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Giant congenital melanocytic nevus[*]
Nevo melanocítico congênito gigante

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Abstract: Giant congenital melanocytic nevus is usually defined as a melanocytic lesion present at birth that will reach a diameter ≥ 20 cm in adulthood. Its incidence is estimated in <1:20,000 newborns. Despite its rarity, this lesion is important because it may associate with severe complications such as malignant melanoma, affect the central nervous system (neurocutaneous melanosis), and have major psychosocial impact on the patient and his family due to its unsightly appearance. Giant congenital melanocytic nevus generally presents as a brown lesion, with flat or mammilated surface, well-demarcated borders and hypertrichosis. Congenital melanocytic nevus is primarily a clinical diagnosis. However, congenital nevi are histologically distinguished from acquired nevi mainly by their larger size, the spread of the nevus cells to the deep layers of the skin and by their more varied architecture and morphology. Although giant congenital melanocytic nevus is recognized as a risk factor for the development of melanoma, the precise magnitude of this risk is still controversial. The estimated lifetime risk of developing melanoma varies from 5 to 10%. On account of these uncertainties and the size of the lesions, the management of giant congenital melanocytic nevus needs individualization. Treatment may include surgical and non-surgical procedures, psychological intervention and/or clinical follow-up, with special attention to changes in color, texture or on the surface of the lesion. The only absolute indication for surgery in giant congenital melanocytic nevus is the development of a malignant neoplasm on the lesion.
Keywords: Nevi and melanomas; Nevus, pigmented; Skin neoplasms

Resumo: O nevo melanocítico congênito gigante é, geralmente, definido como lesão melanocítica presente ao nascimento e que atinge, no mínimo, 20 cm de diâmetro na vida adulta. Sua incidência é estimada em menos de 1:20.000 recém-nascidos. Contudo, apesar de sua raridade, possui importância tanto por estar associado a complicações graves, como o melanoma maligno e o acometimento do sistema nervoso central (melanose neurocutânea), quanto pelo grande impacto psicossocial que ocasiona no paciente e nos familiares, devido a seu aspecto comumente inestético. O nevo congênito gigante, geralmente, apresenta-se como lesão acastanhada, plana ou elevada, de bordas bem definidas e com hipertricose, e seu diagnóstico é eminentemente clínico. Do ponto de vista histológico, porém, os nevos melanocíticos congênitos são diferenciados dos nevos adquiridos, principalmente pelo seu tamanho maior, pela disseminação das células névicas para as camadas mais profundas da pele e pela sua arquitetura e morfologia mais variadas. O nevo congênito gigante é considerado fator de risco para o desenvolvimento do melanoma. Todavia, a real incidência de malignização ainda é controversa. Estima-se que o risco de melanoma ao longo da vida esteja entre 5 e 10%. Diante dessas incertezas e do tamanho das lesões, a abordagem do nevo gigante representa um desafio e deve ser individualizada. O tratamento pode incluir procedimentos cirúrgicos ou não cirúrgicos, intervenções psicológicas e/ou acompanhamento clínico, com atenção a mudanças de coloração, superfície ou textura do nevo. Considera-se que a única indicação absoluta para a intervenção cirúrgica é o surgimento de uma neoplasia maligna sobre a lesão.
Palavras-chave: Neoplasias cutâneas; Nevo pigmentado; Nevos e melanomas

INTRODUCTION

Melanocytic nevi are benign proliferations of melanocytic cells (also known as nevus cells) arranged in nests in the epidermis, dermis or in other tissue.[1,2]

Melanocytic nevus present at birth is, by consensus, defined as congenital. Some authors, however, also include in this definition melanocytic nevi that develop until six months of age, during the first year or even until two years.[1-5] Although congenital melanocytic nevus (CMN) develops during the intrauterine life, the occurrence of these late congenital nevi might be explained by the insufficient initial production of melanin and / or by the small size of the nevus early on, hindering its detection.[6-9]

Giant congenital melanocytic nevus (GCMN) is, generally defined as a congenital melanocytic lesion that will reach, at least, 20 cm in adult life.[10-20]

Despite its rarity, GCMN is important for its association with severe complications such as malignant melanoma and central nervous system (CNS) involvement, as well as a major psychosocial impact on the patient and his family, due to its unsightly appearance.[6,11,21,22] The issue of deciding which is the best therapeutic approach in these cases also causes distress to the medical team, due to the controversies surrounding the treatment of these lesions - which stems largely from the uncertainties about the risks of complications.[13,23]

HISTORY

The interest in studying GCMN has increased over time mostly because of the hypothesis that there would be an increased risk of melanoma among these patients. Reports of individuals (usually children) with GCMN who later developed melanoma from late nineteenth and early twentieth century already raised the suspicion that these two conditions were linked.[20,24-26]

However, factors such as the low incidence rates of GCMN always hindered the quantification of such risk and, even nowadays, it has not been well established in the literature. There are few studies dealing exclusively with GCMN and its relation to melanoma. Most studies also include medium melanocytic nevi or refer to CMN of all sizes (Chart 1). Moreover, among those who included only GCMN, only three research groups published prospective follow-up data.[16,24,27] It is known that prospective studies with extended follow-up of patients would be necessary to establish more precisely the risk of malignant transformation of GCMN.[18,28] Although GCMN is considered a risk factor for the development of melanoma, the real incidence of malignancy is still a controversy.[21,29,30]

EPIDEMIOLOGY

About 1% of live births presents with a CMN.[31,32] The incidence of GCMN is estimated at less than 1:20,000 newborns. The variety "garment-like" of GCMN is even scarcer: 1:500,000.[32]

The majority of published studies show a slightly higher prevalence of GCMN in female patients, with ratios ranging from 1.17:1 to 1.46:1.[12,18,19,33]

PATHOGENESIS

CMN originates between the 5th and 24th weeks of gestation.[7] It is believed that a morphological error occurs in the neuroectoderm during embryogenesis, leading to unregulated growth of melanoblasts, the precursor cells of melanocytes.[34] The histogenesis of melanocytic nevi, however, is still a matter of controversy. Recently, Saida proposed the hypothesis that both CMN and acquired nevus arise from an accelerated proliferation of cells of melanocytic lineage sometime during development.[35] Therefore giant and medium CMN would be formed when proliferation starts, during migration of melanoblasts from the neural crest to the skin. Nevi will be larger and deeper when this process starts during the embryonic or early fetal periods. The later the onset of cell proliferation, the smaller the melanocytic lesion will be.

Small CMN and acquired nevus, in contrast, would arise after melanoblasts have reached the epidermis (which occurs around the 10th week in utero, when cell differentiation begins). If melanocyte located in the dermal-epidermal junction begins to multiply shortly before birth, the result would be a small CMN. If the proliferation begins after birth, it would produce an acquired melanocytic nevus. Thus, the common origin between acquired nevus and small CMN would explain the clinical and histological similarity of these lesions reported in some studies.[31,36,37]

From a molecular standpoint, it is believed that the development of melanocytes is partially controlled by the proto-oncogenes c-met and c-kit. The hepatocyte growth factor (HGF / SF – hepatocyte growth factor or scatter factor) is a cytokine regulator of epithelial cells that express the tyrosine kinase receptor encoded by c-met. Overexpression of this factor is associated with disorders of differentiation, proliferation and migration of melanocytes and could be related to the occurrence of GCMN.[6,38,39]

There is evidence that the proto-oncogene c-kit, that encodes the protein kit (another tyrosine kinase receptor), allowing the binding of the stem cell factor (SCF-stem cell factor) also has an important role in the development of melanocytes.[40] The expression of c-kit was observed even in proliferative nodules which appear

Chart 1: Studies evaluating the occurrence of melanoma associated to giant congenital melanocytic nevus

Authors	Country	Year of publication	Size of CMN included in the study	Number of MM/ total number of patients	% of patients with MM
Conway	United States†	1939	Only GCMN	4/40	10.0%
Greeley *et al.*	United States	1965	Giant and medium CMN	6/56	10.7%
Reed *et al.*	United States	1965	Mostly GCMN	17/55	30.9%
Lanier *et al.*	United States	1976	Giant and medium CMN	5/72	6.9%
Lorentzen *et al.*	Denmark	1977	Giant and medium CMN	3/151	2.0%
Arons & Hurwitz	United States	1983	Giant and medium CMN	0/46	0%
Quaba & Wallace	United Kingdom	1986	Giant and medium CMN	2/39	5.1%
Gari *et al.**	United States	1988	Only GCMN	1/47	2.1%
Ruiz-Maldonado *et al.**	Mexico	1992	Only GCMN	3/80	3.8%
Swerdlow *et al.*	United Kingdom	1995	Only GCMN	2/26	7.7%
Marghoob *et al.**	United States	1996	Only GCMN	3/92	3.3%
Egan *et al.**	United States	1998	Only GCMN	2/46	4.3%
Bittencourt *et al.**	United States	2000	Only GCMN	3/160	1.9%
Bohn *et al.*	Sweden	2000	Giant and medium CMN	1/12	8.3%
Ka *et al.*	Several‡	2005	Only GCMN	0/379	0%
Hale *et al.**	United States	2005	Only GCMN	4/170	2.4%
Bett	Several‡	2005	Giant and medium CMN	16/991	1.6%
Zaal *et al.*	Holland	2005	Giant and medium CMN	4/320	1.3%
Chan & Giam	Singapore	2006	Giant and medium CMN	0/39	0%
Kinsler *et al.**	United Kingdom	2009	Only GCMN	4/122	3.3%
Total		1939-2009		73/2644	2.8%

CMN: Congenital melanocytic nevus; GCMN: Giant congenital melanocytic nevus; MM: malignant melanoma.
* Prospective studies.
† Also included cases reported in the literature.
‡ Internet patient registry.
Notes: - The studies by Gari, Marghoob, Bittencourt and Hale are follow-ups from the same prospective registry (New York University Giant Congenital Melanocytic Nevus Registry). In order to calculate the toatl number of cases and MM in this box, only the most recent data, from Hale *et al.* were included.
- Kinsler *et al.* evaluated several sizes of CMN, however it was possible to extract data regarding GCMN.
Modified and updated source: Marghoob *et al.* (2000)[21]

in CMN.[41] Although there are reports of familial cases of CMN, most of these lesions occur in at random.[7,42]

CLINICAL FEATURES

GCMN usually presents as a brownish lesion with well-defined borders and hypertrichosis (Figure 1). In newborns it may have a lighter coloration and present few or no hair follicles, occurring as a macule or as an elevated lesion.[17,43] The surface of the nevus may be papular, roughed, warty or cerebriform.[17,44-46]

Although GCMN can affect any region of the tegument, its most frequent location is the torso, followed by the limbs and head.[13,16,19,24,27,47-49] Commonly, however, GCMN affects more than one body segment.[27] Some peculiar locations led to the term "GCMN in garment". These nevi are described as "bathing trunk", "stole" or "coat sleeve," for example (Figure 2).[50,51]

The presence of smaller pigmented lesions scattered over the skin surface, known as satellite lesions,

is common in individuals with GCMN, occurring in up to 78% of the cases (Figure 3).[16,33,48]

Although usually GCMN is an asymptomatic lesion, patients may complain of pruritus, whose mechanism is not fully understood. It is believed that symptoms may be explained by the local and inter-mittent stimuli of afferent sensory fibers, which would be caused by xerosis and hypohidrosis second-ary to the functional impairment of adnexal structures such as sebaceous and eccrine glands.[11,52] The presence of nevus cells may also lead to the disruption of the normal skin architecture, leading to cutaneous fragili-ty that would be responsible for the occurrence of ero-sions and superficial ulcerations.[11,53]

GCMN may also have important psychological consequences, especially when the lesions are very extensive and / or are located in visible areas such as the face.[54] A study evaluating psychosocial aspects of

FIGURE 1: Giant congenital melanocytic nevus in "bathing trunk" with evident hypertrichosis, irregular surface and nodular areas

FIGURE 3: Child with multiple satellite lesions associated to giant nevus, affecting even the oral mucosa (A) and plantar areas (B)

FIGURE 2: A. Giant congenital melanocytic nevi "in garment": A) "in bathing trunk"; (B) "in coat sleeve"; (C) type "shirt"

children with GCMN revealed that emotional or behavioral problems occur in up to 26% of cases, and social problems affect about 30% of patients.[22] These issues arise as a result of an impaired self-image caused by the presence of the nevus, the anxiety over the risk of complications such as melanoma, the discomfort caused by multiple invasive treatments and even by the unsightly appearance of surgical scars. Cutaneous symptoms eventually caused by the melanocytic lesion, contribute to the exacerbation of emotional disorders. Parents and other family members also often present with psychological symptoms associated with the difficulty in accepting the congenital problem and dealing with its implications.[7,22,54]

One of the serious complications of GCMN is neurocutaneous melanosis (NCM), a rare syndrome with just over 100 symptomatic cases described in the literature. It is characterized by the presence of benign or malignant melanocytic proliferations in the CNS associated with the occurrence of congenital melanocytic lesions. Melanocytic cells are found in large number (in nodules or diffusely distributed) in the leptomeninges of the brain and / or spinal cord. Although the location of these cells is similar to that occurring under physiological conditions (in up to 85% of individuals), the extent of infiltration differentiates these patients from the normal population.[6,19,55-58]

The diagnostic criteria for NCM currently accepted are those of Kadonaga & Frieden:[58]

1. Presence of one GCMN or three or more CMN, associated to meningeal melanosis or meningeal melanomas.
2. No evidence of cutaneous melanoma, except in patients in whom meningeal lesions are histologically benign.
3. No evidence of meningeal melanoma, except in patients with skin lesions subjected to histological examination, and confirmed as benign.

The cases with histological confirmation of lesions in the CNS are considered final, while the others are called provisional.[58,59]

Several alterations on skin and other organs have been described, albeit with low frequency in association with GCMN.[6,60] It is believed that, in most cases, these occur in a random way. Case reports describe individuals who, in addition to GCMN, present with diffuse lipomatosis, hypertrophy of cranial bones, atrophy of limbs, skeletal asymmetries involving hyper-or hypoplasia of soft tissues, scoliosis, urinary tract anomalies, capillary vascular malformations, cafe-au-lait spots, ectopic Mongolian spots, fibroepithelial polyps and atopic dermatitis.[4,27,54,58,60-63] The reduction on the circumference of the limb affect-

ed by GCMN is common and attributed to the replacement of subcutaneous fatty tissue by nevus cells.[27]

Some cases of depigmentation have been reported around the nevus region (halo phenomenon), in nevus and / or in skin areas distant from it. This depigmentation is interpreted as an autoimmune phenomenon, involving a response of the immune system to melanocyte's antigens.[27,54,60,64,65]

Other structural CNS malformations may be found, such as arachnoid cysts, choroid plexus papilloma, cerebellar astrocytoma, spinal dysraphism (associated with GCMN located in the lumbosacral region) and type I Arnold-Chiari (herniation of cerebellar tissue through the foramen magnum). Dandy-Walker malformation may be associated with NCM or occur in the absence of CNS involvement by melanocytic cells. It is characterized by cystic enlargement of the fourth ventricle, aplasia or hypoplasia of the cerebellar vermis and an increase of volume of the posterior fossa with or without hydrocephaly.[6,19,54,58,60,62,66]

CLASSIFICATION

Attempts to classify CMN according to their size derive mainly from the fact that the risk of complications is proportional to the diameter of the nevus.[6,9,12,16,20,67]

Various criteria have been used by different authors to define a CMN as giant (Chart 2).[5,18,20,25,26,28,32,37,58,68-75] Kopf *et al.*[20] proposed an arbitrary classification of CMN according to their largest diameter in adulthood, dividing them into: small (<1.5 cm); medium (from 1.5 cm to 19.9 cm); and large (or giant: ≥20 cm).

The classification system proposed by Kopf *et al.* is the most accepted nowadays and, although the reason for the choice of values is subjective, Swerdlow *et al.* have shown in a retrospective study, that malignization occurred only in nevi with a diameter ≥20 cm.[10-19 25] Moreover, the ease of obtaining the diameter of the nevus during physical examination, the accuracy of measurement in centimeters and the applicability of this classification to both adults and children make it useful for the medical practice.[18]

More recently, Ruiz-Maldonado[67] suggested a modification to the system created by Kopf *et al.*, defining as medium the CMN with an average size between 1.5 and 10 cm; naming as large those which diameter varies between 11 and 20 cm, and ranking as giant the nevi with more than 20 cm. The GCMN would be further subdivided into three categories: G1 (21 to 30 cm), G2 (31 to 40 cm) and G3 (more than 40 cm). Patients with giant nevi and more than 50 satellite lesions would go up a level from the category in which they were classified taking into account only the size of the nevus. The author's goals were to

increase the classification accuracy and facilitate the comparison between different studies. This proposal, however, has not yet been incorporated in studies published to date.

In order to enable the classification of CMN in children, and considering that the majority of these lesions increases as the body grows, Dedavid *et al.* calculated the diameter of the skin surface for both sexes in different age groups, creating curves that allow us to estimate which size a CMN will reach in adulthood (Figures 4 and 5).[9,20,37,46,76,77,78]

Another way of obtaining an estimate of the size of CMN in adult life is multiplying the diameter of the lesion in the infant by a numerical factor that varies according to the location of the nevi (Table 1).[9,49,77,79]

HISTOLOGY AND OTHER COMPLEMENTARY EXAMS

GCMN diagnosis is mainly clinical. From the histological standpoint, however, CMN is generally differentiated from acquired nevus mainly by its larger size, the dissemination of nevus cells into the deeper layers of the skin (including subcutaneous tissues) and its varied architecture and morphology.[30,43,80,81]

The epidermal alterations of CMN are often similar to those of the acquired nevus. The most common findings are hyperkeratosis and hyperplasia, elongation of epidermal ridges associated with an increased number of melanocytes and hyperpigmentation (lentigo-like alterations) and presence of melanocytes arranged in nests in the epidermis.[30,43,82]

CHART 2: Giant congenital melanocytic nevus classification

Author	Criteria
Pers (1963); Lorentzen *et al.* (1977)	CMN larger than the pacient's palmar area when located on head or neck and twice the size of the palm when located anywhere else
Greeley *et al.* (1965)	CMN ≥ 900 cm2
Rhodes *et al.* (1981); Arons & Hurwitz (1983)	CMN that cannot be removed with primary closing in one single surgical procedure
Kaplan (1974)	CMN that cannot be removed without causing deformities
Lanier *et al.* (1976)	CMN affecting 30% or more of total body surface
Kopf *et al.* (1979)	≥ 20 cm in its larger diameter in adulthood
Solomon (1980)	> 2 cm
Castilla *et al.* (1981); Bauer & Vicari (1988)	> 4 cm
Zitelli *et al.* (1984)	> 120 cm^2
Illig *et al.* (1985)	> 10 cm
Quaba & Wallace (1986)	> 2% of total body surface
Kadonaga & Frieden (1991)	>9 cm, when located on the head and >6 cm when located on the body, in children
Swerdlow *et al.* (1995)	> 5% of total body surface

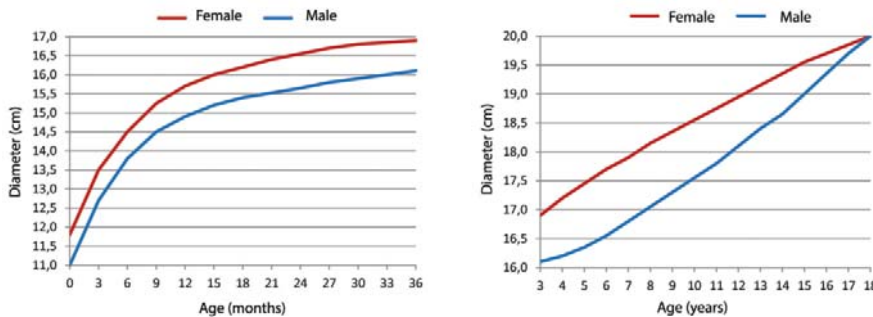**CMN**: congenital melanocytic nevi

FIGURE 4: Size of giant congenital melanocytic nevus located on the head, according to the age
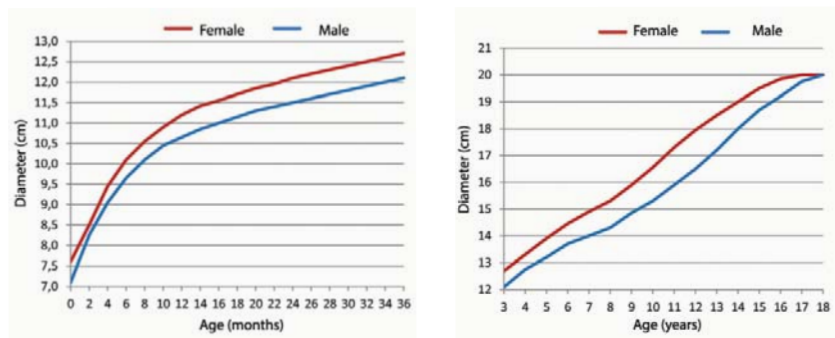
Figure 5: Size of giant congenital melanocytic nevus located on the body, according to the age

Table 1: Estimated size of CMN in adulthood based on its diameter in infancy

CMN location on infant	CMN diameter at birth (cm)*	Factor†
Head	11.8	1.7
Hands, feet, torso, forearms, arms, hips	7.2	2.8
Thighs	5.9	3.4
Legs	6.1	3.3

CMN: Congenital melanocytic nevus.
* Diameter in which the nevus would reach at least 20 cm in adulthood.
† Factor that should be multiplied by the CMN diameter in infancy to obtain its estimated size in adulthood
Modified source: Marghoob *et al*.[49]

Among the findings that help differentiate CMN from acquired nevus are: presence of nevus cells in the lower two thirds of the dermis and subcutaneous tissue; arrangement of these cells as isolated elements or "in Indian line" among the collagen bundles of the lower reticular dermis; the involvement of sebaceous glands, blood vessels, erector muscles of hair follicles, eccrine glands and lymphatic vessels (typically, the nevus cells are present in many units and more than one cutaneous appendage, nerve or capillary vessel), and also the occurrence of perivascular, perifollicular and / or around the eccrine glands distribution, which often simulates inflammatory infiltrates.[6,17,43,82] The involvement of collagen by nevus cells in the middle and deep reticular dermis is a CMN feature with high sensitivity (85.7% to 98.3%) and specificity (72.5% to 96.7%). The finding of greater specificity, however, reaching 100%, is the occurrence of nevus cells within the sebaceous glands, nerves and blood vessels in the deep reticular dermis.[43,82]

While these characteristics are present in CMN of all sizes, they are generally more pronounced in GCMN, to which they can be applied as diagnostic criteria with great accuracy.[17,20,36,83,84]

GCMN also presents a great variety of histological elements. In addition to the usual compound or intradermal melanocytic nevus pattern, other arrangements such as neural, blue nevus or Spitz nevus patterns may occur. In the neural subtype, there are areas

of neuroid tissue differentiation - with microscopic structures formed by fibrillar collagen in an arrangement resembling Meissner corpuscles or Verocai bodies - and the lesion may resemble a neurofibroma. In the blue nevus GCMN type, cellular elements may resemble those of a common blue nevus or those from the cellular or giant nevus varieties. In the case of CMN with Spitz nevus features, there is a proliferation of spindle or epithelioid cells in the reticular dermis, which may associate to common nevus cells or neuroid cells, producing what is known as a combined nevus.[6,17,43,51,58,85] The diversity of histological elements in GCMN could be explained by the fact that these lesions originate oftentimes from a pluripotent stem cell, which can differentiate into multiple cell types.[1]

Dermoscopy is a more useful tool for evaluating small to medium CMN. Regarding GCMN, its histological peculiarity of presenting nevus cells located deeper in the skin is one of the reasons for the low application of dermoscopy. Most giant nevi show a brownish homogeneous background with darker pigmentation islands. Other dermoscopic findings include hypertrichosis, perifollicular hypo or hyperpigmentation, pseudomilia and vascular structures.[6,86]

Complementary tests that aid in the diagnosis of NCM are magnetic resonance imaging (MRI) and cerebral spinal fluid (CSF) analysis. MRI is much more sensitive than CT for the detection of melanin, and it is the best method to evaluate the involvement of the

leptomeninges. On examination, there is focal shortening of T1 relaxation time and, less frequently, of T2. T1 shortening can be seen without the use of contrast. The study of CSF rarely identifies melanocytic cells or free melanin. It is more usual to find low CSF glucose, high protein concentration and sterile leukocytosis. Cytological analysis of CSF, however, should not be performed for routine diagnosis.[55,57-59,87,88]

EVOLUTION

Over time, GCMN can undergo a process of darkening or lightening, develop a more heterogeneous or homogeneous pigmentation, present with an increase in hair growth, acquire a more irregular surface or, more rarely, spontaneously regress.[7,14,89] Some authors observed an initial tendency to darkening of the lesions through adolescence, followed by a significant lightening, associated to an increase in surface roughness, appearance of nodules and hypertrichosis.[24,46,90] Generally, lesions tend to become thicker over time.[17,44-46] The appearance of nodules in the nevus usually corresponds to the proliferation of neuroid tissue elements.[45,74]

A major concern regarding patients with GCMN is the possibility of developing melanoma. Currently there is in the literature ample evidence that these individuals are at increased risk of developing the tumor. Although the value of the incidence rate of malignancies in GCMN may still be a matter of dispute, it is estimated that for these individuals the lifetime-risk for developing melanoma is between 5 and 10%.[16,21,29,30] Although the probability that patients with GCMN develop melanoma throughout their life may seem small, the relative risk of the tumor in these patients compared to the general population, ranges from 52 to 2,600.[15,16,18,19,24,25,49,81,91]

Cutaneous melanoma that affects patients with GCMN presents some peculiarities. Unlike other melanomas that arise in the epidermis, the melanocytic neoplasia associated to GCMN has a non-epidermal origin in up to two thirds of cases, usually occurring in the dermis or in deeper layers.[3,72,92]

Cancerization can occur in extracutaneous melanocyte deposits, particularly in the CNS. The retroperitoneum and gastrointestinal tract mucosa may rarely be affected.[4,19,93] In up to 24% of cases, the origin of melanoma can not be identified.[94] Dedavid et al. studied 289 patients with GCMN described in the literature and found 67 cases of melanoma, of which 50.7% appeared on the nevus; 3% were cutaneous melanomas, but originated in clinically normal skin; 31.3% were primary CNS tumors and 15% were metastatic tumors of unknown primary site.[48]

Some characteristics of patients with GCMN are associated with a higher risk of developing melanoma. Evidence points to an increased incidence of neoplasia in patients with multiple congenital satellite lesions and / or GCMN with a paravertebral or axial location, such as the back, neck or head.[7,15,16,33,48]

It is believed that the increased incidence of melanoma in individuals with GCMN - compared to those who have acquired nevi and small CMN - is explained by the significantly larger number of melanocytic cells or by a different biological behavior of melanocytes in GCMN.[43,45,55,95-99] Changes in gene regulation associated with deoxyribonucleic acid repair mechanisms or tumor resistance to chemotherapy were observed in giant congenital melanocytic lesions.[98] Furthermore, evidence has shown the importance of structural chromosomal abnormalities in the process of malignant transformation of these lesions.[100]

The probability that a patient diagnosed with GCMN develops melanoma is not constant throughout life and most evidence points to an increased risk in early childhood.[5,46,48,49] Marghoob et al. reviewed the literature and found that about 70% of melanomas associated with GCMN were diagnosed before puberty, whereas less than 1% of all melanoma cases in the U.S. population occurs at this age.[49] In a review conducted by Dedavid et al., which included 289 patients with GCMN, it was found that about 50% of melanomas were diagnosed before the age of five.[48] Some recent studies, however, point out that the risk does not disappear during adulthood.[15,81,95]

Other tumors, benign or malignant, can occur in patients with GCMN. These neoplasms often exhibit the same complex histology as seen on GCMN. Thus, the ambiguous tissue differentiation (with elements of melanocytic lineage and other neuroids, for example) can be present in tumors that originate in nevus, hindering the diagnosis.[100,101]

In the group of benign tumors, lipomas - sometimes of intraspinal location- are found as well as benign schwannomas.[54,62,102] Among tumors with some degree of malignancy, the following can be identified: malignant cellular blue nevus, minimal deviation melanomas, sarcomas, malignant schwannomas, liposarcomas and undifferentiated spindle cell neoplasms.[30,92,101,103] Although mesenchymal elements (non-melanocytic and non-neuroids) are rarely described in association with CMN, it is known that sarcomas occur more frequently in patients with GCMN when compared to the general population.[7,101]

Particularly in the neonatal period, various types of melanocytic tumors may arise on GCMN, many of which are considered distinct from melanomas (although they often mimic this neoplasm). These proliferative lesions have varied sizes and can present rapid growth and ulceration. However, at this stage of life, even tumors with the

most worrisome clinical features tend to have a benign behavior, showing stabilization (or regression) after a period of rapid growth.[80,92,100] Nodules appearing on GCMN in newborns can be very difficult to classify histologically, but despite the similarity with melanoma-simulating lesions, they usually show some maturation and do not exhibit the same degree of atypia or the high mitotic rate observed in malignant melanocytic neoplasms. Findings such as inflammatory infiltrate, cellular necrosis and perineural invasion are also suggestive of malignancy.[13,17,80,100] Moreover, unlike melanoma, in which structural changes of chromosomes are found in most cases, the aberrations present in the benign proliferative nodules are predominantly numerical.[100]

Regarding NCM, the frequency of clinically manifested illness among patients with GCMN was estimated by literature reviews to be 4.5% to 11.4%.[78,104] Bittencourt *et al.,* in their prospective study of 160 patients with GCMN, calculated at 2.5% the cumulative risk over five-years for the development of NCM in these individuals.[19]

Clinical manifestations of NCM occur most frequently in the first two years of life. They usually result from increased intracranial pressure secondary to obstruction of the ventricular system foramen, subarachnoid cistern or arachnoid granulations secondary to melanocytic proliferations. There may also be bleeding or, as suggested by the definition of the syndrome, cancerization of melanocytic cells. The neurological signs and symptoms include headache, lethargy, vomiting, irritability, increased head circumference, seizures, papilledema and occasionally cranial nerve palsies. Disease progression can lead to ataxia, or cause bladder and / or intestinal dysfunction. Severe and chronic psychosis is also described, especially when the disease manifests itself later.[6,19,54,56-59,64,66,78,104,105]

The hypothesis that there could be asymptomatic cases of NCM was confirmed after the development of MRI. Based on the analysis of resonances of patients at risk for developing NCM but without neurological signs or symptoms, it is estimated that at least 4.8% to 26% of these individuals may show characteristic alterations compatible with this syndrome during the exam.[19,59,66] The true prevalence of asymptomatic NCM in patients with GCMN, however, is still unknown, and there is little information about the clinical evolution of these patients.[6,54]

Studies show an association between the risk of NCM and three main features: the location of the CMN in the posterior axis (head, neck and paravertebral regions), greater number of satellite lesions and a large size nevus.[16,58,64,78,105,106]

PROGNOSIS

When melanoma arises in GCMN, the prognosis is especially dismal. Trozak *et al.,* in their literature review that evaluated cases of childhood melanoma, observed that none of the 20 patients whose tumor was associated with GCMN was alive at the end of five years, whereas among 35 other individuals diagnosed with prepubertal melanoma (excluding cases of congenital neoplasm), the survival rate in the same period was 34.3%.[46]

There are some explanations for this unfavorable evolution. The fact that cutaneous melanoma associated with GCMN typically grows in the dermis makes it more difficult to detect in clinical exams. Unlike the malignant transformation that occurs in small or medium CMN, starting at the dermal-epidermal junction, and thus rapidly changing the appearance of a nevus, in the case of GCMN it is often necessary that a large nodule develops or ulceration occurs before the diagnosis of cancer is made.[11,55,107] Moreover, the often rough or nodular surface of GCMN further complicates the early observation of the tumor.[46,72] Another factor that may contribute to the severity of the disease is the great extent of nevic lesions (commonly crossing the midline), which causes their lymphatic drainage to be performed by multiple channels. Moreover, the presence of malignant cells in the deeper layers of the nevus facilitates tumoral spread through the lymph and blood vessels of greater caliber, favoring the occurrence of early metastases.[46] Besides, the occurrence of the disease in extracutaneous sites may contribute to the delay in its recognition. The difficult clinical detection of the tumor contributes to the fact that in 24% of cases, melanoma will already be metastatic at the time of diagnosis without the primary site being identified.[94]

Prognosis of symptomatic NCM is also poor. More than half of the patients will die within three years after the onset of symptoms and 70% before 10 years of age. The median age at death is 4.5 years.[19,57,58,78,104] The use of chemotherapy and radiation therapy are not effective in modifying the course of the disease. Palliative treatments, such as the use of shunts to reduce intracranial pressure and administration of anticonvulsants may however be used.[55,57,58,104]

TREATMENT

The approach to GCMN represents a challenge and should be individualized taking into consideration: age of the patient, size and location of the lesion, risk of melanoma, possibility of concomitant NCM; presence of changes suggestive of malignancy on the nevus; possible functional impairments resulting from

invasive procedures and the psychological impact associated with CMN or the surgical scars, often unsightly. Thus, treatment of patients with GCMN may include surgical or non-surgical procedures, psychological and / or clinical interventions, with the utmost attention in changes of color, texture or in the surface of the lesion.[6,7,28,103]

The decision of whether or not a patient should undergo surgical treatment involves both the technical difficulties of performing such procedures (especially when considering the cosmetic motivations) and the uncertainties regarding its effectiveness as a prophylaxis against melanoma.

The recommendation of prophylactic surgical excision would be justified based on the assumption that melanoma may arise on the nevic lesion. However, as seen earlier, 50% of melanomas found in patients with GCMN occur elsewhere.[16,48] Therefore, the removal of the nevus does not guarantee protection against malignancy. In addition, the size of "garment" GCMN may prevent the complete resection (Figure 6). It is difficult to measure the impact of total excision of GCMN or other therapeutic measures on the risk of developing melanoma. Probably the reduction of melanocytic cells reduces the incidence of malignancy. However, the heterogeneity of the studies that evaluated the different types of treatment used and their extension prevents a quantitative analysis, so that there is no current evidence that the removal of the nevus has a prophylactic role against the onset of

FIGURE 6: Giant congenital melanocytic nevus "in bathing trunk" submitted to partial surgical removal

melanoma.[15,29,97,105,108] For these reasons, the more aggressive approach to GCMN remains controversial.[13,23] Some authors suggest considering prophylactic excision for the more heterogeneous, thick or rough lesions, or for those that for any other reason are difficult to follow clinically.[103,107]

The size of the lesions makes their removal often dependent on the use of tissue expanders (especially for nevi located on the head or neck), serial interventions, the use of skin flaps, grafts or a combination of more than one type of surgical procedure.[13,50,68,73,75,103,109-112] Postoperative complications include contractures (which can cause functional alterations), requiring the removal of the grafts used to cover the primary defects, seromas (especially in cases where tissue expanders are used), hematomas, infection, ischemic skin flaps, suture dehiscence and formation of keloids.[13,68,109,111,112] Although various surgical techniques are described for the treatment of GCMN, none is universally accepted.[13,30] More recently, synthetic skin substitutes have been used in some cases to treat the defects secondary to the removal of GCMN.[13,109] However, there are no studies evaluating this technique on large samples and results were inferior to those obtained with the use of tissue expanders.[13]

The partial removal of GCMN by procedures such as dermabrasion, skin curettage, tangential excision (shave excision), chemical peels and laser treatment has mostly cosmetic purposes, since only the most superficial cells of the lesion are removed.[6,7,13,27,37,49]

Dermabrasion and skin curettage are most efficient if performed in the first two to six weeks of life, when it is easier to find a cleavage plan between the upper dermis, rich in nevic cells, and the deeper dermis, relatively poor in these cells.[11,113,114]

Dermabrasion may cause permanent (if performed early) or transient reduction in the pigmentation of the nevus, but it is not able to completely treat hypertrichosis.[37,115-117] The procedure is performed under general anesthesia, and infection is the main adverse event described. There is also the risk of tissue loss requiring skin-grafting when dermabrasion reaches the deeper layers of the skin.[115,117]

Studies have reported good cosmetic results after curettage. This is a procedure that can be performed in one session, in contrast to what usually happens with surgical excision. However, this approach also carries the risks of general anesthesia and the authors describe complications such as hypertrophic scars and infection. Furthermore, repigmentation of the treated area usually occurs partially.[113,114,118]

Tangential excision of the upper dermis may cause mild scarring, sometimes with dotted pigmentation, in infants less than nine weeks old. In older

children, however, the cosmetic results are worse. The procedure can be combined with excision of the thickened portion of the nevus.[42,93]

Chemical peels can improve the appearance of lighter GCMN or those whose nevus cells are more superficially located.[103,119] Ruiz-Maldonado *et al*. used phenol peeling (Baker's formula) for the cosmetic treatment of patients who did not want or were not good candidates for surgical treatment.[27] Larger nevi were treated in multiple sessions in order to avoid the cardiac and renal toxic effects of phenol. Scars were the most common complication, usually secondary to the occurrence of infection. The less toxic trichloroacetic acid at 50% concentration has also been used for depigmentation purposes in this study. Hopkins *et al*. treated 20 patients with the phenol solution and obtained good results in 75% of cases. No complications were observed.[119]

The use of laser in the treatment of GCMN is controversial. Lasers that can be used for this purpose are ruby, Q-switched, and carbon dioxide lasers (which can be combined with Q-switched ruby lasers or Nd:YAG). However, though they may improve the aesthetic appearance of some lesions and reduce the number of melanocytic cells, there is some concern that nevus cells exposed to sublethal doses of energy may have a higher probability of malignant transformation. Repigmentation may also occur. Thus, it is recommended to consider using the laser only when an interventional approach is the choice and surgical treatment is not feasible.[23,120]

There is also a discussion whether the techniques that partially remove congenital pigmented lesions could impair or facilitate the detection of abnormalities suggestive of melanoma on the nevus.[7,13,23,115,118] However, there is no doubt that in the event of unwanted hypertrophic or sclerotic scars over the treated area, a possible diagnosis of melanoma originated from the deep dermis or subcutaneous tissue may be delayed.[103] Furthermore, it may be difficult to distinguish between an area of malignancy and a pseudomelanoma (recurrent nevus originated after the incomplete removal of nevic cells) in those GCMN treated with one of these procedures.[7,37,103,115,121]

Even with these caveats, one can consider – to achieve cosmetic goals - alternative therapeutic modalities (such as skin curettage, dermabrasion and chemical peels) instead of surgeries, considering: the often poor aesthetic results of surgeries, the lengthy process necessary to remove a GCMN, involving multiple steps and requiring the use of tissue expanders and extensive grafts, and the high-cost of these treatments.[27,108]

On the other hand, some authors who advocate the removal of GCMN aiming at prophylaxis against melanoma also believe that the excision should occur early on, taking into account not only the increased risk of malignancy in early childhood[50,75,81] but also the possibility of obtaining more satisfactory cosmetic results, due to better healing, when operating in this age group.[75,103] Other studies contradict this recommendation. Kinsler & Bulstrode[97] argue that studies that advocate the early intervention are based on a small number of cases and did not compare these results with those of children who were operated at an older age. Kinsler *et al*., in a prospective cohort consisting of 122 patients with GCMN, did not observe any significant clinical or aesthetical differences between children operated at one, five or 10 years of age.[122] On the other hand, there is evidence that infants under one year of age have a higher risk of cardiac arrest due to anesthesia.[123,124] In addition, there are studies that point to potential neurological damages and learning difficulties in children undergoing procedures with general anesthesia as infants.[6,125]

Despite the controversy about the treatment, it is a consensus that the only absolute indication for surgical intervention in GCMN is the emergence of a malignant neoplasm on the lesion.[6,11,103]

It is known, however, that clinical follow-up of GCMN also has its difficulties, given the tendency of the surface of the lesion to have irregularities and nodules, and often a darken coloration and hypertrichosis.[3,17,24] Therefore, patients and / or their parents should be instructed to perform regular self-examination of skin and anticipate the medical consultation in case there are changes of color, shape, surface or appearance of the nevus or also other abnormal symptoms. The follow-up of patients becomes easier when performed by a multidisciplinary team, including dermatologist, plastic surgeon, radiologist and also with access to psychologists and neurologists, if necessary. During the periodic examination, it is important to perform the palpation of the lesion and lymph nodes. Serial photographs facilitate the monitoring of the evolution of GCMN.[6,11,23,97]

Taking into consideration the risk of extracutaneous melanomas, in the skin area outside the GCMN or even very deeply under the lesion, it is important to note that even patients whose nevus was completely removed must undergo lifelong, regular examinations of all skin and general medical examination, to facilitate the detection of any malignancy in its earliest stages.[6,49,97] ❑

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QUESTIONS

▼

1 - Regarding the origin of congenital melanocytic nevi, it is correct to affirm that:
   a) Its formation begins between the 24th and the 30th weeks of gestation
   b) The presence of nevi in family members indicates its mainly genetic character
   c) Proto-oncogenes c-met and c-kit play a role in its development
   d) It is the translation of a morphologic error in mesoderm

2 - Regarding epidemiology, one can affirm that the giant nevus:
   a) Affects 1 in 1,000 newborns
   b) It is most common in males
   c) The garment-like variant is the most rare one
   d) It is most common in premature children

3 - Those are clinical characteristics of giant congenital melanocytic nevus, except:
   a) Heterogeneous coloration
   b) Irregular surface
   c) Hypertrichosis
   d) Ulceration

4 - Regarding the clinical aspects of giant congenital melanocytic nevus, one can affirm that:
   a) Its most frequent location is on the head and / or neck
   b) It may present depigmentation or even spontaneous regression
   c) Pruritus occurs in the majority of cases
   d) The appearance of nodules in the nevus, although common, deserves investigation

5 - A congenital melanocytic nevus is considered giant when it reaches the minimal diameter of how many centimeters during adulthood?
   a) 10cm
   b) 15cm
   c) 20cm
   d) 25cm

6 - Mark the incorrect affirmation regarding satellite lesions:
   a) They occur in up to 80% of patients with giant nevi
   b) They are associated, when in multiples, to a higher risk of melanoma
   c) They indicate, when in larger numbers, a higher risk of neurologic involvement
   d) They are most commonly associated with nevus on acral location

7 - A patient cannot receive the diagnosis of neurocutaneous melanosis when, besides having a giant congenital melanocytic nevus, he also presents:
   a) Central nervous system's melanoma without evidence of cutaneous melanoma
   b) Cutaneous melanoma and encephalic melanocytic lesion that is benign on histologic examination
   c) Cutaneous melanoma and meningeal melanoma
   d) Benign melanocytic proliferation in central nervous system without evidence of cutaneous neoplasm

8 - Regarding cutaneous and extra-cutaneous alterations associated to giant congenital melanocytic nevus, it is incorrect to state that:
   a) Depigmentation in cases of vitiligo is interpreted as an autoimmune phenomenon, involving a response from the immunologic system to melanocytes' antigens.
   b) The reduction in the circumference of the limb affected by the nevus is due to replacement of fatty tissue by nevus cells
   c) Most alterations reported in the literature have a causal association with the presence of nevic lesions.
   d) Many cases of structural malformation in the central nervous system, such as arachnoid cysts, choroid plexus papilloma, cerebellar astrocytoma and spinal dysraphism, have been reported

9 - Regarding histologic findings in giant congenital melanocytic nevus, one can affirm that:
   a) Their epidermic alterations allow them to be differentiated of acquired nevi
   b) The presence of nevic cells is classically restricted to the papillary dermis
   c) The occurrence of nevic cells inside sebaceous glands, nerve and blood vessels on the dermis is common
   d) The histopathologic pattern usually presents homogenous morphology and architecture

10 - Regarding giant congenital melanocytic nevus dermoscopy, one can affirm all of the following, except:
   a) Pigmentary network is most commonly present in lesions with irregular surface
   b) The depth of nevic cells in the skin hinders the identification of structures in dermoscopy
   c) Most lesions show a homogenous brownish coloration in the background with islands of darker pigmentation
   d) Perifollicular hyperpgimentation, pseudomillia and vascular structures may be observed

11 - Regarding the diagnosis of neurocutaneous melanosis, mark the correct affirmative:
   a) Computerized tomography scan is the most sensitive method to detect melanin
   b) CSF analysis must be routinely performed to detect central nervous system involvement by nevic cells
   c) Detection of free melanin in CSF is usual
   d) The cases in which there is histological confirmation of lesions of the central nervous system are considered final

12 - Regarding the risk of developing melanoma in patients with giant congenital melanocytic nevus, it is incorrect to state that:
   a) There is, in the literature, ample evidence that these individuals are at increased risk of developing the tumor
   b) The rate of incidence of malignancy is well established, thanks to several prospective studies on the subject
   c) It is estimated that for these individuals the lifetime risk of developing melanoma is between 5 and 10%
   d) The risk of developing tumor seems to be directly proportional to the size of the nevus

13 - Regarding melanoma that occurs associated with giant melanocytic nevus, is correct to say that:
   a) It has better prognosis than de novo cutaneous melanomas
   b) It appears usually after puberty
   c) It has an unknown primary site in 25% of cases
   d) It arises most commonly from the epidermis

14 - The following are also tumors that are associated with giant melanocytic nevus, except:
   a) Neurofibroma
   b) Schwannoma
   c) Dermatofibroma
   d) Rhabdomyosarcoma

15 - About the nodules appearing on the giant congenital melanocytic nevus during the neonatal period, it can be said that:
  a) From the histological point of view, they are easily distinguished from melanoma, by the positivity of HMB45
  b) They suffer stabilization or regression after a period of rapid growth
  c) They exhibit the same degree of atypia and high mitotic index observed in malignant melanocytic neoplasms
  d) Most often, they present structural chromosomic changes

16 - Regarding neurocutaneous melanosis, select the incorrect statement:
  a) The prevalence of asymptomatic neurocutaneous melanosis in patients with giant congenital nevus is greater than 40%
  b) Its symptoms appear most often in the first two years of life
  c) Severe and chronic psychosis may be a clinical manifestation of this condition
  d) Its most common signs and symptoms are headache, lethargy, vomiting, increased head circumference, seizures and papilledema

17 - There is evidence that the risk of neurocutaneous melanosis is associated with the following factors, except:
  a) Location of giant congenital nevus on the head, neck and / or paravertebral region
  b) Nevus with a roughness surface
  c) Increased number of associated satellite lesions
  d) The size of the congenital nevus

18 - About the treatment of giant congenital melanocytic nevus, one can affirm that:
  a) The surgical removal of nevic lesion has proven efficient in preventing cutaneous melanoma
  b) The diagnosis of symptomatic neurocutaneous melanosis affects the decision to surgically intervene or not, on the congenital nevus
  c) Procedures such as dermabrasion, curettage and tangential excision have the same effectiveness in removing the nevus cells that of surgical excision
  d) Currently there is a consensus that the interventionist approach on giant congenital melanocytic nevus is the best option for most patients

19 - Regarding the modalities of interventionist approach on giant congenital melanocytic nevus, select the false statement:
  a) Although laser can improve the aesthetic appearance of lesions and reduce the number of melanocytic cells, it is feared that the cells exposed to sublethal doses of energy have greater likelihood of cancerization
  b) Chemical peels can improve the appearance of lighter colored nevi
  c) Surgical excision of the lesions usually depends on the use of tissue expanders, serial execution of operations, the use of skin grafts or flaps or a combination of more than one type of procedure
  d) The dermabrasion and curettage are more effective if performed after 5 years of age

20 - Regarding the monitoring of patients with giant congenital nevus, one can affirm all the following, except that:
  a) Palpation of both nevus lesion and lymph nodes, is an important act during the physical examination
  b) Psychological support may be necessary, given that emotional or behavioral problems affect up to 26% of patients
  c) Patients whose nevus has been completely removed by a dermatologist may be exempted from periodic examinations of the skin
  d) Dermatoscopy may be unnecessary, particularly in the examination of lesions in which nevus cells are situated more deeply

Answer key
Paracoccidioidomycosis: epidemiological, clinical, diagnostic and treatment up-daing (5):700-11.

1) C	**6)** C	**11)** D	**16)** D
2) D	**7)** A	**12)** D	**17)** D
3) B	**8)** A	**13)**D	**18)** D
4) B	**9)** D	**14)**A	**19)** D
5) C	**10)** D	**15)** D	**20)** D

Papers
  Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.