Predictive Value of Café au Lait Macules at Initial Consultation in the Diagnosis of Neurofibromatosis Type 1

Kara S. Nunley, MD; Feng Gao, MD, PhD; Anne C. Albers, RN, MSN; Susan J. Bayliss, MD; David H. Gutmann, MD, PhD

Objective: To evaluate the predictive utility of the number and morphologic appearance of isolated café au lait macules (CALMs) in establishing the diagnosis of neurofibromatosis type 1 (NF1) in a cohort of children referred to an NF1 subspecialty clinic.

Design: Retrospective study of patients seen between the years 2004 and 2007.

Setting: Tertiary care neurofibromatosis referral clinic at St Louis Children’s Hospital.

Patients: The study population comprised 110 patients who presented with CALMs and no other diagnostic features of NF1. The median number of CALMs at initial presentation was 6, while the median age of the patients was 33 months. The median age at the last follow-up examination was 76.5 months.

Main Outcome Measures: Number and morphologic appearance of CALMs and diagnosis of NF1.

Results: Thirty-four of the children met diagnostic criteria for NF1 during the study period. Thirty-two children met criteria prior to age 72 months, and 2 children met criteria after 72 months. The mean number of CALMs at presentation in children eventually diagnosed as having NF1 (11.8 CALMs) was significantly higher than the mean number of CALMs in children not diagnosed as having NF1 (4.6 CALMs). Of the 44 children who had 6 or more typical CALMs at presentation, 34 children met criteria for NF1. Sixty-eight patients had CALMs described as “typical,” while 42 patients had “atypical” CALMs. Only 2 patients with atypical CALMs met criteria for NF1.

Conclusion: The majority of patients with 6 or more CALMs will eventually meet diagnostic criteria for NF1, typically by age 6 years, and this likelihood increases with increasing number and typical morphologic appearance of CALMs.

Arch Dermatol. 2009;145(8):883-887

Eurofibromatosis Type 1 (NF1) is a common autosomal disorder that affects numerous organ systems, including the skin, eyes, bones, blood vessels, and central and peripheral nervous systems. The diagnosis of NF1 is established when individuals present with 2 or more of the following features: 6 or more café au lait macules (CALMs); 2 or more neurofibromas of any type or 1 plexiform neurofibroma; freckling in the axillary or inguinal region; optic glioma; 2 or more Lisch nodules; a distinctive osseous lesion; and a first-degree relative with NF1. However, infants and young children most frequently exhibit CALMs only and cannot be given the diagnosis of NF1 until a second feature develops. Because the second disease-defining manifestation of NF1, such as axillary freckling and neurofibromas, may not develop until later in childhood, it is not uncommon for children with multiple CALMs and no family history of NF1 to be followed up for several years before the diagnosis of NF1 is confirmed or excluded. This presents a particular challenge for both the physician and the family and may limit adequate screening for serious problems seen in this young age group (eg, optic pathway glioma).

There is relatively little information available regarding the natural history and diagnostic outcomes of children presenting only with multiple CALMs. Previous studies have shown that solitary CALMs are common and may occur in as many as 3% of infants and 25% of healthy children. However, the presence of more than 3 CALMs is detected in only 0.2% to 0.3% of children with known evidence of an underlying disorder. Neurofibromatosis 1 is the most common condition associated with multiple CALMs. Multiple CALMs can also be seen in McCune-Albright syndrome, ring chromosome syndromes, Watson syn-
drome, and Bloom syndrome, but these conditions are far less prevalent than NF1. A syndrome with phenotypic features similar to NF1, but caused by mutations in SPRED1, as well as an inherited form of multiple CALMs without other features of NF1, has also been described in the literature. To our knowledge, the largest study to date examined 41 children with 6 or more CALMs. Of these children, 80% were eventually diagnosed as having NF1 by the end of the study period. While this study provided important insights, it did not include children who had fewer than 6 CALMs at initial presentation and did not focus on the diagnostic utility of morphologic appearance or number of CALMs. Moreover, this study did not address the likelihood of rendering the diagnosis of NF1 as either a function of age or number of CALMs. In an effort to address these important clinical issues, we conducted a retrospective analysis of a large group of children who initially visited a tertiary referral neurofibromatosis subspecialty clinic between the years 2004 and 2007 with only CALMs and no other signs of NF1.

METHODS

PATIENTS

This study was performed using an approved Human Studies Committee Protocol at Washington University School of Medicine, St Louis, Missouri. We reviewed the medical records of 191 patients with an International Classification of Diseases, Ninth Revision (ICD-9) code of 709.09 (nonspecific dyschromia) who were seen by a single physician (D.H.G.) in the neurofibromatosis clinic at a large tertiary care pediatric hospital (St Louis Children's Hospital) between the years 2004 and 2007. This ICD-9 code was the code regularly used to designate patients presenting with CALMs who did not carry a known diagnosis of NF1. The diagnosis of NF1 was established using criteria outlined by the National Institutes of Health Consensus Development Conference. All patients had a complete evaluation including history and physical and neurologic examination performed by a single physician (D.H.G.) at the time of initial presentation to the NF1 clinic. In general, patients were followed up on a yearly basis. Patients were referred for an annual ophthalmologic evaluation with a slit lamp examination as a part of routine care, beginning at 1 year of age. Patients were excluded from this study if they met diagnostic criteria for NF1 at their first visit to the clinic, had a first-degree relative with NF1, had physical examination findings consistent with segmental NF1, were incorrectly coded as having CALMs, or had incomplete or unavailable medical records. Data were collected from the time of initial presentation to our clinic through the time of last follow-up examination. Demographic information and clinical characteristics including description of CALMs, date of diagnosis of NF1 (if applicable), and the chronology of developing additional features of NF1 were recorded for each patient.

Similar to previous studies, “typical” CALMs were defined as lesions with uniform pigmentation and distinct, regular borders, while “atypical” or “irregular” CALMs were defined as lesions with irregular, smudgy borders or nonhomogeneous pigmentation (Figure 1). Patients were classified as having atypical CALMs if their lesions were described as atypical or irregular at the first clinic visit.

STATISTICAL ANALYSES

Distributions of the demographic and clinical characteristics across the 3 groups of patients (patients diagnosed as having NF1 during the period of the study, patients with typical CALMs who did not meet diagnostic criteria for NF1 at the conclusion of the study, and patients with atypical CALMs who did not meet diagnostic criteria for NF1 at the conclusion of the study) were summarized using means, medians, or frequencies, as appropriate. For categorical features such as sex or race, the differences among groups were compared using the Fisher exact test. For continuous features such as number of CALMs or age at presentation, the comparison was made using Kruskal-Wallis rank-sum test. P < .05 was considered statistically significant, and all statistical tests were 2-sided.

RESULTS

A total of 191 patients were seen with an ICD-9 code of 709.09 in the NF clinic over the period of this study. Of these patients, 110 met the inclusion criteria for our study. There were 63 male and 47 female children in our patient population (Table). Twenty-four of the children were Afri-
can American, 63 were white, 1 was Asian, and 2 did not have racial information available in the medical record. The median age at initial presentation to our clinic was 33 months (range, 1-206 months). The median age at last follow-up was 76.5 months (range, 4-206 months). No children were diagnosed as having syndromes other than NF1. No undiagnosed children with typical CALMs had a family history of CALMs. One undiagnosed child with irregular CALMs had a parent with CALMs.

The median number of CALMs at presentation of all patients in the study was 6 (range, 1 to ≥20). Thirty-four (31%) of the children met criteria for diagnosis of NF1 during the study period. The mean number of CALMs at initial presentation in children eventually diagnosed as having NF1 (11.8 CALMs; range, 6 to ≥20) was significantly higher than the mean number of CALMs in children who were not diagnosed as having NF1 (4.6 CALMs; range, 1 to 12) during the study (P < .001).

The percentage of children diagnosed as having NF1 increased with increasing numbers of CALMs at initial presentation (Figure 2A). Of the 26 children who had 1 to 5 typical CALMs at initial presentation, none met criteria for a diagnosis of NF1. Of the 44 children who had 6 or more typical CALMs at presentation, 34 (77%) met criteria for a diagnosis of NF1 by the end of the study period.

Sixty-eight patients had CALMs described as typical, while 42 patients had atypical CALMs. Of the 42 patients with atypical CALMs, 27 had 1 to 5 CALMs and 15 had 6 or more CALMs. Thirty-two patients with typical CALMs met criteria for a diagnosis of NF1 during the study period. Two patients with atypical CALMs, both of whom had more than 6 CALMs at initial presentation, met criteria for a diagnosis of NF1 during the study period.

The mean age at diagnosis of NF1 was 33.5 months (range, 1-96 months). The mean age at diagnosis of NF1 was significantly younger than for those in the undiagnosed group (P < .001).

There were no significant differences in sex (P = .61), race (P = .54), or mean age at the last follow-up examination (P = .31), but age at presentation for children in the diagnosed group was younger than for those in the undiagnosed group (P < .001).

In children eventually diagnosed as having NF1, the most common second feature used to establish the diagnosis of NF1 was axillary or inguinal freckling, occurring in 26 (77%) patients (Figure 2C). Other signs to occur as the second (confirmatory) diagnostic feature included the following: Lisch nodules in 6 children, plexiform neurofibroma in 2 children, and tibial pseudarthrosis in 1 child. Following a diagnosis of NF1, children in this clinic population developed the following additional features of NF1 during the course of our study: 33 patients developed axillary or inguinal freckling, 15 developed Lisch nodules, 8 developed neurofibromas, 4 developed skeletal anomalies, 3 developed macrocephaly, 2 developed optic gliomas, 4 developed plexiform neurofibromas, 1 developed precocious puberty, and none developed malignant peripheral nerve sheath tumors or pheochromocytomas; 6 of 8 patients who underwent neuroimaging were noted to have T2 hyperintensities on magnetic resonance imaging.

Because of the association of CALMs with NF1, current guidelines support evaluation of children with multiple CALMs for this common genetic disorder. In some instances, the presence of other associated clinical findings or a positive family history of NF1 will allow a di-
agnosis of NF1 to be made at the initial evaluation. However, a notable number of children will come to medical attention with only CALMs and no other diagnostic features of NF1. At present, there are scant data to estimate the likelihood that a child who exhibits only CALMs will develop NF1. To better characterize the clinical course of these patients, we performed a retrospective analysis of children with CALMs and no other diagnostic features of NF1 who were seen in our NF clinic over a period of 3 years.

We identified 110 children who were referred to our clinic for evaluation of NF1 based on the presence of CALMs. To our knowledge, this is the largest series to date of children presenting with CALMs alone. However, this was a retrospective study and was limited to data collected at the time of the office visits. In this regard, 13 patients with typical CALMs and 17 patients with atypical CALMs who were younger than 6 years at the last follow-up examination remained undiagnosed. Some of these patients may eventually develop other features and meet diagnostic criteria for NF1 at a later date. Thus, our data may underestimate the number of patients with multiple CALMs alone who eventually meet criteria for NF1.

The median age at which children first visited our NF clinic was 33 months, with a median number of 6 CALMs. Several experts recommend referral or further evaluation of children who manifest 3 or more CALMs. In our cohort, the majority of referring physicians appeared to follow this guideline, as 6% of children referred had fewer than three CALMs.

Thirty-four patients (31%) were eventually diagnosed as having NF1 during the follow-up period. This is consistent with a previous large study of all children evaluated at an NF clinic (including children with fewer than 6 CALMs), which found that 67% of patients had only 1 diagnostic feature of NF1, most commonly CALMs, and did not develop other features. In our series, patients with a higher number of CALMs at presentation were more likely to develop NF1: 77% of patients who had 6 or more typical CALMs at initial presentation were eventually diagnosed as having NF1. This is consistent with the one earlier study, in which 75% of 41 patients with 6 or more CALMs were diagnosed as having NF1. These findings suggest that most children with NF1 who exhibit 6 or more CALMs at initial presentation will be diagnosed as having NF1. However, it is important for pediatricians to recognize that there will be a small number of children who present with only 2 to 3 CALMs at an early age and warrant monitoring for the development of additional CALMs or other features of NF1 over time. No children were diagnosed as having syndromes other than NF1. One undiagnosed child with an irregular CALM had a parent with a CALM. It is possible that this represented a case of multiple familial CALMs without other features of NF1; however, there was no information available about other family members and no genetic analysis was performed.

In children eventually diagnosed as having NF1 after an initial presentation with only CALMs, 76% met NF1 criteria by age 4 years, 94% met NF1 criteria by age 6 years, and all patients met NF1 criteria by age 8 years. The 2 children in our series who were diagnosed after age 72 months were both lost to follow-up for a period prior to diagnosis, and it is possible that a diagnosis would have been established prior to age 72 months had they

Figure 2. Likelihood of being diagnosed as having neurofibromatosis type 1 (NF1) based on the number of café au lait macules (CALMs), patient age, and secondary features. A, The relationship between the number of CALMs at initial presentation and the likelihood of establishing a diagnosis of NF1 is shown. Children with irregular CALMs were excluded. B, The percentage of children eventually diagnosed as having NF1 during the study period is shown for each age. C, The frequency of developing a second clinical feature in children presenting with CALMs is shown.
been seen earlier. This is similar to that previously reported by Korf, who found that 75% of patients diagnosed as having NF1 met criteria prior to age 6 years and 92% met criteria prior to age 10 years. In our series, the most common second feature of NF1 to appear was axillary or inguinal freckling, similar to that reported by Korf. Collectively, these data suggest that the majority of children who present with CALMs alone will meet diagnostic criteria by age 6 to 8 years and justifies following these children as though they have NF1 for most of the first decade of life.

Active NF referral centers are often asked to evaluate children with unusually shaped CALMs. In our series, the morphologic appearance of the CALMs was an important indicator of diagnostic outcome. Typical CALMs in children with NF1 are circular or ovoid macules with uniform pigment and well-defined borders. We found that patients with atypical CALMs were less likely to be diagnosed as having NF1. Although 47% of patients with typical CALMs were eventually diagnosed as having NF1, only 2 patients (3%) with atypical CALMs developed NF1. While several experts have stated that the morphologic appearance of the CALMs was an important indicator of diagnostic outcome. Typical CALMs were eventually diagnosed as having NF1, although 47% of patients with typical CALMs were diagnosed as having NF1. With few exceptions, the diagnosis of NF1 is established by age 72 months using the established National Institutes of Health clinical criteria. In addition to number of CALMs, the morphologic appearance of CALMs may also be a useful predictive feature in the diagnosis of NF1. In some cases, genetic testing for NF1 may be useful in providing a definitive diagnosis; however, this analysis remains cost-prohibitive for many patients. In conclusion, our findings regarding the number and morphologic appearance of CALMs should help clinicians provide more accurate counseling to parents with children harboring multiple CALMs in the absence of other features of NF1.

Accepted for Publication: March 11, 2009.

Correspondence: David H. Gutmann, MD, PhD, Department of Neurology, Washington University School of Medicine, Box 8111, 660 S Euclid Ave, St Louis, MO 63110 (gutmann@neuro.wustl.edu).

Author Contributions: All of the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nunley, Bayliss, and Gutmann. Acquisition of data: Nunley and Albers. Analysis and interpretation of data: Nunley, Gao, Bayliss, and Gutmann. Drafting of the manuscript: Nunley and Gutmann. Critical revision of the manuscript for important intellectual content: Gao, Albers, Bayliss, and Gutmann. Statistical analysis: Gao. Administrative, technical, and material support: Albers. Study supervision: Bayliss and Gutmann.

Financial Disclosure: None reported.

REFERENCES