Title: SURGICAL OUTCOMES AND PSYCHOSOCIAL IMPACT OF GIANT CONGENITAL MELANOCYTIC NEVUS SURGERY: A SINGLE-CENTER CASE SERIES OF 136 PATIENTS.

Author names and affiliations:
1. María Carmen Ceballos-Rodríguez[department of dermatology, fundación jiménez díaz university hospital]
Avenida de los Reyes Católicos 2, 28040 Madrid, Spain.
2. Pedro Redondo[department of dermatology, clínica universidad de navarra]
Avenida de Pío XII 36, 31008 Pamplona, Navarra, Spain.
3. Alejandra Tomás-Velázquez[department of dermatology, clínica universidad de navarra]
Avenida de Pío XII 36, 31008 Pamplona, Navarra, Spain.
4. Deysy Cieza-Díaz[department of dermatology, fundación jiménez díaz university hospital]
Avenida de los Reyes Católicos 2, 28040 Madrid, Spain.
5. Juan Carlos López-Gutiérrez[department of pediatric surgery, la paz university hospital]
Paseo de la Castellana 261, 28046 Madrid, Spain.

Corresponding author:
María Carmen Ceballos-Rodríguez[department of dermatology, fundación jiménez díaz university hospital]
Avenida de los Reyes Católicos 2, 28040 Madrid, Spain.
E-mail address: carmen.cebrod@gmail.com
Phone: +34630542694

ABSTRACT

Purpose: The aim of this study was to evaluate the outcomes, complications and psychosocial impact of surgical treatment of giant congenital melanocytic nevus (GCMN).

Methods: Patients with surgically treated GCMN who attended our clinic between May 2014 and May 2018 were included. Patient demographics and data on the characteristics of the nevus, surgical treatment, and the psychosocial impact (including C-DLQI/DLQI questionnaires) were collected.

Results: One hundred thirty-six patients were included (median age 9 years). Mean age at first surgery was 34 (+/- 61.45) months; 5.53 (+/- 3.69) surgical interventions were necessary to completely excise the nevus. The expanded skin flap was the preferred surgical technique in most locations. Complications were common but not severe. Of the patients studied, 70.4% reported that the surgery had had a minor impact on their quality of life (QoL). Patients and caregivers stated that surgical treatment should begin as soon as possible, even in cases where early treatment did not have an impact on their QoL nor on their satisfaction with the surgery ($p < 0.05$). The lower the patient age at first surgery, the higher the surgeon's satisfaction ($p < 0.01$).

Conclusions: Surgical treatment is a safe option for management of GCMN, and has a low impact on QoL. Patients, caregivers, and surgeons agree that the treatment should begin as soon as possible. This is the largest single-center study evaluating surgical treatment in GCMN patients and its psychosocial impact, and the first to take into account the patient, caregivers and dermatologists opinion of surgical results.

KEYWORDS

Giant congenital melanocytic nevus, Surgery, Excision, Quality of life, Phsycosocial impact, Psychology.

LEVEL OF EVIDENCE

Level IV (case series with no comparison group).

Congenital melanocytic nevi (CMN) are neural crest-derived hamartomas that result from postzygotic mutation. Classifications of these nevi are mostly based on the maximal diameter they are expected to reach in adulthood (projected adult size, PAS). Giant congenital melanocytic nevi (GCMN) [1] (or large CMN, depending on the classification [2]) have a PAS larger than 20 cm. GCMN incidence has been estimated at 1 in 20,000 live births [3].

The main clinical complications of GCMN are malignant transformation into melanoma (approximate incidence 2-3% [4–8]) and central nervous system nevomelanocytic deposits (neurocutaneous melanosis, NCM, with and incidence of around 25% [8–13]). Treatment of GCMN is indicated for cosmetic reasons, to alleviate physical discomfort, or to reduce the risk of developing cutaneous melanoma [14], although the latter indication is controversial, since some melanomas arise on the skin around the site of a previously excised GCMN [7] or in an extracutaneous location [6].

The first-line treatment for GCMN is surgical excision, in some cases aided by tissue expanders [15,16] and/or skin grafts. Most of the time, multiple procedures are required to completely excise the lesion, and in certain patients complete excision is impossible due to the size of the lesion. The best age to begin surgical treatment remains controversial, though most authors state that early intervention is better to improve cosmetic outcomes and reduce the psychosocial impact of the disease [17–21].

The GCMN itself and its surgical treatment have a psychosocial impact, and may affect quality of life (QoL) [22,23].

The objective of our study was to evaluate the outcomes, complications, and psychosocial impact of surgical treatment of GCMN.

List of abbreviations
CMN: Congenital melanocytic nevus.
GCMN: Giant congenital melanocytic nevus.
IQR: Interquartile ranges.
NCM: Neurocutaneous melanosis.
PAS: Projected adult size.
QoL: Quality of life.
SD: Standard deviations.

1. Material and methods

1.1. Study design

A case series study was performed. including patients with GCMN who attended the Pediatric Plastic Surgery clinic at La Paz University Hospital between May 2014 and May 2018.

1.2. Clinical assessment

GCMN diagnosis was based on clinical and histological findings.

All patients with GCMN who were being treated surgically or had undergone previous surgical treatment and agreed to participate in the study were included after providing written informed consent (the patients themselves, or caregivers if patients were younger than 18 years of age).

The following data were collected: date of birth, PAS, area and distribution of the GCMN, age at first surgery, surgical procedures and number of surgeries performed, level of satisfaction of the patient (or caregiver if the patient was under age 12 years) and the surgeon with result (using a scale that goes from -5 for lesions that have greatly worsened, to +5 in cases where the lesion has completely disappeared), psychosocial aspects (if patients over 5 years of age preferred the GCMN or the scar, and whether patients over

age 12 or, if younger than 12, their caregiver, thought the scarring was more socially acceptable than the GCMN), and QoL (using the Skindex29, C-DLQI, and DLQI questionnaires, depending on age).

1.3. Statistical analysis

Continuous variables were expressed as mean +/- standard deviations (SD) for symmetric variables or as median and interquartile ranges (IQR) for skewed variables.

For categorial variables, the chi square (χ^2) or Fisher's exact analysis was applied. For continuous variables, the Student's t-test or Mann-Whitney U test was used.

The Shapiro-Wilk test was used to examine if a variable was normally distributed.

Statistical significance was defined by p values of less than 0.05.

All analyses were performed using the Stata/SE statistical package, release 14.0.

2. Results

2.1. Patient inclusion

A total of 136 patients were included, with a median age of 9 years (ages ranged from 1 month to 59 years).

Patient and GCMN characteristics are described in Table 1.

2.2. Surgical techniques, complications, and level of satisfaction with the outcome.

Reconstructive techniques consisted of expanded skin flaps, full-thickness skin grafts, split-thickness skin grafts preceded by a dermal substitute (Integra®), and/or serial excisions. The reconstructive techniques used in this population are described in Table 2. The preferred reconstructive techniques depending on the distribution are detailed in Table 3.

The GCMN had already been completely excised in 56 patients. A mean of 5.53 (+/- 3.69) surgeries were necessary to achieve complete excision. This number was directly proportional to the PAS (Spearman 0.41, $p < 0.01$) and to the area of the lesion (Spearman 0.38, $p < 0.01$), but it was independent of the age at first surgery and the distribution of the nevus.

The mean age at first surgery was 34 (+/- 61.45) months (see Table 4), although the median age was 14 months. This mean age at first surgery was higher for those patients treated only with skin grafts than for those treated only with tissue expanders (51 vs 31 months) (p = 0,029), independently of the nevus size and location. The mean age at the last and definitive (i.e. achieving complete nevus excision) surgery was 36 (+/- 37) months.

The level of satisfaction with surgical results is described in Table 4.

The patient's level of satisfaction was higher in those treated with expanded skin flaps (Fig. 1) compared to those not treated with this technique (3.58 vs 3.21, p = 0.03). There were no differences in satisfaction between those patients who underwent skin graft surgery and those who did not (p = 0.46). The level of patient satisfaction with the surgery was also associated with the distribution of the GCMN: higher levels of satisfaction were obtained from patients with lesions located on the head, and the lowest levels were recorded for those located on an extremity (p = 0.02). Patient satisfaction was independent of age at first surgery (p = 0.58).

For the surgeon, the level of satisfaction was independent of whether we compared expanded skin flaps to other surgical approaches (p = 0.36), but was lower with skin grafts (3.22 in patients treated with skin grafts vs 3.69 in patients treated with other surgical procedures, $p < 0.01$). Surgeon's satisfaction was inversely proportional to the age at first surgery (p = 0.03) and was not associated with the distribution of the GCMN (p = 0.45).

The most common postsurgical complications were as follows: unaesthetic scar (mainly wide scar and hyperpigmentation in 23.46% of the expanded skin flaps and burn-like appearance in 22.58% of the skin grafts), marked asymmetry (13.97%), infection of the

surgical wound (8.64% of expanded skin flaps and 8.06% of skin grafts), and suture dehiscence (9.88% of expanded skin flaps).

In 96.5% of the cases in which the nevus had been completely excised, the dermatologists thought that the scar was less visible than the lesion, independent of the nevus size and location, and surgical procedures. Nevertheless, the only 2 cases in which the scar was more visible, the patients had been treated mainly with skin grafts.

The only complication found to be associated with the distribution of the GCMN was asymmetry, which was more common in the extremities (52.38%), followed by the breasts (21.43%) and the face (14.71%) ($p < 0.01$).

The development of complications was independent of the age at first surgery.

Only fifteen patients (11.03%) had neurocutaneous melanosis, which is roughly half of the rate described in the literature.

Two patients (2.47%) developed melanoma, both with a fatal outcome. One case occurred in an 8-year-old boy in whom the GCMN had been completely excised; the primary melanoma was on the spinal cord. The other arose in a 25-year-old woman, on a GCMN located on the back that had been partly excised.

2.3. Psychosocial impact.

Regarding the impact of surgery on QoL in patients from 4 years of age (item 10 of the DLQI and C-DLQI questionnaires), during the week after the intervention 70.4% of patients reported that the surgery had represented only a little problem in their lives, for 25.9% it had caused quite a lot of problems and for 3.7% it had been very much of a problem. This impact increases proportionally with age at first surgery ($p = 0.02$).

As for the process of decision-making concerning the treatment approach, 92.3% of patients could not participate in the decision because they were too young; in 3.5% of cases the caregivers and the patient arrived at a decision together, and in 4.2% the patients themselves decided to undergo surgical treatment.

Asked when surgical treatment should begin, 89% of caregivers and 99% of patients considered that it should start as soon as possible, and the rest of the responders felt thought that it should begin when the patient could make a rational decision or even delay the decision until adulthood.

When we asked the caregivers (or the patients if they were the ones making the decision) the reason they chose surgery, 28% reported having done so to reduce the risk of melanoma, 17% for aesthetic reasons, and 55% for both reasons.

When we asked the patients (or the caregivers of patients under age 5 years) if they would undergo the surgical treatment again if they had the chance (thus expressing whether they agreed with the treatment chosen by their caregivers or themselves), 89.71% stated that they would make the same decision. PAS, GCMN distribution, age at first surgery, and the number of surgeries did not influence the agreement with the treatment. Patient gender (males had a higher level of agreement than females, 96.61% vs 86.52%, $p = 0.04$) and patient satisfaction with surgical results (more agreement if more satisfied, $p < 0.01$) were associated with the agreement with the decision of surgical treatment.

We asked patients (or their caregivers if the patient was younger than 5 years) if they preferred the GCMN or the scar in terms of cosmetics. We also asked patients (or the caregivers of patients under 12 years of aye) which they thought was more socially accepted. The results are detailed in Table 5.

3. Discussion

Patients with GCMN should be evaluated by a multidisciplinary team compromising dermatologists, surgeons, radiologists, and psychologists.

Surgery is considered the gold-standard treatment for GCMN. To date, several studies have described the best surgical option according to the surgeon's opinion of the surgical

outcome. However, to our knowledge, none of these studies take into account the patient's or the dermatologists' opinion. On the other hand, studies evaluating the impact of surgery on QoL and other psychosocial aspects of children with GCMN are sparse [24–27].

We present a study of 136 patients, most of pediatric age, whose GCMN was surgically treated.

As in most series, GCMN was more common in women (male to female ratio 0.64:1). The number of surgeries required to completely excise the nevus was proportional to the size of the GCMN (PAS and area), but was independent of the age at first surgery and the distribution of the lesion. One might expect that some locations such as the face or the extremities would require a higher number of surgeries [28,29], but we found that all locations had the same level of complexity, each with its own peculiarities. We also must take into account that in this study we evaluated GCMN complete excision, though additional interventions (e.g. subsequent surgery, laser therapy) are often performed to improve the aesthetic outcome of these more exposed locations.

Expanded skin flaps were the preferred surgical technique in most locations, as described in the literature [21,30–32]. However, in GCMN located on the extremities, skin grafts were preferred. This result contrasts with other studies, in which serial excision or expanded flaps were the most common approaches taken in the extremities [21,30,33]; patients preferred skin grafts only in areas of the body where function was at risk, such as the hands or joints [33]. This preference for expanded skin flaps is supported by the greater level of patient satisfaction with the results of this technique. Dermatologists, whose opinion had not been taken into account in previous studies, thought that in the great majority of cases in which the nevus had been completely excised, the scar was less visible than the lesion.

Surgical complications were frequent but not severe.

The arising of a melanoma in a patient with an already excised GCMN also call into question the utility of surgical excision to reduce the risk of this tumor [6].

Most of our patients began surgical treatment before the age of 2 years. The younger the first surgery, the greater the surgeon's satisfaction with the results. Nevertheless, age at first surgery did not influence the number of surgeries required to completely excise the GCMN or QoL or patient satisfaction. This finding contrasts with other articles that recommend early surgical treatment due to its lower psychological impact and effect on QoL [19–21].

The impact of surgery on QoL was slight in the vast majority of patients, and it was proportional to child age at first surgery.

Most patients and caregivers were satisfied with the cosmetic results of the surgery, as reported in other studies [24–27].

A wide majority of patients and caregivers accepted the scar better than the GCMN. They also believed that the scar was less socially stigmatizing, which is likely one of the reasons why they decided to undergo surgery, as they stated in the survey.

Less than 10% of patients were of sufficient age to make a decision on their treatment, yet nearly 90% would have chosen surgery again if the circumstance presented itself, especially males and patients who were more satisfied with the result. These results may be biased in favor of the decision that the patients themselves or their caregivers took [24]. Further survey-based studies should be designed to avoid this confirmation bias.

4. Conclusions

Surgical treatment is a safe option in the management of GCMN, and has a low impact on QoL. Patients, caregivers, and surgeons agree that the treatment should begin as soon as possible, although in this study this did not have an impact on the number of surgeries,

patient satisfaction with the results, or their QoL (though it did influence in the level of satisfaction of the surgeon).

Surgeons, patients and dermatologists, in the great majority of cases, think that the scar is more cosmetically acceptable than the lesion.

This study is limited by its short duration. It would be of interest to perform a longer follow-up of patients, evaluating the psychosocial impact of surgical treatment before, during and after complete excision of the GCMN.

To our knowledge, this is the largest single-center study evaluating surgical treatment in GCMN patients and its psychosocial impact. It is also the first to take into account the patient, caregivers and dermatologists level of satisfaction when evaluating the results of the surgery.

Highlights

· Surgery is a safe treatment for GCMN.
· Expanded skin flaps are the most optimal surgical option in most cases.
· Surgeons, patients, and caregivers agree that surgical treatment should begin in the first months of life.
· Surgical treatment has a low impact on QoL.

References

[1]   Ruiz-Maldonado R. Measuring congenital melanocytic nevi. Pediatr Dermatol 2004;21:178–9. https://doi.org/10.1111/j.0736-8046.2004.21222.x.

[2]   Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. J Am Acad Dermatol 2013;68:441–51. https://doi.org/10.1016/j.jaad.2012.05.043.

[3]   Castilla EE, da Graça Dutra M, Orioli-Parreiras IM. Epidemiology of congenital pigmented naevi: I. Incidence rates and relative frequencies. Br J Dermatol 1981;104:307–15.

[4]   Watt AJ, Kotsis S V., Chung KC. Risk of melanoma arising in large congenital melanocytic nevi: A systematic review. Plast Reconstr Surg 2004;113:1968–74. https://doi.org/10.1097/01.PRS.0000122209.10277.2A.

[5]   Krengel S, Hauschild A, Schäfer T. Melanoma risk in congenital melanocytic naevi: A systematic review. Br J Dermatol 2006;155:1–8. https://doi.org/10.1111/j.1365-2133.2006.07218.x.

[6]   Kinsler VA, O'Hare P, Bulstrode N, Calonje JE, Chong WK, Hargrave D, et al. Melanoma risk in congenital melanocytic naevi. Br J Dermatol 2017;176:1131–43. https://doi.org/10.1111/bjd.15301.

[7]   Vourc'H-Jourdain M, Martin L, Barbarot S. Large congenital melanocytic nevi: Therapeutic management and melanoma risk: A systematic review. J Am Acad Dermatol 2013;68:493–8. https://doi.org/10.1016/j.jaad.2012.09.039.

[8]   Wramp ME, Langenbruch A, Augustin M, Zillikens D, Krengel S. Clinical course , treatment modalities , and quality of life in patients with congenital melanocytic nevi – data from the German CMN registry. J Der Dtsch Dermatologischen Gesellschaft 2017;15:159–67. https://doi.org/10.1111/ddg.12835.

[9]   Bittencourt F V., Marghoob AA, Kopf AW, Koenig KL, Bart RS. Large Congenital Melanocytic Nevi and the Risk for Development of Malignant Melanoma and Neurocutaneous Melanocytosis. Pediatrics 2000;106:736–41.

https://doi.org/10.1542/peds.106.4.736.

[10]   Hale EKK, Stein J, Ben-Porat L, Panageas KSS, Eichenbaum MSS, Marghoob AAA, et al. Association of melanoma and neurocutaneous melanocytosis with large congenital melanocytic naevi — results from the NYU – LCMN registry. Br J Dermatol 2005;152:512–7. https://doi.org/10.1111/j.1365-2133.2005.06316.x.

[11]   Foster RD, Williams ML, Barkovich AJ, Hoffman WY, Mathes SJ, Frieden IJ, et al. Giant congenital melanocytic nevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. Plast Reconstr Surg 2001;107:933–41.

[12]   Agero ALC, Benvenuto-Andrade C, Dusza SW, Halpern AC, Marghoob AA. Asymptomatic neurocutaneous melanocytosis in patients with large congenital melanocytic nevi: A study of cases from an Internet-based registry. J Am Acad Dermatol 2005;53:959–65. https://doi.org/10.1016/j.jaad.2005.07.046.

[13]   Arneja JS, Gosain AK. Giant congenital melanocytic nevi. Plast Reconstr Surg 2009;124:1–13. https://doi.org/10.1097/PRS.0b013e3181ab11be.

[14]   Tromberg J, Bauer B, Benvenuto-Andrade C, Marghoob AA. Congenital melanocytic nevi needing treatment. Dermatol Ther 2005;18:136–50. https://doi.org/10.1111/j.1529-8019.2005.05012.x.

[15]   Bauer, BS; Few, JW; Chavez, CD; Galiano R. The role of tissue expansion in the management of large congenital pigmented nevi of the forehead in the pediatric patient. Plast Reconstr Surg 2001;107:668–75.

[16]   Bauer BS, Margulis A, Adler N. Congenital melanocytic nevi of the eyelids and periorbital region. Plast Reconstr Surg 2009;124:1273–83. https://doi.org/10.1097/PRS.0b013e3181b5a58d.

[17]   Feins NR, Rubin R, Borger JA. Ambulatory serial excision of giant nevi. J Pediatr Surg 1982;17:851–3.

[18]   Fujiwara M, Nakamura Y FH. Treatment of giant congenital nevus of the back by convergent serial excision. J Dermatol 2008;35:608–10. https://doi.org/10.1111/j.1346-8138.2008.00534.x.

[19]   Su JJ, Chang DK, Mailey B, Gosman A. Treatment of a giant congenital melanocytic nevus in the adult: review of the current management of giant congenital melanocytic nevus. Ann Plast Surg 2015;74:S57–61. https://doi.org/10.1097/sap.0000000000000433.

[20]   Zaal LH, Van Der Horst CM. Results of the early use of tissue expansion for giant congenital melanocytic naevi on the scalp and face. J Plast Reconstr Aesthetic Surg 2009;62:216–20. https://doi.org/10.1016/j.bjps.2007.10.045.

[21]   Gonzalez Ruiz Y, López Gutiérrez JC. Multiple Tissue Expansion for Giant Congenital Melanocytic Nevus. Ann Plast Surg 2017;79:e37–40. https://doi.org/10.1097/SAP.0000000000001215.

[22]   Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): a meta-analysis. Br J Dermatol 2016;174:853–61. https://doi.org/10.1111/bjd.14361.

[23]   Berg P, Lindelöf B. Congenital nevocytic nevi: Follow-up of a Swedish Birth Register sample regarding etiologic factors, discomfort, and removal rate. Pediatr Dermatol 2002;19:293–7. https://doi.org/10.1046/j.1525-1470.2002.00086.x.

[24]   Kinsler VA, Birley J, Atherton DJ. Great Ormond Street Hospital for children registry for congenital melanocytic naevi: Prospective study 1988-2007. Part 2 - Evaluation of treatments. Br J Dermatol 2009;160:387–92.

https://doi.org/10.1111/j.1365-2133.2008.08901.x.

[25] Koot HM, Waard-Van Der Spek F De, Peer CD, Mulder PGH, Oranje AP. Psychosocial sequelae in 29 children with giant congenital melanocytic naevi. Clin Exp Dermatol 2000;25:589–93. https://doi.org/10.1046/j.1365-2230.2000.00712.x.

[26] Bellier-Waast F, Perrot P, Duteille F, Stalder JF, Barbarot S, Pannier M. Prise en charge chirurgicale des naevi géants congénitaux : quel retentissement psychosocial sur l'enfant et son entourage ? Ann Chir Plast Esthet 2008;53:408–14. https://doi.org/10.1016/j.anplas.2007.10.002.

[27] Slutsky JB, Barr JM, Femia AN, Marghoob AA. Large Congenital Melanocytic Nevi: Associated Risks and Management Considerations. Semin Cutan Med Surg 2010;29:79–84. https://doi.org/10.1016/j.sder.2010.04.007.

[28] Yamamoto Y, Minakawa H, Sugihara T, Shintomi Y, Nohira K, Yoshida T, et al. Facial reconstruction with free-tissue transfer. Plast Reconstr Surg 1994;94:483–9. https://doi.org/10.1097/00006534-199409000-00010.

[29] Gur E, Zuker RM. Complex facial nevi: A surgical algorithm. Plast Reconstr Surg 2000;106:25–35. https://doi.org/10.1097/00006534-200007000-00005.

[30] Gosain AK, Santoro TD, Larson DL, Gingrass RP. Giant congenital nevi: a 20-year experience and an algorithm for their management. Plast Reconstr Surg 2001;108:622–36.

[31] Arad E, Zuker RM. The shifting paradigm in the management of giant congenital melanocytic nevi: Review and clinical applications. Plast Reconstr Surg 2014;133:367–76. https://doi.org/10.1097/01.prs.0000436852.32527.8a.

[32] Tønseth KA, Filip C, Hermann R, Vindenes H, Høgevold HE. Extraordinary large giant congenital melanocytic nevus treated with integra dermal regeneration template. Plast Reconstr Surg - Glob Open 2015;3:1–3. https://doi.org/10.1097/GOX.0000000000000454.

[33] Corcoran J, Bauer BS. Management of large melanocytic nevi in the extremities. J Craniofac Surg 2005;16:877–85.

Fig. 1. Giant Congenital Melanocytic nevus (GCMN) on the truck treated with

expanded skin flaps: before (A), during (B) and after the treatment (C). A: GCMN with

a PAS of 42 cm covering the left side of the trunk of a 2-year-old girl. B: Two tissue expanders were placed in a subcutaneous plane. C: Results after 7 years follow-up period.