ORIGINAL ARTICLE

Predicting neurofibromatosis type 1 risk among children with isolated café-au-lait macules

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Background: Although isolated cafe-au-lait macules (CALMs) are a common skin finding, they are an early feature of neurofibromatosis type 1 (NF1).

Objective: We sought to develop an algorithm determining the risk of children with CALMs to have constitutional NF1.

Methods: We conducted a retrospective study of patients with isolated CALMs. Diagnosis of NF1 was based on detecting NF1 mutation in blood or fulfilling clinical criteria.

Results: In all, 170 of 419 (41%) and 21 of 86 (24%) children with isolated CALMs who underwent molecular testing and clinical follow-up, respectively, were given a diagnosis of NF1. Presence of fewer than 6 CALMs at presentation or atypical CALMs was associated with not having NF1 ($P < .001$). An algorithm based on age, CALMs number, and presence of atypical macules predicted NF1 in both cohorts. According to the algorithm, children older than 29 months with at least 1 atypical CALM or less than 6 CALMs have a 0.9% (95% confidence interval 0%-2.6%) risk for constitutional NF1 whereas children younger than 29 months with 6 or more CALMs have a high risk (80.4%, 95% confidence interval 74.6%-86.2%).

Limitations: The study was designed to detect constitutional NF1 and not NF1 in mosaic form.

Conclusions: A simple algorithm enables categorization of children with isolated CALMs as being at low or high risk for having NF1. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.02.027.)

Key words: algorithm; café-au-lait macules; neurofibromatosis type 1; prediction.

Café-au-lait macules (CALMs) are detected in 2.7% of newborns,[1] and 28% of school-age children.[2] CALMs are multiple (≥3) in about 1% of children,[3] and 14% of adults.[4,5]

CALMs are a hallmark of neurofibromatosis type 1 (NF1) (Mendelian Inheritance in Man no. 162200), which affects 1 in 2000 to 2500 newborns.[6,7] Other

Abbreviations used:

AUC:	area under the curve
CALM:	café-au-lait macule
CI:	confidence interval
NF1:	neurofibromatosis type 1
NIH:	National Institutes of Health

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characteristics of NF1 are skin fold freckling, iris Lisch nodules, neurofibromas, osseous lesions, and tumors such as optic pathway gliomas and malignant peripheral nerve sheath tumors.[8] NF1 is caused by mutations in the NF1 gene.[9,10] Approximately 50% of NF1 cases result from a de novo heterozygous *NF1* gene mutation present in a parental gamete or acquired early in fetal development, whereas the rest are familial.[11,12]

There are well-established criteria for diagnosing NF1, generated by the National Institutes of Health (NIH),[13,14] but the clinical signs appear gradually.[13,15-17] In the absence of a positive family history, young children with NF1 may not have sufficient findings to make a clinical diagnosis.[16]

CALMs are usually the first clinical feature of NF1 to appear. They are sometimes present at birth, but commonly develop between early infancy and ~2 years of age.[18] The presence of 6 or more CALMs, greater than 5 mm before puberty and 15 mm after puberty in largest diameter is a clinical diagnostic criterion for NF1.[14]

CALMs are found in other genetic conditions such as Legius syndrome,[19] described in about 2% of individuals with 6 or more CALMs and negative *NF1* gene testing.[19] Although other conditions such as Noonan syndrome,[20] constitutional mismatch repair deficiency syndrome,[21,22] and ring chromosomes,[23] may be associated with CALMs, CALMs are not a cardinal feature of these conditions.[4]

In the absence of a positive family history, young children with NF1 often lack sufficient criteria to make a clinical diagnosis.[16] We propose a diagnostic algorithm to allow for the categorization of individuals with isolated CALMs as being at low or high risk for having NF1.

CAPSULE SUMMARY

- Isolated café-au-lait macules are ubiquitous, but are also a hallmark of neurofibromatosis type 1.
- The study provides an algorithm enabling categorization of children with café-au-lait macules as being at low or high risk for having constitutional neurofibromatosis type 1.
- Accurate risk assessment may result in better patient care.

METHODS

Patients

This study comprised 2 groups. The first included individuals younger than 18 years with isolated CALMs and a negative family history of NF1 referred for *NF1* gene mutation analysis to the Medical Genomics Laboratory, Department of Genetics, University of Alabama at Birmingham, between 2010 to 2013 (the molecular cohort). Patients with a referral diagnosis of (possible) segmental NF1 were not included. Information on this group included age at time of referral, number (<6 or ≥6) and size (>5 or 15 mm in largest diameter at prepubertal or postpubertal age, respectively) of CALMs, and the presence of CALMs with irregular margins and ragged borders (atypical CALMs). These anonymized data were extracted from a structured requisition form (http://www.uab.edu/medicine/genetics/images/NF1_Test_Requisition_Form.pdf). Patients were given a diagnosis of NF1 based on the presence of a disease-causing *NF1* gene mutation according to the laboratory's criteria. The study was approved by the local institutional review boards.

The second group included individuals with isolated CALMs who were referred to a tertiary care neurofibromatosis referral clinic at Tel-Aviv Medical Center (the clinical cohort). None of the patients in this group had other clinical diagnostic criteria for NF1 (including a family history), or signs of segmental disease. All were examined by a single physician (S. B-S.). The number of CALMs and the presence of atypical CALMs were defined as above. Patients were given a diagnosis of NF1 based on later positive molecular testing, or meeting the NIH NF1 clinical criteria. Non-NF1 CALMs were defined either by negative *NF1* molecular testing in blood or when the clinical criteria for NF1 were not met when the patient was older than 72 months.

Molecular analysis

Blood samples submitted to University of Alabama at Birmingham underwent comprehensive *NF1* gene mutation analysis using an RNA-DNA-based comprehensive approach complemented by DNA-based dosage analyses, as previously described.[24-27] Mutations were classified and annotated following recommendations of the Human Genome Variation Society.

Statistical analysis

Continuous variables were compared using a 2-tailed Student *t* test and logistic regression. Discrete variables were compared using Pearson χ^2 test. A *P* value of less than or equal to .05 was considered significant. Confidence intervals (CI) at the level of 95% were calculated.

A decision tree, using number of sample in the leaf node and pruning algorithm, was used. The data were divided into 3 groups (a cross-validation