Number of Satellite Nevi as a Correlate for Neurocutaneous Melanocytosis in Patients With Large Congenital Melanocytic Nevi

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Background: Patients with large congenital melanocytic nevi (LCMN) are at risk for neurocutaneous melanocytosis (NCM). Patients with LCMN on the posterior axis or in conjunction with many satellite melanocytic nevi seem to represent subgroups at greatest risk.

Objective: To determine the relationship between LCMN location, number of satellite nevi, and risk of NCM.

Design: Descriptive survey study.

Setting: An Internet Web-based registry of patients with LCMN, maintained by a nevus support group (Nevus Outreach Inc).

Participants: Individuals with LCMN or their guardians visiting the Nevus Outreach Web site were provided the opportunity to complete the questionnaire.

Outcome Measures: Location of LCMN, number of satellite nevi, and NCM as assessed by patient self-report.

Results: A total of 379 patients with LCMN were evaluated, 26 of whom had NCM. A significantly higher percentage of patients with NCM had their LCMN on the posterior axis compared with patients without NCM (96% and 70%, respectively). Patients with NCM had significantly more satellite melanocytic nevi compared with non-NCM patients (median, 68.5 and 18, respectively). Furthermore, patients with LCMN and more than 20 satellites had a 5.1-fold (95% confidence interval, 1.9-14.0) increased risk for NCM compared with LCMN patients with 20 or fewer satellites. Logistic regression analysis, controlling for age, sex, number of satellite nevi, and LCMN location, identified number of satellite nevi as the only significant risk factor for NCM.

Conclusions: The presence of large numbers of satellite nevi is the most important risk factor for NCM in patients with LCMN. Although location of the LCMN on the posterior axis was a moderate risk factor for NCM in univariate analysis, the strength of the relationship was attenuated in the multivariate analysis.

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During normal embryogenesis, melanoblasts migrate from the neural crest to the leptomeninges and skin. Dysregulation within this migratory pathway can result in increased proliferation of melanocytes and abnormal deposition of melanocytes and melanin in the leptomeninges—an entity known as neurocutaneous melanocytosis (NCM). Patients with NCM may also have excess deposits of melanocytes in the skin, which can manifest clinically as the presence of multiple satellite melanocytic nevi, multiple medium-sized congenital melanocytic nevi, or large congenital melanocytic nevi (LCMN). Patients with LCMN, a relatively rare condition affecting approximately 1 in 20,000 newborns, are at significantly high risk for developing NCM. It is reported that LCMN on the posterior axis (paraspinal, head, and neck regions) and in the presence of many satellite nevi may define a subgroup of patients at greatest risk for developing NCM.

Ideally, to help determine the relationship between number of satellite nevi and anatomical location of the LCMN with NCM requires the study of a large number of individuals with LCMN who are selected from the general population, thereby reducing referral center or case selection bias. Toward this end, patient support (advocacy) groups and the Internet may prove to be useful sources that can be used to assist in collecting information on such patients. We report on the first Internet patient support/advocacy group–based (not referral center–based) registry of patients with LCMN. This database was analyzed to determine the relationship between LCMN location and number of satellite nevi and risk of NCM.
Methods

Patients for this study were identified from a registry of patients with LCMN (Nevus Outreach Inc [NOI]-LCMN Registry). Nevus Outreach Inc designed the NOI-LCMN Registry questionnaire in collaboration with one of the authors (A.A.M.). The registry opened for enrollment in November 1998, and continually accrues new members. This analysis, which was performed after obtaining institutional review board approval from the Memorial Sloan-Kettering Cancer Center, New York, NY, is based on patients enrolled in the registry from November 1998 to June 2002.

Nevus Outreach Inc, a nonprofit patient support group for persons with LCMN (http://www.nevus.org), maintains the Internet-based registry. To be eligible for this registry, members are required to have a congenital melanocytic nevus that is or can be expected to measure at least 20 cm in adulthood. Assuming normal growth and surface area expansion of human skin, it can be anticipated that a congenital nevus measuring 6 cm on an infant’s body or 9 cm on an infant’s head will attain a maximum diameter of 20 cm. Registry member information is entered into the database via the Internet by persons with LCMN or parents or guardians if the child is too young to complete the questionnaire. Persons generally find the NOI registry by using Internet search engines, while some are referred to the registry by their physician. Because the registry is Internet based, there is potential for global enrollment. Persons without Internet access who are interested in belonging to the registry complete a paper-based survey, and these data are entered into the registry by NOI.

Data Collection and Analyses

Patients were asked to complete a 6-page questionnaire that included information on the overall description of the main nevus including the size and distribution of the main nevus, changes in characteristics of main nevus, and number and distribution of satellite nevi. The NCM status of nevus each was ascertained, and patients were asked to provide information on neurological symptoms and magnetic resonance imaging (MRI). Information regarding surgical treatments, neurological conditions, MRIs, and personal and family history of melanoma was also collected from all registrants. Patients were asked to measure the largest diameter of largest nevus in centimeters. Distribution of main nevus was assessed by asking the registry members to select the location of the main nevus from a body map divided into 90 distinct areas. These areas were then grouped into the following broader categories: head and neck, extremities, anterior torso, and posterior torso (paraspinal). In the final analysis, location was categorized as posterior involvement (head and neck and posterior torso) vs extremities and anterior torso. Any LCMN that had posterior (paraspinal) involvement was considered a posterior nevus. We categorized the number of satellite nevi as dichotomous (≤20 vs >20 satellite nevi) and in quartiles (0-3, 4-20, 21-70, and ≥71).

Descriptive statistics including means, medians, percent- ages, and 95% confidence intervals were calculated to de-scribe the study population. Differences between groups defined by presence and absence of NCM and categorical independent variables were examined by χ² tests for independence. Continuous variables that were not normally distributed were analyzed by the 2-sample t test. Continuous variables that were not normally distributed were analyzed by the Wilcoxon rank sum test. Univariate analyses were performed to identify predictor variables and potential confounding variables for inclusion in the multivariate model. Logistic regression modeling was performed to examine the relationship between NCM and LCMN location and number of satellite nevi, while adjusting for potential confounding factors.

Results

The analysis included 381 patients who were registered at the time of analysis. Two patients with linear epidermal nevi inadvertently completed the registry form and were excluded from the registry. Thus, the final analyses were based on 379 patients with LCMN from 26 countries. There were 159 (42%) male and 220 (58%) female patients enrolled in the registry at the time of our analysis. Mean age of the patients was 8 years, median age was 3 years, and 75% of individuals were younger than 10 years. The mean diameter of the LCMN was 30.3 cm (median, diameter, 24.7 cm). Of the registrants, 272 (72%) had most of their LCMN on the posterior axis (paraspinal, head, and neck), 27 (7%) had the most on an extremity, and 80 (21%) had the most on the chest or abdomen. The mean number of satellite nevi was 81.5, and the median number was 20 (range, 0-2500).

We compared characteristics of patients with and without NCM. Of the registry members, 26 (7%) had a diagnosis of NCM (22 with symptomatic NCM and 4 with asymptomatic NCM diagnosed by MRI). The median age at diagnosis of NCM was 2.4 years (median, 6 months; range, birth-24.5 years). The 26 NCM patients were compared with the 353 patients without NCM. No differences in the median age or mean diameter of the LCMN were apparent between the 2 groups (Table 1). However, a significantly higher percentage of patients with NCM had their LCMN on the posterior axis compared with patients without NCM (96% and 70%, respectively) (P = .02) (Table 1, Figure 1). The crude odds ratio determined that individuals with LCMN on the posterior axis have a 5.1-fold (95% confidence interval, 1.2-22.2) increased risk for having NCM compared with those with LCMN on the anterior axis or extremities combined.
Twenty-eight patients without NCM failed to document on their registry form the number of satellite nevi that were present on the skin. Thus, the numbers of satellite nevi of the 26 NCM patients were compared with 325 non-NCM patients. The median number of satellites was significantly higher for patients with NCM compared with non-NCM patients (68.5 [mean, 221] vs 18 [mean, 68.4], respectively; P < .001) (Table 1). The distribution of NCM patients is presented by the number of satellite nevi categorized by quartiles (Figure 2). The percentage of individuals with LCMN who were diagnosed with NCM increased as the number of satellite nevi increased (Figure 2). In addition, most patients with NCM had many satellite nevi, with 54% of the NCM cases in the highest quartile compared with 8% in the lowest quartile (P < .001) (Figure 2). In contrast, there was a relatively even distribution of non-NCM patients across each quartile (Table 1). The crude odds ratio revealed that individuals with LCMN who had more than 20 satellite nevi had a 5.1-fold (95% confidence interval, 1.9-14.0) increased risk for having NCM compared with people with 20 or fewer satellite nevi. Logistic regression analysis, controlling for age, sex, number of satellite nevi, and LCMN location, identified number of satellite nevi as the only significant risk factor for NCM (P = .003) (Table 2). The sex of the individual with NCM had borderline significance in both the univariate and the multivariate models, with a greater proportion of male patients with NCM compared with female patients. Location of the LCMN became less statistically significant when the number of satellite nevi was added to the multivariate analysis. A pared-down model including only the number of satellite nevi and location of the large nevus was also explored. The adjusted odds ratios and confidence intervals did not change appreciably for either of these 2 variables.

Figure 1. The anatomical locations of the large congenital melanocytic nevus (LCMN) in patients with neurocutaneous melanocytosis (NCM) and in patients without NCM. Any LCMN that had posterior axis involvement was considered a posterior axis nevus. The numerical values at the base of each bar represent the number of patients within the group.

Figure 2. The distribution of patients with neurocutaneous melanocytosis (NCM) plotted as a function of the number of satellite nevi categorized by quartiles. The raw number of patients within the NCM cohort is given in Table 1. For the entire cohort, the raw numbers for each quartile are as follows: 91 of the 351 patients had between 0 and 3 satellites and 2 (2%) of these patients had NCM, 93 of 351 patients had between 4 and 20 satellites and 3 (3%) of them had NCM, 78 of 351 had between 21 and 70 satellites and 7 (9%) of them had NCM, and 89 of 351 patients had over 71 satellites and 14 (16%) of them had NCM (16%).

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Large congenital melanocytic nevus is a rare pigmented lesion with an incidence of approximately 1 in 20 000 births. Individuals with LCMN are at increased risk for developing NCM, and it is reported that subgroups of patients at particularly high risk for developing this condition are those with LCMN on the posterior axis and those that have many satellite nevi. The importance of LCMN location and number of satellites as NCM risk factors were previously identified by univariate statistical analysis and by review of published cases. However, to our knowledge, these variables have not, before the present study, been subjected to multivariate analyses. To help better define the risk factors for NCM (univariate analysis) and to determine their relationship to each other (multivariate analysis) requires the accrual of a large cohort of patients who have LCMN and NCM. This may be achieved by enlisting the support and involvement of patient advocacy groups in research efforts and by using the Internet to reach as many people with LCMN around the world as possible. The present study is the first to use an Internet patient support/advocacy—based (not referral center-based) registry of patients with LCMN (NOI-LCMN Registry). Within 4 years the NOI-LCMN Registry accrued 379 patients with LCMN from 26 countries and has become the world’s largest LCMN database. We acknowledge that when examining cohorts, if differences exist in case ascertainment (self-enrolled or referred), then the comparison of the cohorts may be problematic. In this population, individuals were all self-selected, regardless of severity of condition or disease status. We acknowledge that patients registering online may be more motivated and educated, have cosmetically problematic lesions, and may have larger lesions; however, we think this cohort will be different (with less extensive disease) from referral centers because large referral centers are, in name and mission, there to treat individuals with extensive or problematic disease.

The analysis of the NOI-LCMN Registry confirms previous reports that LCMN on the posterior axis confers a significant increased risk for NCM. In addition, this study confirms that the presence of many satellite nevi (>20) significantly increases the relative risk for NCM. Unlike previous reports, however, this large database with 379 participants affords researchers the ability to also perform...
multivariate analyses. When the combination of age, sex, location of the LCMN, and number of satellite nevi were analyzed to determine their significance, only the number of satellite nevi remained as a highly significant risk factor for NCM. This finding, if verified, may have important management implications for patients and physicians, such as defining subgroups of neurologically asymptomatic patients with LCMN in whom brain MRI for the presence of NCM should be considered. If the results of this study are confirmed by others, it is reasonable to assume that MRI would be strongly recommended for those LCMN patients who have many satellite nevi irrespective of the location of their LCMN. It is, however, important to acknowledge that some NCM patients will not have any satellite nevi, as was seen in one of the patients in the NOI-LCMN Registry. Thus, clinicians need to continue to maintain a certain degree of vigilance for the presence of NCM in patients with LCMN, and this vigilance should be heightened for those individuals with many satellite nevi. There were 28 patients without NCM excluded from the multivariate analysis because they lacked satellite nevi information. These individuals were similar in sex and location of the large nevus to the responders, although they were slightly older. Since age is not a risk factor for NCM, it is our contention that this difference has a negligible effect on the results.

This study revealed that patients with at least 20 satellite nevi are at highest risk for having NCM, and the risk for having NCM continues to rise as the number of satellite nevi increases (Figure 2). There are a few reasons why the number of 20 satellites should not be viewed as a strict threshold. New satellite nevi can continue to develop for many years after birth; thus, infants born with fewer than 20 satellite nevi may eventually develop over 20 satellites within the first few years of life. Even though new satellite nevi can continue to develop, it may be safe to assume that individuals with more than 20 satellite nevi by age 3 years (the median age of the study population) are the ones at greatest risk for NCM. It should be noted that the registry data are self-reported, and to date there has been little independent confirmation. However, the study population is educated, motivated, and likely to be able to report accurately about this condition. Therefore, misclassification of satellite nevus counts could occur. Differences between physician report and self-report with regard to number of nevi have consistently shown that patients generally tend to underreport nevus counts.10 Thus, nevus count misclassification should not be a major bias affecting our results.

The primary analysis of this data resource provides interesting insights about the relationship between NCM and number of satellite nevi in persons with LCMN. The study is limited by the small number of NCM cases. However, in support of our findings are the relatively large number of LCMN cases in our data set and the consistency of our findings with previous reports.5,7-9 This study reveals that the presence of large numbers of satellite nevi is the most important risk factor/correlate for NCM in patients with LCMN (Figure 3). Although location of the LCMN on the posterior axis was a moderate risk factor for NCM in univariate analysis, the strength of the relationship was attenuated in the multivariate analysis. This finding may have implications as to which patients should be subjected to MRI. This study also illustrates the feasibility of using patient support/advocacy groups and the Internet in collecting data for research purposes.

We encourage all patients with LCMN to register in the NOI-LCMN Registry at http://www.nevus.org.
also encourage physicians encountering patients with LCMN to direct these patients to the NOI-LCMN Registry. To obtain paper copies of the registry form, for people without Internet access, requests can be mailed to the following address: Nevus Outreach Inc; 1601 Madison Blvd; Bartlesville, OK 74006. This registry is designed to continuously accrue new patients, and patients already registered are scheduled to receive a follow-up questionnaire aimed at collecting prospective follow-up data regarding this condition in the future.

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