive trait. There is failure of degradation of hydrogen peroxide which is produced by bacteria, resulting in oxidation of hemoglobin. An infected mucosal tissue is thus deprived of oxygen. Most patients are asymptomatic. A few show ulceration of oral and nasal mucous membranes.

Disorders of metal metabolism

Menke's kinky hair. In this disease which is inherited as a sex-linked recessive trait, the basic defect is in the intestinal transport of copper. The resultant low levels of copper and ceruloplasmin appear to be responsible for the neurodegenerative changes. Main dermatological abnormality is seen on the hair. Coarse stubby hair with abnormalities like pili torti, monilethrix and trichorrehexis nodosa are seen. Seborrhoeic type of eczema and generalised hypopigmentation have also occurred. Hypopigmentation is probably from deficient availability of copper for adequate tyrosinase function.[14] Parenteral copper therapy has been tried but without appreciable success.

Acrodermatitis enteropathica (AE). Disturbance of zinc metabolism occurs as an inherited disease. Deficiency of oligopeptidase secreted by the normal enterocyte but not that of the AE patient is postulated as the biochemical abnormality.

The disease manifests typically in children at the time they are weaned from the mother's breast. Hence it presents at about the age of six to nine months. Alopecia and scaly inflammatory dermatitis in the acral and periorificial areas are associated with diarrhoea. Zinc is curative.

Multiple sulfatase deficiency. Ichthyosis is the only skin change in this disease with a single mutant gene affecting 9 distinct enzymes. Clinical features like deafness, hepatosplenomegaly and coarse facial features overshadow the skin changes.

Steroid sulfatase deficiency. All patients who had pedigree documentation of X-linked ichthyosis had steroid sulfatase deficiency.[15, 16] Onset of ichthyosis is in infancy. Ichthyosis involves extremities and trunk with frequent involvement of scalp and neck. Palms, soles and hair are spared. Scales are dark and large. There is increased formation of structurally normal keratohyaline. Characteristic corneal opacity of deep stromal type which does not affect visual acuity, develops in a majority of the patients in the second or third decade.

Disorders involving connective tissue

Ehlers-Danlos syndrome (EDS). This represents

a group of conditions sharing the phenotypic features of hyperextensibility of skin and joints, poor wound healing, easy bruisability and occasional fragility of large blood vessels of skin and viscera. The inheritance pattern is autosomal dominant, autosomal recessive or X-linked recessive. Abnormalities in collagen synthesis have been demonstrated in four of the eight types of EDS. Among the four, hydroxylysine deficiency is seen in type VI EDS and procollagen peptidase deficiency in type VII EDS.[17]

Cutis laxa (Dermochalasia). Cutis laxa also is a rare group of disorders inherited as autosomal dominant, autosomal recessive or X-linked recessive. In this disease, skin gives the appearance of being too large for the rest of the body. Skin tends to sag especially on the face around the eyes. Low pitched cry, hernias, gastro-intestinal and genito-urinary diverticulae are common.

Most severe manifestation is progressive emphysema leading to cor pulmonale and death. Diminished synthesis of lysyl oxidase by the fibroblasts has been shown but causative relationship between this and the syndrome is yet to be established.

Disorders of the immune system

Hereditary angioedema. Although generally transmitted as an autosomal dominant trait, hereditary angioedema, occasionally results from mutation. The biochemical abnormality is the deficiency of the inhibitor of the activated first component of complement. There are two forms of the disease, one in which the inhibitor protein and its function are lacking, another in which the protein is present and only its function lacks. The disease is characterised by recurrent spontaneous episodes of transient edema of the skin, upper respiratory tract and gastro-intestinal tract. Cutaneous swelling comes anywhere and subsides within 48-72 hours. The odema is non-pitting and non-pruritic. Death by asphyxiation is possible. There is no associated urticaria.

Several other disorders of immune system have skin manifestations as a result of an increased susceptibility to pyogenic infections. These are X-linked agammaglobulinemia, chronic granulomatous disease, leucocyte G6PD deficiency and myeloperoxidase deficiency.

New discoveries are being made and fresh information is being fed in, on the subject of metabolic disorders and diseases of genetic origin. It has become possible to predict many of these disorders through amniocentesis and fibroblast culture. We are entering a future which may control the unregulated pathways in most of the metabolic disorders by means of enzyme inhibitors or activators. Therefore tomorrow's victims of genetically determined diseases may look forward to better days and near normal life expectancies.

References

1. Drash AL: Metabolic disorders, in: Text Book of Pediatrics, 11th ed, Editors, Vaughan VC, Mckay RJ, Behraman RE et al: WB Saunders Company, Philadelphia, 1979; p 1581
2. Tripathy BB and Sidhartha Das: Disorders of lipid metabolism, in: Text book of Medicine, 4th ed, Editors, Shah SJ, Anand MP, Mehta AB et al. Association of Physicians in India, Bombay, 1986; p 231.
3. Fredriekson DS: Plasma lipid abnormalities and cutaneous and subcutaneous xanthomas, in: Dermatology in General Medicine, 2nd ed, Editors, Fitzpatrick TB, Eisen AZ, Wolff K et al: Mc Graw Hill, New York 1979; p 1112.
4. Waldorff DS, Levy RI and Fredriekson DS: Cutaneous cholesteryl ester deposition in Tangier disease, Arch Dermatol, 1967; 95: 161-165.
5. Moses HW, and Chen WW: Ceramidase deficiency. Farber's lipogranulomatosus, in: The Metabolic Disorders of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngaarden JB, Fredriekson DS et al; Mc Graw Hill, New York, 1983; p 820.
6. Kelley WN, Greens ML, Rosenbloom FM et al: Hypoxanthine-guanine phosphoribosyl transferase deficiency in gout, Ann Int Med, 1969; 70: 155-206.

7. Kelley WN and Wyngaarden JB: Clinical syndromes associated with hypoxanthine-guanine phosphoribosyl transferase deficiency, in: The Metabolic Basis of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngaarden JB, Fredriekson DS et al: Mc Graw Hill, New York, 1983; p 1115.
8. Jung EG: Xeroderma pigmentosum, Internat J Dermatol, 1986; 25: 629-633.
9. Stanbury JB and Dumont JE: Familial goitre and related disorders, in: The Metabolic Basis of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngaarden JB, Fredriekson DS et al: Mc Graw Hill, New York, 1983; p 1261.
10. Frei BJ and Kaloustian VMD: Prolidase deficiency. A metabolic disorder presenting with dermatologic signs, Internat J Dermatol, 1986; 25: 431-433.
11. Witkop JR Jr, Quevedo WC Jr and Fitzpatrick JB: Albinism and other disorder of pigment metabolism, in: The Metabolic Basis of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngaarden JB, Fredriekson DS et al: Mc Graw Hill, New York, 1983; p 301.
12. Hardisty RM and Mills DCB: The platelet defect associated with albinism Brit J Hematol, 1972; 23: 679-692.
13. Bickers DR, Pathak MA and Magnus IA: Porphyrias, in: Dermatology in General Medicine, 2nd ed, Editors, Fitzpatrick TB, Eisen AZ, Wolff K et al: Mc Graw Hill, New York, 1979; p 1072.
14. Danks DM; Hereditary Disorders of Copper Metabolism in Wilson's Disease and Menke's Disease, Basis of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngaarden JB, Fredriekson DS et al: Mc-Graw Hill, New York, 1983; p 1251.
15. Shapiro LJ, Burman MM, Weiss R et al: Enzymatic basis of typical ichthyosis, Lancet, 1978; ii: 756-757.
16. DE Groot WP, Jobsis AC, Marinkovic-Ilsen A et al: Sex linked ichthyosis and placental sulphatase C deficiency, Brit J Dermatol, 1980; 103: 78-79.
17. Pinnell SR and Murad S: Disorders of collagen, in: The Metabolic Disorders of Inherited Disease, 5th ed, Editors, Stanbury JB, Wyngarden JB, Fredriekson DS et al : Mc Graw Hill, New York, 1983; p 1434.