

Case report

Neurofibromatosis type 1 with generalized pruritus

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Abstract Neurofibromatosis is a neurocutaneous condition that can involve almost any organ system. Presenting signs and symptoms may vary widely. We describe a patient who presented with generalized pruritus that was not responding to conventional antihistamines or topical steroids, but responded very well to ketotifen. A brief review of the disorder is also made.

Key word

Neurofibromatosis, pruritus.

Introduction

Neurofibromatosis is an autosomal dominant disorder that affects the bone, the nervous system, soft tissue, and the skin. At least 8 different clinical phenotypes of neurofibromatosis have been identified and are linked to at least 2 genetic disorders. Clinical manifestations increase over time. Two major subtypes exist: neurofibromatosis 1 (NF-1), which is the most common subtype and is referred to as peripheral NF, and neurofibromatosis 2 (NF-2), which is referred to as central NF. These descriptions are not especially accurate because NF-1 often has central features.¹⁻³ NF-1 is the most common type, affecting about 90% of those people with NF. It was first described by a German doctor named Frederich von Recklinghausen in 1882 and thus the condition is also known as von Recklinghausen's disease.⁴ Worldwide, NF-1 occurs in approximately 1 of 2500-

3300 live births, regardless of race, sex, or ethnic background. The carrier incidence at birth is 0.0004, and the gene frequency is 0.0002. Male to female ratio is equal. This disease can involve various body systems over time. Signs can range from benign cutaneous manifestations to profound disfigurement.¹⁻³ People who are affected by NF1 have a mutation in a gene, called NF-1 gene, which is on chromosome 17.⁵ A number of different mutations have been found in people affected with NF1. In about half of all cases, NF is inherited from an affected parent. The remainder results from spontaneous mutation and the affected person is then the first person in a family to be affected with NF. That person will then be able to pass on the mutation to his/her children.^{6,7} The mortality rate is higher than that of the healthy population because of the increased potential for malignant transformation of diseased tissues and the development of neurofibrosarcoma. Patients with NF-1 have an estimated 3-15% additional risk of malignant disease in their lifetime.^{8,9} The most common characteristic of NF-1 is the presence of flat, brown patches on the skin

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(called "café-au-lait" spots which means "coffee with milk" in French). These usually arise in childhood. People with NF1 also develop freckling under the arms and in the groin. These spots and freckles pose no threat to a person's health. The neurofibromas which are characteristic of this disorder may grow on nerves in many different parts of the body: they may occur on, or just under, the skin, and occasionally in deeper parts of the body. Neurofibromas can appear at any age but very often appear during adolescence and in women during pregnancy. They are usually not painful. Overgrowths of groups of nerves are called plexiform neurofibromas. These benign (non-cancerous) tumours are often located in the deeper tissues and occur in around 25% of people with NF-1 and may cause cosmetic disfigurement. Small clumps of pigmented cells in the iris of the eye (called Lisch nodules) are often seen. However, these nodules can only be detected by an ophthalmologist using a slit lamp. They do not affect vision. Bony changes, particularly in the long bones of the lower legs, can produce bowing in the long bone and/or fractures known as a pseudoarthrosis or artificial joint. This is a rare complication of NF1, affecting about 2% of patients and may require surgical correction. The majority of children with NF1 will have a degree of learning difficulty, particularly in the area of language and reading ability. The diagnostic criteria are met if 2 or more of the features listed are present: (i) Six or more café au lait macules larger than 5 mm in greatest diameter in prepubertal individuals and those larger than 15 mm in greatest diameter in postpubertal individuals, (ii) Two or more neurofibromas of any type or 1 plexiform

neurofibroma, (iii) Freckling in the axillary or inguinal regions, (iv) Optic glioma, (v) Two or more Lisch nodules (iris hamartomas), (vi) A distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis, (vii) A first-degree relative with NF-1 according to the above criteria.^{1-4,8,10} Treatment of NF1 is primarily symptomatic and cure is not yet possible. Multicenter trials of medications to limit growth of optic nerve gliomas and plexiform neurofibromas are underway.^{3,10}

Case history

A 57-year-old lady reported in skin outdoor of PAF Hospital, Sargodha with history of generalized itching all over the body but more marked over her trunk. Itching started about two years ago but increased in intensity during last six months. It was episodic, would occur at any time and would not subside satisfactorily with various antihistamines and topical steroidal preparations. There was no history of jaundice, weight loss, urinary or bowel complaints. On physical examination she was found to have multiple café au lait spots and neurofibromas scattered all over her body, being more marked over the trunk area (**Figure 1**). Axillary freckles were present and slit lamp examination of eyes also revealed multiple Lisch nodules. She also gave history of similar skin lesions in one of her four siblings. There were few excoriation marks over lower back. Systemic examination was unremarkable and laboratory investigations (blood complete picture, liver function tests, renal function tests, chest x-ray and ultrasound abdomen) did not reveal any abnormality. Her pruritus was assumed to be associated



Figure 1 Multiple neurofibromas and café au lait spots dispersed over whole back of the patient

with existing neurofibromatosis. She was given various combinations of antihistamines along with topical steroidal and soothing preparations but she did not show satisfactory response to these regimens. It was only when ketotifen was added, she started showing marked improvement in her symptoms and finally she was well maintained with ketotifen alone.

Discussion

NF-1 is a disorder with variable phenotypic expression. Some patients may primarily have cutaneous expression, while others may have life-threatening or severely disfiguring complications. Pruritus is a rare symptom that can be seen in NF-1. The possible cause of itching is histamine and other mediators liberated from mast cells, as these cells are present in large number in the skin of NF-1 patients.^{8,11} The beneficial effects of antihistamines and mast cell stabilizing agent in relieving this symptom has been reported earlier.^{12,13} The patient described here had the disease for decades, but she was not concerned much about the stigmata of the disease as she never had

any symptom related to the pre-existing characteristic skin lesions of the disease. She only became worried when she started having severe itching especially over sites, where skin lesions of NF-1 were more concentrated. No other cause of her pruritus could be elicited. Unresponsiveness to various combinations of antihistamines and prompt relief of itching with ketotifen (a mast cell stabilizer) gives evidence about the etiological role of mast cell in producing symptoms (e.g. pruritus) in patients of NF-1. A relatively large number of mast cells are seen in and around skin tumours (neurofibromas) in NF-1 patients.¹¹ It is assumed that these have a pathogenic role in formation and growth of tumour, because some of the mast cell mediators are known to act as growth factors. Moreover, a mast cell stabilizer, ketotifen has been shown to decrease neurofibroma growth, pruritus, pain and tenderness.^{12,13}

Conclusion

NF1 is an extremely variable disorder that can be compounded by a broad spectrum of manifestations and pruritus is one of these rare presentations.

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