Giant congenital melanocytic naevi: definition, malignant transformation and treatment modalities
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Chapter 7

Summary and General discussion
Giant congenital melanocytic naevi (GCMN) are rare and estimated to occur once in every 20,000 live births.\(^1\) They are by definition noted at birth or within the first weeks of life, and commonly they are defined by measuring more than 20 cm in greatest diameter or exceeding one percent of body surface area in the face or two percent elsewhere.\(^2,3\) Apart from imposing a significant cosmetic and psychosocial burden, they are associated with an increased risk of melanoma.

In chapter 2 we show that lack of consensus for the definition of GCMN, impedes good interpretation of data concerning malignant transformation and histology and as a consequence parents cannot be informed properly. We found that in the literature 14 different definitions are used for GCMN. Some have chosen not to use a numerical size parameter as cut-off point between subgroups, while others have based the subdivision on the feasibility of primary excision in one procedure or on size relative to body size. We think that the use of the percentage of total body surface area (TBSA) covered by the naevus is the best measure of the size of a congenital naevus, with further subdivision relating to affected body site.\(^2\) Subdivision by size only does not take into account the patient’s body size and its major changes during growth, especially in the younger pediatric patient group.

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 and the extension of the naevus cells into the deep dermis and underlying tissues, especially in the larger lesions. Of course, the histological 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 of GCMN is enhanced by the uncertainty regarding the risk of malignant transformation and it continues 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.

In chapter 3 we describe a retrospective study based on a nation-wide pathology database, in order to estimate the number of cases of malignant transformation occurring in CMN in the Dutch population from January 1\(^{st}\) 1989 until December 31\(^{st}\) 2000 and assess clinical details. The cases were detected with a query in the comprehensive automated pathology archive (PALGA) with which almost all Dutch pathology laboratories
are linked, and which stores the pathology reports of all participating laboratories. To our knowledge, this is the first study in which standardised incidence rates for malignant melanoma (MM) arising in naevi have been calculated in patients with CMN and GCMN by sex, age and location. These standardised incidence rates are more accurate than a calculation of a general incidence in percentage, in which patients of different ages and sex, patients with different locations of CMN and with different follow-up periods are being compared. So, in other words, we not only considered characteristics of the sample, but also the time period used for the incidence calculation. Furthermore, we took into account the age and sex of the patient, location of the CMN and GCMN and calculated these features separately. Furthermore, we were able to compare our data of MM with the database of the National Cancer Registry (NCR). So we could calculate the increased risk of developing a MM in (G)CMN patients compared with the general population. Our total analytic cohort (of CMN and GCMN) has a 12 times higher risk compared with the incidence in the general population. In our analytic cohort women have a higher risk for developing a MM compared with men (14.1 and 6.4 respectively). This is in close relation with the incidence rates of the NCR. In concordance with the literature, our data show that GCMN have a much higher risk for developing a MM. We found a 51 fold increase in melanoma risk. It should be borne in mind that a melanoma may develop in a (G)CMN at any age; the belief that the risk disappears once the patient reaches adulthood is erroneous. There is no convincing evidence in this study to suggest significant age-related differences in frequency of malignant transformation of (G)CMN. In this nation-wide retrospective study we analysed the standardised incidence rates of melanoma for the largest group of CMN thus far reported in the literature (3929 patients) with 19253 person-years by sex and location. However only a major and very long-term prospective study of untreated CMN would provide definitive data regarding the life-time risk of malignant transformation of CMN. Obviously, such an ideal long term randomised study seems unfeasible, since it seems to be unethical to withhold treatment to a control group. Thus, we have to accept that available data can only provide an approximative estimate of the risk.

Based on retrospective data, early excision seems indicated and preferable at young age. 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, location and size of the CMN, and the definitive choice should be individualised accordingly.

In chapter 4 we evaluated the long term cosmetic and oncological results of excision and subsequent reconstruction in 17 cases of GCMN on scalp and periorbital region after early tissue expansion. We paid special attention to the prevalence of major and minor
complications, since these are seldom described in literature. We showed that GCMN of the scalp or forehead can be excised completely after early tissue expansion. By means of a validated evaluation tool for evaluation of scars, we showed good cosmetic results. In seven patients (18% of the tissue expanders) expander related complications occurred; exposure of the expander, implant failure or infection which all caused a short interruption in the reconstruction program. Our complication rate is comparable with the data of 9 to 24% reported in previous publications. In five patients minor (reconstruction) complications developed, in two as a minor elevation of the eyebrow. Although seemingly obvious, GCMN located at a temporal or frontal region are prone for disturbing the symmetry of the brow position. In our study re-pigmentation very rarely occurred and implicates the accurate and complete removal of the GCMN.

Frieden and colleagues advocate to make an MRI scan of all patients with GCMN at the scalp or back, in order to detect neurocutaneous melanosis (NCM). Neurocutaneous melanosis is a rare phakomatosis characterised by CMN associated with leptomeningeal melanin-deposits. We now know that neurologic asymptomatic patients with NCM characteristics shown at MRI, do not have a worse prognosis than patients without NCM. We doubt whether an MRI under general anaesthesia is indicated in asymptomatic patients; since in asymptomatic patients the presence of NCM does not influence our choice of treatment nor their survival. In summary tissue expansion is a good method for removing GCMN located at the scalp or forehead with a good cosmetic end-result. Performing tissue expansion at a young age is advisable.

Unfortunately, it is not always feasible to excise a GCMN even after TE or serial excision due to the size and deep spread of GCMN; in such instances, superficial ablative techniques as curettage are indicated. The primary aim of curettage treatment is the improvement of the cosmetic result; also, it is hoped that the reduction of numbers of naevus cells reduces the risk of malignant transformation.

In chapter 5 we investigated the long term cosmetic and oncologic results of curettage of GCMN. In nine years eight neonates were treated, with a mean follow-up period of 5.6 years. In only one patient no re-pigmentation did almost occur, and four patients (50%) developed severe re-pigmentation. Except for the patient without re-pigmentation, all other patients underwent additional surgery because it was not possible to perform satisfactory complete curettage at the borders. Almost all patients and parents were satisfied with the cosmetic improvement by the curettage, despite the re-pigmentation. No malignant transformation was discovered during our follow-up period. Curettage of GCMN at a very early age has been based upon the supposedly superficial location of naevus cells and the finding of an easy cleavage plane between the upper and lower dermis during first weeks of life. Moss noted that this cleavage plane is not present in
the normal skin and that it is not located at the junctional area of the naevus. Mark et al. mentioned in 1973 that in the reticular dermis and subcutis, naevus cells in CMN are usually disposed as single cells between collagen bundles and fat cells, but also found naevus cells in the hair follicles which are surrounded by collagen sheaths with anchors in the subcutis, and in erector pili muscles. In fact, in our experience the histological features of GCMN in infancy are variable, and may include the presence of large numbers of naevus cells arranged in densely cellular masses within the dermis. Such cellular masses, which contain little collagenous stroma, present a plausible explanation for the plane of cleavage found by the surgeon, since in contrast to normal collagen-rich reticular dermal tissue, such naevus cell masses provide little resistance to the physical trauma of the surgeon. The plane of cleavage would thus lie in the level where cellularity of the naevus is high; this is in accordance with our finding of many naevus cells in the post-curettage biopsies mentioned above. The disappearance of the “cleavage” plane after a few weeks of life can be explained by the gradual emergence of more collagen-rich stroma within the main mass of the naevus. De Raeve published in a period of 14 years, a total amount of 19 neonates treated by curettage. The author mentioned in her study that naevus cells in the superficial component of the GCMN, were more proliferative, and this component was more vascular compared with its deep component and with MCMN, which were not removed after curettage.

Apart from curettage, there are two other incomplete removal treatments of GCMN; dermabrasion, and laser therapy. The disadvantage of dermabrasion is that it is followed by re-pigmentation if performed (too) superficially, but produces hypertrophic scares when performed too deeply. The same is true for laser treatment which has been justified on the basis of the superficial position of the majority of the pigment in GCMN. Again the deeper naevus cells in the deep dermis and subcutaneous fat remain. Also, the naevus cells are repeatedly damaged by the laser treatment and thereby repeatedly inducing re-activation of the deeper located naevus cells. Long term follow-up on cosmetic and oncologic results are lacking until now. We do know that the created hypopigmentation due to the laser treatment, makes it very hard to discover a malignancy.

In conclusion the presence of re-pigmentation shows that it is unrealistic to aim at removal of all naevus cells with curettage. Long term follow-up and close monitoring of pigmentation remains essential to detect malignant transformation at an early stage.

In chapter 6 we described two families with familiar clustering CN. The molecular mechanism underlying melanocytic neoplasia remain unknown, but various mechanisms have been postulated and consequently CMN formation is likely to be a multifactorial process. Most cases of GCMN are sporadic, but there are several reports of familial
clustering leading to the suggestion that at least some genetically inherited basis exists.\textsuperscript{15} Reports of identical twins discordant for GCMN, however, confound this issue.\textsuperscript{16,17} It is suggested that GCMN reflect a cutaneous mosaic of the ‘GCMN trait’. This trait is neither dominant, as it does not display a Mendelian pattern of inheritance, nor recessive as a homozygous phenotype has never been observed and is probably not viable. Rather, it is paradominant: such a trait does not manifest in a heterozygous individual and can thus be transmitted unperceived in families, until loss of heterozygosity occurs due to a postzygotic mutation leading to a mosaic in which the disease manifests. However, no such trait has been identified.

Future perspectives

At the start of our research we tried to set up a protocol for the diagnosis and treatment of GCMN. Working our way through, we understood that there is a lack of consensus how to define CMN and therefore we first sought for a proposal for the definition of GCMN, calculate the chance for malignant transformation and described specific treatment results (this thesis). We feel that it is necessary to set up a nation wide database (as in New York and Germany) for registration of patients with GCMN. This registration should be performed by for example midwife’s, general practitioners, and by medical specialists. Of course these physicians must be informed properly and get familiar with the database. Further patients and their relatives should be informed properly and be able to get in contact with physicians through the website, so there is a possibility for cross linking for registration of patients. Data should be controlled and analysed, for example, by a research centre.

Recently, the explanation for malignant transformation for GCMN has been sought in genetic mutations (BRAF oncogene and NRAS mutations). Michaloglou showed in vitro and in vivo in our own CMN BRAF (V600E) expressing melanocytes.\textsuperscript{18} Hopefully further research in this field will give us more information concerning malignant transformation. The extensiveness of GCMN poses physicians for a major reconstructive challenge, since (early) prophylactic excision has gained more and more acceptance. Integra ®, a permanent dermal replacement, provides an alternative to the traditional reconstructive choices. The use of a bioengineered, cell-free dermal matrix expands reconstructive options and after engraftment, epidermal coverage can be restored with a thin split-thickness skin graft. Since in naevus excision the dermis is also excised, Integra can provide a rigor and better cosmetic result.
Also further research in familiar inheritance is needed, since familiar clustering is known and parents and their relatives have a great urge for knowledge in this field. A nation wide registry could be helpful in analysing the genetic components of familiar clustering GCMN.
References


16. Voigtlander V and Jung EG. Giant pigmented hairy nevus in two siblings. Humangenetik 1974;24:79-84
