Giant congenital melanocytic naevi: definition, malignant transformation and treatment modalities
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Chapter 6

Familial clustering of giant congenital melanocytic naevi

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Abstract

Giant congenital melanocytic naevus (GCMN) is an infrequently occurring congenital malformation. GCMN generally occurs isolated but rare familial occurrence points to a genetic background. We present two cases of familial GCMN: one with two affected siblings and another with two affected double second cousins. Familial occurrence of GCMN reported in literature is reviewed, and an overview of the embryology and proliferation is given, illustrating the plethora of factors that might lead to GCMN formation. The pattern of inheritance is likely not Mendelian, and discordance in identical twins and the segmental distribution of lesions suggest a postzygotic mutation. A polygenic paradominant inheritance explains the clinically observed transmission pattern best. Candidate genes include those influencing neural crest development and melanocyte proliferation.
Introduction

Giant congenital melanocytic naevi (GCMN) are benign proliferations of cutaneous melanocytes, present at birth or within the first weeks of life, with a minimum size of 1% total body surface area (TBSA) at the head or 2% elsewhere.\(^1\) Size, location, macroscopy, and histology can vary remarkably.\(^2\) GCMN are infrequent, the frequency at birth being estimated as one in every 20,000 live born children.\(^3\) GCMN frequently impose a significant cosmetic and psychosocial burden to affected persons. In addition, they are associated with an increased risk of malignant melanoma\(^3,4\) and may be associated with neurocutaneous melanosis (NCM).\(^5,6\)

Almost all GCMNs occur sporadically, but familial clustering has been reported.\(^7-10\) Discordant identical twins however are also known.\(^11-14\) Etiology and pathogenesis remain unknown, and various mechanisms have been postulated such as erroneous neural crest development,\(^15,16\) activating mutations of melanocyte proliferation,\(^17-20\) cutaneous mosaicism and paradigmatic inheritance.\(^21-23\)

Here we report on two familial cases of GCMN, and review familial occurrences and the various hypotheses regarding aetiology and pathogenesis.

Materials and Methods

The Department of Plastic, Reconstructive and Hand Surgery of the Academic Medical Centre in Amsterdam serves as a referral centre for children and adults with GCMN. We surveyed files of all patients in search for familial occurrence of GCMN. Medline and Embase databases were systematically searched by combining relevant search terms and synonyms for GCMN, familial occurrence, consanguinity, chromosome abnormalities, and the co-occurrence of pigmentation or other disorders.

Results

Patient Survey

From 1991 to date, 120 patients with GCMN were treated. There were two families with more than one member affected by GCMN. Other, likely unrelated, disorders that were present in patients were cleft palate, congenital cataract and phenylketonuria. The latter patient also had trisomy 21. No other chromosome abnormalities were identified.

The first patient was a boy with a typical GCMN located on the occipital region, covering approximately 1% TBSA (Fig. 1). The lesion had an evenly brown colour with hairy patches, was excised, and follow-up was uneventful. The boy did not have any other
abnormalities. A subsequent sister of the patient (Fig. 2) was born with a large GMCN of the back and buttocks covering approximately 10% TBSA (Fig. 3). The lesion was hairy and unevenly coloured, and excised in three stages with serial tissue expansion. The girl was otherwise healthy and follow-up was uneventful.

The second patient was a girl with a GCMN of the abdomen, back, buttocks and upper legs covering approximately 30% TBSA (Fig.4). The lesion was hairy, unevenly coloured and had several satellite lesions. In addition, a soft tissue hypotrophy of the right upper leg was noted, as well as two hypertrophic masses over the sacrum and mons pubis. These soft and painless masses were pigmented, hairless and had a stuck-on appearance. Most of the GCMN and both hypertrophic masses were removed in three stages using a combination of curettage, excision and split-thickness skin grafting.

Figure 1: Family I, patient 1. A congenital pigmented lesion of the occiput measuring 3 x 7 cm.

Figure 2: Pedigree of Family I.
Figure 3: Family I, patient 2. A hairy, unevenly pigmented lesion of the back measuring >20 cm across.

Figure 4: Family II, patient 1 at birth showing a large, unevenly pigmented lesion of the back, buttocks and left upper leg as well as a hypertrophic area over the sacrum (Remainder of lesion not shown).
Histologically, the large protuberant mass on the back was found to result from a markedly increased amount of pale myxoid matrix accumulating between the scattered naevus cells, which themselves were unremarkable and devoid of nuclear atypia (Fig. 5). The overall picture was reminiscent to but still different from diffuse cutaneous neurofibroma. The localisation within the congenital naevus and the presence of focal pigmentation strongly suggest the lesion was an integral part of the congenital melanocytic naevus. Similar masses have previously been described and were thought to represent neurofibromas or neurotized naevi, based on clinical and histological examination. \textsuperscript{24-26} This feature can be explained by the common origin of melanoblasts and neural precursors from the neural crest.

![Figure 5: Histopathological analysis of the protuberant mass from Case 1 from family II, showing a marked increase of pale myxoid matrix accumulating between the normal nevus cells.](image)

As one mass was positioned over the mons pubis, an endocrinological work-up was conducted. This initially suggested a mild non-classical 21-hydroxylase deficiency, but repeat analysis at the age of seven years gave normal results. The girl had no other features of 21-hydroxylase deficiency. Follow-up was uneventful.

The family history showed the daughter of the sister of the mother also had a GCMN (Figure 6). This patient had a circular pigmented lesion of the entire right arm excluding the palm, a 10 cm lesion over the left elbow and a 15 cm lesion over the left lower leg, in total covering approximately 11% TBSA (Fig. 7). In addition, approximately 75 0,5-3 cm satellite lesions all over her body were present. The lesions were all hairy and unevenly
coloured. In addition, a soft tissue hypotrophy of the entire right arm was noted. She had no other abnormalities, notably no hypertrophic masses, and was otherwise healthy. An endocrinological work-up gave normal results.

**Figure 6:** Family II, patient 2 at age 12 showing a circular pigmented lesion of the entire right arm.

**Figure 6:** Pedigree of family II. Please note IV:4 and IV:5 are double second cousins.
No other cases of GCMN occurred within the two families. All patients’ parents were physically examined for the presence of naevi and the extended family was interviewed telephonically; a significantly increased number of naevi was not reported. No skin cancer, pigmentation disorders or other major disorders occurred in two families.

**Literature Survey**

Literature search yielded four reports on familial occurrence of GCMN (Table 1). In each family only two closely related members were affected, and in none associated physical or genetic abnormalities were mentioned. Danarti et al. reviewed a further three cases of which there was no full-text availability. A survey amongst several patient organizations showed that there are no known familial cases in the NYU-LCMN registry, Nevus Outreach support group or the Nävus-Netzwerk registry.

In none of these reports the patients were born to consanguineous parents; sporadic GCMN from consanguineous parents however has been reported by Goodman et al. In addition, there are three reports on twins with GCMN; all were discordant same-sex monozygotic twins. Reports on chromosome abnormalities in GCMNs are infrequent. Dessars et al. found two balanced translocations involving the BRAF gene and one deletion of the long arm of chromosome 6 out of 27 GCMNs. Heimann et al. analyzed a single GCMN and found 22% of mitoses to be polyploid and 4% with chromosome rearrangements involving 1p, 12q and 19p. Finally, Bastian et al. found no chromosomal aberrations in eight GCMN without foci of proliferation.

In addition to the previously mentioned neurocutaneous melanosis, a variety of co-occurring disorders has been associated with GCMN, including structural brain abnormalities (Dandy-Walker malformation, hemimegalencephalopathy, meningohydroencephalocele, Table 1: Summary of reported familial clustering of giant congenital melanocytic naevi.

<table>
<thead>
<tr>
<th>Author</th>
<th>Familial relation</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Nevi in family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecht (1981)</td>
<td>Double first cousins</td>
<td>Male; hairy naevus covering half of the scalp</td>
<td>Female; hairy naevus covering half of the scalp</td>
<td>None</td>
</tr>
<tr>
<td>Voigtländer (1974)</td>
<td>Siblings</td>
<td>Male; hairy naevus encircling the wrist</td>
<td>Female; hairy naevus Parents &lt; 10 small covering abdomen, hairless naevi buttocks and thigh. Multiple satellite naevi</td>
<td>Parents unaffected</td>
</tr>
<tr>
<td>Beck (1921)</td>
<td>Grandson/grandmother</td>
<td>Male; ‘tierfell’</td>
<td>Female; similar distribution</td>
<td>Parents unaffected</td>
</tr>
<tr>
<td>Gould (1896)</td>
<td>Siblings</td>
<td>Male; hairy naevus covering the trunk and thighs. Hundreds of satellite naevi</td>
<td>Female; hairy naevus covering the entire back. Hundreds of satellite naevi</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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lissencephaly\textsuperscript{38} and microcephaly\textsuperscript{39}) spina bifida occulta,\textsuperscript{24} polydactyly,\textsuperscript{39} linear epidermal naevus syndrome,\textsuperscript{40} segmental neurofibromatosis,\textsuperscript{24,41-43} encephalocraniocutaneous lipomatosis,\textsuperscript{37} general lipomatosis,\textsuperscript{32} placental nevomelanocytosis,\textsuperscript{44-46} Hirschsprung disease\textsuperscript{47} and hypotrophy of the underlying bone\textsuperscript{48} or subcutaneous fat.\textsuperscript{49,50}

**Discussion**

Out of 120 patients, two cases of familial clustering and one chromosomal aberration were identified. The results from the literature search underscribe that, albeit rare, familial clustering of GCMN does occur and leads to suggest that some inheritable factor is implicated. In order to discuss inheritance, first the embryology and proliferation of melanocytes and GCMN will be briefly reviewed.

**Embryology**

Melanoblasts are derived from the neural crest and proliferation, differentiation and migration is regulated by a complex network of interacting genes, such as the microphthalmia-associated transcription factor gene (Mitf)\textsuperscript{51} and the c-kit proto-oncogene.\textsuperscript{52} Mutations in this network may deregulate the pigmentary system during embryogenesis, resulting in various congenital pigmentation disorders. This mechanism is thought to explain the deposition of melanocytes in the leptomeninges\textsuperscript{53} and placenta\textsuperscript{44-46} of GCMN patients, and possibly also the co-occurrence of structural brain abnormalities,\textsuperscript{38} spina bifida, neurofibromatosis,\textsuperscript{24} encephalocraniocutaneous lipomatosis\textsuperscript{54} and Hirschsprung disease.\textsuperscript{47} Of interest, it has been hypothesized that as the c-met / hepatocyte growth factor scatter factor (HGF/SF) signaling pathway influences melanoblast proliferation and migration,\textsuperscript{13} a morphogenic error of this pathway with overexpression of either factor may result in abnormal distribution of melanocytes and formation of GCMN or NCM.\textsuperscript{15,16,55}

The rare occurrence of divided naevi sheds some light on the time of congenital melanocytic nevus formation. These naevi are seen at adjacent parts of the body that were fused at some point during embryogenesis, such as the eyelids\textsuperscript{56-58} or the glans penis and prepuce.\textsuperscript{59-61} The current hypothesis is that, after melanoblast migration to the epidermis in the 7\textsuperscript{th} week of gestation,\textsuperscript{62} a single nevus was formed in the period of embryological fusion, which is between the 9\textsuperscript{th} and 20\textsuperscript{th} week for the eyelids and the 11\textsuperscript{th} and 14\textsuperscript{th} week for the penis. After embryological division, proliferation continues as two separate naevi.

An other explanation might be that a propensity to develop GCMN is present in all body cells, and gives rise to an increased chance to obtain a second mutation that will lead to
the GCMN itself. This may be compared to a likely similar mechanism in Klippel-Trenaunay syndrome, in which often an upper and a lower limb are affected but not the trunk in between, indicating these to be separate events in the limbs.\textsuperscript{63} This hypothesis does not necessarily exclude the former hypothesis.

### Proliferation

The proliferation of melanocytes is partially controlled by the RAS-RAF-MAPK pathway, which induces proliferation and melanogenesis in response to UVB radiation and the binding of $\alpha$-melanocyte stimulation hormone ($\alpha$-MSH) to the melanocortin-1 receptor (MC1R).\textsuperscript{64} Various activating mutations in this pathway with a higher kinase activity have been identified.

The somatic $\text{BRAF}^{V600E}$ mutation\textsuperscript{65} has been shown common in both melanoma and different types of melanocytic naevi\textsuperscript{66-69} suggesting it is an early event in melanocytic neoplasia. Germline mutations of the BRAF-gene have not been found in melanoma or naevus patients;\textsuperscript{70,71} however chromosomal translocation was identified as a mechanism of BRAF activation in GCMNs.\textsuperscript{20,72} On the other hand, germline mutations of the BRAF-gene and several other components of the RAS-RAF-MAPK pathway have been identified in cardio-facio-cutaneous syndrome,\textsuperscript{73,74} which is associated with skin hyperpigmentation and frequent naevi.\textsuperscript{75} This substantiates the relationship between these mutations and inherited pigmentation disorders.

There is some evidence that somatic $\text{NRAS}$ mutations in codon 61, which have also been implicated in melanocytic neoplasia,\textsuperscript{76,77} are correlated with congenital melanocytic naevi: Bauer et al.\textsuperscript{17} identified the NRAS mutation in 26 out of 32 congenital naevi, Ichii-Nakato et al.\textsuperscript{19} in 9 out of 20 medium-sized congenital naevi and Dessars et al.\textsuperscript{20} in 18 out of 24 GCMNs. However, the absence of congenital pigmented abnormalities in patients with germ-line NRAS mutations suggest these findings to be secondary phenomena.

In contrast to previous reports\textsuperscript{66,67} very few BRAF mutations were identified in these studies or a study by de Raeve et al.,\textsuperscript{18} who detected no BRAF mutations in 19 GCMNs. Bauer et al.\textsuperscript{18} suggested the previous observations might be due to use of a different definition of ‘congenital’ such as occurring within the first two years of life or based on histological criteria, thereby essentially falsely designating these as truly congenital.

The final component of the RAS-RAF-MAPK pathway that has been implicated in melanoma is the polymorphic germline mutation of MC1R.\textsuperscript{78} Papp et al.\textsuperscript{76} identified MC1R variants in 3 out of 17 CMN, but other germline mutations associated with melanoma and dysplastic naevi\textsuperscript{79} such as CDKN2A and CDK4 were not found.
Inheritance

Based on the occurrence of multiple or medium-sized naevi in the relatives of GCMN patients,\textsuperscript{32} autosomal dominant transmission with variable expression was suggested as a possible explanation for the familial occurrence. However, in the present cases and other reports on familial clustering,\textsuperscript{7-10} no significantly increased number of naevi was observed in the relatives, arguing against such a mode of inheritance.

An autosomal recessive trait is also unlikely, as there is a lack of reports on GCMN patients born to consanguineous parents, and the incidence of familial cases does not fit this model.

Among the discordant and familial cases reported in the literature and those reported here, there was no obvious sex predilection (male:female=5:8 for the familial cases and male:female=2:1 for the discordant cases) and there is also no known difference in severity between affected males and females, making X-linked inheritance less likely.

The occurrence of monozygotic twins discordant for GCMN argues against any Mendelian pattern of inheritance (although this does not rule it out completely), and suggests a postzygotic event might be involved, producing a genetic mosaic in which the disease manifests. For several autosomal dominant skin disorders\textsuperscript{80-82} a segmental pattern of involvement due to cutaneous mosaicism resulting from a postzygotic loss of heterozygosity\textsuperscript{22} has been proved.

As GCMN are likely to be neither dominant nor recessive, the concept of ‘paradominant inheritance’ was introduced. This offers an explanation for the occasional familial occurrence of otherwise sporadic conditions, and also for the discordance in monozygotic twins.\textsuperscript{21} A paradominant trait does not manifest in a heterozygous individual and can thus be transmitted unperceived in families. It is only when a postzygotic mutation causes loss of heterozygosity that the disease manifests in the ensuing mosaic (Fig. 8). This mechanism has also been suggested for other conditions.\textsuperscript{83}

One can speculate mutations disturbing neural crest development are involved, because of their function in melanocyte depositions and the nature of co-occurring disorders. Possibly mutations in genes with different functions are involved, giving rise to polygenic paradominant inheritance:\textsuperscript{84} one or more mutations or polymorphisms segregate on either side of a patients family and each in themselves do not cause GCMN; it is only when a second postzygotic mutation in another gene occurs that a GCMN develops. In this context, the observed somatic mutations of melanocyte proliferation could confer an increased viability to a cell carrying the mutations or polymorphisms.
Conclusion

The multitude of factors implicated in the embryology and proliferation of melanocytes illustrates the plethora of possibilities that might lead to GCMN formation. GCMNs generally occur isolated, but the two familial occurrences described here and the infrequent occurrence reported in literature raise suspicion that an inheritable factor is implicated. The discordance in monozygotic twins and the segmental pattern in which the disease manifests suggest a postzygotic mutation. A polygenic, paradigmatic inheritance can explain the clinically observed transmission pattern. Possibly mutation(s) in gene(s) influencing neural crest development will play a role. However, the exact etiology remains to be elucidated.
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