Introduction

Children with metabolic diseases often present with nonspecific clinical and biochemical changes. Cutaneous manifestations of metabolic diseases are sometimes difficult to diagnose. Dermatologists and pediatricians must be aware of the signs and symptoms of these associations so that they can make early diagnosis, thus preventing, in some cases, the progression to a severe and fatal disease. There are many metabolic disorders with skin manifestations related to infants and children for example acrodermatitis enteropathica, lipoidoproteinosis, phenylketonuria, Wilson disease, skin signs of diabetes mellitus and diseases of the thyroid ***(Ramos-e-Silva et al., 2002).***

Acrodermatitis enteropathica is a rare disease caused by alteration of zinc metabolism, either hereditary by autosomal recessive transmission, or acquired ***(Neldner, 1999).***

Hands and feet are rapidly affected in acrodermatitis enteropathica, presenting paronychia, dermatitis in fingers and palms, and accompanied by annular lesions with a desquamative collar ***(Mallory, 1996).***

Cutaneous manifestations of lipoid proteinosis are sometimes precipitated by vaccination or other illnesses of benign nature. Nodules, hyperkeratotic verrucous plaques of yellowish-white, and varioliform scars and crusts occur more frequently on the face, neck, hands and knees, possibly due to frequent trauma in those regions ***(Lapiere`, 1999).***

Phenylketonuria is a rare, hereditary, autosomal, and recessive disease. It is caused by deficiency of the phenylalanine hydroxylase enzyme or its cofactors ***(Erlandsen, 2001).***

Newborns presenting phenylketonuria have blond hair, blue eyes, and hypopigmented skin. Eczematoid and sometimes scleroderma-like lesions are frequent, and it is believed that the increase of manifestations of atopic dermatitis is due to the existent vasoconstriction ***(Goldsmith, 1999).***

Wilson disease is an inherited copper metabolism dysfunction disease characterized by cirrhosis and central nervous system findings. Skin pigmentation and a bluish discoloration at the base of the fingernails (azure lunulae) have been described in patients with Wilson disease. Spider nevi, palmar erythema and digital clubbing also occur ***(Manolaki et al., 2009).***

Diabetes mellitus is a common disease with cutaneous manifestations present in 82% of the patients. Diabetic dermatopathy is characterized by pretibial pigmented maculae, occurring in 50% of diabetic adults and very rarely in children. The lesions start with small papulae that evolve into brownish-red and later yellowish maculae, which may be depressed ***(Freinkel, 1999a).***

Congenital hypothyroidism affects 1:4000 newborns, affects equally both sexes, and is the greatest cause of mental retardation. There are few clinical symptoms at birth; the children tend to be docile with cold, xerotic, and vasoconstricted skin and frequently presenting cutis marmorata ***(Freinkel, 1999b).***

Children with congenital hypothyroidism may present with a condition called myxedema, characterized by a yellowish skin, resulting from a combination of anemia, icterus, and carotenemia, attributed to the hepatic defect in conversion of beta-carotene into vitamin A, besides infiltration of mucopolysaccharide acids, hyaluronic acid, and chondroitin sulfate ***(Lucky, 1995).***

In Grave's disease, pretibial myxedema lesions are pink nodules with well-defined borders, shiny, and bilateral but not symmetric, usually in the front of the tibia ***(Freinkel, 1999b).***

Aim of the Work

To review the metabolic diseases in children with skin manifestations regarding the following objectives:

- Etiology, pathogenesis and causes of metabolic diseases in children with skin manifestations.
- Diagnosis and differential diagnosis of metabolic diseases in children with skin manifestations.
- Types and methods of diagnosis of different skin lesions in metabolic diseases in children.
- Management of metabolic diseases in children with skin manifestations.

Chapter (1)
Lysosomal Storage Diseases

A-Fabry Disease

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal**α**-galactosidase A activity. It is a devastating, progressive inborn error of metabolism with, particularly in the early stages, important roles being played by cellular dysfunction and microvascular pathology induced by lysosomal glycosphingolipid deposition in a variety of cell types, including capillary endothelial cells, renal (podocytes, tubular cells, glomerular endothelial, mesangial and interstitial cells), cardiac (cardiomyocytes and fibroblasts) and nerve cells ***(Germain, 2010).***

FD is pan-ethnic, but due to its rarity, determining an accurate disease frequency is difficult. Reported incidences, ranging from 1 in 476,000 to 1 in 117,000 ***(Meikle et al., 1999).***

Diagnosis:

Clinical picture:

Early signs and symptoms: Fabry disease at the pediatric age

Early neural damage primarily involves small nerve fibers of the peripheral somatic and autonomic nerve systems with onset of related symptoms generally occurring at an earlier age in boys than in girls. Pain is experienced by 60-80% of classically affected boys

and girls and is one of the earliest symptoms of FD. Two types of pain have been described: episodic crises ("Fabry crises") characterized by agonizing burning pain originating in the extremities and radiating inwards to the limbs and other parts of the body, and chronic pain characterized by burning and tingling paraesthesias ***(Charrow, 2009).***

Patients may complain of abdominal pain (often after eating), diarrhea, nausea, and vomiting, which are a significant cause of anorexia ***(Hoffmann et al., 2007).***

Tinnitus may be an early symptom and hearing loss has been reported in children ***(Keilmann et al., 2009).***

Early signs of cardiac and cerebrovascular abnormalities may be present during adolescence in both genders. Signs of involvement of the sinus node and conduction system (e.g. shortened PR interval, arrhythmias, impaired heart rate variability, and mild valvular insufficiency) have been demonstrated ***(Kampmann et al., 2008).***

Renal impairment often begins with microalbuminuria and proteinuria in the 2nd to 3rd decade of life which, like in diabetic nephropathy, are believed to directly contribute to the progression of the Fabry nephropathy. With advancing age, proteinuria worsens ***(Fervenza et al., 2008).***

Dermatological manifestations

Angiokeratomas (AGK) are present in 66% of male and 36% of female patients with FD ***(Orteu et al., 2007)***. Appearing as

nonblanching red to blue-black lesions from 1 to 5mm in diameter, they are not always covered by fine white scales as their name would suggest being also macular or just palpable. In classically affected males, the earliest lesions are observed during childhood on the hands, knees, elbows and flanks. Their number increases during adolescence with lesions on the genitals, involving the penis, scrotum and groins in men, and the lumbosacral area, gluteal cleft and trunk in both sexes (Fig.1) ***(Zampetti et al., 2012).***

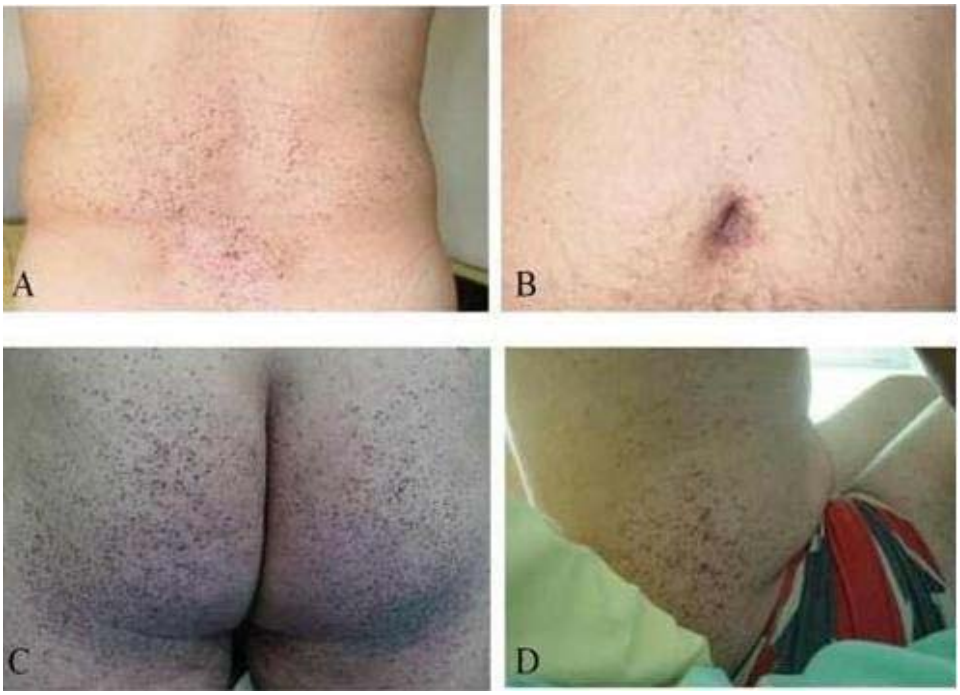

Figure (1): Angiokeratoma: the angiokeratoma are small, raised, dark-red spots that increase in number and size with age and can occur singly or in clusters. They are typically found on the lower back (A), buttocks (C), groin, flanks (D) and upper thighs but their distribution may be restricted to a limited area, such as the umbilicus (B) ***(Germain, 2010).***

Later in life AGK can appear on the lips, umbilicus, periungual areas and palms and there may be macular angiomas. More lesions are usually observed in men. Females frequently have AGK on the upper back and chest and rarely on the genitalia ***(Zampetti et al., 2012).***

The histology of AGK shows a vascular proliferation within the papillary dermis with an overlying acanthotic and orthokeratotic epidermis encircling thin-walled vascular channels occasionally filled with erythrocytes. Common cherry haemangiomas (CH) are usually more dome shaped with an associated oedematous or fibrotic stroma. Histology can potentially differentiate AGK from CH but not from AGK of different pathogenesis because lipid inclusions are usually dissolved during the preparation of the sample ***(Elder et al., 2007).***

Electron microscope Shows lamellated intracytoplasmic vacuolar inclusions called 'zebra bodies'. Ultrastructural analysis of skin biopsies obtained from patients with FD after enzyme replacement therapy (ERT), shows the disappearance of the intracytoplasmic globotriaosylceramide (Gb3) inclusions ***(Navarro et al., 2006).***

Telangiectasiae are the second commonest skin manifestation and occur most commonly on photo damaged areas such as the face and the V of the neck. Occasionally, in patients with widespread AGK, they are found on sun protected sites such as the flanks and antecubital fossae. In some patients, mucosal lesions on the inner aspect of the lips or tongue can be observed ***(Zampetti et al., 2012).***

Absence of sweating (anhidrosis) or a decreased ability to sweat (hypohidrosis) ***(Orteu et al., 2007)*** with decreased skin impedance ***(Gupta et al., 2008)*** is a significant problem for patients and can cause heat and exercise intolerance ***(Eng et al., 2006).***

Laboratory diagnosis

Enzyme activity:

The demonstration of a deficient activity of α-galactosidase activity in plasma or leukocytes is the reference laboratory method which should systematically be used to confirm the clinical diagnosis of FD in males in whom the result will be conclusive. In contrast, affected girls and adult females may have their enzyme activity falling within the normal range. Therefore, all females should have their status determined by genotyping (analysis of the GLA gene mutation) ***(Germain et al., 2010).***

Globotriaosylceramide measurement:

Plasma Gb3 has also been proposed and used in the biochemical diagnosis of FD, but this method is time- consuming and in females, plasma Gb3 levels are generally lower than in males and usually in the normal range.Urinary Gb3 is a more reliable marker allowing diagnosis in the majority of both male and female patients ***(Touboul et al., 2005).***

Genotyping:

In female heterozygotes, α-galactosidase activity may be within the normal range and therefore, the definitive diagnostic confirmation should be made by genetic analysis in suspected cases ***(Linthorst et al., 2005).***

Treatment:

Conventional medical treatment and adjunctive therapies for FD related morbidities:

Patients with neuropathic pain may benefit from avoidance of circumstances triggering acute pain attacks, e.g. significant physical exertion and temperature changes. Carbamazepine, oxcarbazepin, gabapentin, pregabalin and phenytoin are classically used to manage pain in FD ***(Eng et al., 2006).***

Gastrointestinal symptoms:

Gastrointestinal problems resulting from delayed gastric emptying and slow bowel movements may respond to metoclopramide, and changes in eating habits, e.g. small and frequent meals. Some success has been achieved by managing dyspepsia with H-2 blockers ***(Eng et al., 2006).***

Enzyme replacement therapy:

In Europe, there are currently two commercially available enzyme preparations for FD: agalsidase alfa, produced using cultured human skin fibroblasts and registered for use at a dose of 0.2 mg/kg biweekly, and agalsidase beta, produced by the expression of human α-galactosidase cDNA in Chinese Hamster Ovary (CHO) cells and registered for a use at 1.0 mg/kg biweekly ***(Sakuraba et al., 2006)***.

B-Fucosidosis

Fucosidosis is an inherited autosomal-recessive metabolic disorder. Affected individuals are deficient in the lysosomal enzyme L-fucosidase. Symptoms result from the accumulation of fucose containing glycoproteins, oligosaccharides, mucopolysaccharides, and glycolipids within organs, including the brain ***(Alex, 2010).***

Diagnosis

Clinical picture

The clinical manifestations of this disorder include delayed intellectual and motor development, progressive neurological decline, coarse facial features, and musculoskeletal findings typical of dysostosis multiplex. The clinical course has been divided into fucosidosis type 1, with an early presentation and rapid progression, and type 2, which has a somewhat later presentation and slower progression that allows survival into early adulthood ***(Alex, 2010).***

Dermatological manifestations

Cutaneous features include mainly AGK; this is present in 52% of patients and manifests with vascular lesions that are mainly located over the lower abdomen, external genitalia, and the perineum, but may spread to the limbs (Fig.2), the palms, and soles. The frequency and extension of AGK lesions tend to increase with age. Other cutaneous findings include widespread telangiectasias, acrocyanosis, purple transversal distal nail bands, increased palmoplantar vascularity, sweating abnormalities (hyper- or hypo-hidrosis), and dry, thin skin ***(Fleming et al., 1997).***

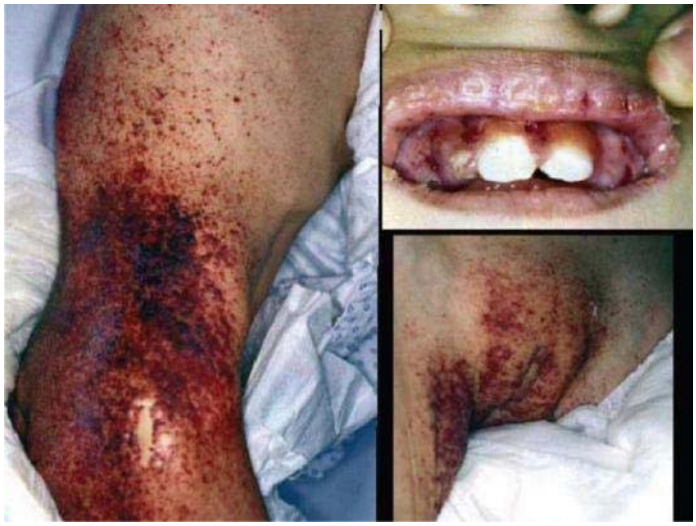

Figure (2): Diffuse AGK lesions present on the trunk (left panel), the external genitalia (right lower panel), the gums, and lips (right upper panel) ***(Kanitakis et al., 2005).***

From a pathologic point of view, AGK of fucosidosis manifest as proliferative ectatic blood vessels that are lined by a flattened endothelium and are filled with erythrocytes. They are located in the papillary dermis underneath a thickened, papillomatous epidermis overlaid by a thickened horny layer. This aspect is similar to AGK found in other metabolic diseases. EM examination may help to exclude Anderson- Fabry's disease, because this disease is the only one among metabolic diseases with AGK to show electron-dense, lamellar (zebra-like) inclusions within endothelial and other cell types ***(Kanzaki, 1995).***

By EM, it was observed that endothelial cells of fucosidosis AGK contain electron-lucent vacuoles, found also in several other cell types, not only in the skin but in other tissues as well, including liver, peripheral nerves, rectal mucosa, eye, and peripheral lymphocytes. The reason why

AGK develops in the setting of metabolic diseases (such as fucosidosis) remains unclear. It can be speculated that the accumulation of pathologic material within the cytoplasm of endothelial cells induces their apoptosis, followed by continuous reactive regeneration, leading to the formation of newly formed ectatic capillaries ***(Kanitakis et al., 2005).***

Laboratory diagnosis

Enzyme activity

Biochemical examination, showing greatly reduced or absent activity of the deficient enzyme L-fucosidase within leukocytes, skin fibroblasts, or other tissues such as the liver ***(Kanitakis et al., 2005).***

Treatment

The treatment of fucosidosis is not yet well established. some patients with fucosidosis received allografts of allogeneic bone marrow or stem cells with promising results, consisting of a progressive rise of enzymatic levels and improvement of psychomotor development ***(Krivit, 2004).***

C-Hurler syndrome(Mucopolysaccharidosis1)

Mucopolysaccharidosis-I (MPS-I)is a lysosomal storage disorder inherited as an autosomal-recessive condition and is caused due to deficiency of the lysosomal enzyme α_1- iduronidase, which results in the progressive accumulation of glycol-saminoglycans (GAG) within the lysosomes, subsequently leading to multiorgan dysfunction and damage ***(Muenzer et al., 2009).***

Patients affected with MPS I are unable to degrade the GAG, dermatan sulfate and heparan sulfate, which provide structural support to the extracellular matrix and cartilaginous structures such as joints and heart valves. MPS I has an estimated incidence of 1 case per 100, 000 live births.MPS 1 has been classified into two groups, severe MPS I (Hurler Syndrome) and attenuated MPS I (Hurler-Scheie and Scheie syndromes) ***(Muenzer et al., 2009).***

Diagnosis:

Clinical picture:

Children with severe MPS I usually die within the first decade of life as a result of cardiorespiratory failure and progressive neurological disease. On the contrary, most patients with attenuated MPS I survive into adulthood. However, cases of attenuated MPS I show wide variation with respect to age of presentation, symptoms and disease course ***(Hopkin and Grabowski, 2005).***

The clinical presentation may be limited to growth failure, cloudy corneas, mild coarsening of facial features, hepatomegaly and micrognathism in MPS I Hurler-Scheie (H/S). Skeletal changes of hands and spine are minimal. The typical features appear at about the age of 12 years, including macrocephaly and coarse facies, and restriction of joint mobility with deformities becomes apparent at the age of 12-15 years. Frequent upper and lower respiratory tract infections are common and occur secondary to enlargement of tonsils and

adenoids and enlarged tongue. Patients with MPS I H/S may show dental abnormalities including enamel defects, carious teeth, dentigerous cysts and abscesses ***(Tatapudi et al., 2011).***

Cardiac abnormalities are common among patients with MPS I, and worsen with age. It has been recommended to undergo cardiac evaluation every 1 or 2 years after an initial diagnosis ***(Muenzer et al., 2009).***

Dermatological manifestations:

Patients with Hurler syndrome have facial dysmorphism, with a broad saddle nose, thick lips, and a large tongue. The skin is thickened, with ridges and grooves, especially on the upper half of the body. Fine lanugo hair is profusely distributed all over the body. Dermal melanocytosis, characterized by extensive, blue pigmentation with both a dorsal and a ventral distribution, indistinct borders, and a persistent and or progressive course, occurs in some patients with lysosomal storage disease, including patients with Hurler syndrome ***(James et al., 2006).***

The most common lysosomal storage disease associated with generalized mongolian spots is Hurler syndrome. The mongolian spots result from entrapment of melanocytes in the dermis because of arrested transdermal migration from the neural crest into the epidermis. Through activation of receptors with tyrosine kinase properties, exogenous peptide growth factors regulate this migration. Some experts observed that accumulated