

Referral practices of primary care physicians regarding children with multiple café-au-lait spots

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ABSTRACT

Background: Neurofibromatosis type-1 (NF1) is an autosomal dominant genetic disorder with an incidence of 1:3000. In 1988, the National Institute of Health (NIH) established strict diagnostic criteria for NF1 including six or more café-au-lait spots (CALs) \geq 5mm in prepubertal individuals. Current recommendations are that any child with five or more CALs should be evaluated for this disorder. Although the use of NIH criteria permits diagnosis of virtually all NF1 patients by age 20, the diagnosis of very young children is challenging, and as many as 35% of children with NF1 remain undiagnosed by age 5.

One challenge is that multiple CALs can be seen in other disorders and a few spots are not uncommon among normal, healthy individuals. Also contributing to diagnostic delay is the fact that many other features of NF1 are either uncommon or do not develop until late childhood or adulthood. Although there is currently no preventative therapy for NF1, early diagnosis is critical for the pre-symptomatic detection of treatable optic gliomas and for genetic counseling and family planning. This study explored primary care referral practices regarding young children with multiple CALs in an effort to determine whether lack of knowledge of the significance of CALs and other features of NF1 contributes to delays in diagnosing young children. Study Design and Methods: One hundred and twenty four primary care physicians in the Seattle metropolitan area received a self-administered questionnaire exploring their referral practices regarding young children with multiple CALs. Results: Sixty-eight valid surveys were collected. One hundred percent of respondents reported that suspicion of NF1 based on multiple CALs alone

would cause them to refer to specialty care for further evaluation. The mean number of CALS leading to referral in a child with no other disease features and no family history of the disorder was 5.02 (SD \pm 1.56, 95% confidence interval 4.64 – 5.40). A positive family history would influence 78.8% percent to refer with fewer spots. For the majority of surveyed physicians, the presence of subcutaneous nodules (89.7%), seizure (85.3%), parental concern (81.8%), developmental delay (80.6%), axillary freckling (76.5%) and macrocephaly (51.5%) would reduce the number of CALS needed to prompt a referral.

Conclusions: Our results demonstrate that primary care physicians are appropriately referring children with CALS for suspected NF1. Delays in the diagnosis of young children with NF1 do not seem to result from lack of knowledge of the significance of CALS, nor from reluctance to refer. However, knowledge of the sensitivity and specificity of axillary freckling and subcutaneous nodules coupled with CALS appears to be deficient. An expectation of 100% referral rate should be reasonable for these features.

INTRODUCTION

Neurofibromatosis type-1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the NF1 gene on chromosome 17. The incidence of NF1 is currently estimated at 1:3000⁸, with one-half of cases representing new mutations². Clinical manifestations of NF1 include the development of benign nerve tumors, or neurofibromas, that typically present as subcutaneous nodules. Patients with NF1 are also at an increased risk for the development of malignant tumors including neurofibrosarcomas, astrocytomas, medulloblastomas, Wilm's tumors,

rhabdomyosarcomas and childhood leukemias. Forty percent of patients with NF1 have some type of mental deficit such as attention deficit, seizure or behavioral disorders⁸.

In 1988, the National Health Institute Consensus Conference established diagnostic criteria for NF1 (Table 1).

Table 1: NIH Criteria for Diagnosis of NF1

Diagnostic criteria are met with two or more of the following:

1. Six or more café-au-lait spots larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in postpubertal individuals.
2. Two or more neurofibromas of any type, or one plexiform neurofibroma
3. Inguinal or axillary freckling
4. Optic glioma
5. Two or more Lisch nodules
6. Distinctive osseous lesion such as sphenoid wing dysplasia or cortical thinning of long bones
7. A first-degree relative who meets the NF1 diagnostic criteria

Multiple café-au-lait spots (CALs) are one of the earliest signs of NF1 and as many as 99% of NF1 patients have six or more CALs greater than 5mm in diameter by age one². CALs are round to oval with sharply defined borders and are generally less than two centimeters in their greatest diameter³. They are milky brown in color and are more common on the trunk, buttocks and lower limbs. Although CALs are usually apparent at birth or within the first year of life, they may increase in number during early childhood and increase in size after puberty. In fair skinned children, examination with a Wood's lamp can visualize CALs not visible in standard light. Although more than six CALs almost always indicates NF1, there are several other diseases that are also associated with multiple CALs including McCune-Albright syndrome, neurofibromatosis-2, Watson syndrome and autosomal dominant CALs.

Histologically, CALS show an increased amount of melanin, either free or within melanocytes or keratinocytes in the basal cells of the epidermis. The melanocytes produce an increased number of melanosomes that aggregate to form macromelanosomes. These macromelanosomes are present both within CALS and in the normal appearing skin of patient's with NF1. However, they are also found in skin biopsies of normal, healthy individuals²³.

Even though multiple CALS are strongly associated with NF1, they are also present in the general population. CALS are visible in 0.4-2.7% of newborns³. Among children less than ten years of age, 13% of Caucasians and 27% of African Americans have at least one CALS¹. Although multiple CALS appear more commonly in African-American children, five or more CALS, in any child, is exceedingly rare and occurs in only 0.003-1 percent of children who have no other signs of NF1³. Based on the prevalence of CALS in the general population, current recommendations are that more than three CALS in Caucasian children should prompt evaluation for development of a multi-system disorder and any child with five or more CALS should be closely monitored for the development of NF1⁴.

One challenge to the diagnosis of NF1 in young children is that many of the clinical findings listed in the NIH diagnostic criteria do not develop until late childhood or adolescence, or occur in only a small percentage of children with NF1. Early onset of multiple neurofibromas appears to be associated with a deletion of the NF1 gene¹⁰. The majority of affected children do not develop neurofibromas until puberty¹⁰. Neurofibromas are found in 48% of NF1 patients by age 10 and 84% by age 20². Axillary or inguinal freckling (Crowe's sign) appears in 90% of NF1 patients by age

seven². Optic gliomas develop within the first three years of life but occur in only 4% of NF1 patients². Lisch nodules are characteristic NF1 lesions of the iris that are visualized by slit-lamp exam and are present in more than 70% of NF1 patients by age 10². Osseous lesions, such as sphenoid dysplasia or thinning of the long bone cortex, usually present within the first year of life but occur in only 14% of NF1 patients². Another factor that complicates diagnosis is that one half of cases represent new mutations². These sporadic cases of NF1 do not have affected first-degree relatives and are, therefore, more difficult to diagnose during early childhood before other features of the disease are apparent.

The NIH diagnostic criteria for NF1 were developed under strict guidelines to avoid misclassification of patients and facilitate the linkage studies that were then being performed to try to map the NF1 gene. These criteria have proven useful in the diagnosis of NF1 with 97% of affected children fulfilling NIH criteria by age eight and virtually all affected individuals doing so by age twenty². Yet since many of the clinical features of NF1 do not appear until mid to late childhood, diagnosis of the younger child with NF1 will be delayed for a significant proportion when using the NIH criteria. A recent study found as many as 46% of sporadic cases fail to meet NIH criteria by age 1². In another study, 35% of NF1 children remained undiagnosed by age 5, even though multiple CALS were present in the majority of cases before age one⁷.

Although NF1 currently has no preventative treatment, 93% of surveyed parents of children with NF1 indicated that they would appreciate early diagnosis even in the absence of symptoms⁷. Early diagnosis of NF1 is critical for the pre-symptomatic detection of rare, but treatable, optic gliomas. Additional benefits of early diagnosis

include opportunities for parental education, genetic counseling, family planning and opportunities for learning interventions during early education.

Given that 46% of sporadic NF1 patients fail to meet diagnostic criteria by age one², other clinical features of NF1 have been proposed to facilitate earlier suspicion for the diagnosis of NF1 in children. These include short stature (less than or equal to the 3rd percentile), macrocephaly (greater than or equal to the 97th percentile), and thorax abnormalities⁵. Unfortunately, these features have very low specificity for NF1, especially when compared to those contained in the NIH diagnostic criteria.

It has been suggested that one of the problems leading to a delay in the diagnosis of NF1 in children is failure of primary care physicians to recognize the significance of CALS and other features of NF1. We were interested in trying to determine whether failure to refer for suspicion of NF1 was based on lack of familiarity with NIH criteria, misconception regarding the sensitivity of NIH criteria or disinclination to refer in general.

MATERIALS AND METHODS

Study Population

Each year Children's Hospital and Regional Medical Center publishes a Physicians Directory listing Western and North Central Washington physicians in both pediatrics and family practice. Pediatricians included in the directory are members of the Children's Medical Staff, referrers to Children's or are members of the American Academy of Pediatrics, Washington State Chapter. Family physicians in the directory are either referrers to Children's or members of the American Academy of Family Practice,

Washington State Chapter. Study participants were selected from the 1999 listing of practitioners within the King County region.

Pilot Testing

The initial survey format was tested and revised via an in person pilot survey administration. Pediatric and family medicine practices within the King County region were selected randomly from the directory and contacted by phone to determine willingness to participate in the pilot study. During June of 2002, six pediatric practices and three family medicine practices participated in the pilot study and generated twenty-four completed surveys (seventeen pediatric and seven family medicine). The pilot study resulted in minor format changes to the questionnaire to facilitate survey completion and data interpretation.

Following pilot study completion, 100 physicians (50 pediatric, 50 family medicine) were randomly selected from the 1999 Children's Directory. Excluded from consideration were practices that participated in the pilot study and practices that indicated a specialty care (allergy, developmental/behavioral etc) versus primary care focus. Random selection then consisted of totaling the remaining directory listed physicians in King County and dividing that total by fifty to obtain the nearest whole number. This resulted in the selection of every third eligible pediatrician and every seventh eligible family medicine physician for participation in the study.

Survey Methods and Questionnaire Content

In July 2002, a self-administered anonymous questionnaire (Table 2) was mailed to the 100-targeted physicians. Each questionnaire was accompanied by a cover letter explaining our interest in understanding how CALS influence physician referral

Table 2: Neurofibromatosis Type-1 Survey

1. If a child under age 3 presents with multiple café-au-lait macules as the only clinical finding, and you suspect neurofibromatosis type-1, do you refer to specialty care (ophthalmology, genetics, dermatology, radiology or other) for further work-up?

_____ Yes _____ No

If yes, skip to question 4.

2. If no, please explain your approach to this patient:

3. What would lead you to make a referral to specialty care for suspected neurofibromatosis type-1?

Skip to question 14.

4. In a child under age 3 with café-au-lait macules as the only clinical finding, how many café-au-lait macules ≥ 0.5 cm at the largest diameter would result in your referral to specialty care for suspected neurofibromatosis type-1?

1 ___ 2 ___ 3 ___ 4 ___ 5 ___ 6 ___ 7 ___ 8 ___ 9 ___ 10+ ___

5. In a child under age 3 with a first-degree relative diagnosed with neurofibromatosis type-1, how many café-au-lait macules ≥ 0.5 cm at the largest diameter would result in your referral to specialty care for suspected neurofibromatosis type-1?

0 ___ 1 ___ 2 ___ 3 ___ 4 ___ 5 ___ 6 ___ 7 ___ 8 ___ 9 ___ 10+ ___

6. Would parental concern lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
7. Would developmental delay lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
8. Would axillary freckling lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
9. Would seizure lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
10. Would subcutaneous nodules lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
11. Would macrocephaly lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
12. Would short stature lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____
13. Would thorax abnormality lead you to refer with fewer café-au-lait macules than indicated above? Yes _____ No _____

14. Specialty: Pediatrics _____ Family Medicine _____

15. Year Graduated from Medical School _____

practices. Included in the mailing was an unlabeled self-addressed stamped envelope for survey return and a separate labeled self-addressed stamped post card to document survey completion and maintain physician anonymity. Four weeks after the initial mailing, non-responders were sent a reminder letter and a replacement questionnaire. Twenty-eight physicians responded to the first mailing. An additional sixteen surveys were returned after the second mailing. The questionnaire included 13 fixed response questions and two open-ended questions exploring the relationship between CALS and referral practices. The first question was a yes/no response to determine whether physicians refer children to specialty care for evaluation when NF1 is suspected based on the presence of multiple CALS. Questions 2 and 3 were open-ended questions exploring approaches to patients if the physicians indicated that they would not refer to specialty care in question 1. Questions 4 and 5 assessed the number of CALS that prompt referral both when CALS are the only clinical finding and when the patient has an affected first-degree relative. These questions allowed physicians to indicate on a numeric scale the threshold number of CALS, in each case, that results in referral. Questions 6 through 13 were yes/no response questions that explored whether parental concern, developmental delay, axillary freckling, seizure, subcutaneous nodules, macrocephaly, short stature, and thorax abnormality result in referral with fewer CALS than previously indicated. The final two questions gathered data on physician characteristics including specialty (pediatrics or family medicine) and the year graduated from medical school.

Data Analysis

Valid survey responses were compiled and analyzed using SPSS (SPSS Inc, Chicago, Ill) for Windows, version 10.0. The survey required simply placing a check

mark to indicate a response, and all questions with responses were considered valid. In several instances, physicians chose not to respond to one or more of the survey questions. Questions left blank were considered invalid responses and excluded from data analysis for that question only. For questions 4 and 5, several physicians selected more than one response. In all instances these multiple responses were two consecutive numbers on the numeric scale. These responses were entered into our database using the average of the two responses in order to avoid skewing the results in favor of fewer or more CALS. For example, if the physician selected both 5 and 6, a response of 5.5 was entered. Years in clinical practice were calculated by subtracting the year of graduation from medical school from 2002. These were then grouped into four categories to facilitate comparison: 1) 10 or fewer years in practice (1992-2002), 2) 11 to 20 years in practice (1981-1991), 3) 21 to 30 years in practice (1970-1980), 4) 31 or more years in practice (1969 or before).

RESULTS

Physician Characteristics

Of the 100 surveys mailed, 18 were undeliverable, indicating the targeted physician was no longer with the practice, or the practice was no longer in business. One survey was returned from a physician practicing internal medicine. Since we were interested in referral practices regarding young children, the internal medicine survey was considered invalid and was not included in our analysis. Of the remaining 81 mailed surveys, 44 (54%) were returned. These were then added to the 24 surveys generated from the pilot study to yield 68 surveys for final analysis (55% response rate). The physician distribution in the final analysis included 22 family medicine physicians

(32.4%), 44 pediatric physicians (64.7%) and 2 physicians who did not indicate their specialty (2.9%).

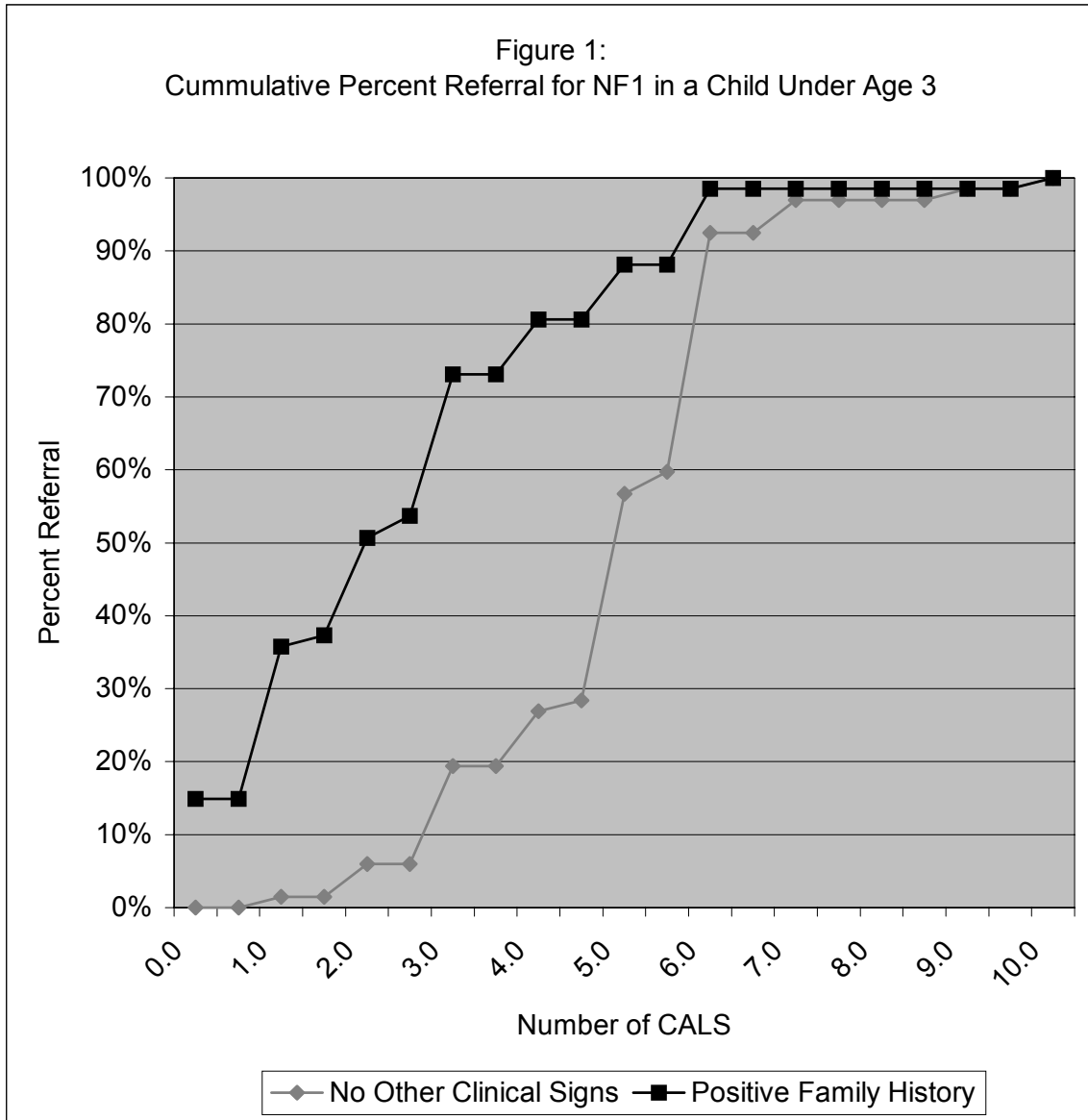
Referral Practices

Since the primary purpose of the study was to determine the number of CALS prompting physicians to refer a child for further evaluation for suspected NF1, it was important to first assess whether physicians actually make referrals when they suspect this disorder. This turned out to be a valid assumption as 100% of surveyed physicians indicated that they would refer to specialty care (ophthalmology, genetics, dermatology, radiology or other) for further work-up if they suspected NF1.

Next, using a numeric scale, we investigated the threshold number of CALS leading to referral in a child with no other clinical signs, and in a child with a positive family history of NF1 (Figure 1). Sixty-seven physicians responded. In children under age 3 with CALS as the only clinical finding, the mean number of CALS ≥ 0.5 cm at the largest diameter that would result in a referral to specialty care for suspected NF1, was 5.02 (SD ± 1.56 , 95% confidence interval 4.64 – 5.40). In response to this question, 92.5% of surveyed physicians reported that they would refer with six or fewer CALS.

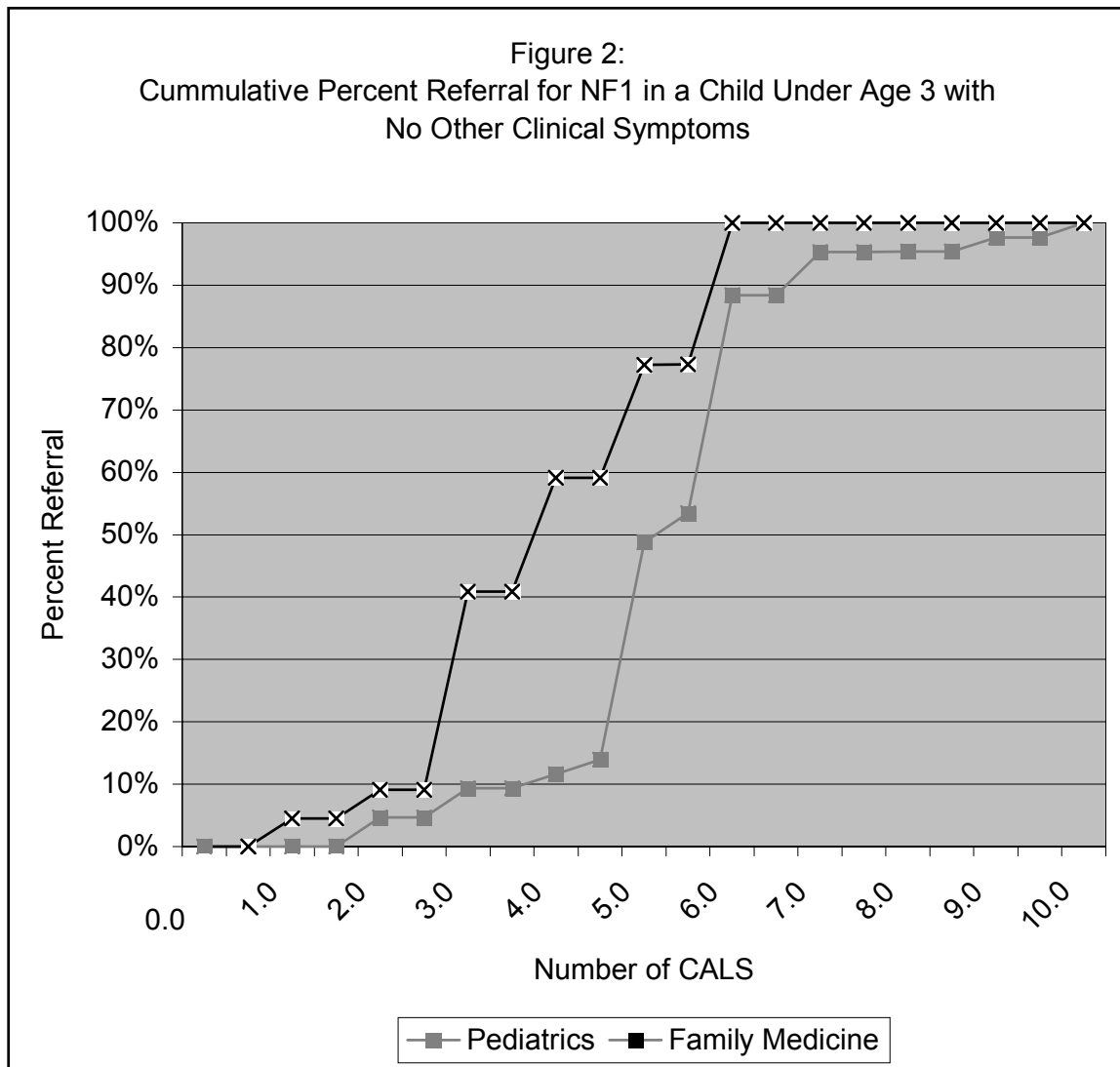
We also assessed the threshold number of CALS leading to referral in a child with a first-degree relative diagnosed with NF1 using a scale from zero to ten. The scale was changed in this instance because some physicians automatically refer children with a family history of NF1 for further evaluation, even when no CALS are present. As in the previous question, sixty-seven physicians responded. In children under age 3 with a first degree relative diagnosed with NF1, the mean number of CALS ≥ 0.5 cm at the largest diameter that would result in referral to specialty care for suspected NF1 was 2.60 (SD \pm

2.08, 95% confidence interval 2.10 – 3.11). This number is significantly lower than the number leading to referral in a child with no family history of the disease.



We analyzed responses by both specialty and years in practice. In children who have no other signs of NF1, family medicine physicians tend to refer with fewer CALS than their pediatric colleagues (Figure 2), with a mean of 4.09 (SD ± 1.44, 95% confidence interval 3.45 – 4.73) for family medicine compared to a mean of 5.45 (SD ±

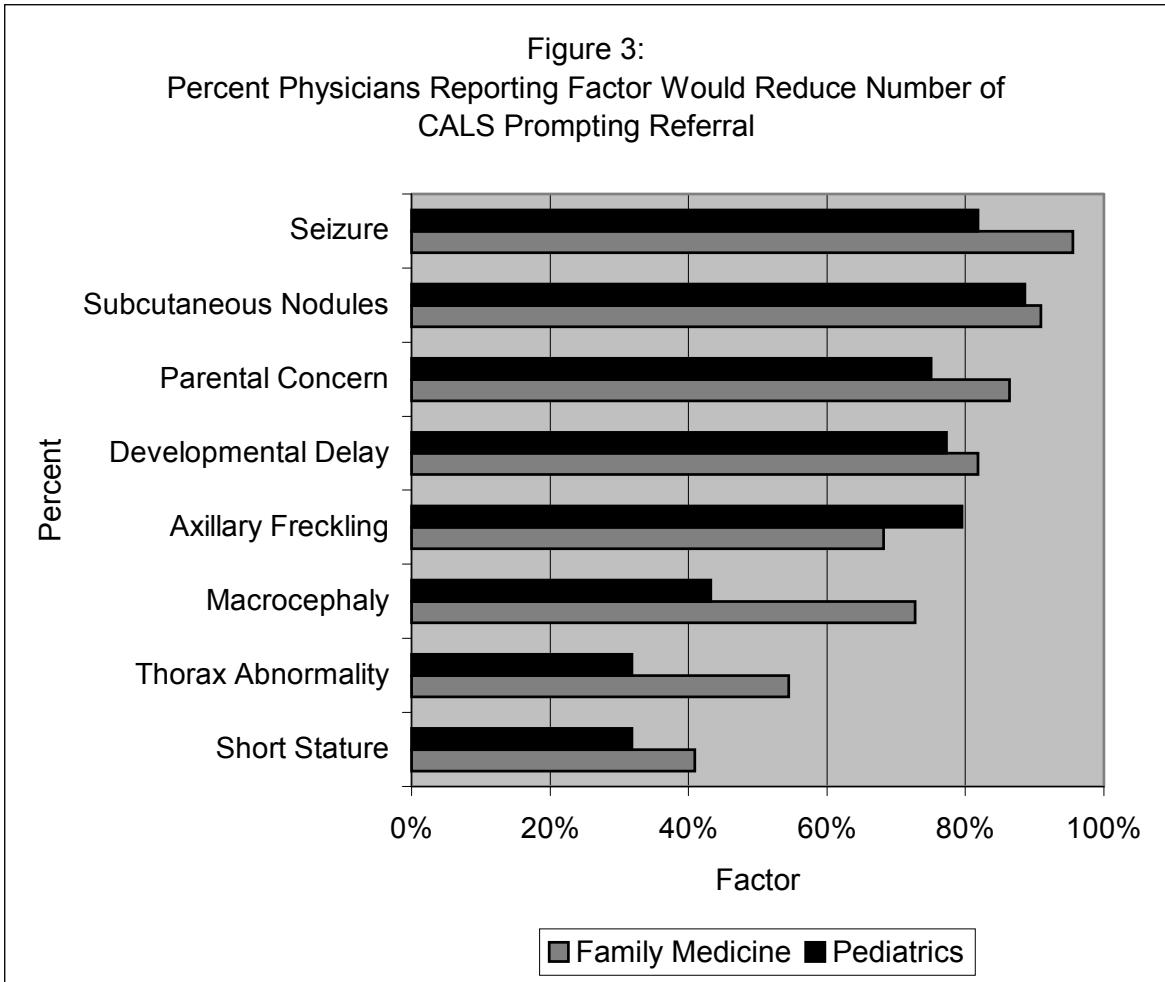
1.44, 95% confidence interval 5.01 – 5.90) for pediatrics [$p = 0.001$ (2-tailed)]. This trend continues when the child has a positive family history of NF1 with a mean of 1.68 (SD \pm 1.32, 95% confidence interval 1.10 – 2.27) for family medicine, and a mean of 2.92 (SD \pm 2.19, 95% confidence interval 2.24 – 3.59) for pediatrics [$p = 0.018$, (2-tailed)].



When we compared the threshold for referral by physician experience there was a statistically significant correlation between the number of CALS prompting referral and

the number of years in practice [$p = .021$ (2-tailed)]. The mean number of CALS resulting in referral among physicians with 10 or fewer years in practice was 4.20 (SD \pm 1.81, 95% confidence interval 2.90 – 5.50). For physicians with 11 – 20 years of experience the mean was 4.91 (SD \pm 1.16, 95% confidence interval 4.41 – 5.42). Those in practice 21 – 30 years had a mean of 5.08 (SD \pm 1.64, 95% confidence interval 4.31– 5.84). Finally, the mean for physicians with 31 or more years in practice was 5.71 (SD \pm 1.65, 95% confidence interval 4.76 – 6.67). Physicians with fewer years in practice tend to refer children with fewer CALS as compared to their less recently trained colleagues. Regardless of experience, the majority of physicians (92.5%) refer children with 6 or fewer CALS for evaluation of NF1 when no other clinical signs are present.

Using these numbers as the physician threshold for referral, we then explored factors that, in the presence of multiple CALS, would reduce this threshold (Figure 3). The majority of surveyed physicians reported that following factors would lead them to refer with fewer CALS than previously indicated: subcutaneous nodules (89.7%), seizure (85.3%), parental concern (81.8%), developmental delay (80.6%), axillary freckling (76.5%) and macrocephaly (51.5%). The presence of short stature (33.8%) and thorax abnormalities (38.2%) result in referral with fewer CALS only among a minority of physicians surveyed. There was a statistically significant correlation at the 0.05 level [$p=0.023$ (2-tailed)] between specialty and response to the presence of macrocephaly: 43.2% of surveyed pediatricians, in contrast to 72.7% of family practice physicians, indicated that macrocephaly would reduce the number of CALS prompting referral.



DISCUSSION

Our data demonstrate that physicians appropriately refer children with multiple CALs for specialty evaluation. The mean number of CALs resulting in referral was 5.02 (SD ± 1.56, 95% confidence interval 4.64 – 5.40). This corresponds well with the current recommendation that children with 5 or more CALs be closely monitored for NF1⁴. It also indicates that referral practices regarding children with multiple CALs do not explain diagnostic delay in children with NF1 once the presence of CALs is appreciated (primary care providers may overlook CALs if examination does not include use of a

Wood's lamp). Delay of diagnosis may not be due to failure of referral as shown by the willingness of respondents to refer.

Diagnostic delay may occur at the level of the specialists. With the exception of CALS, many of the diagnostic features for NF1 occur later in childhood or in a small percentage of children who have NF1. This make diagnosis challenging even when physicians are aggressively referring children with multiple CALS for specialty evaluation. Although our data indicate that physicians are actively investigating the possibility of NF1 in children with five or more CALS, it is unclear if even more aggressive referral practices, such as referral of children with three or more CALS would significantly reduce diagnostic delay.

It has been proposed that minor disease features such as macrocephaly, short stature and thorax abnormalities should be considered for use to trigger earlier detection of NF1 in children who fail to meet NIH diagnostic criteria⁵. It is recognized that both the sensitivity and specificity of these features for NF1 is low and our data indicate that the majority of physicians (with the exception of family practice physicians encountering macrocephaly in a child with multiple CALS) do not currently alter their referral practices based on these features.

In contrast to macrocephaly, short stature and thorax abnormalities, both axillary freckling and subcutaneous nodules are highly specific for NF1, and as such, should lower the threshold for referral close to 100% of the time. Axillary freckling only reduced the number of CALS resulting in referral in 76.5% and subcutaneous nodules in only 89.7% of surveyed physicians. This clearly indicates a need for increased physician

education regarding the relationship between axillary freckling, subcutaneous nodules and NF1.

The small number of surveyed physicians limits this study. Our results are difficult to generalize with only 68 surveyed physicians from one metropolitan area. However, several interesting trends were apparent in our data. These include a tendency for pediatricians to require a higher number of CALS to trigger a referral than family medicine physicians. This is also true for physicians with more years in practice compared to their more recently trained colleagues. This could reflect differences in either training or experience with NF1. Regardless of differences between specialties or years of experience, both pediatricians and family medicine physicians appear to be appropriately referring children with multiple CALS for further evaluation, based on self-report.

Our study did not address the differences in CALS frequency among different populations of children and the impact these differences may have on referral practices. Multiple CALS are much more frequent in African-American children compared to Caucasian children. The number of CALS physicians regularly encounter in their patient populations undoubtedly affects their referral practices and their index of suspicion for NF1. We did not ask physicians to describe their practice populations and could not factor this into our analysis. Any child with five or more CALS should be evaluated for NF1 regardless of skin color or racial background. Our data indicate that this is occurring.

When a child has a family history of NF1, the threshold for suspicion for NF1 becomes lower as evidenced by a mean of 2.60 CALS resulting in referral when the child

has a first-degree relative with NF1 compared to mean of 5.02 CALS when they do not. The diagnostic challenge occurs when physicians are not looking specifically for CALS. CALS can be difficult to identify in fair skinned children and may, in some cases, require Wood's lamp examination for visualization. Our survey did not determine whether all children with multiple CALS are correctly identified. We were able to learn what physicians would do; our self-administered questionnaire could not determine what they actually do.

Nonetheless, the results of our study indicate that primary care physicians are appropriately referring children with multiple CALS for further evaluation and are aware of the diagnostic significance of multiple CALS. Therefore, we cannot argue that diagnostic delay in children with NF1 results from delays in referral to specialty care for thorough evaluation once CALS are identified. In order to better understand why some children with NF1 experience diagnostic delay, a retrospective chart review of children diagnosed with NF1 would be a useful next step. In such a study, one could determine the number of CALS identified by the primary care physician and the age at which CALS were first identified. Then one could better outline the steps undertaken that ultimately led to the diagnosis of NF1 and identify any factors potentially causing diagnostic delay. Early diagnosis of children with NF1 is highly desirable and there is still much to be learned regarding how children are diagnosed and what interventions can be used to facilitate earlier detection. It is clear from our study that the delay in referral, if it truly exists, is not due to a failure to educate physicians regarding the significance of multiple CALS.

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