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SHORT COMMUNICATION

Clinical Characteristics of Pruritus in Neurofibromatosis 1

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Neurofibromatosis 1 (NF1) is an autosomal dominant disease that affects approximatively 1/3,000 people worldwide (1). This disease results from a germline mutation in the NF1 tumor suppressor gene encoding a Ras-GTPase activating protein neurofibromin, which is expressed throughout the nervous system. The manifestations of NF1 are extremely variable, even within a family. NF1 is clinically characterized by tumour formation leading to the generation of optic gliomas, neurofibromas, malignant peripheral nerve tumours, and an increased incidence of rare cancers. NF1 is a cause of pruritus, which frequency has been evaluated at 19.4% in people with NF1 (2). The aim of this study was to evaluate, with a questionnaire, the characteristics of pruritus in patients with NF1.

MATERIALS AND METHODS

Patients were recruited via two ways: (*i*) in two consultations specialised in NF1: at the University Hospital of Brest ($n = 13$) and Créteil (Henri Mondor) ($n = 6$), patients completed the questionnaire during the consultation; and (*ii*) via the French National Association on Neurofibromatosis (Association Neurofibromatoses et Recklinghausen): members of the Association received an e-mail with an information sheet on study details to propose them to complete the questionnaire on the website ($n = 21$).

The questionnaire comprised two parts (Appendix S1[1]). The first part used an exploratory approach with a questionnaire in French adapted from previous questionnaires (3) that have been used in other studies to investigate characteristics of pruritus in 5 dermatoses (4) and in small fiber neuropathies (5). It contained questions about the chronology, localization, intensity, treatment, disruption of daily activities, and characteristics of scratching. The second part was the 5-D itch scale, validated in 2010 (6), the French version is not validated yet.

RESULTS

From November 2013 to June 2014, 40 patients were included. The mean age was 46.5 years (range 20–75). There were 16 men (40%) and 24 women (60%).

Pruritus appeared daily in 35% of the patients, almost daily in 35% of the patients and less frequently for others. Pruritus tended to appear more frequently in the evening, with the symptom being reported as experienced "often" or "always" in the evening for 70% of the patients, at night for 35% of the patients, in the morning for 33% of the patients and in the afternoon for 30% of the patients.

Only 5 patients were treated for their pruritus: an emollient was used by 4 patients (for one, emollient had no effect, and for the 3 others, the emollient had a short term effect), and 1 patient took an oral anti-histamine.

The intensity of pruritus was assessed by a visual analogic scale. At its worst, pruritus was intense (6.7/10), and at its best, pruritus was mild (1/10). The mean intensity of pruritus was rated as 3.8/10.

The most common symptoms accompanying itching were heat sensations (in 23.5% of the patients) and pain (in 17.6% of the patients). The other sensory symptoms accompanying itching are presented in Fig. S1[1].

The effects of normal daily activities on pruritus are shown in Fig. S2[1]. For the question "Do you scratch?," 27.5% of the patients answered "very often," 60% of the patients answered "often," and 12.5% of the patients answered "rarely".

Scratching was considered highly pleasurable for 12.5% of the patients, moderately pleasurable for 52.8% of the patients, neutral for 15.0% of the patients, moderately unpleasant for 12.5% of the patients, and highly unpleasant for 7.5% of the patients. For 52.5% of the patients, pruritus was localized on neurofibromas.

The results of the second part of the questionnaire (i.e., the 5-D itch scale) are presented in Table SI[1]. The mean of the 5-D itch scale was 12.8 and ranged from 7 to 21.

DISCUSSION

In the literature, very few data are available on pruritus in patients with NF1. Khosrotehrani et al. (2) included 703 patients with NF1, itch was reported in 19.4% of them without any other data on its characteristics. Pruritus was associated with higher mortality in children but not in adults. In 2010, Sbidian et al. (7) established the NF-1 score, a prediction score for internal neurofibromas in NF1, but pruritus was not evaluated. Pruritus in NF1 has been reported to be associated with NF1 complications, with localized pruritus being a presen-

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ting symptom of a spinal cord tumour (8) or a brainstem glioma (9, 10). The association of generalized pruritus with NF1 and cholestatic liver dysfunction has also been described (11).

However, NF1 is considered to be a cause of neuropathic pruritus (12), although there are few data on this relationship. Chronic pruritus is considered to be neuropathic when nerve fiber damage is responsible for the symptom. The nerve fiber damage usually causes overlapping symptoms of pruritus and pain and is associated with other abnormal sensations. The pathophysiology of pruritus in NF1 is not completely elucidated. O'Brien et al. (13) studied pain and itch behaviour in a mouse model of NF1 with a targeted heterozygous NF1 gene deletion that lacked tumours. They concluded that NF1 heterozygosity alone is not sufficient to increase pain and itch sensation in mice. Mast cells probably play an important role in the generation of pruritus as they are present in the neurofibromas microenvironment and appear to contribute to tumour initiation, progression and angiogenesis (14). However, in our study, only 52.5% of the patients presented a pruritus localized on neurofibromas.

Neuropathic pruritus is seldom the only symptom with which the patient presents: the itch is usually associated with other symptoms, such as pain, allodynia, paraesthesias, hyperaesthesia, hypoaesthesia, and/or electric shock-like sensations (11).

NF1 leads to a significant reduction in patients' overall quality of life (QoL), as demonstrated in a study of 129 patients (15). The visibility of cutaneous neurofibromas is the main complication that impacts QoL. Chronic pruritus can be an independent factor for altered QoL, and may be comparable to that of pain. In the question about disability on the 5D itch scale, pruritus frequently or always affects sleep, leisure/social, housework/errands, or work/school for 27.5% of the patients and occasionally affects one of these activities for 35% of the patients.

The limitations of this study are the relatively small size of the sample, and a selection bias due to the recruitment of patients in two different ways (consultation in two university hospitals and through the National Association of patients with NF1). It would have been interesting to compare clinical features of NF1 (because the disease is highly variable), with pruritus characteristics, but due to low frequency of NF1 patients with pruritus, it was not possible. Patients who completed the questionnaire on the website were not examined.

This study supports many previously unknown and interesting data about the clinical characteristics of itch in patients with NF1 and underlines that pruritus is not only present opposite neurofibromas. This raises questions about the pathophysiology of pruritus.

Health care workers often do not take pruritus into consideration, but this is an important symptom from the patient's point of view that is frequent and can cause impaired QoL.

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