Case report

Generalized morphea in a child with harlequin ichthyosis: a rare association

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ABSTRACT

Introduction: Harlequin ichthyosis (HI) is a severe and rare hereditary congenital skin disorder characterized by excessive dryness, ectropion and eclabion. The association of ichthyosis with systemic sclerosis has been described in only three children. No patient with generalized morphea (GM) associated with harlequin ichthyosis was described.

Case report: A 4-years and 6-months girl, diagnosed with harlequin ichthyosis based on diffuse cutaneous thickening, scaling, erythema, ectropion and eclabion since the first hours of birth was described. She was treated with acitretin (1.0 mg/kg/day) and emollient cream. At 3 years and 9 months, she developed muscle contractures with pain on motion and limitation in elbows and knees, and diffuse sclerodermic plaques on the abdomen, back, suprapubic area and lower limbs. Skin biopsy showed rectified epidermis and mild hyperorthokeratosis, reticular dermis with perivascular and peridendal infiltrates of lymphocytes and mononuclear cells, and reticular dermis and sweat gland sclerosis surrounded by a dense collagen tissue, compatible with scleroderma. The patient fulfilled the GM subtype criteria. Methotrexate and prednisone were introduced. At 4 years and 3 months, new scleroderma lesions occurred and azathioprine was associated with previous therapy, with no apparent changes after two months.

Discussion: A case of harlequin ichthyosis associated with a GM was reported. The treatment of these two conditions is a challenge and requires a multidisciplinary team.

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Morfeia generalizada em uma criança com ictiose arlequim, uma associação rara

RESUMO

Introdução: Ictiose arlequim é uma doença cutânea congênita grave, autossômica e rara, caracterizada por ressecamento excessivo da pele e hiperqueratose. A associação de ictiose
com esclerose sistêmica foi descrita em apenas três crianças. Ainda não foi descrito nenhum paciente com morfeia generalizada (MG) associada à icterise arlequim.

Relato de caso: Menina de quatro anos e seis meses de idade com diagnóstico de icterise arlequim baseado em espessamento cutâneo difuso, com fissuras, descamação, eritema e sangramento da lesão desde as primeiras horas de vida. A paciente foi tratada com acitretina (1,0 mg/kg/dia) e creme emoliente. Aos três anos e nove meses, desenvolveu contraturas musculares com dor à movimentação e limitação nos cotovelos e joelhos e placas esclerôdémicas difusas no Abdômen, nas costas, na região suprapúbica e nas extremidades inferiores. A biópsia de pele mostrou epiderme retificada e hiperqueratose leve, derme reticular com linfócitos, infiltrado mononuclear perivascular e perianexial e esclerose da derme reticular e glândula sudorípara rodeada por um tecido colágeno denso, compatível com esclerodermia. A paciente preencheu os critérios para o subtipo MG. Metotrexato e prednisone foram introduzidos. Aos quatro anos e três meses, apresentou novas lesões esclerodérmicas, associando-se azatioprina à terapêutica anterior, sem resposta após dois meses.

Discussão: Um caso de icterise arlequim associada à MG foi descrito. O tratamento dessas duas condições é um desafio e requer uma equipe multidisciplinar.
lesions in abdomen (Fig. 2), lower limbs, back and supra-pubic areas and azathioprine (3.0 mg/kg/day) was introduced along with prednisone and methotrexate with no improvement after two months of therapy. Topical corticosteroid was not used. At present, her follow-up is composed of a multidisciplinary team with a rheumatologist, dermatologist, ophthalmologist, geneticist, physiotherapist and occupational therapist.

Discussion

To our knowledge, we describe herein the first case of harlequin ichthyosis associated to GM diagnosis. This congenital disease occurred previously to the scleroderma diagnosis, not in agreement with the rare cases of acquired ichthyosis and scleroderma reported in the literature.5,6

According to the new classification criteria, localized scleroderma has four different subtypes: plaque morphea, GM, linear scleroderma and deep morphea.9-10 The GM is defined by the presence of four or more plaques, with individual plaques greater than 3 cm and involving at least two out of seven anatomic sites,2 as evidenced in our patient that presented lesions occurring in upper and lower limbs, and trunk.

Furthermore, ichthyosis is composed of cutaneous keratinization diseases that can be inherited or acquired.3 Congenital ichthyosis is often associated with a variety of typical neonatal phenotypes with scaling and erythema. The main subtypes are congenital ichthyosiform erythroderma, lamellar and harlequin ichthyosis, including overlapping phenotypes. The mild subtype is congenital ichthyosiform erythroderma with fine and white scaling, and different degrees of erythema. Coarse and brown/dark scaling are observed in lamellar ichthyosis, generally with collodion membrane and ectropion. The harlequin ichthyosis is a more severe subtype associated with very scaling erythroderma, collodion membrane and pronounced ectropion.5,11 Of note, a collodion baby is defined by erythroderma, shiny and tight skin, like parchment, covering the entire body at birth. It is an initial presentation of several genetic conditions, including congenital ichthyosis,19 as observed in our case.

The disease course is generally severe with multiple joint contractures.13,14 Our patient presented contractures mainly in elbows and knees, possibly due to association with GM.

One limitation of the present case was the absence of electronic microscopy in the skin biopsy and genetic evaluations, since this is an autosomal recessive congenital disease.5 ABCA12 mutation analysis showed that 52% of survivors had heterozygous mutations, and all deaths were associated with homozygous mutations, while missense mutations are usually related with milder phenotypes.5,15,16 The association between harlequin ichthyosis and scleroderma, an autoimmune disease, is probably coincidental.

Of note, acquired ichthyosis with systemic sclerosis has been described in four patients after this autoimmune diagnosis,6,7 however the rare subtype of harlequin had not been previously reported. Other associations between harlequin ichthyosis and autoimmune chronic disorders have been rarely described without a clear relationship with pathogenesis of autoimmunity, such as hypothyroidism,13 celiac disease17 and juvenile idiopathic arthritis.13,14

The ichthyosis treatment is based on the severity of the disease and included topical formulations and oral retinoids,18 as indicated in our patient with unsatisfactory response. Moreover, the cutaneous juvenile scleroderma includes pharmacological (glucocorticosteroids and methotrexate) and non-pharmacological (physical exercises and early physiotherapy) therapies.19 Azathioprine may also be administered in refractory cases,20 as used in the present case. The difficulty
of the treatment concomitantly of these two severe and rare conditions should have contributed to the poor response ther-apy in our case.

The outcome of harlequin ichthyosis is generally related to stillbirth or first weeks of life death due to prematurity, renal failure, respiratory insufficiency and infection. To our knowledge, only eight cases with isolated harlequin ichthyosis or associated with juvenile rheumatoid arthritis survived the neonatal period, with a median of current age of 4 years (ranged from 6 months to 14 years).  

In conclusion, we reported the first case of harlequin ichthyosis associated with a rare type of juvenile scleroderma. The treatment of these two simultaneous illnesses is very challenging indeed and requires a multidisciplinary team.

Conflicts of interest

The authors declare no conflicts of interest.

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