Juvenile xanthogranuloma: A possible diagnostic criterion for Neurofibromatosis type 1 in young children

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To the Editor,

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder affecting 1 in 3000 people (Dunning-Davies & Parker, 2016). According to the National Institute of Health (NIH), the diagnosis relies on the presence of at least two of the seven clinical criteria (Anonymous, 1988). However, the late onset of clinical features and the lack of familiality in half of the cases, due to the de novo occurrence of the mutation, make the NIH criteria of limited value in children under the age of 2 years, where café au lait spots are often an isolated sign (Dunning-Davies & Parker, 2016). In addition, recent studies and clinical observations suggest that a significant percentage of individuals with multiple café au lait spots does not have NF1 (Bernier et al., 2016).

Juvenile xanthogranuloma (JXG) is a benign, self-involuting form of non-Langerhans cell histiocytosis, consisting of an asymptomatic yellow, orange, or reddish papule or nodule, most commonly affecting the head and neck and typically occurring in young children. Although its actual incidence in the general population is difficult to determine due to its spontaneous regression over a few years, it has frequently been reported in children with NF1. Consequently, some authors proposed to adopt JXG as an adjunctive NF1 diagnostic criterion (Ferrari et al., 2014). Finally, although later denied (Liy-Wong et al., 2017), an association of JXG with juvenile myelomonocytic leukemia (JMML) had been hypothesized in patients with NF1 (Zvulunov et al., 1995).

We evaluated the frequency, age at presentation, and clinical features of JXG, in a series of subjects affected by NF1. Clinical records of these patients followed at the Department of Paediatrics of the Institute for Maternal and Child Health, IRCCS Burlo Garofolo, of Trieste, Italy, between January 1, 2007, and December 31, 2018, were retrospectively assessed. The diagnosis of NF1 was established according to the presence of at least two NIH criteria. JXG was defined as an asymptomatic yellow-brown papule or nodule with negative Darier sign and diffuse, homogeneous, orange-yellowish hue, surrounded by slight erythema at dermoscopy. Age at diagnosis of JXG, gender, number and location of JXG, family history of NF1, and personal history of JMML were recorded.

Out of 106 patients with NF1 (52 males), 17 (9 males) were diagnosed with JXG. Table 1 shows the age at the detection and the site of JXG. Lesions were solitary in 12 (70.6%) cases. Ten (58.9%) of the 17 patients had already received the diagnosis of NF1 at the time of the detection of JXG. A familiality for NF1 was present in 8 of the 17 patients with JXG. No patient developed JMML during the follow-up, which had a medium duration of 8.2 years (range 3.1–15.3 years).

This case series confirmed the high frequency of JXG in children with NF1. Remarkably, among the seven patients without a previous diagnosis of NF1, six were younger than 2 years, and three had no familiarity for NF1. These patients could have benefited from an earlier diagnosis of NF1 if JXG had been endorsed as a diagnostic criterion.

According to the previous reports (Ferrari et al., 2014), this study showed that JXG should reinforce the suspicion of NF1 in children with any other sign of the disease, namely café au lait spots. If future studies confirm these data, JXG could be included as a diagnostic criterion, allowing for earlier diagnosis of NF1 in younger children.

No patients in this series presented JMML at the time of JXG diagnosis or developed it during follow-up. Thus, these data support the results of previous studies in denying an increased risk of JMML in patients with NF1 and JXG (Ferrari et al., 2014).

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

TABLE 1 Number and site of juvenile xanthogranulomas (JXG), gender, age at diagnosis of JXG, Neurofibromatosis type 1 (NF1) already diagnosed at the time of the detection of JXG, and family history of NF1

Patient no.	Sex	Age at diagnosis of JXG (years)	Number of JXG	Site of JXG	NF1 already diagnosed at the time of detection of JXG (yes/no)	Familiality for NF1 (yes/no)
1	M	1.8	1	Head	No	No
2	F	0.6	1	Trunk	No	Yes
3	M	4.6	4	Head, neck, leg	Yes	No
4	M	3.0	>5	Diffuse	Yes	No
5	F	1.1	1	Head	No	Yes
6	M	13.6	>5	Diffuse	No	No
7	F	4.4	1	Trunk	Yes	No
8	F	2.0	1	Trunk	No	Yes
9	M	3.0	1	Neck	Yes	Yes
10	F	6.3	2	Head	Yes	No
11	M	3.3	1	Leg	Yes	No
12	M	1.3	1	Trunk	Yes	Yes
13	M	1.3	1	Head	Yes	Yes
14	M	8.0	2	Head	Yes	Yes
15	F	6.5	1	Hand	Yes	No
16	F	1.5	1	Trunk	No	No
17	F	1.7	1	Trunk	No	Yes

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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