

## CONTROVERSIES IN DERMATOLOGY

# Controversial Issues in Congenital Nevi

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**Abstract.** Congenital melanocytic nevi are very common lesions that nevertheless pose many controversial questions. A systematic review of the literature suggests that the risk of developing melanoma on giant congenital melanocytic nevi (GCMN) is lower than previously thought given that, in the most recent series of GCMN, only 2 % of patients developed melanoma and most did so before the age of 5 years. Therefore, prophylactic surgery should be considered on an individual basis according to the degree of clinical suspicion of melanoma and the esthetic and functional consequences. In extensive reviews of series of biopsies of melanoma, small congenital melanocytic nevi have been associated with 7% to 8% of cases. Many authors believe that these might represent a significant risk of malignant conversion from 10 years onwards and so recommend regular control visits during infancy and prophylactic exeresis in puberty.

**Key words:** congenital melanocytic nevus, neurocutaneous melanosis, melanoma.

## CONTROVERSIAS EN EL NEVUS CONGÉNITO

**Resumen.** Los nevos melanocíticos congénitos son lesiones muy frecuentes, pero que todavía plantean muchas cuestiones que son motivo de controversia. Una revisión sistemática de la literatura sugiere que el riesgo de desarrollar melanoma sobre nevos melanocíticos congénitos gigantes (NMCG) es inferior al que se postuló históricamente. En las series de NMCG más recientes sólo un 2 % de pacientes desarrolló un melanoma y la mayoría lo hizo antes de los 5 años de edad. Por tanto, su tratamiento quirúrgico profiláctico debe ser individualizado en función de la sospecha clínica de melanoma y de las consecuencias estéticas y funcionales. En revisiones amplias de biopsias de melanoma se han encontrado NMC pequeños asociados en un 7-8 % de los casos. Muchos autores consideran que podrían tener un riesgo de malignización significativo a partir de la segunda década de vida, por lo que recomiendan la vigilancia periódica durante la infancia y la exéresis profiláctica en la pubertad.

**Palabras clave:** nevus melanocítico congénito, melanosis neurocutánea, melanoma.

## Introduction

In spite of the many articles that have been published about congenital nevi, many questions still remain unanswered. What is the real incidence of melanoma in giant congenital nevi? Is the risk of melanoma greater in small and medium-sized congenital nevi than in acquired melanocytic nevi? Which lesions should be resected?

Does surgical treatment completely eliminate all risk of malignancy? When is the best time to excise a lesion? Is it possible that superficial treatments that do not completely remove a lesion may alter its subsequent biological behavior and increase the risk of melanoma?

The importance of finding answers to these questions is that these answers would enable us to establish a consensus that would facilitate the therapeutic management of such lesions. In this article we present a systematic review of the literature in order to clarify some of these questions, and critically examine the conclusions, results, and recommendations published to date. In addition, we propose new studies that would further our understanding of the prognosis and biological significance of congenital nevi.

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## Review

### Definition of a Congenital Melanocytic Nevus

Congenital melanocytic nevi (CMN) are, by definition, lesions composed of pigmented cells that are produced during ontogenesis and are present at birth.<sup>1</sup> These lesions are now thought to be hamartomas derived from the neural crest, the result of postzygotic mutations that result in defective cell migration and/or differentiation.<sup>2</sup>

Histologically, they differ from acquired melanocytic nevi as follows:

1. They are generally larger.<sup>2-4</sup>
2. In young children the intraepidermal pattern of the lesion is usually lentiginous with the nevus cells forming a single-file array along the dermoepidermal junction.<sup>4,5</sup>
3. Congenital nevi have a dual melanocytic population<sup>6</sup> with a) an epithelioid component that adopts a junctional pattern, expands the adventitial dermis, and evolves towards maturation and involution, and b) a neuromesenchymal component with lymphocyte-like cells that infiltrate more deeply, extending into the lower two-thirds of the dermis and the subcutaneous cell tissue. These cells are dispersed among the loose collagen bundles or form a single-file array. They tend to be exocentric, angiocentric, and neurocentric, and do not display maturation or involution.<sup>2,4,5,7</sup>

However, since some lesions with these characteristics only become clinically visible after birth, it may be preferable to use the term “CMN pattern.”<sup>7,8</sup> Some authors have referred to this subgroup of nevi that only become apparent some time after birth as “tardive CMN”; such lesions are almost always visible before the infant reaches 2 years of age.<sup>2</sup>

Conversely, lesions called “early-onset nevi” may be present at birth but have the characteristics of an acquired nevus, justifying the use of the term “acquired pattern nevus.”

CMN are classified according to size using a number of arbitrary methods; these include surface area, relationship with other structures (such as the palm of the hand), largest diameter, and the difficulty of surgical resection.<sup>2</sup> The classification currently in use is the system proposed by Kopf<sup>9</sup>: small CMN (<1.5 cm), medium CMN (≥1.5 cm and ≤20 cm), and giant CMN (>20 cm).

In addition to these 3 types of CMN, there are also a number of special variants. The term “garment nevi” is traditionally used to refer to a giant congenital nevus on the trunk when the largest diameter is greater than 40 cm.<sup>1</sup> The divided nevus or kissing nevus affects opposing parts of the upper and lower eyelids in such

a way that it looks like a single lesion when the eye is closed. These CMN develop between the ninth and twentieth week of gestation when the eyelids are still fused.<sup>7</sup>

Although giant CMN are easily distinguished from other forms by their size, small congenital nevi may be very similar to acquired melanocytic nevi.<sup>2,3,7</sup> Furthermore, all the typical histologic characteristics may not always be found in small CMN.<sup>3,8</sup> In clinical terms, CMN are oval lesions with well-defined limits and a smooth, rugose, papular, verrucous, or cerebriform surface.<sup>7</sup> With age, thick dark hair appears, the nevi tend to darken, and nodules may develop on the surface of the lesion.<sup>7</sup>

CMN, especially the giant forms, have been associated with a number of different syndromes. Cases have been reported of Carney syndrome, epidermal nevus syndrome, type 1 neurofibromatosis, premature ageing syndrome, occult spinal dysraphism, scoliosis, atrophy, anatomic asymmetry, elephantiasis, and hypertrophy of the cranial bones.<sup>7,10-12</sup> Neurocutaneous melanosis or leptomeningeal melanocytosis is a rare congenital syndrome characterized by the association of a) a giant nevus (>20 cm in an adult, >9 cm on the scalp, or >6 cm on a child’s body) or more than 3 small CMN in association with meningeal melanosis or melanoma; b) no evidence of cutaneous melanoma (except in patients with histologically benign meningeal lesions); and c) no evidence of meningeal melanoma (except in patients with histologically benign cutaneous lesions).<sup>13</sup>

### Prevalence

The prevalence of CMN is difficult to estimate because of the lack of well-defined differences between small CMN and acquired nevi and because CMN present many different histologic patterns.<sup>2</sup> The prevalence of histologically confirmed CMN ranges from 0.64% to 2.7%.<sup>2</sup>

The incidence and prevalence for giant CMN are estimated to be 1 per 20 000 live births<sup>14</sup> and 0.005%, respectively.<sup>2</sup> The most common anatomical location is the trunk, followed by the limbs, and then the head and scalp.<sup>15,16</sup> CMN are often associated with multiple small satellite nevi (76%<sup>15</sup>–91%<sup>17</sup>).

### Risk of Developing Melanoma

Although in theory all CMN are susceptible to malignant change, the relationship between the size of the nevus and the risk of developing melanoma is still a matter of debate.

**Table 1.** Childhood Melanoma: Cases Associated with Melanocytic Nevi

| Author                               | Year | Number of MM | Age, y                 | CMN (%)    | Giant CMN (%) | Small and Medium-Sized CMN (%) | Follow-Up, mo          |
|--------------------------------------|------|--------------|------------------------|------------|---------------|--------------------------------|------------------------|
| Pratt et al <sup>120</sup>           | 1981 | 31           | ≤21; μ:14 (0.17-20.75) | 12 (38.7%) | ND            | ND                             | ND                     |
| Rao et al <sup>121</sup>             | 1990 | 33           | ≤20; μ:12 (0.3-20)     | 3 (9.1%)   | 3 (9.1%)      | 0 (0%)                         | ND                     |
| Mehregan et al <sup>122</sup>        | 1993 | 6            | ≤14; μ: 9.1 (2-13)     | 2 (33.3%)  | 2 (33.3%)     | 0 (0%)                         | ND                     |
| Tate et al <sup>123</sup>            | 1993 | 48           | ≤20                    | 5 (10.4%)  | 1 (2%)        | 4 (8.4%)                       | μ: 48 (1-210)          |
| Davidoff et al <sup>124</sup>        | 1994 | 85           | ≤18                    | 2 (2.4%)   | 2 (2.4%)      | 0 (0%)                         | ND                     |
| Spatz et al <sup>125</sup>           | 1996 | 60           | ≤16; μ: 10.4 (1-16)    | 4 (6%)     | ND            | ND                             | μ: 60; (0-324)         |
| Naasan et al <sup>126</sup>          | 1996 | 50           | ≤18                    | 4 (8%)     | 0 (0%)        | 4 (8%)                         | ND                     |
| Scalzo et al <sup>37</sup>           | 1997 | 22           | ≤15                    | ND         | ND            | 0 (0%)                         | ND                     |
| Saenz et al <sup>127</sup>           | 1999 | 40           | ≤18; μ: 15 (3 -17)     | 15 (37.5%) | 2 (5%)        | 13 (32.5%)                     | μ: 216 (24-576)        |
| Sander et al <sup>128</sup>          | 1999 | 126          | <20                    | 5 (4%)     | 0 (0%)        | 5 (4%)                         | (51-271)               |
| Gibbs et al <sup>129</sup>           | 2000 | 27           | ≤16                    | 3 (11.1%)  | 0 (0%)        | 3 (11.1%)                      | μ: 62 (5-108)          |
| Schmid-Wendtner et al <sup>130</sup> | 2002 | 36           | ≤18;μ: 16 (2-17)       | 8 (22.2%)  | 8 (22.2%)     | 0 (0%)                         | μ: 79.2                |
| Mones et al <sup>131</sup>           | 2003 | 11           | ≤10;μ: 5.2 (1-10)      | 0 (0%)     | 0 (0%)        | 0 (0%)                         | μ: 19.9 (2-37)         |
| De Sá et al <sup>132</sup>           | 2004 | 32           | ≤18;μ: 12.63 (0-18)    | 5 (15.6%)  | 5 (15.6%)     | 0 (0%) <sup>a</sup>            | μ: 43.14 (1.71-198.32) |
| Jafarian et al <sup>133</sup>        | 2005 | 13           | ≤17; (<10: 7, ≥ 10: 6) | 2 (15.4%)  | 0 (0%)        | 2 (15.4%)                      | μ: 26 (7-219)          |
| Ferrari et al <sup>134</sup>         | 2005 | 33           | ≤14;μ: 11 (3-14)       | 7 (21.2%)  | 0 (0%)        | 7 (21.2%)                      | μ: 122                 |
| Total                                |      | 653          |                        | 77 (11.8%) | 23 (3.52%)    | 38 (5.81%)                     |                        |

<sup>a</sup>In this study there were 9 children (28.1%) with small melanocytic nevi, but these lesions were not directly related to the melanoma. Abbreviations: CMN, congenital melanocytic nevus; MM, melanoma; μ, mean; ND, no data.

## Giant Congenital Nevi

Historically, the risk of developing melanoma in giant CMN has been overestimated to the extent that some authors have asserted that up to one-third of melanomas affecting prepubescent children originate within a giant nevus.<sup>18</sup> To ascertain the real percentage of melanomas arising in CMN during infancy we reviewed the principal case series of childhood melanomas published in the literature, a total of 653 cases (Table 1). A congenital nevus was present in only 11.8% of these patients, and in many of these cases this information had been obtained retrospectively from medical records and had not been confirmed histologically. Of these cases, 3.52% were associated with a giant nevus and 5.8% with a medium or small CMN (a ratio of 5 to 3).

The reason for this overestimation of the risk of giant CMN becoming malignant was probably a bias towards under recording of cases of giant CMN in which melanoma did not develop<sup>19,20</sup> and because many cases of giant CMN associated with atypical melanocytic proliferations were diagnosed erroneously as melanomas.<sup>21,22</sup>

There are 2 types of benign proliferation that can appear on CMN: proliferative nodules and hamartomatous lesions.<sup>22</sup> The biological behavior of proliferative nodules is benign,<sup>23</sup> especially in the case of nodules that appear during the neonatal period. There remains some debate, however, about whether patients with proliferative nodules have a higher risk of developing melanoma.<sup>7</sup>

From a clinical standpoint, 2 types of proliferative nodules have been described:<sup>22</sup>

1. Small proliferative nodules (<1 cm), which are usually present at birth but may appear at any time of life, especially during infancy. These lesions are usually covered by intact epidermis and vary in color from pale pink to dark brown.<sup>22</sup> Histologically, they are benign proliferative or expansile nodules that are sharply demarcated, hypercellular, and composed of large epithelioid cells.<sup>22</sup> What distinguishes such lesions from melanoma is that they have a low mitotic index and no atypical cells, inflammatory infiltrate, or necrosis.<sup>7,22,24</sup> Unlike what occurs in the case of melanoma, the transition between these nodules and the normal cells of the congenital nevus is gradual rather than abrupt.<sup>22,25</sup>
2. Large nodular proliferations, (>1 cm) which are deeply pigmented, initially grow very rapidly, and occasionally ulcerate.<sup>22</sup> Histologically, these are tumoral dermal nodules and subcutaneous nodules.<sup>22</sup> They may be composed of monomorphous melanocytes with epithelioid or spindle cell morphology<sup>22</sup> or balloon cells.<sup>26</sup> Occasionally, they show neural or mesenchymal differentiation, and hamartomatous elements may be present, including adipose cells and cartilage.<sup>22</sup> These proliferations may have an elevated mitotic index but, unlike the case of melanoma, the mitoses are not atypical.<sup>22,27</sup> A differential diagnosis with malignant blue nevus or malignant epithelioid schwannoma must sometimes be established.<sup>7</sup> By contrast, true melanomas are usually composed of small cells with scant cytoplasm that resemble “blastic” tumors<sup>2</sup> and they present atypical mitosis.

In spite of their initially alarming appearance, with time these proliferative nodules regress spontaneously, their size and mitotic activity decline gradually, and they may even disappear entirely.<sup>25,28</sup>

Another focal change that can affect CMN during childhood is ulceration, which can occur in cases without any clinical or histologic evidence of malignancy.<sup>29</sup>

Differences in the criteria used in the different case series of melanomas arising on giant CMN preclude meta-analysis of the data,<sup>30</sup> and there are to date only 4 systematic reviews in the literature.<sup>1,20,30,31</sup> We have broadened the scope of these reviews by including all the main case series of giant CMN published in the literature to date (Table 2). Overall, 46% of the patients with giant CMN were under 10 years of age when melanoma was diagnosed (mean age 14.4 years). The risk of developing melanoma ranges from 0% to 10% in the different case series (mean 1.75%) and mortality was 35.2% during a mean follow-up of approximately 9.2 years.

Most of the studies did not specify the following information: the total number of CMN in the sample, length of follow-up period, or the number of cases of melanoma arising in small or medium CMN.<sup>30,32</sup> Neither was the

risk of developing melanoma calculated by age, sex, or the location of the nevi.<sup>32</sup> Other factors that complicate the interpretation of the results of these studies include the absence of any uniform criteria, arbitrariness in the definition of the size of the nevi, the bias introduced by the selection of high risk cases in tertiary level hospitals, the reduced potential for malignant degeneration after partial or complete resection of the lesion, the lack of prospective comparative studies, and the presence of atypical histologic findings during the neonatal period.<sup>15,19-21,30,32,33</sup>

Some authors have suggested that larger giant CMN<sup>34</sup> and nevi with more satellite lesions<sup>34</sup> are associated with an increased risk of malignancy. The authors of 1 study found that melanoma was less likely to develop in giant nevi that affected only the head or one limb.<sup>34</sup>

### Medium-Sized Congenital Nevi

In a retrospective study of 230 medium CMN, Sahin et al<sup>35</sup> detected 3 melanomas (1.3%). In another series of 239 patients with medium CMN,<sup>32</sup> no cases of melanoma were detected in 25 years of follow-up. On the basis of these results, some authors only recommend surgical resection in cases that are difficult to monitor because of the site of the lesion (scalp) or when substantial cosmetic changes occur or atypical clinical characteristics are detected.<sup>35</sup> However, other authors are of the opinion that it is impossible to draw any conclusions from the data obtained from these studies because the small size of the case series and the short follow-up.<sup>36</sup>

### Small Congenital Nevi

Some authors are of the opinion that the risk associated with small CMN is no greater than that associated with acquired melanocytic nevi. In a review of 22 children diagnosed with melanoma over a 30-year period, in no case did melanoma arise in association with a precursor lesion with a diameter of less than 5 cm.<sup>37</sup> A number of isolated cases of melanomas arising within small CMN in both children<sup>8,38,39</sup> and adults<sup>40,41</sup> have, however, been reported in the literature. In a review of 3922 CMN (146 of which were giant), only 1 patient (who had a 3 × 3 cm nevus) developed melanoma, which metastasized and was ultimately fatal.<sup>42</sup>

The question of whether prophylactic removal of these lesions is justified was first raised in 1980.<sup>43,44</sup> In 1984, it was established in a consensus conference that they could be managed by regular clinical follow-up and monitoring because malignant transformation was uncommon.<sup>45</sup> In 1982, Rhodes et al<sup>46</sup> undertook a retrospective histologic study of 234 melanomas and found evidence suggestive of associated CMN in 8% of these cases. In another group of 134 patients with melanoma, an association with a

**Table 2.** Proportion of Cases in Which Melanoma Originated Within Giant Congenital Nevi (GCMN) and Associated Mortality

| Authors   | Year       | No. of GCMN | No. of MM (% of GCMN)   | Age <sup>a</sup>   | Deaths (% of GCMN) | Mean Follow-Up, y      |
|---|------------|-------------|-------------------------|--|--------------------|------------------------|
| Greeley et al <sup>135</sup>  | 1965       | 56          | 6 (10.7%)               | 1 y, 1 y, 10 y, 10 y, 30 y, 38 y   | 3 (5.36%)          | NA                     |
| Lorentzen et al <sup>136</sup>  | 1977       | 151         | 3 (1.98%)               | 28 y, 38 y, 40 y   | 3 (1.99%)          | 23                     |
| Arons et al <sup>137</sup>  | 1983       | 46          | 0 (0%)                  | NA   | NA                 | ND (1-17)              |
| Zitelli <sup>106</sup>  | 1984       | 6           | 0 (0%)                  | NA   | NA                 | 1.25                   |
| Quaba and Wallace <sup>33</sup>   | 1986       | 39          | 2 (5.13%)               | 2 y, 6 y   | 2 (5.13%)          | 8.6                    |
| Hori et al <sup>138</sup>   | 1989       | 154         | 7 (4.54%)               | ND   | ?                  | ND                     |
| Ruiz-Maldonado et al <sup>10</sup>  | 1992 (P)   | 80          | 3 (3.75%)               | 8 mo, 2.3 y, and 14 y  | 3 (2.5%)           | 4.7 <sup>b</sup>       |
| Swedlow et al <sup>132</sup>  | 1995       | 33          | 2 (6.06%)               | 18 y, 20 y   | 2 (6.06%)          | 23.7                   |
| Dawson et al <sup>139</sup>   | 1996       | 133         | 0 (0%)                  | NA   | NA                 | 6.7                    |
| Ingordo et al <sup>140</sup>  | 1997       | 157         | 0 (0%)                  | NA   | NA                 | NA                     |
| Egan et al <sup>15</sup>  | 1998       | 46          | 2 (4.35%)               | 2.7 y, 3.5 y   | 1 (2.17%)          | 7.3                    |
| Bohn et al <sup>98</sup>  | 2000       | 12          | 1 (8.3%)                | 5 y  | 0 (0%)             | ND (1-16)              |
| Foster et al <sup>62</sup>  | 2001       | 46          | 0 (0%)                  | NA   | NA                 | 5                      |
| Berg and Lindelöf <sup>42</sup>   | 2003       | 146         | 0 (0%) <sup>b</sup>     | NA   | 0 (0%)             | 10 <sup>c</sup> (0-21) |
| Ka et al <sup>21</sup>  | 2005       | 379         | 0 (0%)                  | NA   | NA                 | NA (2-6)               |
| Hale et al <sup>34</sup> (includes Gari et al, <sup>85</sup> Marghoob et al, <sup>16</sup> DeDavid et al, <sup>31</sup> and Bittencourt et al <sup>17</sup> ) | 2005 (P)   | 205         | 3 (1.46%) <sup>d</sup>  | 1 mo, 36 y, 52 y   | 1 (0.49%)          | 5.3                    |
| Bett <sup>60,86</sup>   | 2005, 2006 | 1,008       | 19 (1.88%) <sup>e</sup> | Birth, birth, 3 mo, 7 mo, 9 mo, 17 mo, 3 y, 4 y, 7 y, 8 y, 9 y, 24 y, 26 y, 34 y, 39 y, 39 y, 58 y, ND | 4 (0.40%)          | 5.6                    |
| Chan <sup>29</sup>  | 2006       | 39          | 0 (0%)                  | NA   | NA                 | 16.9 (1-38)            |
| Total   |            | 2736        | 48 (1.75%)              |  | 17 (35.2%)         |                        |

Modified from Kregel et al<sup>1</sup> and Watt et al.<sup>30</sup> Abbreviations: MM, malignant melanoma; NA, not applicable; ND, no data; P, prospective study. <sup>a</sup>Age when melanoma was diagnosed. <sup>b</sup>In 1989, a patient was diagnosed with minimal-deviation melanoma, but when the case was reviewed in 2003 the diagnosis was changed to congenital melanocytic nevus with a benign nodular proliferation. <sup>c</sup>Mean. <sup>d</sup>In this study 5 patients developed melanomas in other locations (2 in the central nervous system [CNS], 1 retroperitoneal, 1 on normal skin, and 1 of unknown origin) with a fatal outcome in 4 cases. <sup>e</sup>In this study 5 patients developed melanomas in the central nervous system and died.

preexisting congenital nevus was found in 56% of cases.<sup>47</sup> These findings imply a 3-fold to 21-fold increase in the lifetime risk of developing melanoma and a cumulative risk at 60 years of age of between 0.8% and 4.9%, respectively.<sup>47</sup> In a later study, Betti et al<sup>48</sup> examined

the biopsies of 190 patients with melanoma and found evidence suggestive of CMN in a similar percentage of cases (7.8%).

In a study of 52 cases of melanoma arising in CMN, Illig et al<sup>49</sup> found 48 (92.2%) of them to be associated

with a nevus having a diameter of under 10 cm. Of these cases, 61% were melanomas of the superficial spreading type, most of them eccentric to the congenital nevus. Unlike what occurs in the case of giant CMN, none of these melanomas developed before puberty. In a series of 667 biopsies of melanomas,<sup>5</sup> an associated CMN was detected in 57 (8.5%) cases, all of which were diagnosed in adulthood. These findings have led many authors to conclude that the risk of malignant change in small CMN becomes significant after 20 years of age and increases with age.<sup>50</sup>

Other authors consider that it is difficult to estimate the risk of melanoma in small CMN. As we commented earlier, there are no pathognomonic pathological findings that can be used to distinguish small CMN from acquired melanocytic nevi in all cases.<sup>4,32</sup> In a review of 124 melanomas, Harley et al<sup>51</sup> found 24% to be associated with preexisting nevi, of which 55% were acquired and 28% were small CMN. It was, however, impossible to make this distinction in 17% of these cases. Prospective studies starting at birth are needed to obtain reliable data and minimize the bias produced by underdiagnosis.<sup>32</sup>

### *Histogenesis of Melanoma Arising in CMN*

Initially, it was thought that melanoma could originate in either the epidermal or the dermal component of a congenital nevus.<sup>34,52,53</sup> However, in view of the fact that most of the melanomas that develop within giant CMN are located in the dermis, it was later suggested that they must arise from the cells located in this layer.<sup>7,54</sup>

This debate was decisively influenced by the consideration of nodular proliferative lesions in giant CMN as a sign of malignant transformation because of their histologic appearance, although the benign biological behavior of such nodules was subsequently confirmed.<sup>25,28</sup>

Today, the view of many authors is that only the junctional component is potentially malignant<sup>55</sup> and that melanoma never, or only very rarely, develops within the dermal component of a giant congenital nevus.<sup>56</sup>

Melanomas associated with small CMN originate in the epidermis, resemble superficial spreading or nodular melanoma and have contiguous banal melanocytic proliferation with a congenital pattern.<sup>7,49</sup>

Cases have been described involving other types of malignant tumors that may arise in giant CMN, including poorly differentiated small round cell tumors, malignant cellular blue nevi, mesenchymal differentiation (rhabdomyosarcoma, liposarcoma), and spindle-cell malignant carcinoma with lamellar cell (“pseudomeissnerian”) differentiation.<sup>15,57</sup>

### *Risk of Developing Neurocutaneous Melanosis*

Neurocutaneous melanosis is a rare syndrome; approximately 100 cases were reported in the literature up to the year 2000.<sup>16</sup> In 91% of these cases, the nevi were in a posterior axial location and in 78% they were accompanied by satellite lesions.<sup>58</sup> As in the case of melanoma, some authors have suggested that risk of developing neurocutaneous melanosis is higher when giant CMN are accompanied by multiple satellite lesions.<sup>34,59</sup> In a series of 1008 patients with giant CMN or neurocutaneous melanosis,<sup>60</sup> 7.5% of the patients who had a giant nevus on the trunk had symptomatic neurocutaneous melanosis, as compared to only 0.8% of those in whom the nevus was located on the head or a limb. Multiple satellite nevi were present in 87% of the cases in this series.

The prevalence of symptomatic neurocutaneous melanosis in patients with giant CMN has been reported to be 11.4%.<sup>2</sup> In patients with asymptomatic disease, magnetic resonance imaging (MRI) should be used to rule out involvement of the central nervous system (CNS),<sup>17,28</sup> which has been detected in between 4.5%<sup>61</sup> and 30%<sup>60,62,63</sup> of cases in the series reviewed. Electroencephalography revealed abnormalities in 20% of these patients.<sup>10</sup>

In 66% of patients with neurocutaneous melanosis, neurological manifestations occur in the first 5 years of life (mean age of onset, 2 years).<sup>58</sup> Most of these manifestations are attributable to increased intracranial pressure resulting from the proliferation of leptomeningeal melanocytes, which obstructs the circulation of cerebrospinal fluid and prevents its reabsorption in the arachnoid villi.<sup>13,16,34</sup> The most common signs and symptoms are hydrocephalus (3%),<sup>60</sup> convulsions (2.7%),<sup>61</sup> papilledema, headache, microcephaly, paresis, and mental retardation.<sup>58,61</sup>

Neurocutaneous melanosis may also be associated with symptoms secondary to associated neurological diseases, including intracranial tumors, intracerebral and subarachnoid hemorrhage, and spinal malformations, as well as fusion defects, intraspinal lipomas, arachnoid cysts, and syringohydromyelia.<sup>12,63</sup> At least 13 cases have been described in the literature of association with Dandy-Walker malformation.<sup>12,64-75</sup>

The mortality rate for neurocutaneous melanosis is estimated to be 92%<sup>13</sup> secondary to onset of melanoma or neurological damage caused by progressive melanocytic proliferation in the CNS.<sup>63</sup> In 50% of cases, death occurs before 5 years of age (mean age at death was 3 years).<sup>58</sup> In the study cited above of 1008 patients with giant CMN or neurocutaneous melanosis, mortality was 45% in patients with neurocutaneous melanosis and no giant nevus, 2.3% in patients with a giant nevus on the trunk, and 0% in patients in whom the nevus was located on the head or a limb.<sup>60</sup>

In patients with neurocutaneous melanosis, melanomas

may develop on the giant nevus in 2.5%<sup>60</sup> and in the CNS in between 50%<sup>17</sup> and 64%,<sup>58</sup> with an associated mortality of 90%<sup>58</sup> to 100%.<sup>16</sup> In the review published by DeDavid et al,<sup>31</sup> 8.4% of patients developed CNS melanomas. All these patients had a giant nevus in a posterior axial location and had been diagnosed with neurocutaneous melanosis; 50% were younger than 3 years of age at diagnosis. Overall, 90% of the patients died, almost 50% before 5 years of age.

## Treatment

The treatment of CMN remains a matter of considerable debate. There is still no consensus on their treatment, the optimum age for resection, or the indications for removal.

Three types of indications have been proposed in the literature<sup>76</sup>:

1. Curative: when malignant transformation of the nevus is suspected
2. Prophylactic: depending on the patient's estimated risk of developing melanoma
3. Cosmetic: to prevent the consequences of the psychological and social stigmatization that can occur as a result of these lesions

The chief justification for prophylactic resection of CMN is to eliminate the risk of malignant change. The dual object of treatment is therefore to maximize ablation of the potentially malignant cells and to minimize possible sequelae.<sup>77-79</sup>

Treatment of CMN for cosmetic reasons is also controversial. Some authors defend the removal of giant CMN because they are disfiguring and unaesthetic and may have negative psychological repercussions. These physicians consider that the scars arising from treatment are better tolerated by the children than the original nevi.<sup>77</sup>

## Surgery

Surgical excision of the congenital nevus is the safest method of removing all potentially malignant cells.<sup>30,80</sup> As the incidence curve for melanoma arising within CMN is bimodal, the ideal time to perform surgical resection will depend on the size of the lesion.<sup>50</sup>

Since almost half of the melanomas arising within giant CMN described in the literature appeared during the first 5 years of life, prophylactic treatment should be implemented as early as possible.<sup>55,30,81</sup> Moreover, abstention from treatment and careful monitoring is a complicated option because the nevus usually has

a verrucous and polylobulated surface, making early detection of melanoma difficult.<sup>7,82</sup>

However, implementing this recommendation is not simple for the following reasons:

1. Complete resection of giant CMN generally requires a series of complex surgical interventions<sup>19,83</sup> that usually result in a cosmetic or functional deficit.<sup>30,84</sup>
2. In some cases, satellite lesions are so numerous that it is difficult to obtain donor skin for the grafts needed to cover the surgical defect<sup>19</sup>; the risk of melanoma associated with satellite nevi is not known.<sup>85</sup>
3. The psychosocial impact of repeated hospital admissions and surgical interventions on the child and his or her family should also be considered.<sup>19,83</sup>
4. Some authors<sup>52,53,86</sup> consider that surgical treatment does not completely eliminate the risk of melanomatous transformation if the patient has neurocutaneous melanosis or when nevus cells have infiltrated deeply into the fascia or muscle.

In the case of inoperable lesions, or when any of these factors are present or the family decides to adopt an approach of watchful waiting, careful monitoring of the patient is recommended including serial photography every 3 to 6 months during the first 5 years of life and every 6 to 12 months thereafter (Figure 1).<sup>19,83</sup>

In recent decades, technical advances in the repair of surgical defects have reduced the technical difficulties and morbidity associated with resection. These include the use of tissue expanders,<sup>87</sup> cultured epithelial autografts<sup>88</sup> and allografts,<sup>89</sup> as well as dermal and/or epidermal skin substitutes.<sup>90</sup> Tissue expanders are particularly indicated on the scalp because any other technique will produce areas of hairless scar tissue.<sup>91,92</sup> The advantage of this technique is that it uses tissue adjacent to the defect for the reconstruction. The disadvantages are the greater technical complexity, the need for multiple surgical interventions, the long period before the lesion can be completely eliminated (1-6 months), and the risk of complications (infection, ischemia, seromas, haematomas), discomfort, pain, and psychological intolerance.<sup>93</sup>

Gosain et al published algorithms for the surgical management of giant CMN.<sup>90,94</sup> When total resection of the lesion would result in loss of function or mutilation of the area involved, partial resection is recommended.<sup>94</sup> When the nevus can be excised in 2 or 3 interventions without affecting contiguous anatomical structures, they recommend the use of serial excision or of repeated procedures separated by intervals of at least 6 months.<sup>90</sup> When the resection is performed in more than 3 stages, tissue expansion during periods of 3 to 6 months is recommended. Those authors recommended the use of different surgical techniques depending on the anatomical

location of the nevus<sup>90,94</sup>; on the scalp they recommend the use of transposition flaps expanded from the temporal or occipital area towards the line of implantation; for the face, expanded full thickness skin grafts taken from the supraclavicular fossa; on the anterior trunk, abdominoplasty; and on the posterior torso, expanded transposition or advancement flaps. They report better results on the proximal areas of limbs with transposition flaps or pedicle grafts, and on the distal areas with expanded full thickness skin grafts.<sup>94</sup>

Twenty years ago, 50% of dermatologists recommended early resection of small CMN and only 27% advised careful monitoring.<sup>95</sup> Today, however, since the risk of prepubertal malignant transformation is thought to be very small, the recommended strategy is periodic monitoring throughout childhood and prophylactic resection in puberty unless morphologic changes are detected during the early years of life or the nevus is located in an area that is difficult to access (Figure 2).<sup>8,50,54,55,82,94</sup> Dermoscopy can be a useful technique for monitoring CMN<sup>93</sup> but, unlike in the case of acquired nevi, the presence of abrupt polycyclic borders in a congenital nevus should not be interpreted as indicative of malignancy.<sup>96</sup>

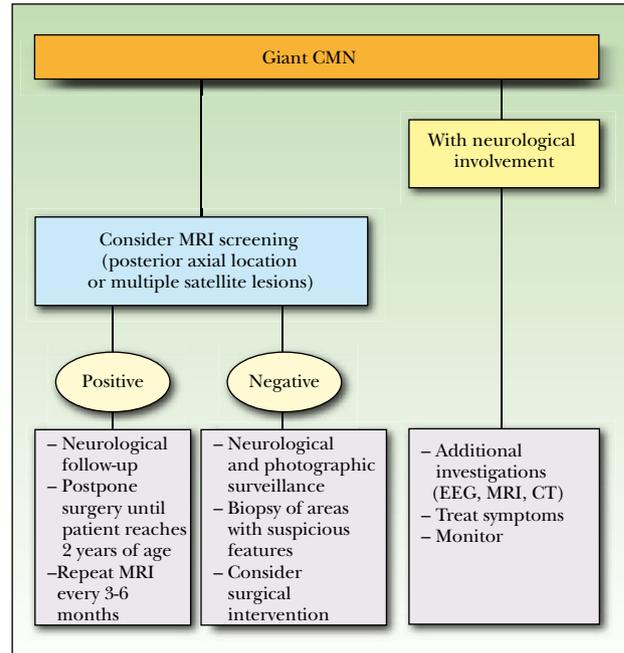
In a retrospective study of 192 patients with CMN carried out in 2002, it was found that 40% of the cases reviewed had been treated with surgical resection and that the larger the lesion, the earlier it was excised.<sup>97</sup> Malignant transformation was not found in any of these cases, which may be an indication that the lesions were excised for essentially cosmetic reasons, or it may be indirect evidence that surgical treatment performed at an optimum age reduces the risk of melanomatous transformation.

The most controversial question is the management of medium-sized CMN because the evidence in the literature does not support any specific therapeutic strategy. Some authors recommend resection of these lesions during puberty to reduce the risk of malignant transformation while minimizing the risk associated with anesthesia<sup>7</sup> (Figure 2).

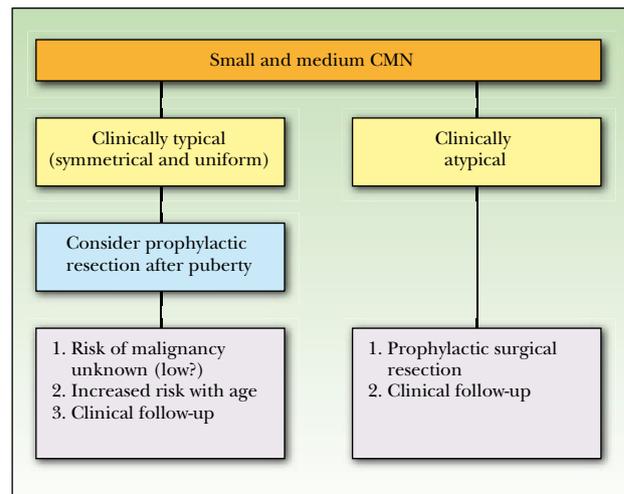
### Curretage, Dermabrasion, and Laser Treatment

Treatments that remove only the superficial component of giant CMN (curretage, chemical peeling, dermabrasion, and laser treatment) achieve good cosmetic results, although in some cases a focal and histologically atypical repigmentation of the clinical lesion is observed.<sup>98-100</sup> There is considerable debate about the safety of these techniques and their possible effect on the development of melanoma.

In studies in which a skin biopsy was obtained following superficial treatment, it was usually found that nevus cells persisted.<sup>79,91,99-105</sup> Some authors consider that removing the superficial portion of the lesion not only



**Figure 1.** Algorithm for the management of giant congenital melanocytic nevi (CMN). Taken from Marghoob et al.<sup>141</sup> CT indicates computed tomography, EEG, electroencephalogram; MRI, magnetic resonance imaging.



**Figure 2.** Algorithm for the management of small and medium congenital melanocytic nevi (CMN). Taken from Marghoob et al.<sup>141</sup>

does not eliminate the risk of malignant change<sup>34,106</sup> but that it may even increase this risk by destroying the layer that provides protection against ultraviolet radiation.<sup>104</sup>

In a recent study, however, the cells of the dermoepidermal junction were found to be more proliferative and vascular than those of the deeper component.<sup>55</sup> The implication of this finding is that curretage not only lowers the risk

of malignancy by reducing the number of melanocytes in the lesion but also eliminates the most “active” cells. Although only 4 cases of melanoma have been detected after dermabrasion,<sup>42,86,98,107</sup> the short follow-up of most cases makes it impossible to draw any conclusions about the safety of these therapeutic modalities.

In order to remove most of the melanocytes, the recommended approach is to perform the curettage during the first 2 weeks of life because during this period there is a cleavage plane between the upper dermis (the area that contains most of the nevocytes) and the deeper dermis.<sup>55,77,91,99,101</sup> However, the risks associated with general anesthesia in neonates must also be taken into consideration.<sup>99</sup>

Dermabrasion obtains similar results to curettage during the first 12 months of life. It is, however, a more aggressive technique that causes more bleeding and only removes a more superficial portion of the nevus. This is because once the dermoepidermal junction is breached there is a risk of hypertrophic scarring in 15% of cases, especially in the case of dorsal CMN.<sup>76</sup>

Another technique that has been used is shave excision of the epidermis and superficial dermis using the technique used to obtain lamellar grafts.<sup>108</sup> However, pale scars and spotted pigmentation were reported when this intervention was performed before 9 weeks of age.<sup>92</sup>

Authors who have used the phenol chemical peel technique obtained very variable cosmetic results.<sup>109</sup> The drawback of this technique is that no histopathologic study is possible and there is a risk of cardiac, hepatic, and renal toxicity.<sup>93</sup>

Various types of lasers have been used to treat giant CMN considered unsuitable for surgical excision. The types most often used were normal-mode ruby lasers<sup>110</sup> and carbon dioxide (CO<sub>2</sub>) lasers,<sup>78,111</sup> but these are painful procedures and the cosmetic results are unpredictable.<sup>77,110,111</sup> Today, the UltraPulse CO<sub>2</sub> laser<sup>112,113</sup> is generally used to eliminate the layers of tissue with the highest concentration of pigmentation, and this is followed by additional treatment with more selective lasers.<sup>77,100,114,115</sup> In a study of 5 CMN it was found that the Q-switched ruby laser more effectively removed superficial nevus cells than Q-switched neodymium:yttrium-aluminum-garnet (Nd:YAG) laser systems.<sup>102</sup> Other authors have combined Q-switched ruby laser with normal-mode ruby laser and reported that this combined therapy removed more melanocytes than normal-mode ruby laser alone.<sup>103-105</sup> Erbium-doped yttrium aluminium garnet (Er:YAG) lasers have been used successfully in the treatment of giant CMNs<sup>79</sup> and inoperable facial CMN.<sup>116</sup> CO<sub>2</sub> laser can also be used to complement curettage in the treatment of satellite lesions in which the cleavage plane is not clearly defined.<sup>80</sup>

It has recently been reported that the use of cultured epidermal autografts after treatment with Er:YAG laser or

curettage induced rapid reepithelization and reduced the risk of hypertrophic scarring, granulation tissue formation, and the length of stay in hospital.<sup>84</sup>

### Treatment of Neurocutaneous Melanosis

As we saw earlier, when a giant congenital nevus is in a posterior axial location, normal-mode ruby laser treatment should be carried out in the first 6 months of life (before normal myelin deposition hides the melanin deposits)<sup>117</sup> and followed up with periodic neurological surveillance (Figure 1).<sup>83</sup> The optimum age for surgical resection of CMN in children with neurocutaneous melanosis is also still a subject of debate. The intervention should, however, be postponed until at least 2 years of age in asymptomatic children with evidence of leptomeningeal melanosis on magnetic resonance imaging. It should also be noted that most melanomas arising from giant CMN also appear around this age.<sup>58</sup>

The treatment of symptomatic neurocutaneous melanosis is palliative, and essentially consists in the administration of anticonvulsants. In cases with associated obstructive hydrocephalus, ventriculoperitoneal shunts are placed to drain cerebrospinal fluid.<sup>61</sup> Some authors have unsuccessfully tried combination treatment with radiotherapy and chemotherapy.<sup>118,119</sup>

## Conclusions

The conclusions of this review of the literature are summarized in Table 3.

1. The mean risk of developing melanoma within a giant congenital nevus is 2%.
2. Associated small CMN have been found in 7% to 8% of melanoma biopsies.
3. The incidence curve for melanoma arising within a congenital nevus is bimodal; the first peak occurs before 5 years of age and corresponds to malignant change in giant CMN; the second peak occurs between puberty and adulthood in association with small CMN.
4. Only 11.8% of cases of childhood melanoma are associated with a precursor lesion. Of these, 3.52% are associated with a giant nevus and 5.8% with a small or medium-sized congenital nevus (ratio 5:3).
5. Surgical treatment of giant CMN is controversial, and the appropriateness of such an intervention should be decided on a case-by-case basis taking into account the clinical suspicion of melanoma and the cosmetic and functional repercussions of the proposed surgery.
6. Since the current view is that there is only a low risk of prepubertal malignant change in small CMN, the recommended approach for these lesions is periodic

**Table 3.** Questions Frequently Asked About Melanocytic Nevi

|  | <i>Small and Medium CMN</i>  | <i>Giant CMN</i>   |
|--|--|--|
| What is the risk of developing melanoma?                           | The risk is unknown, but evidence of CMN has been found in 7% to 8% of biopsies of melanoma. | 2 %  |
| Where does melanoma start?   | At the dermoepidermal junction   | At the dermoepidermal junction. And, exceptionally, in the dermis?                                       |
| At what age does melanoma appear?                                  | During or after puberty  | Before puberty   |
| In which patients is the risk of neurocutaneous melanosis highest? | ≥ 3 CMN  | Axial location   |
| What are the treatment options?                                    | Monitoring   | Monitoring   |
|  | Self-examination   | Self-examination   |
|  | Prophylactic resection (after puberty)   | Prophylactic resection (early)   |
| What are the available techniques?                                 | Surgery (simple or staged, using skin grafts or tissue expanders)                            | Surgery (simple or staged, using skin grafts or tissue expanders). Curettage during the neonatal period? |
| How can melanoma be diagnosed early?                               | Clinical examination   | Clinical examination   |
|  | Dermoscopy   | Palpation  |
|  | Monitoring with serial photography   | Monitoring with serial photography   |

Modified from Marghoob et al.<sup>117,141</sup> Abbreviations: CMN, congenital melanocytic nevi.

monitoring during childhood and prophylactic removal in puberty.

- While the cosmetic results obtained with treatments that only remove the superficial component of giant CMN (curettage, dermabrasion, and laser therapy) are good, there is still no consensus about whether such interventions may increase the patient's risk of developing melanoma.
- In patients with a giant nevus in a posterior axial location, an MRI scan should be obtained within the first 6 months of life and the patient should be periodically screened for neurocutaneous melanosis.

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## Conflict of Interest

The authors declare no conflicts of interest.

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