Giant Congenital Melanocytic Nevi: Selected Aspects of Diagnostics and Treatment

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Background: Treatment of giant melanocytic nevi (GMN) remains a multidisciplinary challenge. We present analysis of diagnostics, treatment, and follow-up in children with GMN to establish obligatory procedures in these patients.

Material/Methods: In 24 children with GMN, we analyzed: localization, main nevus diameter, satellite nevi, brain MRI, catecholamines concentrations in 24-h urine collection, surgery stages number, and histological examinations. The t test was used to compare catecholamines concentrations in patient subgroups.

Results: Nine children had “bathing trunk” nevus, 7 had main nevus on the back, 6 on head/neck, and 2 on neck/shoulder and neck/thorax. Brain MRI revealed neurocutaneous melanosis (NCM) in 7/24 children (29.2%), symptomatic in 1. Among urine catecholamines levels from 20 patients (33 samples), dopamine concentration was elevated in 28/33, noradrenaline in 15, adrenaline in 11, and vanillylmandelic acid in 4. In 6 NCM children, all catecholamines concentrations were higher than in patients without NCM (statistically insignificant). In all patients, histological examination of excised nevi revealed compound nevus, with neurofibromatic component in 15 and melanoma in 2. They remain without recurrence/metastases at 8- and 3-year-follow-up. There were 4/7 NCM patients with more than 1 follow-up MRI; in 1 a new melanin deposit was found and in 3 there was no progression.

Conclusions: Early excision with histological examination speeds the diagnosis of melanoma. Brain MRI is necessary to confirm/rule-out NCM. High urine dopamine concentration in GMN children, especially with NCM, is an unpublished finding that can indicate patients with more serious neurological disease. Treatment of GMN children should be tailored individually for each case with respect to all medical/psychological aspects.

MeSH Keywords: Catecholamines • Melanosis • Nevus, Pigmented

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Background

Giant congenital melanocytic nevi (GMN) occur in approximately 1 in 20,000 newborns. They typically affect trunk and proximal parts of the limbs (bathing nevus), scalp, and neck, but may involve any skin surface. According to the definition, their diameter must exceed 9 cm (20 cm in adulthood) or 2% of body surface. Additionally, in most cases multiple, smaller satellite lesions are present in proximity to the main nevus. The pigmentation of nevi can range from tan to dark brown and depends on concentration and kind of melanin, a natural pigment produced from the amino acid tyrosine in the skin (in the basal layer of the epidermis). The histological characteristics may be heterogeneous within 1 nevus. Nevus cells (melanocytes) extend from the dermal-epidermal junction into the deep part of the skin and sometimes to subcutaneous tissue. Risk for melanoma arising in GMN is about 5–15%. Melanoma may develop early in infancy or in childhood. The other major medical concerns with GMN are the increased risk of associated neurocutaneous melanosis (NCM). NCM is a rare, congenital phakomatosis, characterized by the proliferation of melanocytes in the central nervous system (CNS) that worsens prognosis of patients with GMN. Criteria for NCM were established by Kadonaga and Frieden in 1991 [1]. The risk of developing NCM is not exactly known but is assessed to range from 3% to 12% in the reviewed groups of patients with GMN [2,3]. Neurological manifestations of NCM depend on localization and extension of the lesions and usually occur before the age of 2 years; less frequently, symptoms appear in the 2nd or 3rd decade of life. The most characteristic CNS symptoms include: increased intracranial pressure, seizures, motor deficits, aphasia, and hydrocephalus. In case of spinal localization, myeloradiculopathy, and bowel or bladder dysfunction may occur. Prognosis in symptomatic NCM is poor, but asymptomatic patients have a more unpredictable course. In the literature, most of the symptomatic patients died before the age of 10 years [1,4]. One of the management options in GMN is their surgical removal, which in most cases is impossible in 1 stage. Therefore, it is crucial to have the most exact information about each aspect of this rare congenital disease before initiating multistage surgical treatment.

The pathogenesis of GMN and associated NCM is not clear, but it is generally known that both disorders affect structures of neuroectodermal origin. During early fetal development (5–25 weeks of pregnancy) melanoblasts deriving from the neural crest cells migrate to the basal layer of the epidermis, then they enter epidermis and differentiate into melanocytes. Neural crest cells are also responsible for the formation of leptomeninges; therefore, in the brain melanocytes are normally seen in the pia mater, reticular formation of the medulla, and the substantia nigra. It has been also reported that neurotransmitters (catecholamines) present in human epidermis may influence the metabolism of neuronal cells, as well as human melanocytes. In a study by Takayama in animal and human models, abnormal expression of hepatocyte growth factor/scatter factor (HGF/SF) was detected in extensive pigmented nevi, which may suggest that deregulation of HGF/SF-Met signaling may play a crucial role in the development of GMN and NCM [5].

The purpose of this study was to analyze the diagnostics, treatment, and follow-up in children with giant melanocytic nevi to establish the obligatory procedures in these patients.

Material and Methods

This study included 24 children (14 girls, 10 boys) with giant melanocytic nevi treated between 2004 and 2012 in the Clinic of Pediatric Surgery of Children and Adolescents of the Institute of Mother and Child in Warsaw. The age of the patients at the time of the first operation ranged from 2 days to 7 years.

The data collected from medical documentation included the following: localization of main nevus: bathing trunk (back and/or buttocks and/or abdomen and/or proximal limbs), only back, only head and/or neck, other localization), the biggest diameter of main nevus, presence of satellite nevi, the results of magnetic resonance imaging (MRI) of CNS with regard to the presence or absence of neurocutaneous melanosis (NCM), concentrations of catecholamines (CA: adrenaline – A, noradrenaline – NA, dopamine – DA, vanillylmandelic acid – VMA) in 24-h urine collection, number of operations needed to complete excision of main nevus, and histological examination of the main nevus. The follow-up in relation to presence of melanoma arising in GMN, changes in MRI in case of NCM, and general cosmetic results was performed.

The test was used to compare the mean values of urine catecholamines concentrations (A, NA, DA, and VMA) in the following groups of patients:
- in the whole study group (n=20);
- in the subgroup with brain lesions (n=6) and subgroup without them (n=14);
- in the subgroup with the largest size of the main nevus (bathing trunk and back localization of the nevus [n=14]) and subgroup with smaller size of the main nevus (head and/or neck and other localizations [n=6]).

Results

Localization of the main nevus and presence of the satellite nevi is shown in Table 1 (Figure 1). Nine children (37.5%) had main “bathing trunk” nevus, with the biggest diameter exceeding 20 cm; in 7 cases the main nevus was located on the
Table 1. Localization of main giant melanocytic nevus and presence of satellite nevi.

| Localization of main nevus | Bathing trunk | Back | Head and/or neck | Other localization |
|----------------------------|---------------|------|------------------|--------------------|
| n=24                       | 9             | 7    | 6                | 2 (neck + shoulder neck + thorax) |
| The biggest diameter of main nevus | >20 cm | 10–20 cm | 10–15 cm | 10–15 cm |
| Presence of satellite nevi | 9             | 6    | 2                | 2                  |

Figure 1. Localization of main nevus: (A) – bathing, trunk, (B) – back localization, (C) – head and/or neck, (D) – other localization: shoulder and neck.
back, in 6 on the head and/or neck, and in 2 patients the neck and shoulder and neck and thorax were involved. Diameters of the main nevi ranged from 10 cm to 30 cm. Nineteen children (79.2%) had also multiple satellite nevi. MRI of the brain was performed in all the patients and it revealed NCM in 7 children (29.2%). Localization of melanin deposits in the brain is shown in Table 2 (Figure 2). On clinical examination, 6 of these patients so far are asymptomatic and 1 has seizures. Level of catecholamines in 24-h urine collection was obtained from 20 patients (aged from 1 month to 13 years). Thirty-three samples were examined (from 8 patients, 2 or 3 samples were collected). Dopamine (D) concentration was elevated in 28 of 33 samples (19 patients), noradrenaline (NA) concentration was elevated in 15 of 33 samples (14 patients), adrenaline (A) concentration was elevated in 11 of 33 samples (7 patients), and vanillylmandelic acid (VMA) concentration was elevated in 4 of 33 samples (Figure 3). In 1 patient with a nevus on the head, concentrations of all CA were normal.

In the entire analyzed group, the average concentration of DA was 309.55 ug/24 h (42–765; standard level with respect to age: 61–250 ug/24 h), average concentration of NA was 39.53 ug/24 h (7.9–161; standard level with respect to age: 11–51 ug/24 h), average concentration of A was 4.57 ug/24 h (1.2–11.8; standard level with respect to age: 1.3–7.1 ug/24 h), and average concentration of VMA was 3.57 ug/24 h (0.8–10.6; standard level with respect to age: 0.1–11 ug/24 h).

In the group of patients with NCM (n=7), catecholamine concentrations were obtained in 6 children (11 samples). In 1 of these children, CA concentrations were normal (head localization of the nevus). In the remaining 5 patients, 8 of 11 samples showed elevated level of DA, 7 of 11 samples showed increased level of NA, 4 of 11 samples showed increased level of A, and 1 of 11 samples showed increased level of VMA.

In 6 children with NCM, concentrations of all the catecholamines were higher as compared to patients without brain lesions (DA: 359.6 ug/24 h vs. 284.52 ug/24 h, NA: 39.87 ug/24 h vs. 39.35 ug/24 h, A: 4.82 ug/24 h vs. 4.45 ug/24 h, and VMA: 4.34 ug/24 h vs. 3.19 ug/24 g, respectively), but the t test showed these differences were not statistically significant (Tables 3 and 4).

In the subgroup of 16 patients with the largest size of the main nevus (bathing trunk and back localization), concentrations of A, NA, DA, and VMA were significantly higher than in the group with smaller size of the main nevus (head and/or neck and other localizations, n=6). These results are shown in Table 5.

Among the entire group of 24 analyzed patients, surgical treatment of the main nevus is finished in 8 children (2 of them with NCM). Only 1 of them had 1-stage excision of the nevus. Four patients required 3–6 operations, and 3 patients needed 6–12 stages of operative repair. In 4 of these patients, new satellite nevi are constantly observed. The remaining 17 patients are in the course of stage excision of a giant nevus (at present, 3–13 stages of excision). The example of final cosmetic result is presented in Figure 4.

### Table 2. Localization of melanin deposits in the central nervous system of the children with NCM.

| Age*/localization of main nevus | Sex | Neurological signs | Amygdala | Pons | Cerebellum | Other intraparenchymal localization | Cortex/leptomeninges | Leptomeninges | Contrast enhancement |
|--------------------------------|-----|------------------|---------|-----|------------|-------------------------------|---------------------|--------------|---------------------|
| 1 12 days/ head                | M   | –                | –       | –   | +          | + (Temporal lobes)           | +                   | +            | Gd not given       |
| 2 4/12/ bathing                | M   | +                | +       | +   | –          | –                             | –                   | –            | –                   |
| 3 9/12/ bathing                | F   | –                | +       | –   | +          | –                             | –                   | –            | –                   |
| 4 9/12/ back                   | F   | –                | +       | +   | +          | + (Thalamus)                 | +                   | –            | –                   |
| 5 1.5/12/ back                 | M   | –                | +       | +   | –          | –                             | –                   | –            | –                   |
| 6 4/12/ bathing                | F   | –                | –       | –   | –          | –                             | –                   | –            | –                   |
| 7 7/ bathing                   | F   | –                | –       | –   | +          | + (Thalamus)                 | –                   | –            | –                   |

* At the moment of the first MRI.
In all patients, histological examination of the excised nevi revealed compound nevus. In 15 cases a neurofibromatic component was diagnosed in the deeper part of the dermis, and in 3 of them neurofibromatic lesions were also seen in satellite nevi (Figure 5).

In 2 patients (with bathing trunk and head localization, aged 6 months and 17 months, respectively) melanoma arising in GMN was diagnosed on histological examination after subsequent stage of nevus excision (Figure 6). After broadening the margins of surgical excision, both patients underwent complex oncologic diagnostics. At 8-year and 3-year follow-up, respectively, both patients remain without signs of recurrence or metastatic lesions.

Four of 7 patients with NCM had more than 1 MRI examination during the follow-up period (from 15 months to 62 months). In 1 child a new melanin deposit in the left auditory canal was found on the third MRI. In 3 patients no progression of CNS lesions was observed, and even decrease of some foci was seen. In the symptomatic patient, the ventricular system was dilated in the first MRI examination and its width systematically decreased over the course of 5-year observation.

Discussion

The decision concerning the best way of management the child with GMN is complicated because it involves a multidisciplinary medical team without certainty of success in every patient. The kind of treatment must be tailored individually for each case. The most important medical concerns include: cosmetic implications of having GMN and cosmetic results after their surgical removal, risk of repeated general anesthesia, psychological aspects of needing frequent diagnostic investigations and often multistage operative treatment, risk of developing malignancy, and risk of developing symptomatic NCM [4,6]. An additional factor is parents’ pressure for early surgical intervention deriving from fear of potential transformation to malignant melanoma within the nevus and psychosocial aspects of cosmetic appearance of the child. Therefore, various authors present their own algorithms for management.

![Figure 2. MRI of the brain in patients with NCM. SE sequence, T1-weighted images. Melanin deposits are seen in the amygdala (A), in the cortical/leptomeningeal localization (B), and in the pons (C).](image-url)
Table 3. Concentrations of CA (dopamine, noradrenalin, adrenaline) in 24-h urine collection and localization of main nevus in 6 patients with NCM.

| Localization of main nevus | Age (months) | DA (61–250)* | NA (11–51)* | A (1.3–7.1)* | VMA (0.1–11)* |
|----------------------------|--------------|--------------|-------------|--------------|--------------|
| Head                       | 1            | 42 N         | 7.9 N       | 1.2 N        | 0.1 N        |
| Bathing trunk              | 67           | 160.7 N      | 84 H        | 7.6 H        | 1.7 N        |
|                            | 75           | 92.9 N       | 6 N         | 0.5 N        | 0.8 N        |
|                            | 84           | 347 H        | 48.9 H      | 10.9 H       | 5.4 N        |
| Back                       | 31           | 360.9 H      | 38.7 H      | 2.2 N        | 2.6 N        |
| Bathing trunk              | 60           | 591 H        | 36.7 H      | 3 N          | 6.8 H        |
|                            | 66           | 353 H        | 56.1 H      | 10.7 H       | 3.3 N        |
|                            | 71           | 520 H        | 80 H        | 2.2 N        | 3.9 N        |
|                            | 77           | 262.5 H      | 28.7 N      | 2.9 N        | 3.5 N        |
| Bathing trunk              | 84           | 389.6 H      | 20.8 N      | 2.4 N        | 5.5 N        |
| Bathing trunk              | 156          | 765 H        | 74.1 H      | 8.7 H        | 10.6 N       |

H – increased concentration with respect to age; N – normal concentration with respect to age; * – standard level range (ug/24h).
of GMN with respect to its localization and total size, clinical presentation, and other problems, including potential malignancy or melanosis of the central nervous system. Surgical interventions also include various possibilities – full-thickness excisions, partial-thickness excisions, dermabrasions, curettings, and laser treatment – but there is no agreement about the best age at which to begin the surgery, and the evaluation of which option at which age is best [6–8].

In the presented study, 24 children were diagnosed and surgically treated due to GMN. Their greatest diameters exceeded 20 cm in case of “bathing” nevi and 10 cm in case of other localizations. Additionally, 19 of them had multiple satellite nevi on the entire surface of the body at start of treatment. Generally, we prefer the early surgical management because of ease of performing more radical excision and better late cosmetic results. The age of our patients at the time of first intervention ranged from 2 days to 7 years and depended on the time of the first consultation in our outpatient department and on the clinical presentation of the nevus. Most of the parents of the presented group of children did not accept the suggestion of observation of the lesions and delayed surgery, and wanted to start surgical excision early. Children and parents accepted multistage surgical procedure and even not perfect cosmetic results much better than the presence of thick, rugous, dark skin. They were also afraid of potential malignancy because in most cases nevus appearance was not homogenous and in the first histological examination dysplastic changes within it were found. In the analyzed material in 2 patients (8%), melanoma arising in GMN was confirmed. We did not suspect malignancy in these very young children before subsequent stages of nevus excision because no sudden changes in nevus appearance were observed. The reported risk of transformation of nevus excision because no sudden changes in nevus appearance were observed. The reported risk of transformation of malignant melanoma ranges from 3% to 40% in the literature [7–10]. Such a wide range can be explained by severity of disease in these cases, difficulties of histological evaluation of giant nevi leading to over-diagnosis of malignancy, and inclusion of melanomas outside of the nevi [7,11].

### Table 4. Average concentration of CA (adrenaline, noradrenaline, dopamine and vanillylmandelic acid) in 6 patients with NCM and 14 patients without NCM.

| Localization of main nevus (number of patients) | Average age (months) (min–max) | Average Adrenaline* concentration (ug/24 h) (min–max) | Average Noradrenaline* concentration (ug/24 h) (min–max) | Average Dopamine* concentration (ug/24 h) (min–max) | Average Vanillylmandelic acid* concentration (ug/24 h) (min–max) |
|-----------------------------------------------|-------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------|
| Head/neck, other (n=6)                         | 70.36 (1.0–156.0)             | 4.82 (0.5–11.8)                                      | 39.87 (6.0–161.0)                                       | 359.00 (42.0–765.0)                               | 4.34 (0.8–10.6)                                        |
| Patients with NCM (n=6)                        | 42.00 (1.0–12.0)              | 4.45 (1.1–11.8)                                      | 39.35 (11.2–161.0)                                      | 284.52 (112.0–550.0)                              | 3.19 (1.3–5.7)                                        |
| Patients without NCM (n=14)                    | 42.00 (1.0–12.0)              | 4.45 (1.1–11.8)                                      | 39.35 (11.2–161.0)                                      | 284.52 (112.0–550.0)                              | 3.19 (1.3–5.7)                                        |
| p-value                                       | P=0.779                      | P=0.964                                              | P=0.233                                                | P=0.126                                         |

* Standard level range with respect to age: A (1.3–7.1 ug/24 h), NA (11–51 ug/24 h), DA (61–250 ug/24 h).

### Table 5. Average concentration of CA (adrenaline, noradrenaline, dopamine and vanillylmandelic acid) in the subgroup of 14 patients with the largest size of the main nevus (bathing trunk and back localization) and the subgroup of 6 children with smaller size of the main nevus (head and/or neck and other localization).

| Localization of main nevus (number of patients) | Average age (months) | Average Adrenaline* concentration (ug/24 h) | Average Noradrenaline* concentration (ug/24 h) | Average Dopamine* concentration (ug/24 h) | Average Vanillylmandelic acid* concentration (ug/24 h) |
|-----------------------------------------------|----------------------|---------------------------------------------|-----------------------------------------------|-------------------------------------------|-------------------------------------------------------|
| Bathing trunk, back (n=14)                    | 55                   | 5.29                                        | 45.41                                         | 299.54                                    | 2.91                                                  |
| Head/neck, other (n=6)                         | 21                   | 1.58                                        | 14.32                                         | 141.0                                     | 1.86                                                  |
| p-value                                       | 0.046                | 0.001                                       | 0.001                                         | 0.001                                     | 0.006                                                 |

* Standard level range with respect to age: A (1.3–7.1 ug/24 h), NA (11–51 ug/24 h), DA (61–250 ug/24 h).
MRI of the brain with intravenous administration of the contrast agent should be performed in all patients with GMN [4,12,13]. In the fatal cases in symptomatic patients, MRI demonstrates thickening of the leptomeninges and their strong contrast enhancement after gadolinium administration. The only symptomatic patient in our study group who presented with seizures showed no leptomeningeal enhancement. In our material, NCM was confirmed in 7 of 24 patients with GMN (29%), which is a high incidence rate compared to that reported by other authors. Our patients showed typical intraparenchymal localization of melanin deposits (temporal lobes – mainly regions of amygdala, cerebellum, pons), but also atypical lesions in thalami. In 5 cases, focal leptomeningeal location of melanin deposits was also seen [12]. NCM was diagnosed in 4 of 9 patients with bathing trunk localization (44%), in 2 of 7 patients with back localization (28%), and in 1 patient of 6 with the nevus on the head and/or neck (16%). Six of these patients were below 1 year of age at the time of the first MRI study. During the follow-up period in 1 patient, a new melanin deposit was found in a very uncommon localization never reported before (in the internal auditory canal) and in 3 other
patients decrease of some foci was observed [12]. There is no clear explanation of such findings, but most authors accept the theory that with age, melanotic lesions become less visible due to progressing myelination of the white matter. Therefore, “regression” of brain changes in the course of NCM should be carefully assessed in relation to clinical neurological symptoms [12–15].

We did not find papers in the literature considering plasma or urine concentrations of catecholamines in children with GMN, although high plasma CA level or impaired catecholamines metabolism were frequently reported in other melanocytes-dependent skin disorders because CA and melanin have the same metabolic precursor – tyrosine. Increased CA concentrations were found in diseases with melanin deficiency such as vitiligo, as opposed to our findings in the disease with increased amount of melanin in the skin (GMN) or in skin and brain (NCM). In vitiligo, dopamine shows cytotoxic effect and may induce apoptosis in melanocytes [16–18]. The mechanism of the reverse action in case of GMN and NCM remains to be explained. Gillbro et al. proved presence of noradrenaline line synthesis in human melanocytes leading to melanogenesis. Authors also conclude that melanin production can mirror the stress response [19]. Dopamine has been found to be the most toxic monoamine in inducing apoptosis in neuronal cells [20]. We are at the beginning of this part of evaluation of children with GMN, but initial data are interesting, particularly with respect to dopamine levels. Higher dopamine concentrations in children with GMN and brain lesions (NCM) may help predict the patients with potentially more serious neurological course of this neuroectodermal disease. The statistically significant correlation between larger area of the main nevus (which means higher content of melanin) and higher concentrations of the tested catecholamines in patients with GMN confirms metabolic disturbances of various metabolites deriving from tyrosine.

Conclusions

Parents of children with giant melanocytic nevi prefer early, multistage surgical management because of their constant concern about potential malignancy of the nevus.

Clinical evaluation of changes in giant nevi with thick, not homogeneous, surface in relation to potential malignant transformation is difficult. Therefore, early excision with detailed histological examination of excised parts can speed diagnosis of melanoma.

MRI of the brain is necessary in each child with GMN to confirm or rule out neurocutaneous melanosis, especially its most severe and lethal form, with leptomeningeal contrast enhancement.

The high concentration of dopamine in 24-h urine collection in children with giant melanocytic nevi, especially in those with NCM, has not been published before now, and it is an interesting finding that can help predict patients with more serious neurological course of disease. Treatment of children with giant melanocytic nevi still remains a multidisciplinary challenge. It should be tailored individually for each case with respect to all medical concerns and psychological aspects of management.

Conflict of interest

The authors declare that they have no conflicts of interest.

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