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Lysosomal storage disorders (LSD) are characterized by the accumulation of partially degraded insoluble metabolites within lysosomes. GM1-gangliosidosis type 1 is a particularly severe LSD with marked central nervous system involvement.

Dermal melanocytosis encompasses a clinical spectrum of cutaneous diseases such as Mongolian spots, naevus of Ota, naevus of Ito and acquired symmetrical dermal melanocytosis of the face (1).

The association of dermal melanocytosis with LSD is uncommon and still poorly understood (2). We report here a case of dermal melanocytosis associated with GM1-gangliosidosis type 1.

CASE REPORT

A 7-month-old mestizo girl from Brazil was referred for evaluation of extensive and unusual slate-blue macules resembling Mongolian spots. All areas of the skin, with exception of the face, scalp, palms and soles, were involved. Lesions were macular, grey to blue-black, non-hairy, usually sharply demarcated and varied in shape and size from a few millimetres to several centimetres in diameter. Larger lesions were distributed over the anterior and posterior trunk and dorsal sides of the hands and feet (Fig. 1). The lesions were present at birth and their number did not increase with time.

She was the first child of healthy non-consanguineous parents, with no past history of complications during the perinatal or delivery period. Moreover, no family history of any congenital anomalies or genetic disorders was reported. In addition to the skin lesions, the infant had coarse facial features with palpebral oedema, strabismus, low nasal bridge, broad nose, long philtrum, gingival hypertrophy, short neck, hepatomegaly and hirsutism. At 1 year of age she presented generalized muscle hypotonia, pyramidal signs, lethargy and progressive developmental delay, with mental retardation.

A 3-mm punch biopsy was obtained from one of the hyperpigmented cutaneous macules, revealing dermal melanocytosis and vacuolated eccrine gland cells. Electron microscopy revealed ubiquitously distributed membrane-bound clear vacuoles in fibroblasts and eccrine gland epithelial cells (Fig. 2). Bone X-ray imaging showed vertebral deformities, with hypoplasia and anterior beaking at the thoracolumbar region and slightly wide-ned ribs. Cranial computed tomography (CT) scan showed enlargement of the ventricular system. Ophthalmological examination revealed macular cherry-red spots and corneal clouding.

Definite diagnosis of GM1-gangliosidosis was made on typical urinary oligosaccharides chromatographic profile and low level of β-galactosidase activity in leukocytes and cultured skin fibroblasts. Normal urinary excretion and chromatography of glycosaminoglycan and level of α-iduronidase could rule out mucopolysaccharidosis (MPS) type I.

The patient is now 1 year and 8 months of age and has been hospitalized several times due to pulmonary infections. She also presents generalized hypotonia with severely delayed acquisition of motor milestones.

DISCUSSION

GM1-gangliosidosis (OMIM 230500) is a rare autosomal recessive lysosomal storage disorder caused by a deficiency of β-galactosidase (3). Although its incidence is not known, the infantile form (type 1) can affect 1 in 3700 live births in the Maltese Islands population (4). Type 1 GM1-gangliosidosis is usually diagnosed in early infancy, when developmental arrest or delay becomes evident. Definite functional deterioration of the nervous system follows within several months. Generalized muscle hypotonia, present at the initial stages, evolves into spasticity with frequent convulsive seizures. The patient becomes vegetative and death ensues within a few years. Macular cherry-red spots, corneal clouding and optic atrophy can also be observed. Hepatosplenomegaly is often reported and, in typical cases, dysmorphism and generalized skeletal
dysplasia are evident and progressive. Later onset cases have been grouped as late infantile/juvenile form (type 2) or adult/chronic form (type 3), characterized by a protracted clinical course (3).

Mutations in GLB-1, the β-galactosidase gene, are responsible for GM1-gangliosidosis and Morquio disease type B, a generalized dysostosis without central nervous system involvement. In GM1 gangliosidosis, β-galactosidase defects result in progressive accumulation of ganglioside GM1 in the brain (5). In Morquio B disease and GM1-gangliosidosis patients, high amounts of oligosaccharides derived from keratan sulphate or glycoproteins are detected in the visceral organs and urine (6).

Gangliosides are sialic acid-containing glycosphingolipids expressed in the plasma membrane of cells and mediate a variety of modulatory interactions (7). They may exert effects on proliferation and differentiation modulating tyrosine kinase growth factor receptors, such as epidermal growth factor receptor and fibroblast growth factor receptor (8, 9). Recent evidence suggests that the unfolded protein response can be induced by the unfolded protein response can be induced by the unfolded protein response can be induced by GM1 increase in neural crest cells during development might be involved in its pathogenesis (6). In this context, cell culture experiments demonstrating that addition of cholera toxin induces the differentiation of melanoblasts into mature, pigmented melanocytes are particularly interesting (12). The fact that this effect is known to be mediated by GM1 gangliosides (7) provides a link between GM1 increase and melanocyte differentiation. Though nerve growth factor (NGF) has been implicated (11), the true effect of GM1 on NGF signalling is not known (13, 14).

Although cure is still not possible for GM1-gangliosidosis, early diagnosis and intervention allows proper genetic counselling and anticipatory guidance regarding the typical course of the disease (2).

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