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Narrative Review

The Three Most Important Things to Tell Parents of a Child With Café-au-lait Macules

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KEYWORDS

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McCune Albright Syndrome

ABSTRACT

Café-au-lait macules are common pigmented lesions, either congenital or acquired during the first years of life, and should not necessarily be regarded as indicators of an underlying syndromic condition. Their main distinguishing features from other hyperpigmented lesions are described, and all syndromic disorders associated with the presence of café-au-lait macules are reviewed.

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Introduction

The macula belongs to the group of elementary lesions (macula, papule, nodule, vesicle, pustule, pompho) and differs from the blotch/spot only in size (macula > 1 cm, spot < 1 cm); it is a flat, circumscribed non-palpable lesion with sharp, regular margins, round, oval and sometimes irregular in shape.

The normal colour of the skin is given by the chromatic superimposition of four pigments: melanin brown, carotene yellow, oxyhaemoglobin bright red and reduced haemoglobin red-blue.

Café-au-lait macules (CALMs)

CALMs belong to the group of hypermelanosis or genetic epidermal melanodermias, they are "hyperchromic lesions" due to the accumulation or altered distribution of melanin with unchanged numbers of melanocytes.

Melanin is produced by melanocytes (dendritic cells located at the dermoepidermal junction) and transferred in granules (melanosomes) to keratinocytes.

The colour shade of skin lesions of melanocytic origin will be a function of the depth of melanin deposition: superficial layers of the epidermis (black), dermal-epidermal junction (dark to light brown), superficial dermis (slate grey blue), deep dermis (electric blue).

Priority need for a differential diagnosis between coffee-milk spots and other hyperchromic spots, such as Hyperchromic Nevus due to a mutation occurring during foetal life, homogeneous brown colouring, generally single with variable extension (a few centimetres to many decimetres up to affecting a haemithorax or limb with blaskoid distribution) with indented margins and irregular outline; or with Ephelides multiple macules < 5 mm, round or oval, irregular borders, localised on the face or other photo-exposed sites, frequent in children with light-coloured hair and eyes.

If observed in young children, a differential diagnosis with Congenital Melanocytic Nevus (NMC) at onset must be made. Dermoscopy (globular or reticular pattern for increased melanocyte number that is absent in CALMs) and Wood's light (CALMS increased melanin with Wood's ++ finding) can be useful for diagnosis.

CALMs are homogeneous light-brown flat lesions, sometimes almost invisibility, wich may be present at birth or in the first years of life (Fig.1 a, b). We need not worry if less than three are present in a normal child in the absence of a family history of genetic disorders (1). About one third of healthy school-age children have at least one CALM (2).

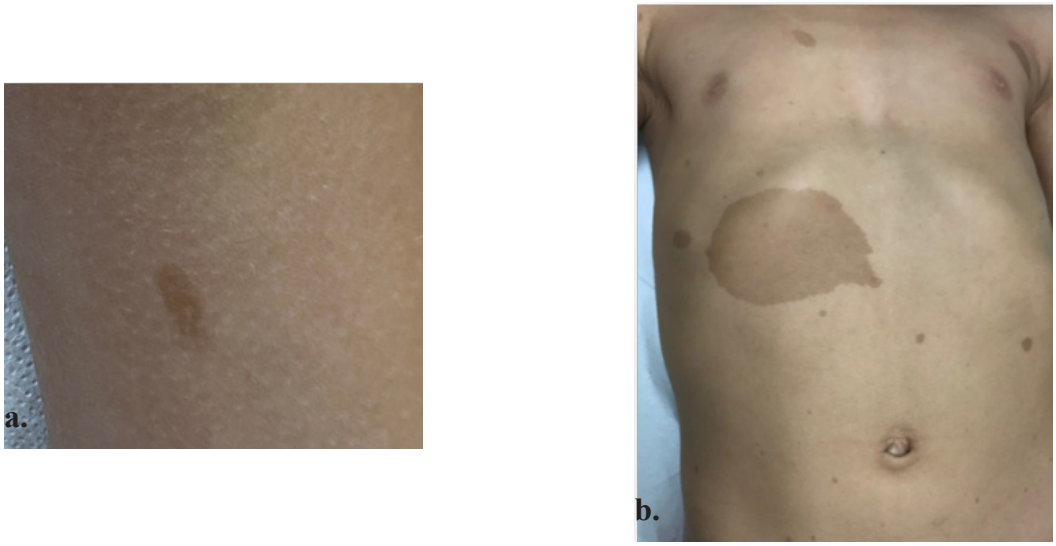

Fig. 1. *Presence of single (**a**) and multiple (**b**) café-au-lait macules on the skin.*

It is necessary to investigate when we have ≥6 patches >5 mm (before the age of 5) familiarity for genetic disorders (check parents), neurological signs, skin nodules, axillary or inguinal freckles, CALMs atypical in shape or distribution (3).

Note that 'typical' CALMs (homogeneous pigmentation and well-defined borders) are better predictors of underlying genetic disease than 'atypical' CALMs (irregular pigmentation and poorly defined borders).

CALMs are a suggestive but not exclusive sign of Neurofibromatosis type 1 (NF-1) and their presence generates anxiety and concern also as a consequence of increasing access to the web as a source of information.

In a minority of cases, certain pathologies may be associated with them, as shown in Table I.

Table I. *Syndromes with CALMs.*

Syndromes	Associated Anomalies
Multiple Familial CALMs	None. Only CALMs and freckling with no other signs of NF1
Legius Syndrome (NF1-like)	None. Only CALMs and freckling with no other signs of NF1
NF1 e and 2	Lisch nodules, optic nerve gliomas, skeletal anomalies, benign and malignant neoplasms
Watson Syndrome	Pulmonic stenosis, intellectual disability, short stature, relative macrocephaly, Lisch nodules, neurofibromas
McCune-Albright Syndrome	Fibrous dysplasia of the bone, precocious puberty (several endocrinopathies)
LEOPARD Syndrome	Congenital heart anomalies, pulmonic stenosis, abnormal genitalia, growth retardation, skeletal anomalies
Westerhof-Beemer-Cormane Syndrome	Hypopigmented skin patches, Intellectual disability, hort stsature, skeletal and sometimes neurological abnormalities
Tuberous Sclerosis	Hypopigmented macules, facial angiofibromas, periungual fibromas, cortical tubers (neurological disorders)
Bloom Syndrome	Short stature, photosensitivity and predisposition to tumor development
Ataxia-telangiectasia Syndrome	Cerebellar ataxia (lack of coordination), telangiectasias (dilated blood vessels), immunodeficiency, and an increased risk of cancer
Fanconi anemia (bone marrow aplasia**)**	Skeletal anomalies, microcephaly, endocrine, renal and genitourinary system abnormalities. predisposition to the development of leukemia and tumors

Neurofibromatosis type 1

Von Recklinghausen disease is part of a heterogeneous group of neuroectodermal diseases. It has an incidence of 1:2500-1:3000; equal incidence between the sexes, mutation in an oncosuppressor gene (17 q 11.2). The diagnosis is based on the presence of at least 2 of the criteria encoded by the National Institutes of Health (NIH). Full penetrance is age dependent, expressivity variable and the course unpredictable.

CALMs are the first and earliest manifestation of NF-1(<95%), sometimes detectable at birth, usually appearing by 2 years of age; followed by Freckling or axillary or inguinal freckles (at school age), Lisch iris nodules and cutaneous Neurofibromas (pre-puberty).

A presentation of at least 6 CALMs (diameter greater than 5 mm before puberty and 15 mm after puberty) fulfils one of the NIH clinical diagnostic criteria for both NF1 and Legius syndrome (NF1- like) (4).

Although there are no guidelines for how long to monitor patients with less than 6 CALMs, children older than 29 months with less than 6 CALMs have a 0.9% risk of developing NF1 and almost all patients with NF1 will meet the diagnostic criteria by the age of 8 years (5).

CALMs of NF1 have a homogeneous light brown to dark brown colour, regular margins, rounded or oval (typical CALMs such as "*California Coast*"), varying diameter from 0.5 to 50 cm, growing proportionally to the affected body segment those present in the first year of life, then smaller ones will appear with random distribution.

Legius syndrome (NF1- like)

Is rare and transmitted in an autosomal dominant manner, the mutation is in the SPRED1 gene on chromosome 15, > 6 CALMs (> 80%) + intertriginous freckles (50%) no typical NF1 manifestations (neurofibromas, Lisch nodules, optic gliomas, nor neoplastic and bone complications), macrocephaly and neurobehavioral disorders may be present (6).

McCune Albright Syndrome (SMA)

Is characterised by large CALMs with jagged edges like the 'Maine Coast' that do not cross the midline and follow the Blaschko lines. It has a prevalence of 1:30.000 and is due to a mutation in the GNAS gene. The clinical signs are age-dependent: CALMs (almost always present at birth), precocious puberty (50% probability in females within 4 years) and bone dysplasia (50% probability of onset within 8 years).

Café-Au-Lait Macules (CALMs) do not have an evolutionary character and therefore treatment for aesthetic improvement only with Q-switched laser can be proposed.

Practical course for the paediatrician in the face of CALMs:

a. Observe number, size and shape;
b. Complete examination for associated neurological or cutaneous signs;
c. Accurate family history;
d. Early classification of atypical cases, if suspected send to centre;
e. Do not alarm families unnecessarily (early diagnosis is of little use);
f. The key to management is monitoring over time.

The three most important things to tell parents

1. CALMs are innocent and very frequent lesions; 1/3 of healthy children have ≥ 1; If they create discomfort in the future, they can be removed by laser.
2. It is not justified to think of NF1 when the typical ones are less than six.
3. In the vast majority of cases, the involvement is exclusively cutaneous and life can be completely normal. Complications are rare and mostly treatable.

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