

# Lysosomal storage diseases, diagnosis from skin lesions

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## ABSTRACT

Lysosomal storage disorders form an heterogeneous group of more than 40 hereditary diseases due to the deficiency of various lysosomal enzymes in charge of the metabolization of substances inside lysosomes. These macromolecules are stored inside the organelles of multiple organs and produce different symptoms. A great number of these diseases may have cutaneous manifestations, and in many cases the dermatologist may be the one to suggest the diagnosis.

We describe eight patients with lysosomal storage diseases diagnosed at our hospital during 2009 and 2010, on whom the cutaneous lesions were the clue to the diagnosis.

Five patients were diagnosed with Fabry disease (1 male and 4 females), one with type II mucopolysaccharidosis (male), one with b-mannosidosis (male) and the last one with galactosialidosis (female). Angiokeratoma was the most frequent cutaneous manifestation, and the key to the diagnosis of Fabry disease, b-mannosidosis and galactosialidosis, while aberrant Mongolian spots on the trunk, some of which were lenticular, led us to the diagnosis of type II mucopolysaccharidosis.

On four patients the diagnosis was confirmed through enzyme blood tests in filter paper, leukocytes and/or urine examination. On five patients -one of whom had already been diagnosed through biochemistry- a genetic study was also performed. Tests were performed on all the patients to evaluate the extension of the systemic disease and the need for specific treatment (for those diseases in which it is available). One of the patients with Fabry disease started the treatment soon after the diagnosis.

It is the aim of this paper to present different LSDs in which the role of the dermatologist in diagnosis proved fundamental. We would like to stress not only the academic importance of the discussion of these rare diseases but also the possibility of providing many patients with specific enzyme replacement treatment. (*Dermatol. Argent.*, 2011, 17(3): 221-229).

## Keywords:

*lysosomal storage disorders, cutaneous manifestations.*

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## Introduction

Lysosomes are intracellular organelles which contain enzymes responsible for the degradation of different types of compounds such as mucopolysaccharides, sphingolipids and glycoproteins. Partial or total deficiency of these enzymes leads to progressive accumulation of the non-degraded substrates in the affected organs<sup>1</sup>. Lysosomal storage diseases (LSD) are a group of metabolic innate errors, each caused by a particular enzymatic deficiency<sup>2</sup>, with an estimated incidence of 1,500 to 7,000 neonates<sup>1</sup>. They form a heterogeneous group of monogenic diseases of predominantly autosomal recessive inheritance, except for Fabry disease and type II mucopolysaccharidosis, which are X-linked. They generally involve multiple organs with different degrees of severity. Although each of these disorders bears particular characteristics, they all tend to have different types of multisystemic manifestations depending on their severity and the organ affected<sup>3</sup>. Many of them present neurological, cardiac, hepatic, renal and articular signs, among others<sup>4</sup>.

In many of these entities skin is affected and a great number of cutaneous manifestations have been described. Even though few of these manifestations are pathognomonic of these diseases, certain phenotypes, such as bathing suit angiokeratomas or a specific type of Mongolian spot, are directly associated with these disorders and should call for clinical attention<sup>5</sup>. The advent of new therapeutical technologies, such as enzyme replacement therapy (ERT), has encouraged interest in diagnosis given the fact that now some patients may be offered specific treatment.

The present paper describes eight patients with different lysosomal storage disorders whose diagnoses were reached through cutaneous lesions.

### Patient 1, mucopolysaccharidosis type II

One year 10 months male patient born to non-consanguineous parents, from China, who arrived in Argentina one month before consultation. He is referred to the Pediatric Dermatology Department at Hospital Ramos Mejía due to dorsal hyperpigmented macules.

Clinical examination showed macrocephaly, slightly coarse facial features, some articular contractures, globular enlargement of the abdomen with organomegaly revealed by palpation, and bilateral inguinal hernia. The patient evidenced motor retardation -he stood in tripod position- and marked retardation in language acquisition. The dermatological examination revealed steel blue hyperpigmentation, in association with dermal melanocytosis (Photo 1), which extended from the sacral region to both shoulders. He also presented some lesions which reached the front abdominal area. The lesions were big macules and other similar, smaller, lenticular lesions on the same areas.



**Photo 1:** Extensive dermal melanocytosis on MPS2 patient.



**Photo 2:** Angiokeratomas on lateral side of thigh. Galactosialidosis patient.



**Photo 3:** Angiokeratomas on back of penis and scrotum.  $\beta$ -mannosidosis patient.



**Photo 4:** Umbilical angiokeratomas on hemizygotic Fabry disease patient.



**Photo 5:** Vulvar angiokeratomas on heterozygote Fabry disease patient.

As lysosomal storage disease was suspected, laboratory tests were carried out and the results were: 0,2 mol/l/h iduronate-2- sulfatase (normal value >15) and enhanced release of mucopolysaccharides in urine. Having diagnosed type II multipolysaccharidosis (MPS2), other tests included brain computerized axial tomography (CAT) scan, thorax and long bones X-rays, abdomen ultrasonography, which evidenced hepatosplenomegaly, and heart evaluation by electrocardiogram and cardiac ultrasound, which were normal. As it proved to be a lysosomal storage disease for which there is specific treatment, the patient was referred to the Ricardo Gutiérrez Children's Hospital day care service to complete staging and begin treatment.

### Patient 2, galactosialidosis

Twenty-six-year-old female, born to non-consanguineous parents, from Peru, referred to the Hospital Ramos Mejía Dermatology Department due to slightly hyperkeratotic dark red to blue-black papular lesions. The patient had a non-relevant family history and was under follow-up care by the Abnormal Movement Section of the Neurology Department.

Physical examination evidenced short stature, coarse facial features, generalized hypertrichosis, predominantly bathing-suit angiokeratomas (from waist to thighs) (Photo 2), some isolated lesions on oral mucosa, palms and soles and prominent bones.

Biopsies of the cutaneous lesions were carried out, which confirmed the angiokeratomas diagnose. With the clinical diagnosis of angiokeratoma corporis diffusum, metabolic laboratory tests with enzymatic and urine studies were carried out and galactosialidosis was diagnosed. Skin electron microscopy revealed radiolucent endothelial deposits. Evaluations by ophthalmology, otorhinolaryngology, traumatology, endocrinology, cardiology, hematology, brain CAT scan and abdominal ultrasonography were all within normal range. As there is no specific treatment for this disease, symptomatic treatment of neurological manifestations was started and the patient decided to return to her own country.

### Patient 3, $\beta$ -mannosidosis

A Twenty nine -year old male, born to non-consanguineous parents, without relevant family history and a personal history of global mental retardation, hyperactivity and aggressiveness was referred to our hospital for the evaluation of generalized dark red to blue-black papular lesions, some of them warty. Physical examination revealed peculiar facies, short stature, erythematous-purple hyperkeratotic papular lesions mainly distributed on thighs, buttocks and genitalia (Photo 3), and softer lesions on back, palms and soles. The lesions had developed slowly over the previous 10 years. There were also telangiectasias on



ears and vascular tortuosities on eyes. A skin lesion biopsy confirmed the angiokeratoma diagnosis.

Due to the patient's clinical characteristics -mental retardation and angiokeratoma corporis diffusum- blood and urine metabolic laboratory test were performed and the  $\beta$ -mannosidosis diagnosis was reached. The ophtalmological, otorhinolaryngological and hematological evaluations were all within normal range. As there is no current specific treatment for this disease, its neurological manifestations were treated symptomatically.

### Patients 4 to 8, Fabry disease

7-year-old patient without relevant family history. The consultation was due to the presence of dark red to blue-black plain papular lesions on back of both legs. They had developed over more than a year and were asymptomatic. Physical examination evidenced similar lesions on umbilicus (Photo 4). Inquiry revealed the patient suffered from diarrhea and frequent abdominal pain which had been diagnosed as recurrent abdominal pain of probable psychogenic origin, recurrent fevers of unknown origin and crises of acute acral pain, especially after exercise. The definitive diagnosis of Fabry disease was established by demonstration of low levels of  $\alpha$ -galactosidase through

enzyme blood tests in filter paper. This study was complemented with genetic analysis, which evidenced a W399X mutation in Fabry's gene (GLA) and showed a TGA mutation -stop codon- instead a TGG in 399 codon.

Ophthalmological evaluation evidenced posterior cataract - Fabry's cataract-, MRI neurological evaluation was normal, Quantitative Sensitive Testing (QST) to test fine fiber conduction was normal, otorhinolaryngological tests including tone audiometry was normal and nephrological laboratory and renal ultrasonography also tested normal. ERT with Fabrazyme<sup>®</sup> 1 mg/kg every 14 days was started. After administering 4 doses without any adverse reactions and due to lack of supply of the medication, it was replaced by Replagal<sup>®</sup> 0,2 mg/kg, which was very well tolerated.

Family screening through mutation studies evidenced Fabry disease in four female patients, the mother, two of the mother's sisters and a cousin of the index case. Dermatological evaluation of all of them showed vulvar angiokeratoma in both aunts (Photo 5). Ophthalmological, nephrological, cardiological, neurological and otorhinolaryngological evaluations were also carried out and their results are shown on Table 1.

On the basis of the disease extent study, two of the patients will be starting ERT shortly.

**TABLE 1**

|   | Sex | Age | AK  | GI  | Cardio   | Opht.          | AP  | PSE    | CNS | Renal | ORL | T         |
|---|-----|-----|-----|-----|----------|----------------|-----|--------|-----|-------|-----|-----------|
| 1 | M   | 7   | Yes | Yes | No       | Yes, cataract  | Yes | Alt    | No  | No    | Yes | Yes       |
| 2 | F   | 34  | No  | No  | No       | Yes, CVerticil | Yes | Normal | No  | No    | Yes | No        |
| 3 | F   | 36  | Yes | No  | No       | Yes, CVerticil | Yes | Alt    | No  | No    | No  | Initiated |
| 4 | F   | 38  | Yes | No  | Yes, RBB | Yes, CVerticil | Yes | Normal | No  | No    | No  | Initiated |
| 5 | F   | 7   | No  | No  | No       | No             | No  | Normal | No  | No    | No  | No        |

### Abbreviations

**AK:** angiokeratomas  
**Alt:** altered  
**AP:** acroparesthesias  
**Cardio:** cardiological

**CNS:** central nervous system  
**CVerticil:** Cornea verticillata  
**GI:** gastrointestinal  
**Ophtal:** ophtalmological

**ORL:** otorhinolaryngology  
**PSE:** peripheral sensory evaluation  
**RBB:** right branch block  
**T:** treatment

## Discussion

As mentioned in the introduction, LSD are extremely infrequent hereditary disorders which manifest through multiple systemic symptoms and which, at times, may involve the skin<sup>6</sup>. They form a heterogeneous group of diseases which, even if sharing some clinical features, each has its own clinical traits secondary to the enzymatic deficit itself and to the accumulated substrate.

Among the almost 50 recognized storage diseases, at least 13 of them have evidenced skin involvement (Table 2). It is beyond the aim of this paper to describe all these pathologies at length, so we will only focus on the disorders manifested in our patients, such as progressive aberrant Mongolian spots and generalized angiokeratomas (angiokeratoma corporis diffusum).

A certain kind of aberrant Mongolian spot which has been described in 4 different types of LSD differs from the spots usually observed in neonates in that it is very large and can even involve the anterior abdominal area, is progressive and not involucional<sup>7</sup>, and is accompanied by lenticular lesions<sup>8</sup>. In our case, this type of spot was the key cutaneous manifestation of the MPS2, but it has also been described in gangliosidosis gm1 (GM1), mucopolysaccharidosis i (MPS1) and mucopolipidosis II<sup>9</sup>.

Among the hypotheses that have attempted to explain this association is Hanson's et al<sup>8</sup>, who suggested that provided the heparan sulphate binds to the nerve growth factor (NGF) with high affinity, the latter would remain free and, as melanocytes also have receptors for this substance, it would produce an arrest of its migration in the dermis, thus giving the affected skin its bluish colour secondary to the Tyndall effect.

MPS2 is a LSD belonging to the mucopolysaccharidoses group. These disorders are glycosaminoglycan metabolism errors with direct accumulation of the macromolecules inside lysosomes due to different enzymatic deficits<sup>10</sup>. Clinically, all types share some characteristics: multisystemic involvement affecting the cardiovascular, pulmonary, skeletal, ocular, hepatic and nervous systems.

MPS2 presents X-linked inheritance and its clinical manifestations are due to the iduronate 2-sulfatase enzyme deficit and successive heparan and dermatan sulfate deposit in tissues<sup>11</sup>. From the point of view of dermatology, the MPS group tends to progressively develop thickened, unable to fold skin<sup>10</sup>. Besides, it is likely to present hypertrichosis and gargoyle-like facies<sup>12</sup>. Firm, whitish to normal-skin colour to, bright papules or nodules called "pebbling"<sup>13</sup> are other cutaneous lesions which may appear in MPS2, or Hunter syndrome. These lesions are generally symmetrically distributed on back and limbs and appear gradually. From the histological point of view, the toluidine blue staining of the papules evidences metachromatic material deep in the reticular dermis. It is suggested that

physiopathogenesis would be secondary to the coalescence of cytoplasmic vacuoles with further rupture and release of intravacuolar material<sup>14</sup>. Even if similar changes have been observed in a patient with MPS1<sup>13</sup>, the "pebbling" should point to MPS2 diagnosis. Esclerodermiform changes on hands and feet have also been described within this MPS group. Fortunately, there is at present specific enzyme replacement therapy available through the iduronate 2-sulfatase enzyme (Elaprase<sup>®</sup>)<sup>15</sup>.

Another cutaneous manifestation shared by a number of LSD which was key to the diagnosis of most of our patients is angiokeratoma corporis diffusum (ACD). Formerly synonym of Fabry disease, ACD is currently considered a phenotype shared by different LSD among which are galactosialidosis<sup>16</sup>,  $\beta$ -mannosidosis<sup>17</sup> (as is the case of the patients described in our paper), aspartylglucosaminuria<sup>18</sup>, GM1<sup>19</sup>, fucosidosis type 2<sup>20</sup> and Kanzaki disease<sup>21</sup>.

Fabry disease is the second most common LSD after Gaucher disease, of X chromosome-linked inheritance, characterized by the progressive development of symptoms secondary to globotriaosylceramide deposits in the endothelium of different organs<sup>22</sup>. It generally starts at infancy with imprecise symptoms like diarrhea and recurring abdominal pain -due to the intestinal vasa nervorum involvement-, hypohydrosis and fever of unknown origin due to poor temperature regulation, acroparesthesias and pain crises on hands and feet<sup>23</sup>. Together with these symptoms, typical angiokeratomas develop on bathing suit area<sup>24</sup>. These are dark red to blue-black papular lesions with different degrees of hyperkeratosis on their surface<sup>25</sup>. Even if they could pass unnoticed or be confused with cherry angiomas, purpuric lesions or telangiectasias, the presence of lesions umbilical, as in our index case, is quite distinctive of this disease<sup>6</sup>.

After infancy, patients gradually develop more severe symptoms, like chronic renal failure, cardiac alterations and strokes with high morbidity<sup>26</sup>. As it is an X-linked disease, its manifestations are generally more florid in male patients, although it is known that in female heterozygotes (called carriers in the past), it can range from very mild symptoms to forms as florid as in men<sup>27</sup>. This could be attributed to the so-called lyonization, in which one of the X chromosomes is inactivated randomly while the other provides genetic information<sup>4</sup>. Even if our 4 female patients evidence milder symptoms than the index case, the current symptoms in 2 of them would justify the initiation of ERT.

The diagnosis of this disease requires a high degree of suspicion. In male patients, final diagnosis can be reached measuring the enzymatic activity in leukocytes or in blood drop in filter paper -as in our index case. In female patients, blood enzymatic activity is not a good diagnostic method as due to the above mentioned lyonization, it

TABLE 2

| Disease                | Inheritance | Enzyme                                   | Gene         | Deposited substrate                     | Cutaneous lesion                                                         | Treatment                                       |
|------------------------|-------------|------------------------------------------|--------------|-----------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------|
| Gaucher                | AR          | Glucocerebrosidase                       | 1q21         | Glucocerebrosides                       | Diffuse or localized hyperpigmentation (Type 1); collodion baby (Type 2) | ERT; substrate inhibition                       |
| Fabry                  | X-linked    | $\alpha$ -galactosidase a                | Xq22.1       | Gb3                                     | ACD                                                                      | ERT                                             |
| Fucosidosis II         | AR          | $\alpha$ -L-fucosidase                   | 1p24         | Glycoconjugates rich in fucoside        | ACD                                                                      | BMT                                             |
| Galactosialidosis      | AR          | Neuraminidase + $\beta$ -galactosidase   | 20q13.1      | Long-chain sugars                       | ACD                                                                      | Symptomatic                                     |
| Aspartylglucosaminuria | AR          | Aspartylglucosaminidase                  | 4q32-33      | Aspartylglucosamine                     | ACD                                                                      | Symptomatic                                     |
| GM1                    | AR          | GM1- $\beta$ -galactosidase              | 3p21-23      | GM1                                     | ACD; extensive and progressive dermal melanocytosis                      | Symptomatic                                     |
| Kanzaki                | AR          | $\alpha$ -N-acetylgalactosaminidase      | 22q13.1-13.2 | $\alpha$ -N-acetylglucosamine           | ACD                                                                      | Symptomatic                                     |
| $\beta$ -mannosidosis  | AR          | $\beta$ -mannosidase                     | 4q22-25      | Mannose-n-acetylglucosamine             | ACD                                                                      | Symptomatic                                     |
| MPS1 (Hurler-Scheie)   | AR          | $\alpha$ -iduronidase                    | 4p16.3       | Ds and Hs                               | Extensive and progressive dermal melanocytosis                           | ERT; BMT                                        |
| MPS2 (Hunter)          | X-linked    | Iduronate-L-sulfatase                    | Xq28         | Ds and Hs                               | Pebbling; extensive and progressive dermal melanocytosis                 | ERT                                             |
| Farber                 | AR          | Ceramidase                               | 8p.22-p21.3  | Ceramide                                | Subcutaneous nodules; granulomas                                         | BMT (when there is no neurological involvement) |
| Niemann-Pick A         | AR          | Sphingomyelinase                         | 11p15.1-15.4 | Sphingomyelin                           | Tense, bright-looking skin; xanthomas                                    | Symptomatic                                     |
| Mucopolipidosis II     | AR          | n-acetylglucosamine 1-phosphotransferase | 12q23.3      | GAG, oligosaccharides and sphingolipids | Extensive and progressive dermal melanocytosis                           | Symptomatic                                     |

### Abbreviations

**AR:** autosomal recessive  
**ACD:** angiokeratoma corporis diffusum  
**BMT:** bone marrow transplantation  
**Ds:** dermatan sulfate

**ERT:** enzyme replacement therapy  
**GAG:** glycosaminoglycans  
**Gb3:** globotriaosylceramide  
**Hs:** heparan sulfate

can test normal even in affected women, so final diagnosis should be reached through molecular study of the mutation. In our patients, a W399X mutation was detected as a result of this study. This mutation had been previously described in other countries, but our case was the first Argentine family with this alteration.

Nowadays, it is possible to offer patients specific replacement treatment through which the missing enzyme is replaced, intravenously, every 2 weeks, for life. Even though the treatment is not curative, as it cannot modify

the underlying genetic alteration, it has proved to be effective because it slows down the progression of the disease<sup>28</sup>. There are two types of ERT available: Fabrazyme<sup>®</sup> and Replagal<sup>®</sup>. Both have proved to be effective and safe for the treatment of this disease.

As mentioned above, other LSD can also manifest with ACD. Among our patients, this phenotype was the key to the diagnosis of galactosialidosis and  $\beta$ -mannosidosis. Galactosialidosis is a lysosomal storage disease caused by the combined deficit of two enzymes,  $\beta$ -galactosidase and

neuraminidase due to a defect in the lysosomal enzyme called carboxypeptidase/catepsine protective enzyme, whose function is to bind to  $\beta$ -galactosidase and neuraminidase thus forming a complex which protects them from degradation by proteolysis<sup>29</sup>. Clinically, it can manifest through three different phenotypes: the neonatal phenotype, characterized by fetal hydrops, ascitis, organomegaly and early fetal death<sup>30</sup>; the late infancy phenotype, with organomegaly, growth retardation and cardiac involvement; and a third phenotype, the youth or adult one, characterized by the emergence of ataxia, myoclonias, mental retardation -including loss of previously acquired skills-, angiokeratomas<sup>16</sup>, absence of organomegaly and long life expectancy. Our patient is within this last subtype. In this kind of patients, the ACDs are distributed similarly to other LSDs, on bathing suit area and on contact areas such as elbows and knees<sup>16</sup>, but the presence of telangiectasias on joints has also been reported<sup>29</sup>. At present, there is only symptomatic therapy for this pathology.

$\beta$ -mannosidosis, the third LSD with ACD in our paper, is characterized by the  $\beta$ -mannosidase enzyme deficit and mannose n-acetylglucosamine intralysosomal accumulation<sup>17</sup>. The gene mutation is located in the 4q<sup>21-25</sup> chromosome and its phenotype is heterogeneous. It is the most recently described oligosaccharidosis and at present there are about 13 diagnosed patients reported in the literature<sup>31</sup>. Clinically, it is characterized by mild to severe mental retardation, hyperactivity, aggressive behaviour -as in our patient-, hearing impairment, language acquisition retardation, epilepsy and peripheral neuropathy. Skeletal alterations and facial dysmorphism are also frequent. These patients may also evidence ACD in a similar distribution to Fabry disease, but this is a finding only present in 50% of patients. The literature offers only one previous description according to which the diagnosis was suspected from ACDs. A further skin manifestation could be a greater susceptibility to skin infections and a case has been reported in which it coexisted with pseudoxanthoma elasticum.

Currently, the treatment available for this pathology is just the relief of the symptoms, especially neuropsychiatric ones.

## Conclusions

LSDs are very rare diseases with multisystemic manifestations, whose diagnosis requires a high degree of suspicion. Cutaneous lesions can, at times, be the key to the diagnosis, but they need to be recognized and specific complementary tests which are not usually among routine laboratory tests have to be requested. The fact that we can offer some of the patients specific treatment which alters the natural development of this type of diseases makes our diagnosis ever more relevant.

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