Juvenile Xanthogranuloma and Nevus Anemicus in the Diagnosis of Neurofibromatosis Type 1

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Neurofibromatosis type 1 (NF1) is a hereditary autosomal dominant condition with an estimated incidence of 1 in 3500 births. About half the cases are sporadic. According to the National Institutes of Health (NIH) consensus conference, a diagnosis of NF1 in children is established by the presence of at least 2 of 7 clinical criteria: 6 or more café au lait macules larger than 0.5 cm, 2 neurofibromas or 1 plexiform neurofibroma, axillary or inguinal freckling, optic glioma, at least 2 iris Lisch nodules, a characteristic bone lesion (pseudarthrosis or sphenoid dysplasia), or a first-degree relative with NF1. It later appeared that the presence of T2 unidentified bright objects on brain magnetic resonance imaging also has good diagnostic value. Indeed, NIH diagnostic criteria allow a diagnosis of NF1 in most children at the age of 5 years but are of limited value for earlier diagnosis. Actually, before the age of 2 years, 50% of children with sporadic NF1 have been reported to harbor only 1 NIH criterion, resulting in delayed diagnosis. In this age group, NF1 usually manifests as isolated multiple café au lait spots, which are highly suggestive but not specific for NF1. Additional cutaneous manifestations may occur in children with NF1: juvenile xanthogranulomas (JXG) and nevus anemicus (NA).

Juvenile xanthogranuloma is the most common non-Langerhans cell histiocytosis. It consists of an asymptomatic yellow-brown papule or nodule, usually solitary, preferentially localized on the head and neck. It appears in the early years of life, may be present from birth, and resolves spontaneously. Its association with NF1 was first reported in 1937 by Lamb and Lain. Since then, multiple additional cases have been reported. The presence of JXG in patients with NF1 is considered a warning sign for juvenile chronic myelomonocytic leukemia (JCMML). Patients with NF1 and multiple JXG lesions have a 20- to 30-fold higher risk of developing JCMML than those without JXG lesions. However, in at least 2 retrospective series of JXG in patients with NF1, no increased incidence of JCMML was reported.

**IMPORANCE** The diagnosis of neurofibromatosis type 1 (NF1) is based on 7 clinical criteria. However, they are of limited value before the age of 2 years. Juvenile xanthogranuloma (JXG) and nevus anemicus (NA) are commonly observed in children with NF1 and may be useful diagnostic clues.

**OBJECTIVES** To evaluate the frequency of JXG and NA, to describe their clinical features, and to determine their diagnostic value in patients with NF1.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective medical record review of outpatients seen between January 1, 2005, and December 31, 2011. University hospital dermatology department affiliated with the French NF1 referral center network. Patients with NF1 diagnosed by at least 2 National Institutes of Health criteria and examined at our department.

**MAIN OUTCOMES AND MEASURES** Percentage of patients with NF1 who had JXG or NA categorized into 4 age groups.

**RESULTS** Among 72 patients with NF1 (median age, 15.4 years), 23 had JXG (10%) or NA (25%). Both lesions were more frequent (55%) in those younger than 2 years (JXG, 30%; NA, 35%). Most JXG lesions were multiple and resolved spontaneously. Cephalic and genital involvement was frequent. No patient with JXG developed chronic myelomonocytic leukemia. Nevus anemicus was present on the neck and upper chest in 72% of cases. Among 10 patients (14%) who had only 1 diagnostic criterion at first visit, including 9 younger than 2 years, JXG or NA was present in 8 (80%).

**CONCLUSIONS AND RELEVANCE** We found a high frequency of JXG and NA in patients with NF1, especially in children younger than 2 years with fewer than 2 diagnostic criteria. Hence, JXG and NA appear helpful in improving early diagnosis of NF1 in young children and infants.
Nevus anemicus is a pale macular skin area, often with polycyclic borders, caused by permanent vasoconstriction in the superficial dermis, which may be relieved on injection of an α-blocking agent. It is unassociated with impaired melanization or sensitivity. Nevus anemicus is considered stable throughout life. It appears at birth or during childhood, predominantly on the trunk. It is sometimes associated with an adjacent port wine stain, which is thought to result from a twin spotting phenomenon. Association with neurofibromatosis type 1 was first suggested in 1915 by Naegeli. It was later reported by Schmidt in 1929 and Fleisher and Zeligman in 1969.

Because both signs are present in children, they may represent early diagnostic criteria for NF1. However, no studies have addressed their diagnostic value in NF1. Hence, our objectives were to evaluate the frequency of JXG and NA, to describe their clinical features, and to determine their diagnostic value in patients with NF1.

Methods
Clinical medical records and photographs from patients with NF1 who underwent detailed skin examination at the Department of Dermatology, Dijon University Hospital, Dijon, France, between January 1, 2005, and December 31, 2011, were reviewed. Because the study was performed retrospectively, institutional review board approval was not required. Recorded clinical data were age at first diagnosis of JXG or NA; age at diagnosis of NF1; NIH criteria at first and last visits; sex; personal and family history; mode of inheritance of NF1; type, number, and localization of skin lesions; evolution; and any other associated clinical or laboratory anomalies. Diagnoses of NF1, JXG, and NA were made on a clinical basis. Neurofibromatosis type 1 was defined as the presence of at least 2 NIH criteria. Juvenile xanthogranuloma was defined as asymptomatic yellow-brown papules or nodules, without Darier sign (swelling or redness on rubbing). Nevus anemicus was defined as hypochromic macules devoid of vasodilation on friction. No skin biopsies were performed. The frequency, median age at diagnosis, and sex ratio for each sign (JXG and NA) were calculated in our whole population divided into 4 age groups (<2 years, 2-9 years, 10-19 years, and ≥20 years). Association of JXG and NA with age group, sex, mode of inheritance of NF1, and number of NIH criteria at first visit was determined using the Fisher exact test, with P < .05 considered statistically significant.

Results
Among all 72 medical records of patients with NF1 (33 males and 39 females) seen at the Department of Dermatology, Dijon University Hospital, Dijon, France, between January 1, 2005, and December 31, 2011, a diagnosis of JXG or NA was found in 23 patients (32%). Most patients were children, with the median age at first visit being 15.4 years (range, 1 week to 67.8 years). Seven patients (10%) had JXG (5 males and 2 females), and 18 patients (25%) had NA (11 males and 7 females). Two patients (3%) had both NA and JXG. Among patients younger than 2 years, 11 (55%) had either JXG (30%) or NA (35%). Frequencies in older age groups are shown in Figure 1. Neurofibromatosis type 1 occurred de novo in 38 patients (53%). No significant association was observed between the presence of JXG or NA and the mode of inheritance (inherited vs sporadic).
Juvenile xanthogranuloma was more frequent in males, albeit not significantly (OR, 3.30; P = .23). The median age of patients at diagnosis was 7 years (range, 7 weeks to 57.2 years). Nevus anemicus lesions were asymptomatic, hypochromic, round or elliptoid macules that ranged from 0.5 to 6.0 cm in diameter, rarely noticed by patients or parents before examination by a dermatologist. Most NA is visible only after elicitation of vasodilation in surrounding skin by gentle friction during examination, which enhances color contrast, although some NA is also detectable without friction. In rare instances, NA has been noticed by parents as local absence of redness on skin vasodilation after a warm bath. These lesions mainly involve the neck and upper chest (72%) (Table 1 and Figure 3) and are more often multiple and clustered than solitary (Table 1). The median number of lesions was 2 (range, 1-28). In 3 patients aged 0.1, 1.0, and 15.4 years, NA was associated with an underlying neurofibroma (2 plexiform neurofibromas on the trunk and 1 superficial neurofibroma on the forehead). Evolution of NA with age could not be accurately determined because follow-up was available for only 9 patients, with a median duration of 0.6 year (range, 0-20.7 years). Regression of NA was noted in 1 patient only, at the age of 1 year.

Ten patients (14%) had only 1 NIH diagnostic criterion at the first visit. Eight of these patients had de novo cases and 9 were younger than 2 years (45.0% in this age group). However, JXG or NA was present in 8 patients (80%), raising high suspicion for the diagnosis of NF1, which was subsequently confirmed on follow-up. In addition, JXG was significantly more frequent in patients with only 1 NIH criterion for NF1 (OR, 30; P < .001) than in patients with NF1 who have a definite diagnosis based on 2 or more NIH criteria. However, NA was not significantly more frequent in patients with only 1 NIH criterion for NF1 (OR, 3.77; P = .11). Prevalence of JXG and NA in patients with NF1 who have a definite diagnosis at the first visit was lower. Sixty-two patients (86%) had 2 or more NIH diagnostic criteria at the first visit. Either JXG or NA was present in 15 patients (24%).

**Discussion**

We found a high frequency of NA and JXG in patients with NF1. These conditions were present in more than half the children with NF1 younger than 2 years. Prevalence of JXG and NA in the general population is not precisely known. However, they are certainly much less frequent. Thus, both cutaneous signs appear as good criteria for NF1 diagnosis in infancy and early childhood. In a pediatric series, prevalence of JXG was reported as 3.9% in a series of 357 patients younger than 17 years and 18.2% in a series of 77 patients younger than 3 years. In contrast, in the adult series of Huson et al, prevalence of JXG was only 0.7%. The intermediate prevalence found in our study (10%) reflects a mixed adult and (mostly) pediatric population. Most clinical characteristics of JXG in our study were identical to those previously reported in the general population: predominant cephalic involvement, young
we did not routinely perform magnetic resonance imaging in asymptomatic children.

The high prevalence of NA in NF1 patients (25%) found in our study is difficult to compare with previous results because no series of NA in patients with NF1 or in the general population have recently been published, to our knowledge. In addition, NA may have been overlooked in patients with NF1 because NA is barely visible or invisible unless elicited on skin stroking. However, in the series by Schmidt,43 a prevalence of 11.04% was reported in 462 patients having a diagnosis of neurofibromatosis, although it can be argued that not all of these patients may have had NF1 because diagnostic criteria have evolved over time. In this publication, a study by Fischer is cited, in which a prevalence of 2.36% among 466 patients is reported. Nevertheless, the clinical features of NA in our study agreed with previous articles.33,35,36,39,40,48 These lesions were mostly present on the neck and upper chest. They first occurred during childhood, and although long-term follow-up data were unavailable, they remained stable at follow-up visits despite lower observed frequency in older age groups. In patients with NA, 67% had multiple lesions, whereas they are usually described as solitary lesions. In addition, previously reported female predominance36–40 was not found in our series of patients with NF1 (sex ratio, 1.57). A link between NA and neurofibromas is likely because many NA lesions were overlying neurofibromas, especially of the plexiform type. However, most NA diagnosed in childhood does not seem to evolve into neurofibromas.

In keeping with results of a study from DeBella et al.,45 45% of our population only had 1 NIH criterion (usually multiple Café-au-lait macules) when the first visit occurred at younger than 2 years. Indeed, at this young age, diagnosis of NF1 is often difficult. Because NA and JXG were present in most children with NF1 aged younger than 2 years and were diagnosed in 80% of patients with insufficient criteria for diagnosis at that time, their interest as minor criteria in addition to the previously established NIH criteria could be addressed. Their sensitivity, specificity, and predictive values should be prospectively assessed in a childhood case-control study.