ORIGINAL ARTICLE

Examining Demographic and Clinical Traits in Neurofibromatosis Type 1 Patients: Insights into Vitamin D Levels and Connections with Nevus Anemicus and Neurofibromas

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Abstract

Aim: This article aims to examine the demographic and clinical traits of neurofibromatosis type 1 (NF1) patients, particularly focusing on the potential links between vitamin D levels, BMI, and dermatological features. **Methods:** A retrospective review of medical records involving 128 patients diagnosed with neurofibromatosis type 1 (NF1) over a 3-year-period was conducted. The analysis emphasized investigating the demographic and clinical characteristics of the patients while evaluating key parameters. **Result:** Nevus anemicus was present in 32.8% of NF1 patients, and a significant association was found between nevus anemicus and low vitamin D levels (P = 0.001). We also observed a notable correlation between low vitamin D levels and an increased likelihood of neurofibromas (P < 0.001). Additionally, there appears to be an inverse relationship between serum vitamin D levels and the number of neurofibromas. **Conclusion:** Our study suggests a correlation between lower vitamin D levels and key dermatological characteristics in neurofibromatosis type 1 (NF1) individuals. Specifically, we observed associations with nevus anemicus prevalence and increased neurofibromas. This observation enriches NF1's understanding, offering practical implications for patient management by emphasizing the importance of monitoring and addressing vitamin D levels.

Key Words: *Demographic features, neurofibroma, neurofibromatosis type 1, nevus anemicus, vitamin D, Neurofibromatosis Type 1, Clinical, Nevus Anemiscus, Neurofibromas, Vitamin D*

Introduction

NF1, an autosomal dominantly inherited multisystem disorder, is characterized by distinctive skin lesions, including cafe au lait macules (CALMs) and axillary freckling, along with central and peripheral nervous system tumors.[1] Skin findings play a crucial role in distinguishing NF1 from genodermatoses with minimal skin involvement.[2,3] The primary cutaneous manifestation in NF1 is CALMs, which can be classified as "typical" or "atypical." Typical CALMs are well-demarcated, oval macules or patches with homogeneously colored pigmentation, ranging from light to dark brown. In contrast, atypical CALMs display darker, irregular demarcation and non-homogeneous pigmentation.[4-6] Although lacking a standardized classification system, neurofibromas are broadly categorized into cutaneous neurofibromas (focal or diffuse), subcutaneous neurofibromas, plexiform neurofibromas (nodular or diffuse), and spinal neurofibromas.[1] In NF1 patients, freckles, similar in appearance to sun-induced ones, appear in skin folds like the axillary and groin regions (80%) rather than sun-exposed areas.[1,7] Occasionally, they may be found in other locations, but freckles outside of skin folds are not considered diagnostic criteria.[7]

Neurofibromas are a hallmark of NF1, causing significant morbidity due to their abundance, size, and appearance. In NF1, the presence of thousands of neurofibromas classifies the condition as neurofibromatosis.[8-10] They range from benign dermal and plexiform neurofibromas (PNFs) to malignant peripheral nerve sheath tumors (MPNST).[1,11,12] Unlike individuals without NF1 who may have a single neurofibroma, the NF1 diagnosis requires the presence of at least two neurofibromas.[3,7] PNFs, a distinct neurofibroma type, are present from birth. About 30% of adults with NF1 exhibit PNFs, a percentage that increases

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when internal plexiform neurofibromas are detected using CT or MRI.[13]

Studies suggest that nevus anemicus, a common vascular anomaly, is frequently observed in NF1 patients.[14,15] As diagnosing NF1, especially in those under 2 years old, can be challenging, nevus anemicus is considered a crucial skin finding for suspected NF1 patients.[7,16] Although nevus anemicus is typically found on the trunk, it may also occur on the neck and proximal extremities.[16,17] Additionally, juvenile xanthogranuloma (JXG), a non-Langerhans cell histiocytosis, is another important skin finding in NF1 patients.[18] Ferrari *et al*.[19] suggests using JXG and nevus anemicus for early NF1 diagnosis. JXG can manifest in 0.7-37.5% of NF1 patients within the first 3 years, primarily in the head and neck but potentially anywhere on the body. Early NF1 diagnosis is crucial for informing patients and families about the clinical features, and potential complications, and ensuring appropriate follow-up care.[12]

NF1 is diagnosed based on revised criteria by Legius and colleagues in 2021. These criteria include six or more CALMs (>5 mm prepubertal, >15 mm postpubertal), axillary or inguinal freckling, two or more neurofibromas of any type or one plexiform neurofibroma, optic pathway glioma, two or more Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs) defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging, distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone, and heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.[20] For diagnosis at least two criteria are required. In recent studies, researchers have observed that serum vitamin D levels tend to be low in individuals with NF1. Low vitamin D level has become increasingly prevalent, with an estimated 1 billion people worldwide suffering from vitamin D deficiency.[21] Despite variations in vitamin D levels worldwide,[22] NF1 patients demonstrate a higher prevalence of vitamin D deficiency compared to healthy individuals, although the exact cause remains unclear. Currently, no studies explore vitamin D dynamics in NF1 patients, including uptake, absorption, synthesis, transport, or catabolism. However, there appears to be a strong correlation between the number of skin neurofibromas and serum vitamin D levels, such that those with multiple and larger neurofibromas tend to have lower serum vitamin D levels.[21] Regarding the body mass index (BMI) of NF1 patients, there are limited clinical studies on the BMI of individuals with NF1.[2,23]

The primary aim of our study was to comprehensively evaluate the demographic profile, dermatologic findings, and serum vitamin D levels among individuals diagnosed with NF1. Additionally, we aimed to calculate BMI and investigate potential correlations between these parameters and the clinical manifestations of NF1.

Methods

We reviewed the medical records of 128 patients diagnosed with NF1, following the established criteria outlined earlier. The records pertain to individuals belonging to an NF1 group across Turkey. These individuals undergo comprehensive examinations and control visits once a year at a university hospital. The data spans from January 2014 to September 2017. Patients included in the study had both height and weight recorded during their last appointment and at least one recorded vitamin D level during fall or winter, periods marked by restricted sun exposure due to weather conditions and clothing habits. Vitamin D levels are classified based on serum concentrations as follows: severe deficiency is defined as < 10 μg/L, moderate deficiency ranges from 10 to 20 μg/L, mild deficiency falls within 20 to 30 μg/L, and optimal levels are between 30 and 80 μg/L.[24]

The study excluded individuals with an uncertain NF1 diagnosis based on established criteria, segmental NF1, unmeasured vitamin D levels, and those receiving vitamin D supplementation. Additionally, individuals without recorded weight and height during their last visit were also excluded. Age, gender, first-degree NF1 history, skin findings, serum vitamin D level, and weight-height values were systematically recorded. The severity of vitamin D deficiency was categorized as follows: serum 25(OH) D3 levels below 10 μ/L were classified as severe deficiency, 10-20 μ/L as moderate deficiency, and 20-30 μ/L as mild deficiency.

IBM SPSS (Version 23.0) conducted statistical analyses, expressing numerical variables as mean ± standard deviation or median (25^{th} – 75^{th} percentile) and categorical variables as numbers and percentages. Chi-square or Fisher›s exact test examined relationships between categorical variables, the Mann-Whitney U test analyzed differences in vitamin D levels and demographic/clinical findings, and Spearman›s correlation coefficient assessed numerical variable relationships. The significance level was set at $P < 0.05$.

Results

The distribution of patients by age and gender is given in Table 1. Among the patients, 75% (n = 96) were below the age of 20, indicating a predominant youth population among them.

The distribution of individuals diagnosed with NF1 for the first time is presented according to age and gender in Table 2.

Among patients, only 37.5% (*N* = 48) had a documented family history of NF1. The demographic and clinical features of patients are provided in Table 3.

The study found that 99.2% of the patients had CALMs. The study found that 86.6% (*N* = 110) of patients had CALMs present at birth, while 13.4% of patients (*N* = 17) developed CALMs later. In terms of CALM distribution, 70.9% (*N* = 90) of patients had 6-20 CALMs, while 28.3% (*N* = 36) had 21-50 CALMs, and only 0.8% had over 50 CALMs. CALMs were predominantly found on the lower extremities and anterior trunk. They were also observed on the upper extremities, posterior trunk, face, and neck. Freckles were noted in 93.8% (*N* = 120) of patients, with 90% (*N* = 108) developing them during the first decade of life mostly after the appearance of CALMs. Freckles in the second decade were observed in 9.2% (*N* = 11), and only one patient exhibited freckles after the age of 20 years. Freckling was most common in the axilla [Figure 1] and inguinal region. There was a higher prevalence of freckles among female patients compared to male patients, and this difference was statistically significant (*P* = 0.024).

Additionally, freckles were retrospectively noted on the anterior trunk, posterior trunk, neck, face, upper extremities, and lower extremities of patients. Cutaneous and subcutaneous neurofibromas were present in 36.7% (*N* = 47) of patients [Figure 2]. Among these, 64% (*N* = 30) had exclusively cutaneous neurofibromas, 17% (*N* = 8) had only subcutaneous neurofibromas, and 19% (*n* = 9) exhibited both types.

Neurofibromas were predominantly observed in the first decade of life (64.6%, *N* = 31), followed by the second decade 31.2%, (*N* = 15). A minor proportion, 4.2% (*N* = 2), occurred beyond the age of 20 years. The number of neurofibromas varied, with 42.6% (*N* = 20) having 1-10, 34% (*N* = 16) having 11-50, 14.9% (*N* = 7) having 51-100, and 8.5% (*N* = 4) having over 100. The trunk was the most common site, followed by the lower extremities, upper extremities, and head-neck region. PNFs [Figure 3] were found in 25% (*N* = 32) of patients, with 68.8% (*N* = 22) appearing in the first decade, 18.7% (*N* = 6) in the second decade, and only 2.5% (*N* = 4) beyond age 20. Among those with PNFs, 81.3% (*N* = 26) had a solitary PNF, while 28.7% (*N* = 6) had multiple PNFs.

Nevus anemicus [Figure 4] was identified in 32.8% of patients (*N* = 42). Nevus anemicus occurred as a solitary lesion in 69% (*N* = 29) of cases, while multiple lesions were observed in 31% (*N* = 13) of cases with the highest occurrence on the trunk, followed by the lower extremities, upper extremities, and head-neck region.

Hypopigmented macules [Figure 5] were found in 13.2% (*n* = 17) of patients, primarily on the trunk, followed by the lower extremities, head-neck region, and the upper extremities.

Out of all the patients, only a small percentage 3.1% (*N* = 4) were diagnosed with JXG. Among these, two were located on the head and neck, one on the back of the trunk, and one on the upper extremities.

Table 1: Distribution of patients by age and gender

Gender	*N* (%)	Average Age (year)
Female	69 (53.9)	13.6±9.5
Male	59 (46.1)	14.5±13.2
Total	128 (100)	14±11.3

Table 2: Distribution of individuals diagnosed with NF1 for the first time according to age and gender

Age at Diagnosis	Female	Male	Total	P
	N (%)	*N* (%)	*N*	>0.05
1–10	56 (43.7)	47 (36.7)	103	>0.05
10–20	6 (4.6)	7 (5.4)	13	>0.05
20	7 (5.7)	5 (3.9)	12	>0.05

Table 3: Distribution of patients according to their dermatological findings

Dermatological Findings	Gender						*P*
	Female		Male		Total		
	N	%	*N*	%	*N*	%	
Typical CALMs	66	51.6	54	42.2	120	93.8	>0.05
Atypical CALMs	2	1.5	5	3.9	7	5.4	>0.05
Freckles	68	53.2	52	40.6	120	93.8	0.024
Neurofibroma	24	18.8	23	17.9	47	36.7	>0.05
PNF	18	14.1	14	10.9	32	25	>0.05
Nevus Anemicus	22	17.2	20	15.6	42	32.8	>0.05
Hypopigmented macule	10	7.8	7	5.4	17	13.2	>0.05
JXG*	3	2.3	1	0.8	4	3.1	

N represents the number of patients, while % represents the percentage of patients. CALMs=Café-au-laits macules, PNF=Plexiform neurofibroma, JXG=Juvenile xanthogranuloma. *Due to the small number of individuals with JXG, statistical analysis was not performed

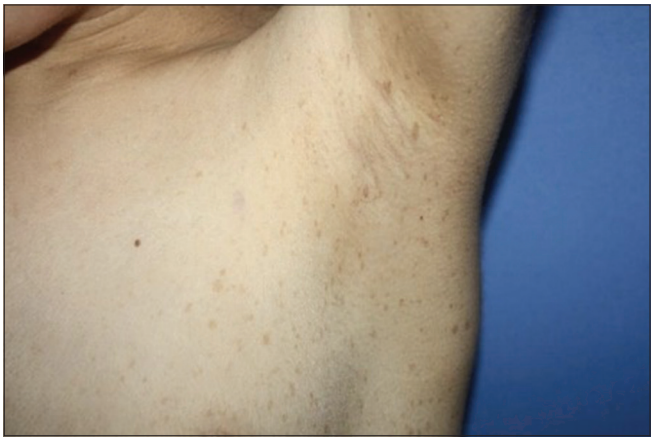

Figure 1: Axillary freckling

Table 4 illustrates the distribution of patients' vitamin D levels by gender.

The median vitamin D level was 15.2 μg/L (10.4-21.9) in women and 16.3 μg/L (12.6-22.5) in men, indicating lower levels in women. This gender difference in vitamin D levels was statistically significant (P = 0.018). There was no statistically significant difference found between patients› serum vitamin D levels and the presence of café-au-lait spots, freckles, and PNFs (P > 0.05). Patients with low vitamin D levels exhibited a statistically significant higher occurrence of nevus anemicus (P = 0.001). Furthermore, the study revealed a significant association between low vitamin D levels and an increased likelihood of neurofibromas (P < 0.001). Additionally, an inverse relationship (rs = −0.251) was observed between the number of neurofibromas and serum vitamin D levels, suggesting that as serum vitamin D levels decreased, the number of neurofibromas increased, although this relationship did not reach statistical significance (P = 0.089).

Table 5 illustrates the findings regarding gender, neurofibromatosis status, and nevus anemicus status in relation to median vitamin D levels.

The distribution of patients' BMI by gender is presented in Table 6.

Discussion

NF1 is a widely recognized disorder impacting multiple body systems, yet limited epidemiological research, especially for the Turkish population, is available. Recent studies have indicated that gender might serve as a prognostic factor for NF1. Two studies noted a 5-10 times higher incidence of visual impairment in females with optic glioma compared to males. Diggs *et al.*[25] reported more frequent neural deficits in female patients and more prevalent learning difficulties in male patients.[24] In our study, females showed higher prevalence in all clinical characteristics, with only freckling showing statistically significant differences (P = 0.024). Notably, the small number of patients without freckles (N = 8) suggests the observed relationship may be by chance.

CALMs are the predominant skin finding in NF1, occurring in 95-99% of patients based on previous studies.[2,3,7,26,27] Our study supports this, revealing a CALM occurrence rate of 99.2%, aligning with the literature.

In NF1 individuals, typical CALMs predominate,[6,28] with limited data on atypical ones. Nunley *et al.*[6] found a 1.8% prevalence of atypical CALMs among 110 patients. Our study aligns with existing findings, showing 93.8% typical and 5.4% atypical cases. CALMs, frequently found on the lower extremities, particularly the buttocks were notably predominant in our study (97.6%), mirroring patterns seen in prior research.[5]

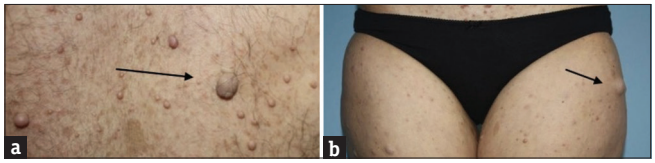

Figure 2: Cutaneous neurofibromas (a) subcutaneous neurofibromas (b)

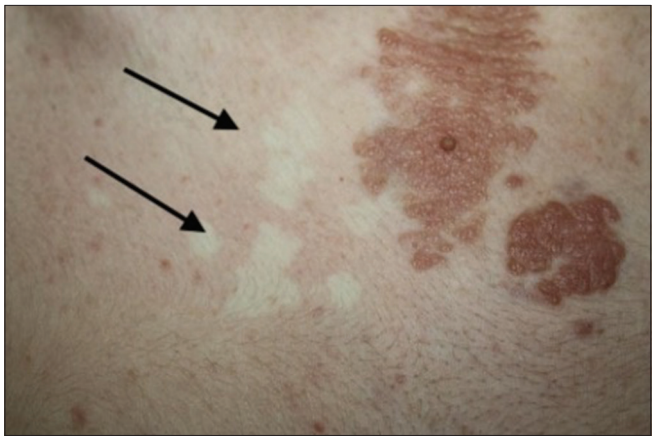

Figure 4: Nevus anemicus

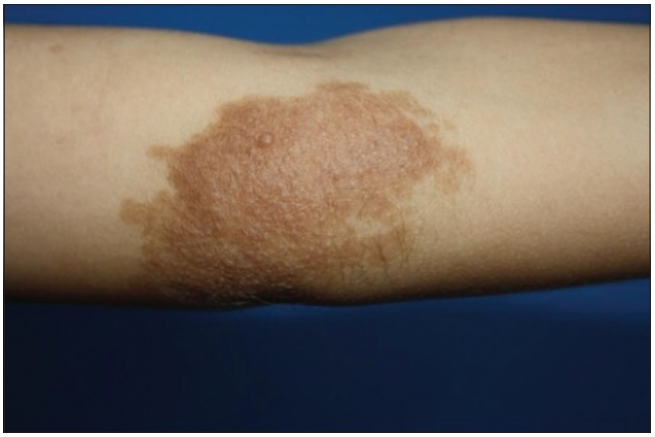

Figure 3: Plexiform neurofibroma

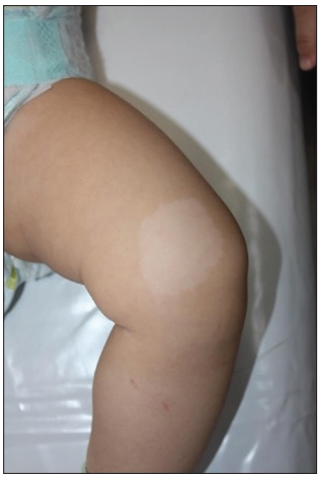

Figure 5: Hypopigmented macule

Table 4: Distribution of patients' vitamin D levels by gender

25 (OH) D3 Level (µg/L)	Gender		Total (*N*=128)
	Female (*N*=69)	Male (*N*=59)	
	N (%)	*N* (%)	*N* (%)
Severe deficiency (<10)	16 (12.5)	10 (7.8)	26 (20.3)
Moderate deficiency (10–20)	33 (25.8)	31 (24.2)	45 (50)
Mild deficiency (20–30)	15 (11.7)	14 (11)	29 (22.7)
Normal (>30)	5 (3.9)	4 (3.1)	9 (7)

Table 5: Relationship between patient conditions and median vitamin D levels with statistical significance

Patients Condition	Vitamin D Level (Median–Range) (µg/L)	*P*
Women	15.2 (10.4–21.9)	0.018
Men	16.3 (12.6–22.5)	
With neurofibromatosis	12.6 (7.8–16.5)	<0.001
Without neurofibromatosis	18.2 (13.6–22.5)	
With nevus anemicus	12.6 (9.3–16.7)	0.001
Without Nevus anemicus	17.6 (13.8–22.5)	

Table 6: The statistical relationship between patients' BMI level and gender

BMI (kg/m^2)	Gender		
	Female (*N*=69)	Male (*N*=59)	Total (*n*=128)
	N (%)	*N* (%)	*N* (%)
Underweight (<18.5)	38 (29.6)	32 (25)	70 (54.6)
Normal (18.5–24.9)	18 (14)	18 (14)	36 (28)
Overweight (25–29.9)	6 (4.6)	9 (7.1)	15 (11.7)
Obese (>30)	7 (5.7)	0 (0)	7 (5.7)

Freckling, a key diagnostic criterion for NF1, typically follows CALM development in 90% of cases.[7,29]

De Schepper found freckles in 80% of NF1 patients,[30] while our study observed freckling in 93.8% of patients, often emerging after CALM appearance. Neurofibromas are a hallmark of NF1, with cutaneous neurofibromas prevalent in 85% of patients, commonly on the trunk and extremities.[6,22,31-34] Subcutaneous neurofibromas, found in the deep dermis, occur in approximately 20% of NF1 patients.[27,35] While the literature reports neurofibromas in 60-90% of NF1 patients,[36] our study found them in only 36.7% of cases. In NF1, neurofibromas can range from a few to thousands.[36,37] In our study, we examined the exact count of neurofibromas, as mentioned earlier, despite the scarce literature on this aspect in NF1.

Prior studies have indicated that PNFs can be identified in up to 30-40% of adult NF1 cases via CT or MRI.[13,38] In our study, 25% of NF1 patients had PNFs. In NF1 patients, both hyperpigmented and hypopigmented lesions can be observed.[39] In an observational case-control study by Javier Garcia-Martinez *et al.*,[40] hypopigmented lesions were observed in 13.9% of NF1 patients compared to 4.38% in the control group. Our study similarly found hypopigmented macules in 13.2% of patients, aligning with Garcia's results.

Existing literature indicates that JXG can occur in 0.7-37.5% of NF1 patients, with a common occurrence on the head and neck,[18,19,41] although they can manifest anywhere.[17,18] Our study observed JXG in 3.1% of patients, predominantly in the head and neck region. In Hirbe *et al.*[15] study, a strong correlation was found between dermal neurofibromas and serum vitamin D levels in NF1 patients, associating lower vitamin D levels with increased number and size of neurofibromas. We also noted a significant link between neurofibroma persistence and low vitamin D levels. Consistent with the findings of Hirbe *et al.*, we observed a negative relationship between neurofibroma count and serum vitamin D levels, although not statistically significant in our study. Studies on NF patients have reported varying prevalence rates of nevus anemicus. It ranges from 8.8% to 51%, with common locations including the upper chest and anterior chest wall.[14,15,19] In our study, nevus anemicus was observed in 32.8% of NF1 patients, predominantly on the trunk. Our study uncovers a significant link between serum vitamin D levels and nevus anemicus occurrence in NF1 patients, suggesting a previously unrecognized association. This highlights the importance of nevus anemicus as a skin manifestation in this population.

There are limited studies on the body mass index (BMI) of NF1 patients, with only a few clinical studies available.[2,23] Koga *et al.* found that the BMI of male NF1 patients was particularly lower.[23] In our study, 54.6% of patients had a low BMI, with a higher percentage in females compared to males.

Conclusion

In summary, despite the study's limitations, such as the absence of a control group and the retrospective nature of our investigation, our findings provide valuable insights. These interesting observations not only enriches our understanding of NF1 but also offers valuable insights for clinicians and researchers. Furthermore, these findings suggest practical implications for the effective management of NF1 patients, highlighting the importance of monitoring and addressing vitamin D levels in clinical practice.

We advocate for further investigation through a prospective study, comparing NF1 patients with a healthy control group regarding nevus anemicus, neurofibromas, and their relation to serum vitamin D

levels. By elucidating these associations, we can enhance understanding of NF1 pathology and refine patient management strategies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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