

Segmental Neurofibromatosis Type 1, a Rare Variant of Neurofibromatosis: Report of Two Cases

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Abstract

Segmental neurofibromatosis type I (SNF-I) is a rare variant of neurofibromatosis (NF). It is classified as NF type V and defined as cafe-au-lait macules and/or neurofibromas in a single, unilateral segment of the body. We report two cases with SNF-I with striking similar manifestations. (*Iran J Dermatol* 2009;12: 22-25)

Keywords: cafe-au-lait, neurofibroma, neurofibromatosis, segmental

Introduction

Inheritance of Neurofibromatosis (NF) follows an autosomal-dominant pattern^{1,2}. It is one of the commonest genetic neurocutaneous syndromes and is highly heterogeneous³. It is manifested by developmental changes in the nervous system, bones and skin¹. At least 7 types of NF^{3,4,8} different clinical phenotypes in some literature² and 5 gene-based types in some other literature⁵ have been described (Table-1), with NF type I (NF-I, Von Recklinghausen's disease) being the commonest (85% of cases with NF¹ and an incidence of 1 in 3,000 live births⁵).

Segmental neurofibromatosis type I (SNF-I) is a rare variant of NF^{6,7,8,9,10}. It was initially classified as NF type V and was defined as cafe-au-lait macules and/or neurofibromas in a single, unilateral segment of the body, with no crossing of the midline, no familial history, and no systemic involvement⁶. Sometimes, SNF-I is characterized by visceral neurofibromas limited to a circumscribed body segment¹¹. Cases that do not conform to these criteria prompt further classification into the following subtypes: true segmental localized with deep involvement, hereditary, and bilateral¹². What is important to understand is that SNF-I should not be regarded as a separate form of NF but as a localized phenotype of NF-I^{13,14,15,16}.

Although the first case of SNF-I was reported in 1937^{2,17}, the total number of reported cases

does not go beyond 150 to date². The prevalence of SNF-I has been estimated to be 1 in 40,000 in the general population¹⁸. As initially described in 1969 by Nicolls, SNF-I results from a somatic mutation in the NF-I gene¹⁹. Ruggieri and Huson have proposed the term "mosaic localized NF-I" for this phenomenon, as an acknowledgement that the pathogenesis of this condition is the post-conceptual mutation leading to somatic mosaicism⁵.

In this report, we described two SNF-I patients with neurofibromas limited to circumscribed segments who interestingly showed relatively similar manifestations.

Case Reports

Case 1

An 18-year-old girl with several nodules on palmar and dorsal aspects of her left hand was referred to the Department of Dermatology, Jondi Shapour University of Medical Sciences. These nodules had gradually developed since 14 years ago. There was no history of systemic disorders including learning disabilities, acoustic problems or seizure. There was no history of NF in her family.

In physical examination, there were some soft, painless, skin-colored nodules of different sizes, from some millimeters to 1 centimeter in diameter, on both aspects of her left hand (figure-1). There were no dermatological manifestations such as



Figure 1: Segmental neurofibromatosis type 1, manifested with multiple soft, painless, skin-colored nodules in left hand (Case 1).

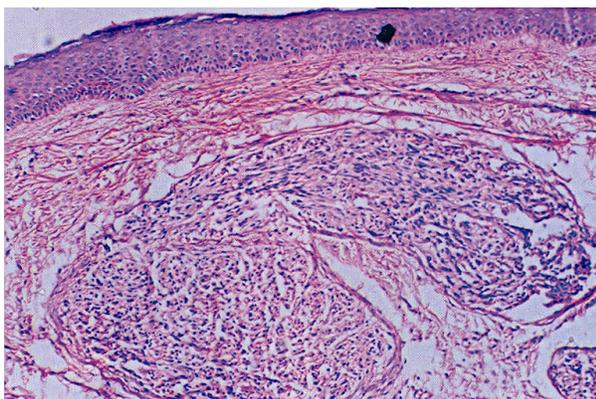


Figure 2: Several nodules in varied sizes in the dermis and subcutis, formed by spindle shaped cells along with thin fibrils and wavy organizations in case 1 (Hematoxylin –eosin $\times 40$).

cafe'-au-lait macules, axillary freckles or skin nodules in other sites of her body. In ophthalmological examination with a slit-lamp set, there were several bilateral Lisch nodules in her irides. Neurological and acoustic examinations were normal.

In histopathological examination of one of the skin nodules, there were several nodules of varied sizes in the dermis and subcutis. These nodules were formed by spindle shaped cells in small sizes along with thin fibrils and wavy organizations (figure-2).

Routine laboratory tests such as hematological and serological findings were totally normal. Results of X-Ray from skull and chest were normal. Magnetic Resonance Imaging (MRI) studies in several sections of brain and spinal cord showed normal results. According to clinical and

histopathological findings, for skin lesions, multiple nodular plexiform neurofibromas was suggested with the final diagnosis of SNF-I.

Case 2

A 74-year-old woman with some nodules on the palmar aspect of her left hand was referred to the Department of Dermatology, Jondi Shapour University of Medical Sciences. These skin nodules had developed since 20 years ago with no history of learning difficulties, acoustic disorders or seizure. She did not also describe any family history of NF. In the past 20 years, she had no problems with these nodules and never referred to any medical centers for them. Since 20 days ago, some of these nodules had become painful and swelled after being exposed to cold weather.

There were some soft nodules of different sizes, between 0.5 to 1.5 centimeters in diameter, in the palmar aspect of her left hand and 3 ones in the volar aspect of her left forearm in physical examination (figure-3). Some of them were skin-colored and not tender in palpation, while some were erythematous, inflamed and tender, especially in the distal phalanx of her third finger. There was only one cafe'-au-lait pigmentation of 1.5 \times 2 centimeters on her lower back, but there were not axillary freckles or skin nodules in other parts of her body. In ophthalmological examination with a slit-lamp set and funduscopy, there were no Lisch nodules or findings suggestive of NF. Neurological examination was intact.

Histopathological evaluation of these nodule showed a well-circumscribed but unencapsulated collection of spindle cells with scanty cytoplasm and elongated wavy nuclei (figure-4).

The patient did not agree to participate in other investigations such as brain MRI or acoustic studying.

According to clinical and histopathological findings, the diagnosis of SNF-I was confirmed.

Discussion

Most patients with SNF (93%) do not have a family history of NF⁶. SNF may arise from post zygotic somatic mutation or loss of heterozygosity (LOH). The gene for NF-I is in the pericentric region of chromosome 17 q 11.2¹. This gene has an unusually high mutation rate, estimated at 2.4 to 10 \times 10 gametes per generation, which is one of the highest rates in known inherited disorders⁵.

When a patient presents with SNF-I, it is critical to determine if the disorder is a result of mosaicism or LOH. In the latter case, the abnormal allele is present throughout the body, with loss of the normal remaining allele in the affected segment¹. In a



Figure 3: Segmental neurofibromatosis type 1, manifested with multiple soft, skin-colored nodules in left hand (Case 2).

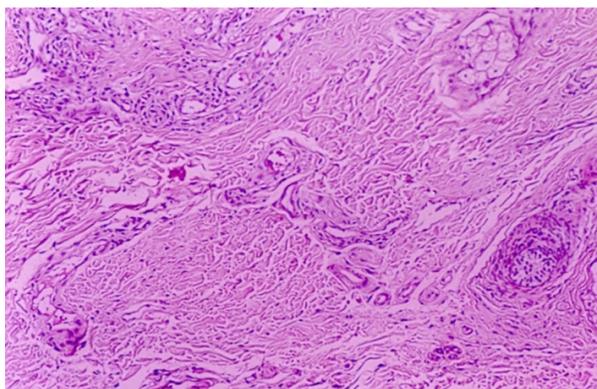


Figure 4: Well-circumscribed, unencapsulated collection of spindle cells with scanty cytoplasm and elongated wavy nuclei in pathological examination of one of nodules in case 2 (Hematoxylin –eosin $\times 40$).

patient who presents with SNF, but has Lisch nodules or axillary freckling, LOH rather than mosaicism is likely to account for the segmental presentation. The risk of passing the gene to a child is roughly 50:50 (as generalized NF-I)¹. However, patients with mosaicism based on post-zygotic somatic gene mutation may or may not have gonadal mosaicism¹. Hence, the risk of gene transmission to a child is not calculable. Gonadal mosaicism is more likely when more than one segment is involved in different parts of the body. According to this pathogenesis theory, it appears that the pathogenesis of SNF-I in our case 1 is probably LOH; on the other hand, if the pathogenesis of SNF in case 1 is mosaicism, the probability of gonadal mosaicism is high because of the involvement of more than one segment.

Hence, a geneticist should be consulted to discuss the risk of transmission¹.

SNF-I occurs in all age groups and has a mean onset age of 28 years⁶. In one study, a mean age of 23.2 years was acquired (age ranged from 9 month to 77 years)²¹. In some literature, its incidence is shown to be slightly higher in women (58% of affected patients with SNF-I)⁶, but in some other, the result is vice versa (male/female ratio =1.14:1)¹³. In our report, both cases were females, with an estimated mean onset age of 29 years that is parallel to other reports.

In SNF-I, clinically, patients may be divided into four groups: those with only pigmentary changes or neurofibromas, those with both pigmentary changes and neurofibromas, and those with isolated plexiform neurofibromas. Lesions are usually unilateral although there are reports of bilateral SNF-I^{22,23}. In this disease, the affected area can vary in size from a narrow strip to an area encompassing half of the body¹⁰.

Clinical disease in SNF-I develops in the same course of time as generalized NF with pigmentary changes, plexiform neurofibromas develop in childhood and neurofibromas develop in adulthood¹³. The plexiform neurofibromas in our case 1 appeared in childhood, when she was 4 years old, and neurofibromas in our case 2 appeared when she was 54 years old, which are both concordant with the existing literature.

Most commonly, patients present with only neurofibromas. They tend to arise in a dermatomal distribution, most commonly cervical, followed by thoracic, lumbar and sacral⁶. In our cases, the neurofibromas were limited to the cervical region, just in-line with other studies.

Pigmentary changes include café-au-lait macules and axillary freckling, with the cervical dermatomal distribution being more common^{2,6,24}, but case 1 had no pigmentary changes.

In one complete ophthalmological study on 72 patients with SNF-I, none of them had typical NF-I ophthalmological manifestations including Lisch nodule, regardless of age at examination²¹. Lisch nodules have been reported in isolated cases – when the eyes were specifically searched for – in previous SNF-I series and were not always unilateral or ipsilateral to the side of NF-I manifestations^{13,20,21,25}. We believe that this phenomenon can be confirmed with LOH theory. Overall, Lisch nodules are rarely seen in SNF-I. Although it is difficult to find a reasonable explanation for these phenomena, it can be

postulated that this probably occurs because the eye is too far from the mutated area with NF-1 lesions in most cases or because the NF-1 (or other "predisposing" or "cooperating" genes) mutation affects tissues or clones different from the eye²¹. Notably, however, patients previously reported to have manifestations of NF-1 restricted only to the face had no Lisch nodules regardless of age at examination^{13,20}. On the other hand, as mentioned earlier, in a patient who presents with SNF-1 but has Lisch nodules, LOH is more likely to account for segmental presentations rather than mosaicism, apparently true for our case 1. In summary, eye involvement in SNF-1 is much less frequent than expected in patients with a generalized disease (about one-quarter of patients under 6 years of age and in 94% of adult patients¹; Therefore, close ophthalmological monitoring in the setting of SNF-1 might be unnecessary²¹.

In summary, there is no specific management strategy for SNF-1. However; genetic counseling should be done and the little risk of transmission to the offspring should be communicated. Careful follow-up is required to monitor disease progression or to delete any systemic complications that may occur in a minority^{2,3}.

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