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Clinical Features and Risks of Congenital Melanocytic Naevi: A Retrospective Analysis of Patients at the Queensland Children's Hospital

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ABSTRACT

Background/Objectives: Congenital melanocytic naevi (CMN) are a risk factor for melanoma. Melanoma risk is dependent on the congenital phenotype. Our primary aims were to assess the clinical characteristics of CMN that indicate a high risk of neurocutaneous melanosis (NCM) and melanoma in an Australian paediatric population group; to identify patient characteristics and clinical features of CMN that trigger further investigations; and to determine the rate of malignancy and other complications for CMN.

Methods: We retrospectively reviewed the electronic medical records of all patients under 18 years who were diagnosed with CMN at the Queensland Children's Hospital between 2014 and 2021.

Results: Eighty-eight patients (38 males and 50 females) were included in the analysis. Eighteen patients (20%) had a biopsy to rule out malignancy. Central nervous system magnetic resonance imaging (MRI) was performed in 16 patients (18%). Five patients (5.7%) experienced complications, of which three had NCM and two had transient neurological symptoms with normal MRI. No cases of melanoma, non-melanoma tumours or deaths were recorded.

Conclusions: CMN size, location over the posterior midline axis and multiple numbers of CMN were found to be significantly associated with the development of complications. CMN size, CMN site, presence of satellite naevi and location over the posterior midline axis were all significantly associated with the likelihood of an MRI or biopsy being performed. Large-scale studies, such as a population-based registry, are recommended to accurately assess the true lifetime risk of complications and associated risk factors.

1 | Introduction

Congenital melanocytic naevi (CMN) are benign cutaneous lesions that develop in utero and vary in size. CMN are a known risk factor for malignant melanoma (MM), with the greatest risk currently thought to be in childhood [1]. The quoted incidence of complications and outcomes has varied over the years. Data from prospective studies of larger groups and systematic literature reviews have suggested an estimated 0.7%–1.15% risk of malignancy for all CMN [2, 3]. The melanoma risk in childhood varies significantly with the severity of the congenital phenotype [4, 5]. Apart from MM, other complications that arise in association with CMN include neurocutaneous melanosis (NCM), benign proliferative nodules and other tumours such as sarcoma.

CMN are currently classified according to largest projected adult size (PAS) in centimetres (cm); small (< 1.5 cm), medium (1.5–20 cm), large (20–40 cm) and giant (> 40 cm) [6]. Patients with giant lesions have been suggested to be at higher risk from complications such as neurological involvement and MM [5]. Other factors that are believed to confer higher risk of NCM are the distribution of the CMN in a posterior axial location and the presence of satellite lesions [7]. The current consensus is that the incidence of adverse clinical outcomes including melanoma in childhood is probably most strongly associated with CMN PAS > 40 cm and satellite lesions at birth [4, 5, 7–9]. The incidence in this group is yet to be definitely established, but a recent study suggests it could be up to 14% in patients with CMN PAS > 60 cm [10].

To date, there has been one Australian case series conducted by Chen et al. in 2012 assessing the clinical characteristics and risks of large CMN among 31 patients at the Sydney Children's Hospital [11]. Given the study's small cohort size and short median follow-up of 12 months, the findings of the study are limited. We aim to assess a larger cohort size and the rate of malignancy and other complications for all CMN irrespective of size. This present study had considerably broader entrance criteria and therefore covers a greater range of clinical phenotypes.

Our study aims to provide an Australian experience on CMN with a focus on the following research goals: to assess the clinical characteristics and risks of CMN in an Australian paediatric population group; to assess the clinical characteristics of CMN over time and identify features that indicate high risk of both NCM and MM in an Australian paediatric population group; to identify patient characteristics and clinical features of CMN that trigger further investigations such as skin biopsy and magnetic resonance imaging (MRI) in an Australian paediatric population group; and to determine the rate of malignancy and other complications for CMN in an Australian paediatric population group.

2 | Materials/Methods

In this retrospective case series, we reviewed the electronic medical records of the Queensland Children's Hospital, identifying all patients under the age of 18 years with a diagnosis of CMN who were reviewed in the Dermatology outpatient clinic over a 7-year period between 2014 and 2021 inclusive.

A list of all patients coded with a clinical diagnosis of CMN regardless of size was generated; 88 patients were identified and included in our study. The following data on patient characteristics were collected and analysed: age, gender, race, CMN location, CMN number, CMN size, absence or presence of satellite naevi and CMN surface characteristics. Hospital notes and clinical photographs were used to identify phenotypic characteristics. Other data collected included: age at initial consultation, follow-up duration, reason for discharge or why the patient was lost to follow-up, total number of consultations, details of central nervous system (CNS) MRI including reason for performing and results, details of biopsies including reason for performing and results, complications (i.e., abnormal neurodevelopment, seizures, MM, NCM, other types of tumour and death), age onset of neurological symptoms, cosmetic/treatment procedures and other specialists involved in patient management.

CMN size was classified according to the size of the lesion at initial presentation: small (< 1.5 cm), medium (1.5–20 cm), large (20–40 cm), giant (> 40 cm) and undefined, if data were missing. CMN location was subdivided into head and neck, torso, upper limbs, lower limbs, multiple, if there was involvement of more than one area, and undefined, if data were missing.

Descriptive statistics were reported depending on the nature of the variable. If the variable was continuous, the following statistics were reported: median, interquartile range and range (minimum/maximum). If the variable was categorical, the counts for each category of the variable were presented, and their corresponding percentage within the outcome groups.

The Mann–Whitney *U*-test was performed to test for differences in size (cm) of the CMN within each of the outcome variables. This test was chosen as opposed to a simple *t*-test because the size of the CMN was heavily skewed, necessitating the use of a non-parametric test.

The association between two categorical variables was explored using the Pearson's chi-squared test for comparisons with large enough expected cells (> 5) or the Fisher's exact test when at least one expected cell ≤ 5 in the contingency table was observed.

3 | Results

Table 1 shows summary statistics of the study cohort. During the period analysed, 88 patients with CMN were identified and included in the analysis: 38 boys (43%) and 50 girls (57%). Median age at first consultation was 16 months (range 0–186 months). The majority of the patient population was White ($n = 73$; 83%); the remaining patients were Asian, African, South American, Melanesian and Indigenous Australian. Ten patients had a giant CMN (12%) classified by a size of greater than 40 cm. Most main CMN (31%) were located in the head and neck region, followed by the lower limbs (30%), torso (28%) and upper limbs (10%). In 14 patients (16%), the main CMN was located over the posterior midline axis. Nineteen patients (22%) had satellite naevi.

TABLE 1 | Summary statistics of the study cohort.

Characteristic	*n* = 88
Gender	
Female	50 (57%)
Male	38 (43%)
Age at initial consultation	
Median (IQR)	16 (4, 60)
Range	0, 186
Ethnicity	
ATSI	1 (1.1%)
Caucasian	73 (83%)
Filipino	1 (1.1%)
Indian	2 (2.3%)
Korean	1 (1.1%)
Nepalese	1 (1.1%)
PNG	1 (1.1%)
Somalian	2 (2.3%)
South American	1 (1.1%)
Thai	1 (1.1%)
Tongan	1 (1.1%)
Venezuelan	1 (1.1%)
Vietnamese	2 (2.3%)
Number of CMN	
Multiple	16 (18%)
Single	72 (82%)
CMN size (cm)	
Median (IQR)	3.0 (1.2, 5.9)
Range	0.4, 23.0
Unknown	22
CMN size at initial consultation	
Giant	10 (12%)
Large	3 (3.7%)
Medium	49 (60%)
Small	19 (23%)
Unknown	7
Main CMN site	
Head and neck	27 (31%)
Lower limb	26 (30%)
Torso	25 (28%)
Upper limb	10 (11%)
Main CMN over posterior midline axis	
Yes	14 (16%)
No	74 (84%)
Satellite naevi present	
Yes	19 (22%)
No	69 (78%)
Complications	
Yes	5 (5.7%)
No	83 (94%)
Complications—neurological symptoms	
Yes	2 (2.3%)
No	86 (98%)
Complications—NCM	
Yes	3 (3.4%)
No	85 (97%)
CNS MRI performed	
Yes	16 (18%)
No	72 (82%)
Biopsy performed	
Yes	18 (20%)
No	70 (80%)

Abbreviations: ATSI, Aboriginal and Torres Strait Islander; cm, centimetre; CMN, congenital melanocytic naevi; CNS, central nervous system; IQR, interquartile range; MRI, magnetic resonance imaging; *n*, number of patients; NCM, neurocutaneous melanosis; PNG, Papua New Guinea.

Patients were followed up for a mean duration of 31.9 months (range 0–94 months, median 26.5 months) and had a mean number of 4.9 visits to the clinic (range 1–26 visits, median 4 visits). Biopsies were performed on 18 patients (20%) to rule out malignancy. Reasons for biopsy included a suspicious area or nodule and a significant change compared to baseline photographs. A CNS MRI was performed in 16 patients (18%). The mean age of patients at their first MRI scan was 9.9 months (range 0–33 months, median 4 months).

Of the total population, 5.7% ($n = 5$) experienced complications. Three patients were found to have abnormal MRI findings without exhibiting focal neurological deficits or impaired neurological development (Table 2). All three patients had NCM. They were referred to neurology for full assessment and follow-up. Two patients had transient neurological symptoms (eye twitching and ataxia, respectively) without abnormality on MRI. There were no cases of MM, non-melanoma tumours arising within the CNS or death in this group of patients over the defined period of follow-up.

TABLE 2 | Clinical and radiological features of patients with abnormal magnetic resonance imaging findings.

Patient	Gender	Number of CMN	Main CMN location	Size of main CMN	Satellites	Neurological symptoms	Other complications	MRI findings
1	Male	Single	Left scalp/forehead	Large	No	No	No	Neurocutaneous melanosis; two superficial T1 hyperintensities in the brain representing leptomeningeal or superficial parenchymal involvement, and third focus in the right optic nerve
2	Female	Multiple	Left scalp	Medium	No	No	No	Neurocutaneous melanosis; leptomeningeal melanocytic deposit—single small 3 mm T1 hyperintensity in the retoclival areas
3	Female	Multiple	Central upper back	Giant	Yes	No	No	Neurocutaneous melanosis; left hemisphere

Abbreviations: CMN, congenital melanocytic naevus; MRI, magnetic resonance imaging.

TABLE 3 | Frequency of treatment types for congenital melanocytic naevi.

	n/88	%
Excision only	17	19.32
Excision + skin graft	2	2.27
Excision + skin graft + microneedling	1	1.14
Excision + skin graft + microneedling + laser + dermabrasion	1	1.14
Total	21/88	23.87

Abbreviation: *n*, number of patients.

Of the 88 patients, 23.9% ($n = 21$) underwent treatment procedures (Table 3); 17 patients (19.3%) had excision only. The remaining four patients received a combination of treatments, including excision, skin grafting, microneedling, laser and dermabrasion. Other specialists were involved in multidisciplinary care. For the 88 patients studied, the following specialists (aside from dermatologists) were consulted regarding the management of CMN and related complications: plastic surgeons, paediatric surgeons, neurologists, paediatricians and ophthalmologists.

Results of comparison between all independent and outcome variables are displayed in Tables S1–S5. Median, minimum and maximum values are reported for numerical variables. Counts and corresponding percentages (within groups) are reported for numerical variables. *p* values are the result of the Mann–Whitney *U*-test for numerical variables and Fisher's exact test for categorical variables. A series of supplementary graphs (Figures S1–S10) displays all statistically significant results for our cohort. CMN size, location over the posterior midline axis and multiple numbers of CMN were significantly associated with the development of complications ($p = 0.044$, $p = 0.027$ and $p = 0.040$, respectively) as shown in Figure 1. Presence of satellite naevi and location over the posterior midline axis were significantly associated with the development of neurological symptoms ($p = 0.045$ and $p = 0.024$, respectively) as shown in Figure 2. CMN size, CMN site, presence of satellite naevi, location over the posterior midline axis and hairy CMN phenotype were all significantly associated with the likelihood of an MRI being performed ($p \leq 0.001$, $p = 0.024$, $p = 0.005$, $p < 0.001$ and $p = 0.004$, respectively). CMN site, presence of satellite naevi, location over the posterior midline axis and female gender were significantly associated with the likelihood of a biopsy being performed ($p = 0.031$, $p = 0.020$, $p = 0.034$ and $p = 0.015$, respectively).

4 | Discussion

Our study shows a female preponderance for CMN with a male-to-female ratio of 1:1.3. Female gender was also significantly associated with the likelihood of a biopsy being performed ($p = 0.015$), and so were CMN site, presence of satellite naevi and location over the posterior midline axis. It is well known that giant CMN are usually associated with the presence of satellite naevi. In our study, 80% of those with giant CMN had satellite naevi. Other characteristics associated with giant CMN in our

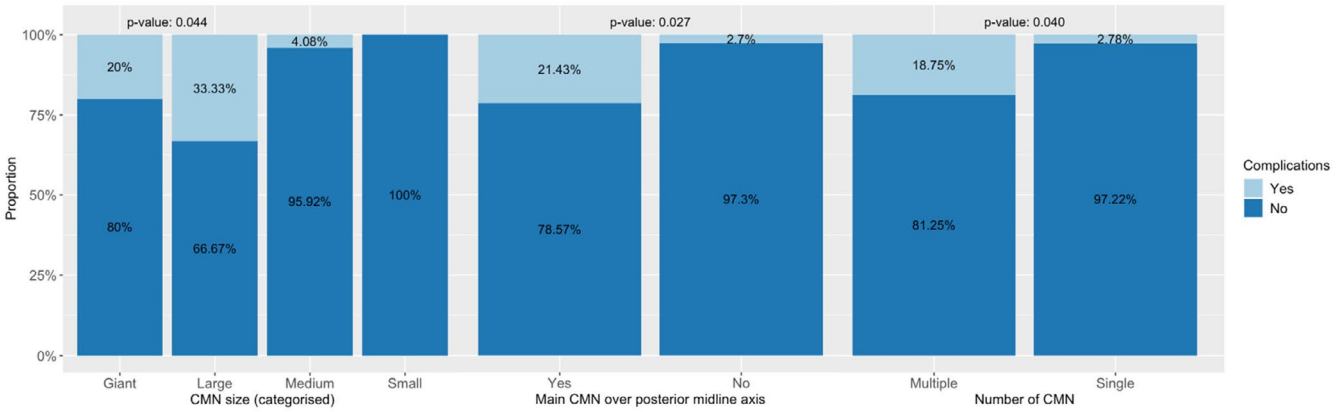

FIGURE 1 | Proportion of individuals with complications for each CMN size category, location of main CMN over the posterior midline axis and per number of CMN. CMN, congenital melanocytic naevus.

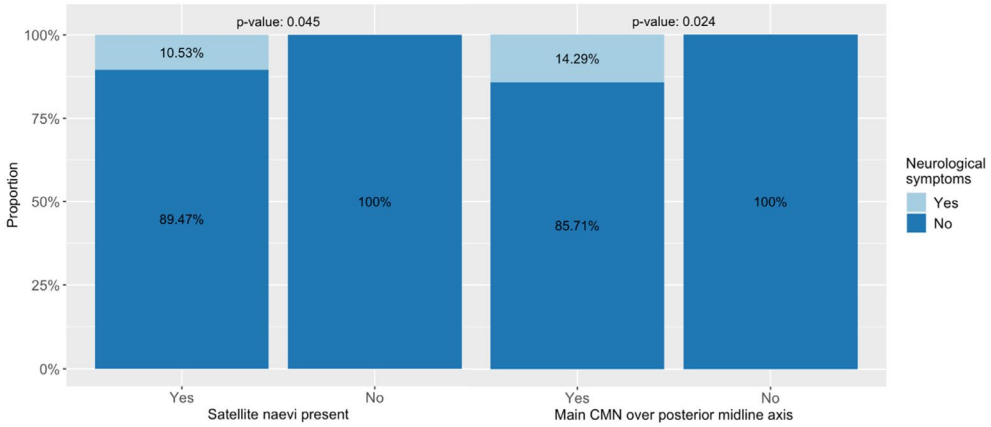

FIGURE 2 | Proportion of individuals with neurological symptoms for the presence of satellite naevi and for the location of main CMN over the posterior midline axis. CMN, congenital melanocytic naevus.

cohort were female gender (90%), location over the posterior midline axis (70%) and hairy phenotype (90%).

Location of the main CMN over the posterior midline axis was significantly associated with the development of complications and neurological symptoms ($p = 0.027$ and $p = 0.024$, respectively), and also the likelihood of an MRI and/or biopsy being performed ($p < 0.001$ and $p = 0.034$, respectively). Together with CMN size, number of CMN and the presence of satellite naevi, our data suggest that the location of the main CMN over the posterior midline axis should prompt clinicians to consider further investigations to screen early for complications.

To predict the size that a CMN will grow to in adulthood (PAS), an established scaling system is ideally used [12]. CMN on patients' heads are predicted to enlarge by a factor of 1.7; on the legs by a factor of 3.3; on the thighs by a factor of 3.4; and on the torso, buttocks, upper extremities and feet by a factor of 2.8. Unfortunately, as the documentation on the size of CMN at birth was inconsistent in our study population, the size of the CMN was calculated and grouped into subcategories based on the initial presentation at the clinic. Irrespective of this, our study found a significant association between CMN size and complication risk ($p = 0.044$). Of those with large and giant CMN, 33.33% and 20%, respectively, experienced complications.

We conducted a literature search yielding 71 relevant articles, as summarised in Table S6, which further informed the results of our study. The Great Ormond Street Hospital for Children Registry for CMN by Kinsler et al. was a prospective study that recruited 349 CMN families, of which only 301 completed follow-up over an average period of 9.2 years. This study also found a female preponderance for CMN, with a male-to-female ratio of 1:1.4. In this case series, abnormal neurodevelopment was recorded in 19% of cases; NCM was not recorded. Five (1.43%) patients developed fatal MM; all had either PAS > 60 cm or multiple CMN. In two of these cases, MM developed within the CMN and in two other cases, MM developed in the CNS [10, 13]. In another prospective cohort study by Kinsler et al., the strongest statistical risk factor for melanoma in childhood was found to be an abnormal screening MRI of the CNS in the first months of life (incidence of 12%) [1]. Screening MRI was not performed routinely as a baseline assessment for every patient in our cohort. Clinical reasons that MRI was performed in patients included CMN overlying the CNS, the presence of neurological symptoms or signs and a routine baseline assessment. The following factors significantly influenced whether or not an MRI was performed: total number of CMN (two or more), CMN size (medium to giant), site (torso or head and neck areas), presence of satellite naevi, location of main CMN over the posterior midline axis and hairy phenotype.

In our cohort, two patients had transient neurological symptoms (eye twitching and ataxia, respectively) without abnormality on MRI. It is unclear whether these findings are related to the presence of CMN or if these patients will develop CMN-related abnormalities in the future. It has been recognised previously that patients with CMN can have neurological abnormalities in the absence of MRI abnormalities [14]. Of note, the presence of satellite naevi and the location of CMN over the posterior midline axis were both significantly associated with the development of neurological symptoms. This can be explained by the aetiology of CMN, which is a result of the maldevelopment of the embryological neural crest cells during their migration along the leptomeninges to the dermis. Thus, the risk of developing NCM is likely to be greater with the presence of a greater number of satellite naevi [11].

Two recent systematic reviews reported a rate of melanoma in patients with CMN of any size to be 0.7%–1.15% [2, 3]. The rate of melanoma in large CMN, as reported in two systematic reviews and a registry of 1008 patients, was higher at 2%–2.9% [8, 15, 16]. The majority of patients who developed MM had CMN of any size located on the trunk, or had melanoma develop within large CMN [3, 16]. These studies suggest that increased PAS is associated with increasing risk of melanoma, and the trunk location of primary CMN is associated with melanoma compared to other locations.

Rate of NCM in large or giant CMN has been reported to be 2.5%–29.17% [17–22]. In the studies without limitation on the size of CMN, the rate of NCM was 2.27%–41.25% [23–28]. However, these studies all differed in methodology, with some studies imaging all patients routinely versus imaging those with specific characteristics. This likely contributes to the wide range in the rate of NCM. Symptomatic NCM was found in 94 of 120 cases of large CMN who had NCM [7, 17–19], five of 19 cases of medium to giant CMN who had NCM [26], one of seven cases of giant CMN [21] and three of five cases of CMN of any size who had NCM [21].

In our study, there were no cases of MM, non-melanoma tumours arising within the CNS or death in this group of patients over the defined period of follow-up. Three patients (3.4%) were found to have abnormal MRI findings without exhibiting focal neurological deficits or impaired neurological development; all three had NCM either in the brain parenchyma or leptomeninges. Sizes of the main CMN ranged from medium to giant, and only one patient's CMN crossed the posterior midline axis. They were referred to neurology for full assessment and follow-up, which was unremarkable.

This study is limited by its retrospective nature, lack of control group, short follow-up duration and low case numbers. The true lifetime risk of complications may be underreported due to the lack of a standardised follow-up period and patients lost to follow-up.

All patients with medium to giant CMN should be referred to dermatology at birth to allow for thorough clinical assessment, including baseline clinical photographs, measurement of CMN and PAS calculation and further investigations if necessary. This will also enable long-term follow-up and a more accurate assessment of the true lifetime risk of complications and the associated risk factors. Patients exhibiting focal neurological deficits or impaired neurological development should have an MRI performed and be referred to neurology urgently. MRI should also be considered when main CMN is medium to giant in size (1.5 to > 40 cm) and present on the head and neck region or torso and/or cross the posterior midline axis with or without the presence of neurological symptoms or when there is the presence of multiple numbers of CMN and/or satellite lesions. Early referral to other relevant specialists is necessary to allow for a multidisciplinary approach to patient care as well as assessment and management of complications.

Overall, our study found that CMN more commonly affected females (57%) and Caucasians (88%). Main CMN was more commonly located on the head and neck (31%), followed by the lower limb (30%), torso (28%) and upper limb (11%). The majority of CMN sizes were medium (60%), followed by small (23%), giant (12%) and large (3.7%). 16% had CMN located over the posterior midline axis. CMN site over the posterior midline axis and the presence of satellite naevi were significantly associated with the development of complications and neurological symptoms. The likelihood of biopsy being performed was significantly associated with female gender, CMN site, the presence of satellite naevi and location over the posterior midline axis. There were no cases of MM, non-melanoma tumours within the CNS or death in this cohort.

The results presented in our study aim to provide an Australian experience on CMN as seen in a large specialist children's hospital providing tertiary-level services for children and young people living in both metropolitan and rural regions. Although we have reported statistically significant results, a cautious approach must be taken given that our sample size is considerably small for true assessment of outcomes. Nevertheless, we hope that our findings may assist clinicians in making decisions and in counselling patients. A large-scale study with long-term follow-up, such as a population-based registry, would be recommended for an accurate assessment of the true lifetime risk of complications and associated risk factors. Furthermore, with the availability of adequate data, a standardised protocol for assessment, management and surveillance of children with CMN will be possible in the future.

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Ethics Statement

Our research presented no more than minimal risk of harm to subjects and involved no procedures. The Children's Health Queensland Hospital and Health Service Human Research Ethics Committee granted an exemption from ethics review for this project on 10 March 2020.

Conflicts of Interest

Professor H. Peter Soyer is a shareholder of MoleMap NZ Limited and e-derm consult GmbH and undertakes regular teledermatological

reporting for both companies. Professor H. Peter Soyer is a medical consultant for Canfield Scientific Inc. and a medical advisor for First Derm. Professor H. Peter Soyer is the former Editor-in-Chief of the Australasian Journal of Dermatology and a co-author of this article. To minimise bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.