Giant congenital melanocytic naevi: definition, malignant transformation and treatment modalities
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Chapter 2

Classification of congenital melanocytic naevi and malignant transformation: a review of the literature

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Mooi WJ
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van der Horst CM

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Abstract

Introduction. Congenital melanocytic naevi (CMN) vary greatly in size, macroscopic appearance and histology. There is a practical need to subdivide CMN according to size, since size differences have a direct bearing on cosmetic and resultant psychological problems, and on therapeutic possibilities, and probably on the chance of malignant transformation. In this review, we summarise the literature on size subgroupings of CMN, with special focus on giant congenital naevi and their risk of malignant transformation.

Materials & Methods. A Medline literature search over the years 1966 through October 2002 was performed. Only English-language studies focusing on CMN in association with melanoma were included. The final strategy consisted of textwords and medical subject heading (MeSH) terms on small, medium, large and giant congenital nevi combined with the textwords classification, histology and melanoma. Additional manual cross-referencing was performed. We excluded articles that dealt only with aspects of treatments.

Results. A wide variety of criteria for size subgrouping of CMN has been put forward in the literature and precludes a direct comparison of reported data (Table I). We identified 35 articles concerning malignant transformation of GCMN in the world literature in which no less than seven different definitions of minimum size of a giant CMN were employed. Histologically, it is difficult or even impossible to conclude that a naevus is congenital or acquired, especially in case of a small lesion, since the differences are not absolute (Table II). Giant CMN have an increased risk for malignant transformation, but the reported incidence rates have differed widely from one to 31% (Table III). Reported melanoma incidence rates have derived from retro-and prospective studies, reviews and case reports, and compared with each other using different definitions. On top of this, patients in different age groups were reported, who were registered in different referral centres.

Conclusion. To allow comparison of study results from different centres, it is essential that the size subclassification of CMN is based on standard and generally accepted criteria. We advise to define GCMN as a CMN covering one percent in face and neck and two percent elsewhere on the body. Based on a review of the world literature we favour prophylactic excision of all CMN, in close communication with patient and family and individualising treatment accordingly.
Introduction

By definition, a congenital melanocytic naevus (CMN) is a benign proliferation of cutaneous melanocytes, which is clinically apparent at birth or becomes so within the first postnatal weeks. CMN affects approximately one percent of all newborns. As a group, congenital naevi vary in size, macroscopic appearance and histology, so there is a need to subdivide these lesions into clinically significant subgroups. Subclassification of CMN has long been a matter of debate, and consensus has not yet been reached. Thus, differences between classifications used by various authors continue to pose an impediment to the comparison of clinical studies from different centres.

Histologically, congenital naevi are distinguished from the far more common acquired naevi mainly by their often larger size and greater cellularity, and by spread of the naevus cells to deep layers of the skin and even subcutaneous tissues, as well as by their more varied architecture and cellular morphology. None of these features, however, distinguishes unequivocally between congenital and acquired naevi, so that in the absence of a history of the presence of the lesion at birth, the congenital nature of a naevus cannot generally be established with certainty. Of course this applies especially to naevi of a size range that might include acquired lesions. Clinical subclassifications of CMN are generally based on size. An often-used subdivision was proposed by Kopf: a small CMN is less than 1.5 cm in largest diameter, a medium sized CMN is between 1.5 and 19.9 cm, and a large or giant congenital naevus (GCMN) is 20 cm or more in largest diameter, all irrespective of patient age and size. The latter subgroup, GCMN, are much rarer than the smaller ones, and affect approximately one in 20,000 newborns.

Continued debate focuses on the life-time risk of malignant transformation and on their optimal treatment. There is no doubt that GCMN have an increased risk of malignant transformation, but there is substantial disagreement about the magnitude of this risk: reported figures having varied widely, from one to 31%. Although there is now general agreement that the risk is limited in the order of a few percent, prophylactic excision of GCMN in order to prevent melanoma has been strongly advocated. Since melanoma may develop within small and medium-sized CMN as well, some authors advise prophylactic excision of these CMN as well.

Not only the risk of malignant transformation of CMN, but also its effect on the patient’s appearance, impacts negatively on the well-being and the psychological development of the patient, especially in case of large CMN. This also constitutes a very important consideration in the decision for treatment.

In this review, we summarise the literature on classification of CMN, with emphasis on giant congenital naevi and on their risk of malignant transformation. We will analyse the differences in reported risks of malignant transformation of CMN, in relation to
the classifications used to describe CMN, the retro- or prospective character of the studies, and their reference centre. Based on this, we will attempt to provide an argued recommendation with respect to the question whether prophylactic excision is required only for GCMN or for all CMN irrespective of size.

**Materials and methods**

A literature search was performed using the biomedical bibliographical database Medline from 1966 to October 2002. Initial searches focused on the textwords congenital naevus, congenital melanocytic naevus, congenital nevocellular naevus, Tierfell naevus and, large and giant congenital (pigmented) naevus. We included English language studies on small, medium and giant congenital naevi in association with melanoma and histology. Final strategy consisted of textwords and medical subject heading (MeSH) terms on small, medium, large and giant congenital naevi combined with the textwords melanoma, histology and classification. Manual cross-referencing was performed additionally. We excluded articles that dealt only with aspects of treatment. Of the articles concerning giant congenital naevi, we listed the classification used, the reported incidence of malignant transformation, the reference centre from which data were reported, the retrospective or prospective character of the study, the average follow-up period, the patient average age and the advice regarding prophylactic CMN excision. The classifications used and the histological features of CMN are listed in table I and II, respectively. The reported figures of malignant transformation in giant CMN are listed in table III.

**Results**

**Subclassifications based on size**

Table I provides a summary of the various definitions of giant or large congenital naevi that have been used. Some authors regard ‘giant’ CMN as a subset of large CMN, others use the terms ‘large’ and ‘giant’ interchangeably. Some have chosen not to use a numerical size parameter as cut-off point between subgroups, but have based the subdivision on the feasibility of primary excision in one procedure or on size relative to body size.

In 1963, Pers, reporting on 110 patients with benign GCMN registered in the Danish Health System in a 40-year period (1915-1955), was the first to use a quantitative parameter for subdivision of CMN. As the distinguishing feature, Pers chose size relative to the body size and considered a CMN to represent a GCMN if the size of the naevus in the face or
neck exceeded that of the palm of the patients hand (one percent), or twice that size if located elsewhere on the body (two percent). Lanier et al.32 and Swerdlow et al.46 also used relative body surface area expressed as a percentage to classify a CMN as GCMN, but these workers chose a substantially higher percentage (Table I). Enhamre proposed a relative area index (RAI). In his definition (Table I), the BSA (body surface area) can be calculated as $7.184 \times 10^{-3} \times W^{0.425} \times H^{0.725}$, with $W$ for body weight in kilograms and $H$ for height in centimetres. 67,68

In contrast to these quantitative parameters, Kaplan, in 1974, chose to take parameters of surgical resectability as the criteria for subclassification (Table I).30 In 1979, Kopf and colleagues established a 'Congenital Nevocytic Nevus Registry' in the Oncology Section of the Skin and Cancer Unit at New York University Medical Centre, with the aim to conduct a long-term prospective study.2 These workers preferred simplicity, and subdivided CMN according to their largest diameter, regardless of age of the patient (Table I).2 Lerner, Illig53 and Reed3 also used diameter in cm, as an absolute measure, to identify GCMN, but these authors used different cut off points to define giant CMN (Table I). Still others have used absolute figures of surface area rather than maximum diameter.10,28

Table I. Overview of clinical definitions used to describe giant congenital naevi GCMN.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Published year</th>
<th>Definition used to describe congenital naevi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conway13</td>
<td>1939</td>
<td>GCMN is a bathing trunk naevus located at the back, which cannot be excised easily. Wound defect cannot be closed primarily</td>
</tr>
<tr>
<td>Pers et al.14</td>
<td>1963</td>
<td>GCMN is a naevus which exceed 1% in the face or neck and 2% elsewhere on the body</td>
</tr>
<tr>
<td>Lorentzen et al.15</td>
<td>1977</td>
<td>GCMN is a naevus which exceed 1% in the face or neck and 2% elsewhere on the body</td>
</tr>
<tr>
<td>Greeley16</td>
<td>1965</td>
<td>GCMN is naevus covering an area of 900 cm2 or more on the trunk or extremity or a major portion of the face or hand</td>
</tr>
<tr>
<td>Lerner et al.17</td>
<td>1972</td>
<td>GCMN is a naevus greater than two cm in diameter</td>
</tr>
<tr>
<td>Kaplan et al.18</td>
<td>1974</td>
<td>GCMN is a naevus which cannot be excised easily and the wound defect cannot be closed by primary closure without deformity</td>
</tr>
<tr>
<td>Lanier19</td>
<td>1976</td>
<td>GCMN is a naevus covering more than 30% of the body surface area</td>
</tr>
<tr>
<td>Kopf et al.2</td>
<td>1979</td>
<td>small sized naevus is &lt; 1,5 cm in diameter, medium sized nevus is between 1,5 cm and 19,9 cm in diameter and a large sized nevus is &gt; 19,9 cm.</td>
</tr>
<tr>
<td>Illig20</td>
<td>1981</td>
<td>GCMN is a naevus larger than 10 cm in diameter</td>
</tr>
<tr>
<td>Zitelli9</td>
<td>1984</td>
<td>GCMN is a naevus larger than 120 cm2</td>
</tr>
<tr>
<td>Enhamre21,22</td>
<td>1986</td>
<td>naevus size expressed in relation with body surface area, using the relative area index (RAI)</td>
</tr>
<tr>
<td>Reed3</td>
<td>1993</td>
<td>GCMN is a naevus larger than 40 mm in diameter</td>
</tr>
<tr>
<td>Swerdlow23</td>
<td>1995</td>
<td>GCMN is a naevus when at least 5% of the body surface area is involved</td>
</tr>
</tbody>
</table>
Histological patterns

CMN (as opposed to melanocytic naevi of other types) is primarily a clinical diagnosis, the essential feature being its presence at or immediately after birth. The histological features of congenital naevi are essentially similar to those of the much more common acquired naevi, which arise later in life; the main differences are their often larger size and greater cellularity, with extension of the naevus cells into the deep dermis and underlying tissues, especially in the larger examples. Both congenital and acquired naevi consist of melanocytes which proliferate, initially at the dermoepidermal junction, from where the cells accumulate at the junction or come to lie in the superficial dermis (Figure 1).

![Figure 1. Congenital naevus. Within the dermis, a densely cellular lesion, consisting of large numbers of nonpigmented naevus cells, is present. Although such large numbers of naevus cells within the dermis suggest a congenital rather than an acquired naevus, this feature by itself provides insufficient basis to designate the naevus as a congenital one.](image)

To a very small extent, naevus cells also proliferate in the immediately subjacent dermal tissue. Some of the accumulated melanocytes, often called naevus cells, spread to deeper parts of the dermis. This spread to deeper tissue layers is generally absent or very limited in acquired naevi but is more pronounced in many congenital naevi, where the deepest cells often permeate the deep dermis and may extend into the subcutis and even deeper body tissues (Figure 2).
After passage of time, often many years, the junctional part of the naevus gradually disappears (resulting in a so-called dermal naevus). A number of studies have systematically evaluated the histological differences between congenital and acquired naevi and a number of additional histological features thought to be more or less characteristic of congenital naevi have emerged from these (Table II). Mark and colleagues compared the histological features of 60 congenital and 60 acquired naevi and identified three features that in their material were characteristic (Table II). Pack and Davis made very similar observations, but in contrast, Lanier stressed that the histological patterns of GCMN were similar to those of acquired naevi. Hendrickson and Ross and Reed et al. stressed the similarity of acquired to congenital naevi, but added that some CMN contain areas of proliferation of immature neural-supportive elements. Walton studied biopsies taken within 72 hours after birth of 11 small CMN (Table II). The implication of Walton’s study is, that the spread of congenital naevi into deeper layers of the skin and the subcutis occurs largely after birth, so that superficial removal of the naevus immediately after birth might prevent this spread to deeper tissues. Zitelli studied six patients with a GCMN and six with a small CMN and classified CMN histologically in two groups (Table II). Interestingly, this study included seven patients under three months of age, where serial biopsies were taken over a subsequent period of

Figure 2. At the base of the same lesion, naevus cells are seen to extend between fat cells of the subcutis, (the fat vacuoles of the subcutaneous lipocytes appear as large rounded empty spaces). This feature of extent of a naevus of this type into the subcutis is thought to be almost pathognomonic of a congenital rather than an acquired naevus.
15 months. The notion of a very early superficial phase of CMN received further support from Silvers and Helwig (Table II). However, in contrast to these studies, Ruiz-Maldonado reported histological patterns of one or more biopsies taken from 62 of the 80 patients with GCMN (Table II). Most of these lesions were predominantly intradermal, also in the neonatal period, thus casting doubt on the hypothesis based on earlier studies, that naevus cells migrate into the dermis during infancy. The variability of the histology of CMN was also evident from a study by Stenn and co-workers (Table II). Again, no significant correlation was found between the histological appearances and the age of the patient. Similarly, there was no relation to sex, anatomic location, or size of the naevus. Barnhill and colleagues concluded that the depth and pattern of naevus cells are directly related to size of CMN in infants (Table II).

When malignant melanoma (MM) arises in CMN, the histological type of the MM relates to the size and extent of the skin involvement of the CMN. Reed and co-workers reported that a MM arising within a CMN usually originated at the epidermal-dermal junction. Illig and co-workers (1985) concluded in their report that all 47 melanomas contiguous with pre-existing CMN limited to the upper two-thirds of the skin were of epidermal

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Histological features of CMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark et al.</td>
<td>1973</td>
<td>60 AN, 60 CMN</td>
<td>naevus cells in lower 2/3 dermis, Indian files, within glands, bloodvessels or nerves</td>
</tr>
<tr>
<td>Lanier et al.</td>
<td>1976</td>
<td>82 CMN</td>
<td>patterns of CMN and AN are similar</td>
</tr>
<tr>
<td>Hendrickson and Ross</td>
<td>1981</td>
<td>6 CMN</td>
<td>CMN and AN are similar, but CMN can contain areas of immature neural supportive elements</td>
</tr>
<tr>
<td>Reed et al.</td>
<td>1965</td>
<td>55 CMN</td>
<td>CMN and AN are similar, but CMN can contain areas of immature neural supportive elements</td>
</tr>
<tr>
<td>Walton et al.</td>
<td>1976</td>
<td>11 CMN</td>
<td>9 small CMN were superficial, 2 small CMN had diffuse penetration into deep reticular dermis</td>
</tr>
<tr>
<td>Zitelli et al.</td>
<td>1984</td>
<td>12 CMN</td>
<td>giant : diffuse pattern of distribution into dermis and often deeper. Small: junctional papillary dermal involvement</td>
</tr>
<tr>
<td>Silvers and Helwig</td>
<td>1995</td>
<td>7 CMN</td>
<td>all showed melanocytic hyperplasia with the epidermis and within pilosebaceous and eccrine sweat units</td>
</tr>
<tr>
<td>Ruiz-Maldonado et al.</td>
<td>1992</td>
<td>62 CMN</td>
<td>51 CMN were predominantly intradermal and 10 CMN were predominantly compound. Nevus cells did not migrate into the dermis during infancy</td>
</tr>
<tr>
<td>Stenn et al.</td>
<td>1983</td>
<td>38 CMN</td>
<td>only upper dermis, or diffuse infiltration upper and deeper dermis, or below reticular dermis</td>
</tr>
<tr>
<td>Barnhill</td>
<td>1995</td>
<td>87 CMN</td>
<td>89% lower half of the reticular dermis, 51% in the subcutaneous tissue</td>
</tr>
<tr>
<td>Nickoloff et al.</td>
<td>1986</td>
<td>29 CMN</td>
<td>6 CMN showed involvement in lower reticular dermal collagen, all 29 naevus cells in adventitia of hair follicles or eccrine ducts in the midreticular dermis or deeper</td>
</tr>
</tbody>
</table>
origin and mainly superficial spreading type. In GCMN, however, melanomas may arise from the deep dermal portion of the naevus. These latter, deeply located malignant tumours, which mostly arise in childhood and early adolescence, may exhibit features of (nonmelanocytic) sarcoma types, such as malignant schwannoma, rabdomyosarcoma, and liposarcoma.

**Malignant transformation of a congenital naevus**

*a. Giant congenital naevus*

Table III lists reported data on melanoma arising in GCMN. Thirty five such articles were identified, and no less than seven different definitions of GCMN were used. In fourteen, the classification proposed by Kopf (GCMN equal to or exceeding 20 cm in largest diameter) was employed. From these, DeDavid et al., Gari et al., and Marghoob et al. and Bittencourt et al. reported prospective studies of respectively 117, 54, 92 and 160 patients from the New York University Registry (NYUR) of large congenital naevi (Table III). These prospective studies were initiated by Kopf in 1979, when he established a ‘Congenital Nevocytic Nevus Registry’, in which patients were entered regardless of age. Ruiz-Maldonado, describing clinical and histopathologic data on GCMN in his prospective study, also used the classification originally proposed by Kopf. He reported on 80 pediatric patients with a mean age at time of consultation of 20 months (range: 2 days - 16 years), from the National Institute of Pediatrics in Mexico City (Table III). In their prospective study on GCMN, Egan et al. used the definition of Kopf in adolescents and adults, but in infants and children GCMN were defined as CMN comprising more than five percent of the body surface area (Table III).

A further five articles used the classification proposed by Kaplan in 1974. The patients were not selected for age. Three of these five articles concerned single case-reports, of which Russell et al. collected another 52 cases of melanoma associated with a GCMN from the literature. Kaplan reviewed the literature of malignant transformation of GCMN and calculated an average incidence of 11%, with 60% of the malignant transformations occurring during the first decade of life.

We found six studies in which GCMN were defined as a percentage of body area, but using different cut off points. From these Pers, Lorentzen and Quaba reported retrospective studies. Swerdlow concluded in his follow-up study that the group of naevi covering at least five percent of the body (33 patients) had a significantly increased risk of melanoma when compared to than the group with smaller CMN. Eighty percent of his patients who developed a melanoma were under three years of age. Egan, who used the same size criterion as Swerdlow, described in a prospective study in which two out of six patients with a GCMN developed a melanoma.
and Reed et al.\textsuperscript{9} collected published cases of malignancy in GCMN, in which GCMN were defined differently. Pack and Reed found that almost half the reported cases of melanoma associated with GCMN not selected for age occurred before the age of five years. In prepubertal metastatic melanoma associated with GCMN, Trozak found that most cases occurred at or before the age of three years.\textsuperscript{51}

\textit{b. Medium and small congenital naevus}

Several case-reports of small CMN (<1.5cm) associated with melanoma have been published.\textsuperscript{61,62} In 1982 Rhodes and Melski reported on 134 patients (age range: 16-75 years) with small CMN, defined according to Kaplan.\textsuperscript{55} Twenty of these patients had developed a melanoma within the small CMN. Reviewing the world literature available at that time, concerning 1161 patients with small CMN, 249 of these patients developed a cutaneous melanoma.\textsuperscript{55} The age of these patients varied from two to 113 months. On the basis of these figures, Rhodes advocated prophylactical removal of all small CMN.\textsuperscript{7,55} Sahin and colleagues followed 227 patients with medium-sized CMN seen from 1955 to 1996.\textsuperscript{56} Indeed in this study, not a single melanoma occurred during the average follow-up of 6.6 years, to an average age of the patients of 25.5 years.

\textit{c. primary melanoma}

In 1985 Illig and co-workers concluded that at least 2.8% of the 570 consecutive melanoma cases studied by them had arisen from a CMN, most of which were less than 10 cm and single, none of the melanomas arose before puberty.\textsuperscript{53} Harley et al. described 124 melanomas in 1996.\textsuperscript{64} In their group, 29 melanomas arose in association with preexisting naevi, of which 55% (16) were acquired and 28% (8) were considered small congenital naevi. Betti and colleagues studied 190 patients with primary melanomas.\textsuperscript{62} Forty of the 190 cases of melanoma were associated with preexisting naevi; of these 40, 15 had congenital features with small CMN (< 1.5 cm). In both studies of Harley and Betti, men were more affected than women, and they concluded that a high percentage of small CMN were found to be associated with melanomas.\textsuperscript{62,64} Schmid-Wendtner and colleagues analysed data of 6931 patients with cutaneous melanoma at the department of dermatology in Munich between 1977 and 1998.\textsuperscript{65} They identified 36 patients in whom cutaneous melanoma developed during childhood or adolescence (< 18 years). In nine of the 36 patients the melanoma was associated with a CMN. Interestingly, Sphall et al. calculated in a national population-based cancer registry, a cumulative risk of malignant transformation of CMN in blacks.\textsuperscript{71} To the age of 75 years this risk was 1/164, and the risk for the age younger than 15 was less than 1:10.000. Massi et al. evaluated 131 patients with invasive melanoma (<4mm in thickness and with a Clark level < V).\textsuperscript{59} Histological evidence of an associated melanocytic naevus was found in 27 out
of 131 melanoma cases (21%). Fourteen (52%) cases showed acquired features, whereas 12 (45%) cases had features of small CMN described by Mark and colleagues.\textsuperscript{12,59}

**Treatment of congenital naevi in order to prevent malignant melanoma**

A key argument for the surgical removal of CMN is their malignant potential.\textsuperscript{2-6,18,72} Various treatment modalities have been advocated, reflecting the divergent personal experiences and preferences of the various authors.\textsuperscript{2-6,9,18,21,26,27,28,29,30,32,33,37,39,46,56,73} These will be briefly reviewed here. An overview of aspects of cosmesis as an argument for removal of CMN, and the cosmetic results of various procedures currently in use, is outside the scope of this review.

Arons and Hurwitz favored a complete one-stage excision of the CMN, including satellite lesions, regardless of lesion size or patient age.\textsuperscript{5} Arons\textsuperscript{5}, Gari\textsuperscript{27}, Pilney\textsuperscript{73}, Ruiz-Maldonado\textsuperscript{39}, and Quaba\textsuperscript{37} all stressed the need for early excision of GCMN, whenever such surgery is feasible and practical. Lanier et al. stated that for complete elimination of melanoma risk, the entire naevus must be excised, down to the fascia, because in CMN, naevus cells commonly extend into the subcutis and fascia.\textsuperscript{32} In addition, these authors advised that the removal of GCMN should be done in the preschool years, in order to minimise the risk of melanoma.

In contrast, Kaplan concluded that those congenital naevi that on biopsy proved to be purely intradermal, could be followed by watchful waiting, because in his experience, such intradermal naevi did not evolve into melanoma.\textsuperscript{30} However, according to the same author, naevi with a histologically proven junctional component or with neuronevus elements should be removed in early life, because of a definite premalignant potential.\textsuperscript{30} Pers summarised his indications for excisional surgery as follows: those lesions on the face and acral portions of the limbs, verrucous lesions, and excessively hairy nevi in women.\textsuperscript{18} Marghoob remarked that even total surgical removal of GCMN does not prevent the development of all melanoma, because melanoma can develop in extracutaneous sites.\textsuperscript{33,34}

Dermabrasion produces favourable cosmetic results in newborns, but Zitelli advised against dermabrasion as a treatment for CMN, since most of the naevus cells are not removed by this procedure, so that it does not prevent melanoma.\textsuperscript{10} Hori went even further and suggested that dermabrasion of GCMN may even provoke malignant transformation, although there is no direct evidence to support this contention and transformation induced by mechanical trauma is biologically implausible.\textsuperscript{29} Rhodes et al. advised prophylactic excision of small CMN as well\textsuperscript{54,55} and recommended that the excision be performed before the age of 12, after which age the risk of melanoma increases.\textsuperscript{7,55} Betti agreed that small CMN can transform to melanoma, but
considered prophylactic removal of all small CMN not feasible, because of their large number and frequency.\textsuperscript{62} However, she advised to remove small CMN as soon as changes are observed on clinical or epiluminescence microscopical evaluation. Goldberg stated that although laser ablation of small CMN may achieve satisfactory cosmetic results, persistence of deeper melanocytes limits the usefulness of this treatment.\textsuperscript{74} Kopf et al. took the position that, because melanoma is so rare in CMN less than 20 cm in diameter, continued observation is sufficient.\textsuperscript{2,58} Similarly, Sahin and colleagues did not consider prophylactic excision mandatory for all CMN, because in their study, medium-sized CMN did not have an increased risk of melanoma.\textsuperscript{56}

### Table III. An overview in literature on melanoma and giant congenital naevi.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>D</th>
<th>GCMN (n)</th>
<th>MM (n)</th>
<th>risk for MM</th>
<th>average age (years)</th>
<th>Average follow-up</th>
<th>C</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopf et al.\textsuperscript{2}</td>
<td>1979</td>
<td>2</td>
<td>443</td>
<td>54</td>
<td>12%</td>
<td>unknown</td>
<td>unknown</td>
<td>a*</td>
<td>review</td>
</tr>
<tr>
<td>Arons et al.\textsuperscript{5}</td>
<td>1983</td>
<td>1</td>
<td>46</td>
<td>0</td>
<td>0%</td>
<td>unknown</td>
<td>unknown</td>
<td>g</td>
<td>retrospective</td>
</tr>
<tr>
<td>Hendrickson\textsuperscript{14}</td>
<td>1981</td>
<td>none</td>
<td>6</td>
<td>6</td>
<td>6.1</td>
<td>8 years</td>
<td>a</td>
<td>morphologic</td>
<td></td>
</tr>
<tr>
<td>Lorentzen\textsuperscript{19}</td>
<td>1977</td>
<td>7</td>
<td>151</td>
<td>3</td>
<td>4.6%</td>
<td>8.2</td>
<td>unknown</td>
<td>g</td>
<td>retrospective</td>
</tr>
<tr>
<td>Baader et al.\textsuperscript{20}</td>
<td>1992</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>birth</td>
<td>10 years</td>
<td>p</td>
<td>case-report</td>
<td></td>
</tr>
<tr>
<td>Bittencourt\textsuperscript{21}</td>
<td>2000</td>
<td>2</td>
<td>160</td>
<td>3</td>
<td>2.3%</td>
<td>1.2</td>
<td>5.5 years</td>
<td>a*</td>
<td>prospective</td>
</tr>
<tr>
<td>Bouffard et al.\textsuperscript{22}</td>
<td>1994</td>
<td>none</td>
<td>1</td>
<td>1</td>
<td>62</td>
<td>1 year</td>
<td>g</td>
<td>case-report</td>
<td></td>
</tr>
<tr>
<td>Conway et al.\textsuperscript{23}</td>
<td>1939</td>
<td>3</td>
<td>40</td>
<td>4</td>
<td>10%</td>
<td>unknown</td>
<td>unknown</td>
<td>g</td>
<td>retrospective</td>
</tr>
<tr>
<td>DeDavid et al.\textsuperscript{24}</td>
<td>1997</td>
<td>2</td>
<td>289 (161 from literature)</td>
<td>34</td>
<td>12%</td>
<td>13.8</td>
<td>unknown</td>
<td>a*</td>
<td>prospective, review</td>
</tr>
<tr>
<td>Dellon et al.\textsuperscript{25}</td>
<td>1976</td>
<td>none</td>
<td>1</td>
<td>1</td>
<td>32</td>
<td>8 months</td>
<td>o</td>
<td>case-report</td>
<td></td>
</tr>
<tr>
<td>Egan et al.\textsuperscript{26}</td>
<td>1998</td>
<td>2 and 4</td>
<td>46</td>
<td>2</td>
<td>4.3%</td>
<td>8.4</td>
<td>7.3 years</td>
<td>o, a</td>
<td>prospective</td>
</tr>
<tr>
<td>Gari et al.\textsuperscript{27}</td>
<td>1988</td>
<td>2</td>
<td>54</td>
<td>1</td>
<td>2%</td>
<td>8.8</td>
<td>53 months</td>
<td>a*</td>
<td>prospective</td>
</tr>
<tr>
<td>Greeley et al.\textsuperscript{28}</td>
<td>1965</td>
<td>5</td>
<td>56</td>
<td>6</td>
<td>11%</td>
<td>15.1</td>
<td>12 years</td>
<td>a</td>
<td>retrospective</td>
</tr>
<tr>
<td>Hori et al.\textsuperscript{29}</td>
<td>1989</td>
<td>2</td>
<td>154</td>
<td>7</td>
<td>4.5%</td>
<td>unknown</td>
<td>unknown</td>
<td>a</td>
<td>retrospective</td>
</tr>
<tr>
<td>Kaplan et al.\textsuperscript{30}</td>
<td>1974</td>
<td>1</td>
<td>360</td>
<td>49 (42 from lit)</td>
<td>10.8%</td>
<td>19.4</td>
<td>5 years</td>
<td>a</td>
<td>retrospective</td>
</tr>
<tr>
<td>Koloske et al.\textsuperscript{31}</td>
<td>1975</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0.6</td>
<td>2.5 years</td>
<td>g</td>
<td>case-report</td>
<td></td>
</tr>
<tr>
<td>Lanier et al.\textsuperscript{32}</td>
<td>1976</td>
<td>6</td>
<td>82</td>
<td>5</td>
<td>6%</td>
<td>20</td>
<td>31.2 months</td>
<td>retrospective</td>
<td></td>
</tr>
<tr>
<td>Marghoob\textsuperscript{33,34}</td>
<td>1995</td>
<td>2</td>
<td>92</td>
<td>3</td>
<td>3%</td>
<td>0.5</td>
<td>5.4 years</td>
<td>a*</td>
<td>prospective</td>
</tr>
<tr>
<td>Pack and Davis\textsuperscript{35}</td>
<td>1961</td>
<td>none</td>
<td>57</td>
<td>10 (6 from lit)</td>
<td>17%</td>
<td>24</td>
<td>unknown</td>
<td>g</td>
<td>review</td>
</tr>
<tr>
<td>Padilla et al.\textsuperscript{36}</td>
<td>1988</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1 year</td>
<td>a</td>
<td>case-report</td>
<td></td>
</tr>
<tr>
<td>Pers et al.\textsuperscript{38}</td>
<td>1963</td>
<td>7</td>
<td>110</td>
<td>2</td>
<td>2%</td>
<td>21</td>
<td>6 years</td>
<td>g</td>
<td>retrospective</td>
</tr>
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DISCUSSION

Since 12 different definitions of GCMN have been used, communication on this subject has been and continues to be still confusing. We identified 35 articles in the world literature concerning the malignant transformation of GCMN in which seven various definitions were used to describe a GCMN (Table III). Incidence rates (1-31%) from patients registered in different referral centres of retro- and prospective studies were compared freely with each other. Discussion remains if all CMN should be prophylactically excised.

Classification according to size

Initial reports of GCMN were descriptive: in 1832, a giant naevus was first mentioned in Alibert’s Monograph of Dermatology, where it was described as a ‘waist coat and drawers type naevus’.66 We feel that terms as ‘bathing-trunk’ or ‘garment’ naevus and Tierfell (animal coat) naevus should be avoided, since they are imprecise and may be offensive to patients and their relatives. As is illustrated in Table I, a wide variety of
criteria for size subgrouping of congenital naevi have been put forward in the literature. The practical classification according to Kaplan\(^30\) is not sufficiently straightforward to distinguish between GCMN and smaller CMN. Their classification can vary between surgeons, depending on their experience with different treatment modalities.

The classification initially put forward by Kopf, which defines a GCMN as a CMN of at least 20 cm in greatest diameter\(^2\) does not take into account the size of the patient.\(^2\) Thus, as congenital naevi tend to enlarge with the general expansion of the skin,\(^70\) a naevus can change in category as the infant grows. The disadvantage of the relative area index (RAI) posed by Enhamre\(^67\) has been pointed out later by Enhamre and Rhodes: a CMN will grow in relation to the affected part of the body,\(^75\) and different parts of the body grow at different rates.\(^67,75\) The percentage of body surface area of the naevus is therefore not entirely constant.\(^18,19\) The surface area of the head expands less and the thighs and legs expand more than the average BSA expansion. However, as a rough guideline with respect to size estimates, it can be said that the surface of the hand (only the palm of the hand) of the patient equals one percent of his/her total body surface area.

### Histological distinction of congenital and acquired naevi

On basis of histology it is hard to predict whether a naevus is a congenital or an acquired lesion.\(^74,75\) The best parameters distinguishing a congenital naevus from an acquired naevus is its presence at birth and its larger size. The recent study of Massi and colleagues is only one of several to illustrate that the histological distinction between congenital and acquired naevi is less than perfect.\(^59\)

Rhodes pointed out that “a classification of histologic patterns is useful only if it is relatively easy to use, accurate, and reproducible”.\(^11\) He pointed out that “it is impossible to compare the histologic studies of Nickoloff\(^13\), Stenn\(^15\), Rhodes\(^54,55\) and Mark\(^12\) because the classifications used to describe histologic patterns of CMN are different”.\(^11\) Mark et al. have stated that “garment naevi need not differ in any way histologically from other small CMN” and that smaller CMN may be as susceptible to the same malignant transformation as garment naevi.\(^12\)

There is room for doubt, whether the histological appearances of a naevus remnant in contiguity with melanoma allows an adequate distinction between acquired and small congenital naevi. The reported data on melanoma with contiguous small congenital naevus appear to be discrepant with prospective, follow-up data. We agree with those who have stated that the similarities of acquired naevi and small congenital naevi are far more striking than the differences and hypothesize that possibly, a naevus remnant may undergo some influence of a nearby melanoma and thus may perhaps come to be misinterpreted as congenital rather than acquired. Whether this is true or not will require
further study, but there can be no doubt that the decision whether a naevus remnant next to melanoma is congenital or not is even more difficult than when the entire naevus, lying in normal skin, is available for study. Of course, the identification of malignancy, or its exclusion, is of far greater importance than the question whether the naevus is congenital or acquired.

**Melanoma risk**

The absence of unequivocal histological indicators of the congenital nature of a naevus makes it difficult to provide reliable data regarding the chance of malignant transformation of a small congenital as opposed to an acquired naevus. The relative risk for the development of a melanoma within GCMN as reported in the literature varies from one to 31%, using seven different definitions. Incidence rates have been based on patients visiting general hospitals, academic referral centres, oncology centres, pediatric centres and public health centres and on top of this, different classifications for GCMN have been used and different age groups of patients. Therefore it is impossible to draw real conclusions on the magnitude of risk on malignant transformation of GCMN.

We first analysed the reported risk for developing a malignant melanoma in relation to the classifications used in literature to describe a GCMN. We calculated an average risk of 8.5% in the nine studies using the definition of Kopf, regardless the character of the study. This risk is 7.5% in articles using the clinical definition proposed by Kaplan, and only 5.3% in articles using the total body surface area to define a GCMN. If we just summarise the reported risks in literature, regardless the classification used, we calculated an overall average risk of 8.2%. Again these rates were calculated regardless the character of the study and kind of referral centres, which are in no doubt of importance with regard to the real risk of the malignant potential of GCMN.

We secondly analysed the different reported risk in relation to referral centres and character of the study. In literature the average risk of malignant transformation of a GCMN in retro- and prospective studies of academic referral centres have varied from 2.3% to 11%. Prospective studies of academic referral centres showed significantly lower average rates of two to five percent, in which the average follow-up period varied from 4.5 to 7.3 years. Important mentioning is that all these prospective studies used the definition proposed by Kopf. Recently Bittencourt et al. calculated an incidence rate of 2.3% in 160 patients with GCMN not selected for age registered in the New York Registry, with an average follow-up period of 5.5 years. Obviously a much longer follow-up period is required to provide an accurate estimate lifetime melanoma risk.
Reported incidence rates of malignant transformation in retrospective studies from general hospitals have been approximately 10%. Several points should however be borne in mind: most studies of general hospitals concerned single case-reports, thus resulting in an inappropriately high number of melanoma associated with GCMN. Similarly, selection bias and small patient numbers in retrospective studies may well have exaggerated the estimates of risk of malignant transformation. From our own analyses it is clear that prospective studies of academic or general centres yielded lower rates of malignant risk than retrospective studies in these centres. Referral bias may additionally have resulted in overestimations of risk. Indeed, the highest incidence rate (31%) were calculated by Reed et al. from a retrospective review of histopathologic materials in an oncology reference centre.

Thirdly we analysed the reported risks in relation to the patient’s age. In general, patients were selected regardless of age, and patients entered the study on time of consultation. Only Ruiz-Maldonado selected pediatric patients younger than 16 years of age. The average age on which patients developed a MM in literature, regardless the classification used, their referral centre and character of the study was 11.1 years. In their review of world literature, Kaplan and colleagues showed that the highest risk of malignant transformation is before the age of ten. Lawrence concluded in his review article that the risk for malignant transformation in a GCMN decreases with age. Apart from the patient’s age, Swerdlow’s cohort-study supported the idea that the risk of melanoma increases with the size of the nevus. Pack and Reed found that almost half the cases of melanoma associated with GCMN not selected for age occurred before the age of five years. In prepubertal metastatic melanoma associated with GCMN, Trozak found that most cases occurred at or before the age of three years. Because of this, Rhodes commented in his article that an early registration of patients with GCMN ensures a realistic estimate risk, while late registration may underestimate the risk. Trozak also found in his study that melanomas usually arise deeply in the naevus, which may cause a delay in its identification.

Finally we looked at melanoma developing in small naevi. According to Rhodes, the estimated cumulative risks of melanoma for persons to the age of 60 with small CMN, are 4.9% by historical assessment and 2.6% if histologically confirmed. Otley criticised the study of Sahin, who had concluded that there is no clinically significant increased risk of melanoma in medium-sized CMN. Otley pointed out that a study many times larger in magnitude of numbers or follow-up duration would be required, and that risk might be underestimated since the most atypical naevi had been selected and removed.
Prophylactic treatment of CMN or not?

Pers reported that 54% of the GCMN patients from his series suffered from significant psychological or emotional distress caused by the naevus. The appearance of a GCMN and the psychological implications are important indications for surgical treatment. Besides their psychological implications, it has been strongly advocated that GCMN should be removed because of their malignant potential. Although several surgical techniques available for treating a GCMN and their malignant potential have been reported by various authors, none of these has gained universal acceptance. A key question is, whether all CMN should be excised, as Rhodes advised, or only GCMN, as is the preference of Kopf. Kaplan advises to use preoperative histological assessment by multiple biopsies as a guide to clinical management, but this approach requires confirmation. Betti found prophylactic removal of all small CMN not feasible, because of their large number and frequency. However, she advised to remove small CMN as soon as changes are observed on clinical or epiluminescence microscopical evaluation. We think that further investigation is necessary before we can safely advise to this wait and see policy and only remove the unequal pigmented and prominent small naevi. In addition, some authors advise MRI scanning of the central nervous system when the GCMN is located on the neck, scalp or medial back, since a GCMN at these sites may be part of neurocutaneous melanosis (NCM), which may be asymptomatic at the time of the diagnosis of the naevus. NCM can present with symptoms of increased intracranial pressure, hydrocephalus and seizures, and carries a poor prognosis. In view of the poor prognosis of the associated central nervous system disorder, such patients should not be burdened with major operations on their cutaneous naevus.

CONCLUSION

So far, no classification of CMN has gained universal acceptance. To compare study results from different centres, it is essential that CMN are subclassified according to and generally accepted criteria. We feel that the use of the percentage of body surface area covered by the naevus is probably the best measure of the size of a congenital naevus, with further subdivision relating to affected body site. Subdivision according to sizes that does not take into account the patient’s body size, does no justice to the major differences in body size especially in the pediatric patient group. Thus, we support the recommendations of Lorentzen and colleagues, that facial naevi covering at least one percent of body surface area, and naevi located elsewhere covering at least two percent of the body surface area are the ones to be classified as GCMN.
The histological features of congenital naevi are essentially similar to those of the much more common acquired naevi, which arise later in life; the main differences are their often larger size and greater cellularity, with extension of the naevus cells into the deep dermis and underlying tissues, especially in the larger examples. Still a congenital naevus is apparent at birth or becomes so within several weeks thereafter. Of course, the identification of malignancy, or its exclusion, is of far greater importance than the question whether the naevus is congenital or acquired.

The controversy concerning the best clinical management, especially of GCMN, and uncertainty regarding on the magnitude of the risk of malignant transformation continue to confuse physicians, patients and parents. Nonetheless, therapy choices have to be made. Physicians should first consider whether there is a need for treatment. Risk of malignant transformation and effects of the presence of the naevus on the patient’s well-being and psychological development are the main issues in this respect. The psychological implications of the CMN will obviously depend not only on the size but also on the location of the naevus. We feel that patients and their responsible family members should be informed as well as is possible, given the uncertainties outlined above, about the risk of malignant transformation. We ourselves advise surgical treatment of all CMN regardless their size, whenever this is feasible. When a GCMN is located at the head or spine, we advocate magnetic resonance imaging to determine the presence of neurocutaneous melanosis (NCM). In the presence of symptomatic NCM, extensive efforts to remove a GCMN are probably not warranted because of its poor prognosis. The choice of treatment depends on a variety of factors, including the experience and preferences of the physician based on the clinical aspects of the CMN, but also the wishes of the patient, and should be individualised accordingly. The establishment of a trusting and open physician-patient relationship is of central importance in this respect. Further systematic prospective studies regarding outcome of surgery on the cosmetic appearance and on the diminution of risk of malignant transformation remain necessary, in order to further fine-tune the choice of therapy. Real conclusions concerning the estimated risk of malignant transformation, are only possible by life time control on treated and untreated patients with GCMN and registration of malignant melanoma in both groups. For obvious reasons, such an ideal long term randomised study seems unfeasible, since the cosmetic results in order to completely excise the GCMN are of utmost importance.
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