Congenital melanocytic nevi: Where are we now?

Part I. Clinical presentation, epidemiology, pathogenesis, histology, malignant transformation, and neurocutaneous melanosis

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Congenital melanocytic nevi (CMN) are present at birth or arise during the first few weeks of life. They are quite common, may have a heritable component, and can present with marked differences in size, shape, color, and location. Histologic and dermatoscopic findings may help suggest the diagnosis, but they are not entirely specific. CMN are categorized based on size, and larger lesions can have a significant psychosocial impact and other complications. They are associated with a variety of dermatologic lesions, ranging from benign to malignant. The risk of malignant transformation varies, with larger CMN carrying a significantly higher risk of malignant melanoma (MM), although with an absolute risk that is lower than is commonly believed. They may also be associated with neuromelanosis, which may be of greater concern than cutaneous MM. The information presented herein aims to help dermatologists determine when it is prudent to obtain a biopsy specimen or excise these lesions, to obtain radiographic imaging, and to involve other specialists (eg, psychiatrists and neurologists) in the patient's care. (J Am Acad Dermatol 2012;67:495.e1-17.)

Key words: congenital nevus; imaging; malignant melanoma; neurocutaneous melanosis; neuromelanosis; tethered spinal cord.

Congenital melanocytic nevi (CMN) are nevi that are present at birth or arise within the first few weeks of life.[1] Small lesions are most often inconsequential, but large nevi can carry a devastating psychosocial burden and increased risks of malignant melanoma (MM). The past few years have seen the publication of several new studies regarding congenital nevi, including a large metaanalysis. The ideal approach to management of these lesions remains debatable. This 2-part review will explore the latest data published on this topic and controversies in management.

CAPSULE SUMMARY

- Congenital nevi are common and typically benign, but when large may be associated with melanoma and neurocutaneous melanosis.
- Literature regarding the clinical, epidemiologic, diagnostic, and prognostic factors of congenital nevi is explored, and an algorithm for their assessment is suggested.
- Even with giant congenital nevi, most patients will not develop melanoma.
- Surveillance is a reasonable option, especially in those in whom surgery is likely to result in poor functional or aesthetic outcomes.

CLINICAL PRESENTATION

Key points

- **Congenital nevi appear at birth or shortly thereafter, changing in appearance over time**
- **They typically occur on the trunk and extremities, and can be quite disfiguring**

Congenital nevi vary in appearance with age. At birth they are often flat and tan, resembling an irregular café au lait spot.[2] The lesions may change during the first few years of life and vary greatly from patient to patient. One common change is the appearance of flat or slightly elevated, small, dark brown macules or papules, respectively, within the parent lesion; this change may remain static into adult life. Compared to benign acquired nevi, CMN are often larger and contain a mottled heterogeneous morphology. Most lesions become elevated, forming plaques. The color may become a shade of dark brown, with the formation of terminal hairs within the plaque. Verrucous changes may be seen in older CMN. Some studies suggest that about 17% of nevi may lighten with age.[3,4]

In 1 series, the distribution of CMN were as follows: 38% on the trunk, 38% on the legs and arms, 14% on the head and neck, and 10% on the feet and hands.[2] Others have also reported similar rates of distribution.[5] About 3% of patients have multiple

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Abbreviations used:

CMN:	congenital melanocytic nevi
CVG:	cutis verticis gyrata
GCMN:	giant congenital melanocytic nevi
HGF/SF:	hepatocyte growth factor–scatter factor
MM:	malignant melanoma
NCM:	neurocutaneous melanosis
PAS:	projected adult size
PN:	proliferative nodule
SEER:	Surveillance, Epidemiology and End Results
TSC:	tethered spinal cord

CMN. In terms of color, nearly all CMN have brown as their primary color, although shades of black, grey, and blue also occur.[2] Seventy-five percent have overlying hypertrichosis with darkly pigmented terminal hairs or, less commonly, with lanugo hairs. Most nonhairy nevi are <5 cm in diameter.[4] Interestingly, a study by Walton et al[6] found that it is not always possible to clinically diagnose CMN by gross appearance early in life. Of 34 pigmented lesions from which biopsy specimens were obtained, only 11 proved to be melanocytic nevi.[6] The others were identified as lentigo (4), café au lait (5), fibrosis and increased capillaries (8), toxic erythema of newborn (2), Mongolian spot (1), nevus sebaceous (1), leiomyoma (1), no identifiable disease (1).[6]

CMN vary in size from small to very large or "giant." Giant CMN (GCMN) have been described at least as far back as 1897,[7] as indicated by Reed.[8] Terms such as "bathing trunk," "vest like," and other garment names have been used to describe their distribution (Fig 1). These GCMN are commonly associated with benign melanocytic growths within the substance of the lesion, termed "proliferative nodules" (PNs).These may be clinically and pathologically confused with MM.[9-12]

In addition to proliferative nodules, GCMN are often associated with "satellite nevi."[13] These are smaller CMN that are present at birth or arise months to years later.[14]

NOMENCLATURE AND CLASSIFICATION

Key point

- **Congenital nevi are divided into small (<1.5 cm), medium (1.5-19.9 cm) and large (≥20 cm)**

A relatively common system for classifying nevi has been to group them into 3 groups: small, medium, and large. Small CMN are those <1.5 cm; medium CMN are 1.5 to 19.9 cm; large CMN are those ≥20 cm in projected adult size (PAS; Table I).[15]

Nomenclature regarding what constitutes a "large" CMN compared to a GCMN has been inconsistent. Some have defined GCMN as those with a PAS of >20 cm[15-17]; others have used varying body surface area measurements or other definitions.[18-22] From this point on, we will use the term GCMN to be synonymous to nevi measuring ≥20 cm because many authorities currently favor this definition.[17] Regardless of how large lesions are defined, many have been found to be associated with satellite CMN, MM, and neurocutaneous melanosis. These associations will be discussed below (Tables II and III).

EPIDEMIOLOGY

Key points

- **The prevalence of CMN varies depending on the study**
- **GCMN are uncommon**

The estimated prevalence of CMN varies widely depending on the study, ranging from 0.5% to 31.7%.[6,23-31] Most are <3 to 4 cm in diameter. Larger ones are less common. GCMN have an estimated incidence of 1 in 20,000 to 500,000 live births.[32,33] Females appear to have a higher prevalence than males in most studies, with a female to male ratio of around 3:2.[3,31,34-36] Other associations are poorly defined.[32]

NONMALIGNANT ASSOCIATIONS

Key point

- **Many associations with congenital nevi have been described, but the most well described are café au lait spots and mucosal nevi**

CMN have various benign associations.[8,37,38] A study by Sigg et al[37] found that 41.7% of patients with CMN also had café au lait spots, a finding that was supported by others.[3] This prompted inquiries of an association with neurofibromatosis. Most cases of GCMN are not linked to neurofibromatosis, but up to 5% of patients with neurofibromatosis have been noted to have GCMN.[39-41]

Other lesions associated with GCMN include mucosal nevi (30%),[42] benign nodules (19%), and plexiform-like overgrowths (6%). Nevi growing on the scalp may be cerebriform in nature, simulating cutis verticis gyrata (CVG).[42,43] Orkin et al[44,45] have estimated that 12.5% of patients with CVG are caused by CMN. Like other forms of GCMN, these have been associated with MM.[46]

Other nonmalignant lesions associated with GCMN include fascicular schwannoma, lipoma, lymphangioma, capillary hemangioma, fibroepithelial polyp, café au lait spots, ectopic mongolian spot,

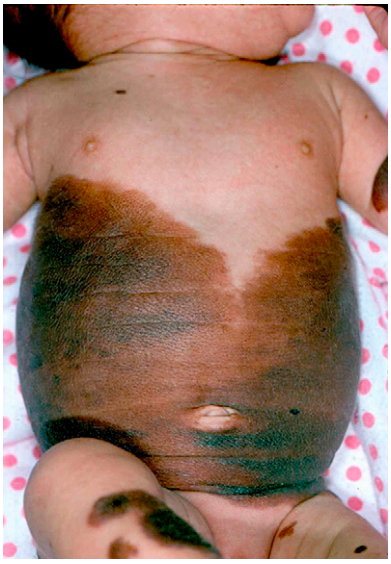

Fig 1. Circumferential garment nevus and satellite nevi in a neonate. (Photograph courtesy of Thomas Stevenson, MD, Division of Plastic Surgery, UC Davis Medical Center, Sacramento, CA.)

Table I. Estimated size of nevus at birth necessary to reach 20 cm in full grown adult

Location of congenital melanocytic nevi	Diameter at birth (cm)
Head	12
Hands, feet, torso, forearms, arms, and buttocks	7
Thighs	5.8
Legs	6

Adapted from Marghoob et al.[86]

atopic dermatitis, vitiligo, neurilemmomas, perinevic leukoderma, and cartilaginous hamartomas.[8,42] Extracutaneous associations include limb hypertrophy (22.5%), electroencephalography abnormalities (20%), cryptorchidism (1%), and central nervous system symptoms (1%).

INHERITANCE

Key point

- **There may be a genetic component to congenital nevi, but data are inconsistent**

Discordant identical twins have been reported, supporting the sporadic nature of CMN.[47-49] However, familial clustering has also been noted.[50] Three of the 60 subjects in a study by Kinsler et al[4] were noted to have relatives who had CMN of similar size, shape, and location. de Wijn et al[50] have reported 2 cases of familial GCMN.[50] They proposed a polygenic paradominant inheritance pattern as an explanation.

ETIOPATHOGENESIS

Key points

- **Nevus cells originate from neural crest melanocytes**
- **Congenital nevi have been found to harbor N-Ras mutations**

Nevus cells are derived from neural crest melanocytes.[51] Murine experiments have shown that melanocytes migrate through the dorsolateral pathway between dermatomes to the overlying ectoderm.[52,53] Migration stops when the melanocytes reach the epidermis and the developing hair follicles, to which they eventually provide melanin.[54,55]

Nevi are benign clonal proliferations of cells of melanocytic origin.[56] Many CMN have been found to harbor N-Ras mutations.[57,58] This differs from acquired nevi and melanomas arising on intermittently sun-exposed skin, which typically have B-RAF mutations.[57,59] In addition, some suggest a genotype–phenotype correlation for CMN size and mutation types.[58] These mutations presumably lead to an excessive number of daughter cells. The mutant daughter cells migrate to subcutaneous, dermal, and epidermal locations. These areas become populated with excess cells.[60] Most believe that congenital nevi migrate in an upward fashion.[61-63] Barnhill et al[64] have suggested that CMN may be the result of extravascular migration of neural crest cells.[64] Mouse studies support this supposition.[65]

Mouse models have been constructed that closely resemble human neurocutaneous melanosis.[66] These mice, which have alterations of the hepatocyte growth factor–scatter factor (HGF/SF)-Met signal transduction pathway, have extensive pigmented nevi and leptomeningeal melanosis. Mice that overexpress HGF/SF have high rates of MM, similar to humans with GCMN.[67,68]

PSYCHOSOCIAL CONSEQUENCES

Key point

- **Because of their appearance, CMN can cause significant psychological burden, especially in larger types**

Though the psychosocial consequences of small congenital nevi appear to be low,[69] GCMN nevi carry a considerable burden. Pers,[20] as indicated by Moss,[70] found that 53.9% of his patients with GCMN had significant psychological and social difficulties as a result of their lesions. In another study of 29 children with GCMN,[71] social problems were

Table II. Frequency, risks and associations of congenital melanocytic nevi

Nevus Size	Frequency	Risks	Associations
Small ($\leq$ 1.5 cm) and medium (1.5-19.9 cm)	0.5% to 31.7%[6, 23-31]	Melanoma: likely less than 1%[3, 5, 19, 103-107, 120] Neurocutaneous melanosis: no epidemiological studies; risk is likely extremely low	Café au lait macule: can co-occur in 40.7%[37] Pineal germinoma: 1 report in a patient with multiple small and medium CMN[182]
Large ($\geq$ 20 cm)	1:20,000 to1:500,000[32, 33]	Melanoma: wide range due to heterogeneity and rarity of large CMN, but likely less than 5%.[31-33, 36, 42, 106, 107, 113, 114, 120, 127] Neurocutaneous melanosis: ranges from 2.5-45%;[36, 113, 127, 139, 143, 164-166] risk varies upon certain factors (see "Risk of neuromelanosis with CMN" section)	Rhabdomyosarcoma: reports[94-98] Neurosarcoma: reports Malignant blue nevi: reports Neurofibromatosis: up to 5% may have large CMN[39-41] Neuroblastoma: reports[42] Mucosal nevi: 31% of large CMN patients[42] Benign nodules: 19% of large CMN patients[42] Cutis verticis gyrata: reports[43] Plexiform-like overgrowths: 6% of large CMN patients[42] Schwannoma and malignant schwannoma: reports[183, 184] Lipoma: reports[185-187] Limb atrophy/hypertrophy: reports[188, 189] Cartilaginous hamartomas: reports Malignant peripheral nerve sheath tumor: reports[190] Vitiligo: reports[187, 190-193] Halo nevi: reports[191, 194] Smooth muscle hamartoma: reports[195] Shokeir syndrome: 1 report[196]

CMN, Congenital melanocytic nevi.

Table III. Recent studies of frequency of melanoma in large congenital melanocytic nevi

Author	No. with melanoma (%)	No. cutaneous vs extra-cutaneous vs metastatic with unknown primary melanoma	Mean F/U time
Ruiz-Maldonado et al, 1992[42]	3/80 (3.75%)	3 vs 0	4.7 y
DeDavid et al, 1997[85]*	6/117 (5.1%)	4 vs 1 vs 1	NM
Bittencourt et al, 2000[36]	3/160 (1.9%)	0 vs 3	5.5 y
Berg and Lindelof, 2003[106]	0/146 (0%)	0 vs NM vs NM	NM
Ka et al, 2005[114]	0/379 (0%)	0 vs NM	NM
Hale et al, 2005[113]	10/205 (4.95)	6 vs 3 vs 1	NM
Bett, 2005[31]	17/1008 (1.7%)	15 vs 1 vs 1	5.6 y
Zaal et al, 2005[107]	4/320 (1.25%)	4 vs NM vs NM	NM
Kinsler et al, 2008[128]	2/120 (1.7%)	1 vs 0 vs 1	8.35 y

This table does not include all studies examining frequency of melanoma in large CMN, but rather more recent studies. Of note, studies by DeDavid et al,[85] Bittencourt et al,[36] and Hale et al[113] used the same database at different times, all employing different study techniques.
F/U, follow up; *NM*, not mentioned.
*Only patients from database are included.

found in 30% of patients and behavioral and emotional problems in 25.9%. Interestingly, problems were not associated with nevus visibility. Sixty-nine percent of mothers indicated they found it awful to have a child born with GCMN. A survey of 192 patients with CMN found that 8% of respondents reported taunting as a result of their nevus and changed their social behavior as a result.[72]

DERMATOSCOPY IN PATIENTS WITH CMN

Key point

- **Various dermatoscopic features for CMN include target network, globules, and perifollicular hypopigmentation**

A large Italian study has helped elucidate dermatoscopic findings that are more prevalent in CMN than in acquired nevi.[73] In comparing small and medium CMN to acquired nevi, observers noted that the following structures helped to discriminate CMN: target network, small globules, vessels, and follicles (Fig 2).[73] In addition, discriminant analysis enabled the distinction between CMN and common nevi with a sensitivity of 82.5% and a specificity of 64%. Other dermatoscopic findings that may be useful in identifying CMN include the focal thickening of network lines, globules in general, skin furrow and/or perifollicular hypopigmentation, and satellite areas.[73,74] A limitation of dermatoscopy is in distinguishing early melanoma from proliferative nodules within CMN. Future studies will hopefully elucidate clues to distinguish these 2 entities.

HISTOLOGY

Key points

- **There are no absolutely specific histologic findings in congenital nevi**
- **Findings that support the diagnosis include a presence of deep nevus cells, particularly within adnexal structures, vessel walls, eccrine glands, or perineurium**
- **Proliferative nodules, which are benign, may develop within congenital nevi and be confused with melanoma**

Mark et al[2] suggested the criteria for histologic diagnosis of CMN in 1973. Included were the presence of nevus cells in the lower two-thirds of the reticular dermis or in the subcutis, dispersal of the deep nevus cells between collagen bundles singly or in linear array, and the presence of nevus cells inside the epithelium of adnexal structures, such as hair follicles, perineurium, or vessel walls (Fig 3). However, other authors later published findings showing that smaller congenital nevi often do not adhere to the Mark et al criteria.[6] In their 1995 study, Barnhill and Fleischli[75] found that the depth and pattern of congenital nevus cells was correlated directly with the size of the nevus. Other studies have shown that acquired nevi may exhibit the same features as congenital ones.[76-80] The most specific findings to help identify CMN according to Cribier et al[76] are the presence of melanocytes in eccrine glands or connective tissue septae. They suggested that CMN could not reliably be identified histologically with the exception of GCMN, which can be differentiated by the presence of massive numbers of nevus cells in the reticular dermis and subcutis. However, even this criterion was not completely specific.

Some studies have shown there may be differences in histology depending on the age of the patient at the time that the biopsy specimen is obtained. Kuehnl-Petzoldt et al[80] looked at CMN

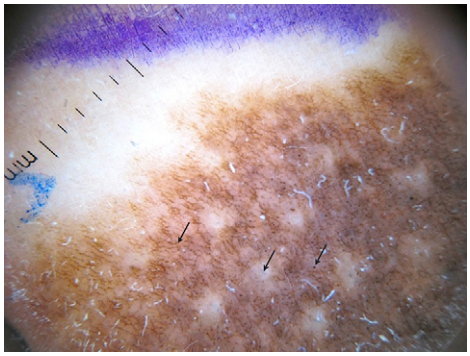

Fig 2. Dermatoscopic image of congenital melanocytic nevus. *Arrows* point to reticular network (*left*), perifollicular hypopigmentation (*center*), and globules contained within empty spaces in the network ("target globules," *right*), features that are reportedly suggestive of congenital melanocytic nevi.

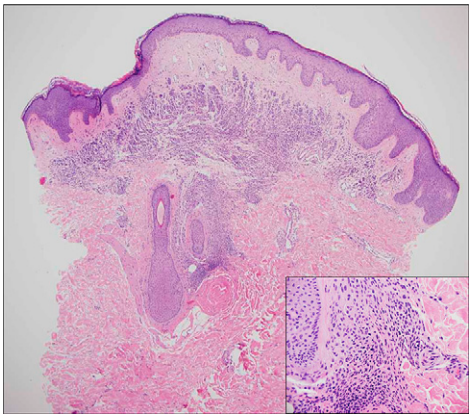

Fig 3. Histologic image of typical congenital melanocytic nevi. Nevus cells are interspersed around hair follicle epithelium and other adnexal structures. (Photograph courtesy of Maxwell A. Fung, MD, Department of Dermatology, UC Davis Medical Center, Sacramento, CA.)

from 14 children <1 year of age and found that like CMN from older patients, there were 2 populations of cells: large superficial pigmented cells and small amelanotic deeper cells.[80] They found in biopsy specimens obtained from older patients that the superficial cell population increases in number while the deeper one stays the same. Other authors have suggested that earlier in life, pigmented nevus cells are primarily restricted to the papillary dermis, but become deeper with increasing age.[6,70,81] However, subsequent studies contradict this assertion, showing that the histologic pattern does not change with advancing age.[2,82,83]

Regarding cellular atypia in CMN, Rhodes et al[77] found 9% of 69 consecutive CMN excised in early childhood to adolescence exhibited atypical melanocytes, similar in number to a group of acquired nevi excised during the same period.[77] Barnhill and Fleischli[75] found a higher incidence of atypia (30%) in their series of 87 CMN, but severe atypia was found in only 2 instances, 1 of which was only focally atypical.[75] CMN have also been associated with benign melanocytic tumors that may arise within them during early childhood.[84-86] Their sizes range widely, and they may exhibit rapid growth with resultant ulceration. However, they frequently stabilize or regress after a period of proliferation.[84,87] These benign secondary proliferations or PNs are readily confused with MM, especially those from patients 1 year of age or younger.[64] Distinguishing features that help differentiate PNs from MMs are the presence of maturation and the lack of atypia or mitotic figures.[11,64,84,87] Others state the MM cells are sharply demarcated from adjacent CMN cells relative to PN.[12] Immunohistochemistry with various antibodies and comparative genomic hybridization have also been proposed as potential methods for discerning PN from MM.[88,89] Despite the worrisome clinical and histologic findings of PN, most laboratory investigations seem to support their benignity.[11,64,84,90]

ASSOCIATED MALIGNANCIES

Key point

- **Aside from melanoma, CMN may be associated with other malignancies**

Reported risks of MM associated with CMN have ranged over the years from 1.1% to as high as 45%, and will be discussed at length below (Fig 4).[8,16,42,83,91-93] At least 5 cases of rhabdomyosarcoma arising within CMN have also been reported,[94-98] all in nevi measuring >12 cm in diameter. Other associated tumors include neurosarcoma, undifferentiated neural tumors, and malignant blue nevi.[8,21,42,93]

RISK OF MELANOMA DEVELOPMENT IN CMN

Key points

- **The risk of melanoma in patients with CMN likely increases with the size of the nevus**
- **While there is evidence that melanomas tend to arise earlier in life in GCMN than in small ones, more data are necessary to fully support this hypothesis**
- **Satellite nevi may also be associated with higher risks of melanoma, but not all studies agree**
- **Melanomas are theorized to originate deep within large CMN and superficially within**

small or medium sized ones, but more data are necessary before drawing conclusions

- **Studies with smaller numbers of patients may have suffered from selection bias and overestimated the risk of melanoma**

Over the past few decades, several dogmas regarding the risk of MMs associated with CMN have arisen. Risks are said to vary by size, numbers of CMN, or even race. In addition, the age of onset and depth of origin of MM may differ from sporadic tumors. The basis for these beliefs will be explored further below.

Small and medium CMN

In 1982, Rhodes and Melski[99] published findings from a retrospective study of small CMN based upon historic and histologic criteria. They calculated the relative risk of cutaneous MM to be 20.9 (based upon history) and 3 to 10 (based on histologic findings), with a corresponding cumulative risk of 4.9% and a ranges of 0.8% to 2.6%, respectively. In a study of 190 patients with melanoma, 15 developed melanomas within small congenital nevi; the average age of melanoma development among these patients was 41.04 years, no cases developed before puberty, and all 15 melanomas were of the superficial spreading type.[100] Aggregated data from several studies have estimated that 19% to 21% of all melanomas are associated with small CMN.[101,102] However, most studies show an incidence rate of melanoma in small and medium CMN of <1%.[3,5,19,103-107] This compares with a general lifetime risk of MM in the United States of 1.97%.[108]

Concerning medium-sized CMN, a prospective study of 230 (1.5-19.9 cm) CMN with an average follow-up of 6.7 years to an average age of 25.5 years found that no MM developed in any of the lesions.[104] However, this study, like others of its kind, may not have had sufficient power from which to draw conclusions.[109]

A large retrospective study of 3929 CMN that segregated nevi into those less than or greater than 20 cm in diameter found that 15 (of which 11 were <20 cm) developed melanoma after a median follow-up time of 4.7 years (19,253 person-years).[107] The incidence rate of melanoma was significantly greater than expected based on population rates, and female CMN patients were more likely than their male counterparts to develop melanoma.

GCMN

Many studies have been conducted on the risk of melanoma associated with GCMN. Estimates have varied markedly (0-50%).[16,19,31,36,42,85,91,110-115]

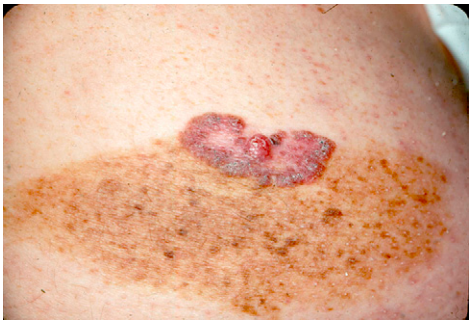

Fig 4. Malignant melanoma arising from a medium-sized congenital melanocytic nevus. (Photograph courtesy of Peter J. Lynch, MD, Department of Dermatology, UC Davis Medical Center, Sacramento, CA.)

Compiling results from several studies (before 1994) of melanoma in children, Williams and Pennella[101] found that GCMN-associated melanomas accounted for <3% of pediatric melanomas. Based on previous data, the authors estimated the lifetime melanoma risk associated with GCMN to be between 5% and 15%. This risk level has been the commonly accepted range for some time, but some researchers have raised concerns regarding the methodologies upon which these estimates are based.[116-118]

In general, more weight may be given to conclusions based on the results of metaanalyses. A 2003 review of 8 studies (432 GCMN patients) found that 12 patients (2.8%) developed melanoma during the reported follow-up periods.[119] Of the 12 patients who developed melanoma, 10 developed it within their GCMN, while data were unavailable/unknown for the other 2 patients. Comparing the incidence of MM in the study populations to the Surveillance, Epidemiology and End Results (SEER) population-based database, they calculated a standardized morbidity ratio of 2599.

In 2006, Krengel et al[120] analyzed 14 studies with a total 6571 CMN patients who were followed for a mean of 3.4 to 23.7 years and found that 46 (0.7%) developed 49 melanomas (mean age at diagnosis, 15.5 years; median age, 7 years). The authors found a markedly increased relative risk (465) of developing melanoma during childhood and adolescence. The early onset of MM echoes the results of many previous studies[86] and has been the basis of recommendations for early surgical excision of CMN. However, this might merely reflect the fact that most patients in these studies have been young.[120] More data on this topic are necessary before firm conclusions can be reached. They also found that melanomas developed within 39 of 1539 CMN >20 cm (2.5%) and 20 of 636 (3.1%) CMN >40 cm. Regarding the location of the MMs, 33 (67%) were

within a CMN, 7 (14%) were metastatic MMs of unknown primaries, and 4 (8%) arose in extracutaneous sites. In only 1 analyzed study were the cutaneous MMs located outside the CMN.

Studies with smaller numbers of patients had statistically significant higher estimates of risks for MM ($P < .0001$), suggesting that selection bias may be responsible for the higher rates of MM that previously shaped the debate of risks associated with CMN.[120] Interestingly, Krengel et al[120] also noted that studies with longer follow-up times did not have higher ratios of melanomas, which may indicate that risk of MM may not be linearly related to time.

Depth of melanoma origin

Concerning the depth of origin of CMN-associated MM, many believe that MM arising within small to medium CMN are more likely to originate superficially, where those arising in GCMN arise from a greater depth.[13] However, data on this hypothesis appears limited at this time.[8,121-123] Prospective data are completely lacking, and there are no large series that compare origins of melanomas among nevi of different sizes. In addition, there is currently no reliable way to differentiate between primary dermal melanomas and metastatic melanomas.[124]

Location

Based on data presented by Bett et al,[31] it is suggested that the risk of MM is greater in those with truncal GCMN than in those with nevi on the head or extremities.[125] In their study, the absolute risk of MM developing in patients with GCMN located on the trunk was 2.9% (15/525), and 0.3% (1/336) for those on the head and limb. However, the percentage of patients with a totally removed nevus was higher in those with head or extremity nevi (39%) compared with those with garment nevi (16%). More data on this topic are necessary before firm conclusions can be drawn.

Age and size

Some studies suggest that melanomas associated with small and medium CMN occur later in life than those associated with GCMN (the fourth and fifth decades of life versus the first and second decades, respectively).[86,102,120,126] However, not all studies note this difference,[107] and the age of patients enrolled in studies looking at the incidence of MM in GCMN was very young, introducing the possibility of selection bias. There are no prospective data comparing age and incidence of melanoma in small versus GCMN; conclusions on this issue should be withheld until more evidence becomes available.

Multiple CMN and satellite nevi

Satellite nevi are CMN that are relatively smaller lesions associated with a GCMN. Multiple CMN are those that lack a GCMN. Data regarding patients with multiple CMN are too limited to draw conclusions.[31,127] The risk of MM may be higher in those with satellite nevi,[113,127] although statistical correlation has not been shown in all studies.[5] While the presence of satellite nevi may be a risk factor for MM, melanomas only rarely arise within satellite nevi.[31]

Early onset nevi

Some investigators suggest that MM risk is associated not with just CMN, but all nevi that arise at <2 years of age.[126] Data on this topic are currently very limited.

Race

People of African and Japanese decent appear to have higher incidences of CMN than Hispanics or whites.[116,127-129] However, like their incidence of MM in general,[130] their chances of a MM arising within a CMN appears very low.[116] Those with darker skin types disproportionally develop MM in nonglabrous skin,[131] where CMN are not common, supporting the notion that CMN are not major risk factors for MM in this group of patients. However, smaller lesions likely make up the majority of CMN seen in these studies; as in patients with lighter skin types, multiple reports exist of patients with MM associated with GCMN.[132-134]

NEUROMELANOSIS AND NEUROCUTANEOUS MELANOSIS

- Neurocutaneous melanosis describes neuromelanosis associated with a congenital nevus
- It can affect various locations in the central nervous system, causing diverse clinical findings, including death

Neuromelanosis (cerebral melanosis), which relates to a congenital error in the morphogenesis of the embryonal ectoderm,[135] describes melanocytic proliferation (benign or malignant, and nodular or diffuse) within the leptomeninges and brain parenchyma.[101,136,137] Neurocutaneous melanosis (NCM) is neuromelanosis associated with CMN.[136-141]

NCM can affect the amygdala, cerebrum, cerebellum, pons, medulla, and spinal cord.[141-143] Those that become symptomatic usually do so before or around 2 years of age,[139,144-147] although symptoms can occur later in life[148] and are associated with increased intracranial pressure (eg, headache, lethargy, recurrent vomiting, and photophobia),[137,140,142,145,149] hydrocephalus,[145,147,150] seizures,[136,137,147,151,152]

cranial nerve palsies (eg, difficulty with vision),[136,137,151] sensorimotor deficits (focal and generalized),[135,150] bowel and bladder dysfunction, and/or developmental delay.[135,150] Symptomatic patients have a poor prognosis with a high mortality rate (secondary to CNS melanoma or mechanical obstruction caused by nonmalignant melanocytes).[136,139,145,153,154] In addition, the Dandy–Walker malformation has been described with NCM and suggests an even more worrisome prognosis.[155-160] Other CNS abnormalities have been reported, including lissencephaly and corpus callosum agenesis.[161] The leptomeningeal spread of a tumor indicates a more diffuse mesenchymal dysplasia and a poorer prognosis.

RISK OF NEUROMELANOSIS WITH CMN

- There is a well-studied association between neuromelanosis and GCMN
- Patients with neuromelanosis may be symptomatic or asymptomatic
- Magnetic resonance imaging is generally the imaging modality of choice, but it neither rules out nor predicts those who will ultimately develop symptoms
- Other than preventing immediate brain stem herniation, treatments can do little to alter the course of symptomatic neuromelanosis

The existing data regarding the risk of neuromelanosis associated with CMN are imperfect but suggest a convincing link. There seem to be 2 peak ages for presentation of complications from NCM. The first peak, which represents the majority of patients, occurs before 3 years of age. The other peak occurs during the second to third decades of life.[143,162,163]

The incidence of NCM has been estimated to range from 2.5% to 45% in patients with GCMN.[36,113,127,139,143,164-166] Risks regarding smaller lesions are not as well defined, but appear to be much lower.[127,156,163] Suggested risk factors for NCM have been reported to be the presence of a GCMN, male sex, satellite nevi or multiple CMN, and head, neck, or posterior midline location (not supported by every study).[127,163,167,168]

Multiple imaging modalities can be used to assess the presence of neuromelanosis,[136,140,141,144,151] but magnetic resonance imaging (MRI) is now the imaging technology of choice (Fig 5).[145,147,155,169] Some suggest that MRI should ideally be performed within the first 4 months of age, before normal brain myelination, which may obscure melanin deposits.[13,143] Others note that the melanotic signal does not necessarily decrease with repeated studies[127]; this issue remains unsettled. Ultrasound is an option for patients in whom MRI is undesirable.[170]

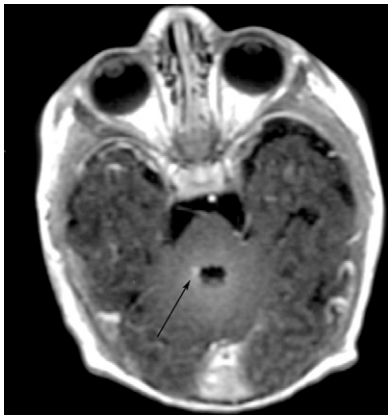

Fig 5. Four-day-old male with neurocutaneous melanosis. Axial T_1-weighted magnetic resonance image at the level of the brachium pontis revealed a nodular area of abnormal T_1 hyperintensity immediately to the right of the fourth ventricle (*arrow*). Contrast enhanced imaging revealed no abnormal enhancement. Given the patient's numerous melanotic cutaneous lesions this finding was considered diagnostic of neurocutaneous melanosis. (Photograph courtesy of Christopher G. Filippi, Department of Radiology, University of Vermont, Burlington, VT.)

Interestingly, not everyone with findings of NCM via imaging studies will develop symptoms (range, 10%-68%).[36,113,127,143,150] The large range of reported findings is likely relates to the small numbers of subjects studied.

It is clear that asymptomatic and symptomatic NCM portend very different outcomes. Many patients with symptomatic NCM die, with more than half of fatalities occurring within 3 years of diagnosis.[139,163] Those without symptoms appear to have few problems.[143] The need for MRI in asymptomatic children remains difficult to assess. In the past, some had suggested its use as a screening procedure. Others argue against this approach, given that there are no proven therapies that appreciably prolong life in patients.[143,149,171] Although the placement of a ventriculoperitoneal shunt can be considered, the threshold of most neurosurgeons for treating asymptomatic hydrocephalus appears to be high.[172] It is also important to note that a negative MRI does not assure normal neurologic function.[127,173]

Other than screening for neuromelanosis, MRI has been advocated to rule out tethered spinal cord (TSC).[143] Like pits, lipomas, and vascular malformations, GCMN have been associated with TSC when located over the midline lumbosacral area. In Foster et al's series[143] of 11 patients with lumbosacral GCMN, 1 was identified with a TSC. This condition

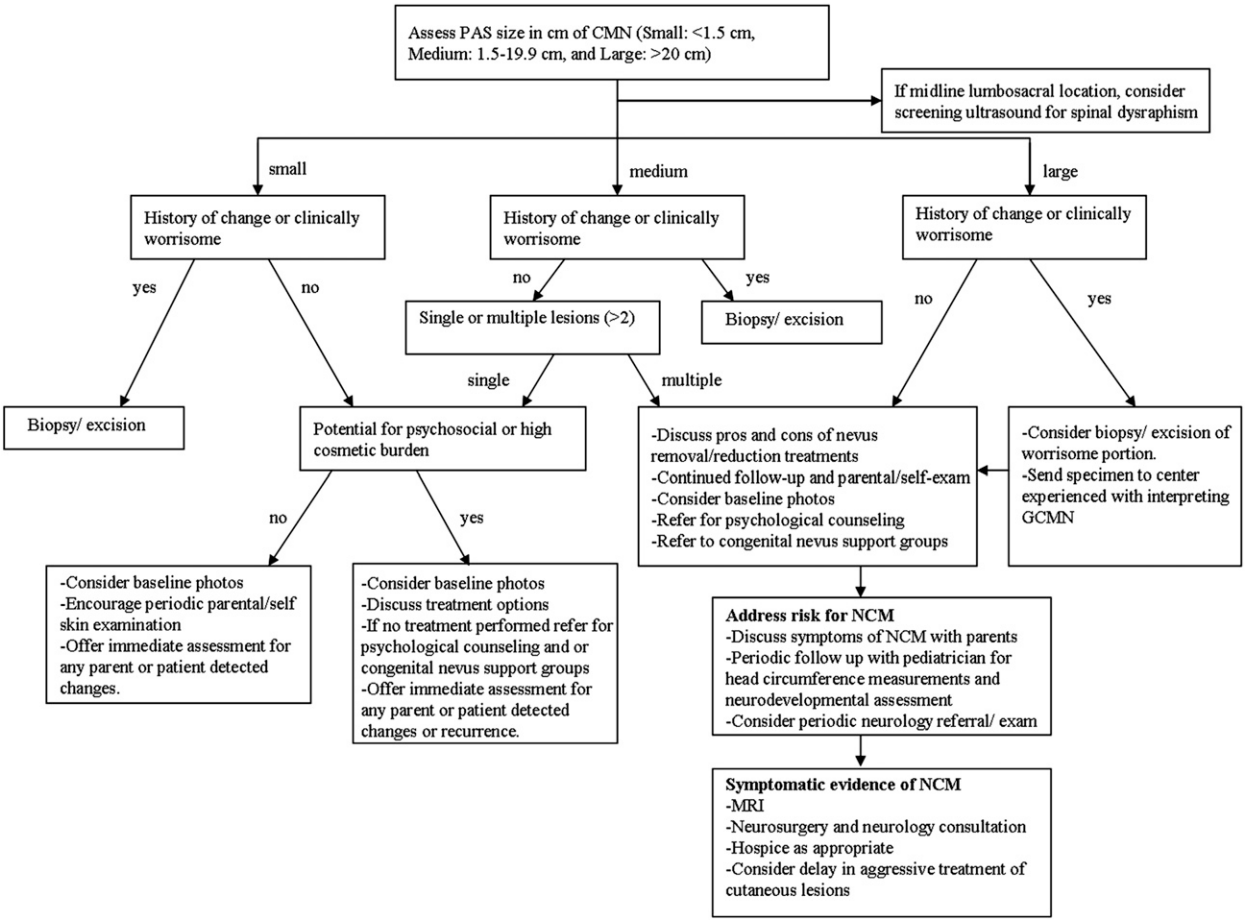

Fig 6. Diagnostic algorithm for assessing congenital melanocytic nevi based on size and other factors. Given that this approach has not been validated in a prospective study, these recommendations should be considered to be based upon level IV evidence, which includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both. *CMN*, Congenital melanocytic nevi; *NCM*, neurocutaneous melanosis.

is potentially treatable with surgery, and the resulting complications are often irreversible once they become symptomatic. With the exception of a case report, there do not appear to be any further data on this topic.[174]

APPROACH TO ASSESSMENT OF CMN

Key points

- **There is no validated approach to assessing congenital nevi**
- **We suggest an approach taking into account size, symptoms, and psychosocial factors**

There is currently no validated approach to the assessment of CMN, and physicians must use their best judgment based on imperfect data. Our own suggestion is shown in Fig 6. There is a large body of evidence that supports the relationship of GCMN with risks of MM and NCM. Satellite nevi, although less well studied, may also be associated. Either of these phenotypes might indicate the need for close follow-up. Given that the risk of MM or NCM with CMN is relatively low for lesions <20 cm,[120] routine follow-up for lesions of small size seems unnecessary. However, we do not encourage rigid cutoff criteria for follow-up, because the difference in risk between a lesion approaching 20 cm and one >20 cm are likely to be small.

Although some authorities[127,164] advocate routine MRI for asymptomatic patients with high-risk CMN, we do not. Imaging does not predict which patients will become symptomatic nor identify those who might benefit from a proven therapy. In addition, MRI often requires general anesthesia for young children. The use of general anesthesia for elective procedures in this age group has recently been called into question. In addition to the increased risk of cardiac arrest in children under 1 year of age,[175,176] there is evidence that general anesthesia might adversely affect neurologic, cognitive, and social

development.[177] However, close follow-up with a pediatrician for head circumference and neurodevelopmental assessment (to screen for NCM) and a dermatologist to monitor for signs of MM is a low-cost way to address high-risk patients. Patients who develop neurologic symptoms (eg, seizures, behavioral disturbances, hemiplegia, headache, vomiting, cranial nerve palsies, papilledema, lethargy, bulging fontanelles, sensorimotor deficits, bowel and bladder problems, or Dandy–Walker syndrome) or fail to meet developmental guidelines should be urgently evaluated by a specialist and with imaging if indicated.[135,154,166,178-182]

The risk of TSC with lumbosacral CMN remains to be defined. Unlike NCM, an effective treatment exists and delayed diagnosis can result in permanent sequelae. Ultrasound, which is noninvasive and can be performed in a child who is awake, can also be used to establish the diagnosis and seems a worthwhile endeavor until more data are available on this issue.

Depending on their location, even small CMN can have significant psychosocial consequences. Referral to congenital nevus support groups (eg, http://www.nevusnetwork.org/) and psychological counseling should be considered where applicable. Treatment of CMN will be discussed in part II of this continuing medical education article.

CONCLUSION

CMN are a diverse group of lesions whose significance ranges from trivial to life threatening when associated with MM or NCM. Accurate calculation of the true lifetime risks of MM for these lesions is difficult with the current data. However, the risk, which appears to be lower than has been espoused in the past, is most significant for GCMN. According to some studies, satellite nevi may also incur risks similar to those with GCMN. Physicians should consider routine neurodevelopmental assessments along with skin examinations for these high-risk patients.

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