Multicenter Study of Wound Healing in Neurofibromatosis and Neurofibroma

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Based on clinical experience, the senior author has become convinced that wounds produced to correct the deformities of patients with neurofibromatosis (NF-1) have produced remarkably good scars, the interesting feature being that progression to keloid or hypertrophic scar is rare. The other point noted was that this situation did not change, no matter the patient's race or skin color. There have been few reports describing or discussing this hypothesis. The purpose of this study was to investigate whether wounds produced in the patients with NF-1 produce keloid or hypertrophic scars. The patients with solitary neurofibroma were also included in this study; these were compared with the NF-1 group. This was conducted as a multicenter study. Patients with neurofibromatosis/solitary neurofibroma, who were operated on from 1990 to 2000, were evaluated by reviewing their medical charts and photographs retrospectively. The patients were treated in centers from five different countries. The analysis was undertaken based on the following points: 1) age and sex at surgery; 2) race of the patients; 3) past and family histories of hypertrophic scar and keloid; 4) surgical site(s); 5) diagnosis, NF1 or solitary neurofibroma; 6) surgical complications; 7) number of reoperations to manage the complications; 8) adjuvant therapy for the tumor; 9) depth of the tumors; and 10) incidence of malignant degeneration. A total of 101 cases with neurofibromatosis or solitary neurofibroma was analyzed. The age at surgery ranged from 1 year 6 months to 74 years; sex ratio was 47 males and 54 females. The racial distribution of the patients was 13 white, 13 black, 3 Hispanic, and 58 Asian. There was no past or family history of hypertrophic scar or keloid. The surgical sites were head and neck in 70 cases, trunk in 20 cases, upper extremities in 22 cases, and lower extremities in 20 cases. The clinical diagnosis was NF-1 in 57 cases, solitary neurofibroma in 35 cases, plexiform neurofibroma in four cases, and no distinct clinical diagnosis in five cases. There were no other types of neurofibromatosis. Hematoma and white wide scar were the main postoperative complications found in six cases of NF-1. Infection was also noted in four cases. However, no patient developed hypertrophic scar or keloid in the neurofibromatosis group, whereas two cases showed hypertrophic scar in the solitary neurofibroma group. The outcome showed that the patients with NF-1 and plexiform neurofibroma, no matter the racial group, produce good scars without keloid or hypertrophic changes, whereas solitary neurofibroma has a potential to cause hypertrophic scar.

Key Words: Neurofibromatosis, neurofibroma, NF-1, von Recklinghausen's disease, wound healing, hypertrophic scar, keloid

Neurofibromatosis (NF) is a neurocutaneous condition of which two types exist. NF type 1 (NF-1, also referred to as von Recklinghausen's disease) occurs in approximately one in 3000 persons and accounts for 96% to 97% of all cases of NF. NF type 2 (NF-2) accounts for approximately 3% of cases and a small fraction of the remaining cases are segmental NF. From extensive clinical experience, some surgeons

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Table 1. Evaluation

1. Age at surgery, sex, race, and surgical sites
2. Past and family histories
Keloid, hypertrophic scar, desmoid and Dupuytren, Peyronie, Ledderhose disease
3. Diagnosis: NF-1 or solitary neurofibroma
4. Complications related to surgery
Hematoma, infection, dehiscence, ulceration, and so on
6. Numbers of reoperations to manage complications
7. Adjuvant therapy
8. Depth of the tumor
9. The incidence of malignant degeneration

NF-1, neurofibromatosis.

have noted that wounds heal very well in patients with NF-1 and seldom, if ever, progress to keloid or hypertrophic scar. However, there have been few reports describing this hypothesis. The purpose of this study was to investigate whether wounds in patients with NF-1 are less prone to keloid or hypertrophic scar formation. The other area to be examined was whether wounds in all racial groups behaved in the same way or was there variation between groups. The patients with solitary neurofibroma (NF-2) were also the candidates for this study, being compared with the NF-1 group.

Materials and Methods

The patients with NF-1 and solitary neurofibroma from five different countries, having been operated on between 1990 and 2000 were registered as a multicenter study. The surgical wound and scar of the cases were analyzed by reviewing the clinical charts, pathology reports, and clinical photographs. The registered institutes and countries were the Craniofacial Institute, Southfield, Michigan; Federal University of Sao Paulo, Brazil; Jikei University School of Medicine, Tokyo, Japan; The Lady Davis Carmel Medical Center, Haifa, Israel; and The University of Science & Technology, Kumasi, Ghana. This group contained examples of most racial characteristics.

Table 2. Results

101 cases	47 males, 54 females
Age at surgery	31.5 years
Follow-up period	3.67 years
Race	
White	13
Black	13
Asian	58
Hispanic	3
Past and family histories	Not remarkable

Table 3. Clinical Diagnosis

NF-1	57 cases
Plexiform neurofibroma	4 cases
Solitary neurofibroma	35 cases
No diagnosis	5 cases

NF-1, neurofibromatosis.

Evaluation of the Cases

The following points were considered in the wound analysis:

1. Age and sex at the time of surgery;
2. Postoperative follow-up period;
3. Race of the patients;
4. Past and family histories of fibroblast-related diseases, including keloid, hypertrophic scar, desmoid and Dupuytren's disease, Peyronie, and Ledderhose diseases;
5. Surgical site(s);
6. Clinical diagnosis of the condition, NF-1 or neurofibroma;
7. Complications related to surgery;
8. Number of reoperations to manage the complications, if any;
9. Adjuvant therapy for the tumor, if any;
10. Depth of the tumors, if applicable;
11. The incidence of malignant degeneration; and
12. Occurrence of keloid and hypertrophic scars (Table 1).

Results

A total of 101 cases with neurofibromatosis or solitary neurofibroma were registered from five different institutions in five different countries. The age at surgery ranged from 1 year and 6 months to 74 years (mean, 31.5 years). The sex ratio was 47 males and 54 females. The races of the patients were 13 white, 13 black, three Hispanic, and 58 Asian. There was no past or family history of hypertrophic scar, keloid, or other fibroblast-related diseases (Table 2). The clinical diagnosis was NF-1 in 57 cases, solitary neurofibroma in 35 cases, plexiform neurofibroma in four cases, and no clinical diagnosis in five cases; all had a pathologic diagnosis of neurofibroma (Table 3).

Table 4. Surgical Sites

Head and neck	70
Trunk	20
Upper limb	22
Lower limb	20

Table 5. Surgical Complications

Hematoma	5 cases
Infection	4 cases
Wound dehiscence	3 cases

There were no other types of neurofibromatosis. With regard to diagnosis of the cases, plexiform neurofibroma is listed as one of the diagnostic criteria for NF-1 and thus this diagnosis led to inclusion in the NF-1 group. If there was no other clinical information available, these cases were classified as NF-1. Surgical sites were head and neck in 70 cases, trunk in 20 cases, upper extremities in 22 cases, and lower extremities in 20 cases (Table 4).

Hematoma was the main postoperative complication followed by four cases of infection, three cases of wound dehiscence, and one case of seroma and bleeding (Table 5). None of the complications required reoperation to solve their problems. All five major complications were found in the NF-1 group; there were no cases that developed hypertrophic scar, whereas two cases of 35 (5.7%) showed hypertrophic scarring in the solitary neurofibroma group. These lesions were found on the surgical scar of the lower leg in a 42-year-old black woman and of the back in a 51-year-old Asian woman (Table 6). There was no keloid formation found in any of the registered cases. Two NF-1 cases of 61 (3.3%) including plexiform neurofibroma showed malignant degeneration of the tumor; they were malignant peripheral nerve sheath tumors (MPNST). The depth of the tumor was documented in 83 cases: 27 cutaneous, eight subcutaneous, one submucosal, and 47 subfascial. In those cases of hypertrophic scarring, tumor was found in subcutaneous layer in one black woman and in the skin layer in one Asian female.

DISCUSSION

Neurofibromatosis type I is one of the most common of the neurocutaneous conditions and there have been multiple papers written on this disease. Within the literature, there have been anecdotal reports from surgeons who have felt that wounds healed better in patients with NF-1. Bleom and van der Meulen[4] reported on three cases stating that the wounds in patients with NF-1 became unobtrusive without a tendency to hypertrophy despite considerable tension on the wound edges. They felt that this was the result of the lack of elastic fibers and to the immature collagen. Ademiluyi et al[5] analyzed the surgical outcome of multiple neurofibromatosis in 30 Nigerian patients and reported that hypertrophic scars and keloid formation were not observed despite poor wound healing and closure of some of the wounds under tension. However, there have been few well-constructed studies set up to investigate this interesting phenomenon. To gain more information, it was decided to conduct a multicenter study. The aim was to investigate whether wounds in patients with NF-1 from a series of different racial groups are less prone to keloid or hypertrophic scar formation.

Keloid or hypertrophic scars represent a benign overgrowth of scar tissue occurring primarily in the dermis. Hypertrophic scars usually appear within 4 weeks after trauma or surgery, whereas the onset of keloids is generally delayed to 3 months, but it can take even longer, up to several years. Hypertrophic scars and keloids develop exclusively in humans with the same prevalence in both male and female sexes and the highest incidence is seen in the second decade. The incidence of hypertrophic scarring is approximately 39% to 68% after a surgical incision and 33% to 91% after burns; this depends on the depth of the wound. In our study, only 5.7% of the patients showed hypertrophic scarring with a solitary neurofibroma, whereas no keloid was found in the NF-1 group. The depth of surgical wound seemed to have no relationship with the occurrence of a hypertrophic scar or keloid in solitary neurofibroma. Keloids are seen in individuals of all races, except albinos, but occur approximately 15 times more often in patients with darker compared with lighter skin. Negroid, Spanish, and Asian people have proved to be more susceptible and develop keloids in 4.5% to 16% of cases. Despite this, Ademiluyi et al reported that 30 Nigerians of African descent who underwent surgical resection of multiple neurofibromatosis did not seem to develop keloid nor hypertrophic scars. In the present study, there were 13 patients of African descent registered, including both NF-1 and solitary neurofibroma, and only one case with a solitary neurofibroma developed a hypertrophic scar; none of the NF-1 group showed keloid or hypertrophic scarring. Keloid formation has been reported in association with numerous dermatologic disorders and palmar, plantar, and penile fibromatosis. Connective tissue diseases are also

Table 6. Occurrence of Keloid and Hypertrophic Scar

	Keloid	Hypertrophic Scar
NF-1 group (plexiform neurofibroma)	0/61	0/61(0%)
Solitary neurofibroma	0/35	2/35(5.7%)

associated with keloid formation. In Ehlers-Danlos, Rubinstein-Taybi, trichorhinophalangeal syndrome, pachydermoperiostosis, scleroderma, and osteopoikilosis, a higher incidence of excessive scar formation has been reported when compared with the normal population, whereas patients with neurofibromatosis showed no evidence of keloid formation in the present study.

Although there are no clear reasons to explain why wounds in NF-1 heal well, there are some mechanisms capable of explaining this better wound healing. Skin involvement may be focal as in the case of café au lait macules or it may be diffuse. Café au lait macules can occur on most sites of the body except the scalp or palms of the hands and soles of the feet. They are uncommonly located on the face. Skin biopsy reveals the presence of giant melanosomes or melanin macroglobulins. In patients with NF-1, café au lait macules contain more of the macroglobulins than does ''normal'' skin in such patients. Even the normal skin contains increased numbers of macroglobulins in comparison with normal skin in nonaffected persons.

Conclusion

The outcome showed that the patients with NF-1 and plexiform neurofibroma produced good scars without keloid or hypertrophic characteristics, whereas solitary neurofibroma has a potential to cause hypertrophic scarring of a variable degree. This information is extremely important because it enables the plastic surgeon to accurately advise the patient before a surgical procedure as to what sort of scars he or she may end up with. Further investigation into this area may lead to a more effective treatment of keloids in the future.

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