Musculoskeletal impairment in adults with neurofibromatosis type 1: an observational study from Southern Italy

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder affecting 1 in 3000 live births. The musculoskeletal system in adult NF1 patients has not been extensively studied. This observational study aimed to characterize musculoskeletal impairment in a cohort of adult NF1 patients. We collected anthropometric data, and data on level of physical activity (PA), muscle strength, muscle performance, bone mineral density, and perceived physical and mental health. The cohort was subdivided according to the patients' level of PA (defined as inactive, sufficiently active, active/very active), and outcomes were compared between the three groups. Eighty-three patients (37 M; 46 F) affected by NF1 were recruited. Seventeen (20.5%) were inactive (Group 0), 38 (45.8%) were sufficiently active (Group 1), and 28 (33.7%) were active or very active (Group 2). When comparing the three groups, statistically significant differences were found between Group 0 and Group 2 ($p < 0.05$) on the three sub-items of the Short Physical Performance Battery. Thirty patients completed the densitometric bone evaluation, which showed osteopenia in 7 patients (23.3%), and osteoporosis/reduced values for sex and age in 4 (13.3%). No statistically significant differences in densitometric findings were found between the three groups ($p > 0.05$). This study provides a musculoskeletal characterization of a cohort of adult NF1 patients from southern Italy. Muscle strength was lower compared with that of the general population, and bone strength was compromised in one-third of our cohort. Physical activity might help to preserve bone health in NF1 patients. Future research should address the long-term effects of PA on bone strength in this population.

KEYWORDS

Neurofibromatosis type 1, physical activity, skeletal muscle, bone mineral density.

Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder (1:3000 individuals) characterized by mutations in the *NF1* gene on chromosome 17q11, leading to loss of function of neurofibromin, a tumor suppressor protein [1]. NF1 is primarily known for its neurocutaneous manifestations and central nervous system (CNS) involvement, which are major contributors to morbidity. Recent studies indicate that NF1 also significantly affects the skeletal and motor systems, leading to bone dysplasia, hypotonia and muscle weakness [2]. Although traditionally attributed to structural and functional CNS changes, these musculoskeletal impairments seem to be related to primary alterations of muscle growth and metabolism resulting from neurofibromin dysfunction, with a consequent reduction of bone strength and skeletal muscle mass [3]. Bone specimens from NF1 patients demonstrate reduced trabecular volume, increased osteoid mass, and elevated undifferentiated osteoblastic/osteoclastic cell count [4]. Young people affected by NF1 are also unable to take part in physical activities to the same level as their peers, experiencing pain and movement-related cramps [5]. Whereas musculoskeletal involvement is well known in children and adolescents with NF1, literature on this aspect in adults is lacking.

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Purpose

This study aimed to characterize musculoskeletal impairment in an adult cohort of NF1 patients.

Materials and methods

Participants

An observational study including consecutive patients ≥ 18 years old affected by NF1 diagnosed according to the National Institutes of Health (NIH) Consensus Conference criteria (National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis 1988) was conducted. The study

received local ethics committee approval (Prot. 0009133/i of 24/03/2023) and was conducted in compliance with the principles of the Helsinki Declaration. Written informed consent was obtained from each participant.

Outcome measurement tools

The patients were evaluated according to our protocol which includes a section covering medical history and anthropometric data, such as age, body mass index (BMI), and clinical features. The latter were categorized as cardinal signs and complications, utilizing an internal phenotypic classification system that divides them into five distinct clinical groups, as described by Napolitano *et al*. [6]. This classification is based on genotype and includes the following details:

- **Group 1 (G1)** consists of patients exhibiting classical NF1 characteristics, defined by the presence of two or more of the following features: six or more café-au-lait macules, axillary and inguinal freckling, two or more Lisch nodules, and neurofibromas, without any other signs of extra-cutaneous or ocular involvement.
- **Group 2 (G2)** encompasses NF1 patients who show two or more of the phenotypic traits listed for G1, along with involvement of the skeletal system (short stature, scoliosis, hyperkyphosis, bone dysplasia), CNS (epilepsy, intracranial vascular malformations, hamartomas or unidentified bright objects) and mental health issues (intellectual disability, anxiety, depression, sleep disorders), as well as vascular complications and anomalies of internal organs, such as heart valve abnormalities and hypertension.
- **Group 3 (G3)** includes NF1 patients with two or more phenotypic features from G1, along with multisystem involvement and a histological diagnosis of malignant peripheral nerve sheath tumor according to the American Joint Committee on Cancer Staging System for soft tissue sarcomas.
- **Group 4 (G4)** is designated for NF1 patients who exhibit two or more of the G1 features, together with multisystem involvement and CNS tumors (such as optic gliomas and pilocytic astrocytomas) as well as peripheral nervous system tumors (e.g., ganglioneuromas and gangliocytomas).
- **Group 5 (G5)** incorporates NF1 patients presenting two or more clinical traits from G1, in addition to multisystem involvement and various organ and system neoplasms of differing grades, including gastrointestinal stromal tumors, endocrine tumors (pheochromocytomas and thyroid carcinoma), genitourinary tumors (ovarian, prostatic, testicular, bladder cancers), hematological tumors, breast cancer, and cutaneous melanoma, as well as ear cholesteatoma.

Moreover, the following clinical and instrumental studies were performed:

- muscle strength measurement (isometric handgrip strength) by means of a hand-held Jamar dynamometer;
- muscle performance assessment by means of the Short Physical Performance Battery (SPPB);
- evaluation of perceived physical and mental health, through the 36-item Short Form Survey (SF-36)
- evaluation of level of physical activity (PA), using the International Physical Activity Questionnaire (IPAQ)
- a densitometric examination, performed using the dual-energy X-ray absorptiometry (DXA) method (GE Lunar), of the bone mineral density (BMD) of the lumbar spine (L1-L4), the left femoral neck (l-FN), and the total body less head. In men over 50 and in postmenopausal women, osteopenia and osteoporosis were diagnosed using the T-score. In females before menopause and males younger than 50 years old, the Z-score was used (-2.0 SD or lower being defined as "below the expected range for age"; and above -2.0 SD as "within the expected range for age") [7].

Based on IPAQ cut-offs expressed in weekly metabolic equivalent (MET) values (< 700: inactive; between 700 and 2519: sufficiently active; >2520: active or very active), patients were categorized into Groups 0, 1 and 2, respectively.

Statistical analysis

Statistical Package for the Social Sciences 25 (IBM Corp., Armonk, NY, USA) software was used to analyze correlations between levels of PA, outcome scores, and densitometric values. All data were presented as mean ± standard deviation (SD), for continuous variables, or as n (%), in the case of categorical variables. The distribution of all variables was tested using the Shapiro-Wilk test. Analysis of variance for multiple samples was carried out using ANOVA in the case of normally distributed variables and the Kruskal-Wallis test in the case of non-parametric variables. The significance threshold was set at p=0.05.

Results

We recruited 83 patients (37 M; 46 F) with an average age of 40.61 ± 15.45 years and an average BMI of 24.34 ± 4.31 kg/m^2, all affected by NF1 (Table I). Most (38%) were classified

Table I Demographic and clinical characteristics of the sample.

VARIABLES	PEOPLE WITH NF1 (*n*=83)
Age (years old)	40.61 ± 15.45
BMI (kg/m2)	24.34 ± 4.31
Handgrip strength (Kg)	27.94 ± 10.17
PHYSICAL ACTIVITY LEVEL	**PEOPLE WITH NF1 (*n*=83)**
Inactive (Group 0) (%)	17 (20.5%)
Sufficiently active (Group 1) (%)	38 (45.8%)
Active or very active (Group 2) (%)	28 (33.7%)
CLINICAL FEATURES ACCORDING TO NAPOLITANO ET AL. [6]	**PEOPLE WITH NF1 (*n*=83)**
G1	29 (34.9 %)
G2	32 (38.5 %)
G3	11 (13.2 %)
G4	4 (4.8 %)
G5	7 (8.4%)

as G2, having classic characteristics of NF1 along with bone involvement. The mean handgrip strength was 27.94 ± 10.17 kg. On analysis of the level of PA, 17 patients (20.5%) were found to be inactive, 38 patients (45.8%) sufficiently active, and 28 patients (33.7%) active or very active.

On comparing the patients stratified by PA (Table II), statistically significant differences were found between Group 0 and Group 2 for the three sub-items of the SPPB ($p < 0.05$).

Thirty patients completed the densitometric examination (14 M; 16 F) (Table III); of these, 19 (63.3%) showed normal mean values for sex and age, 7 had values consistent with a diagnosis of osteopenia (23.3%), while 4 (13.3%) had a diagnosis of osteoporosis/reduced values for sex and age. When comparing the densitometric parameters by level of PA, no statistically significant differences were found between the three groups ($p > 0.05$) (Table IV).

Table II Comparison of scores between patients (n=83) stratified by physical activity.

	GROUP 0 (N=17)	GROUP 1 (N=38)	GROUP 2 (N=28)	*p* VALUE
BMI	24.24 ± 0.82	19.79 ± 11.78	24.34 ± 0.88	0.035
SPPB SCORE	8.06 ± 2.8	9.47 ± 2.36	10.37 ± 1.471	0.008
SPPB Balance	3.18 ±1.35	3.58 ± 0.967	3.92 ± 0.267	0.018
SPPB Gait	2.25± 1.125	2.80 ± 0.98	3.07 ± 0.781	0.032
SPPB SitToStand	2.37 ± 1.38	3.08 ± 1.07	3.37 ± 0.967	0.024
SF-36 Physical activity	75.59 ± 7.37	76.97 ± 6.5	67.86 ± 8.01	0.480
SF-36 Role physical	75 ± 10.05	78.47 ± 38.8	66.6 ± 42.74	0.556
SF-36 Bodily pain	64.7 ± 11.24	66.28 ± 6.94	63.71 ± 7.47	0.981
SF-36 General health	50 ± 6.10	51.96 ± 3.63	58.96 ± 4.94	0.281
SF-36 Vitality	66 ± 7.15	62.18 ± 3.08	68.14 ± 7.53	0.629
SF-36 Social functioning	74.21 ± 7.39	69.37 ± 4.46	70.5 ± 5.58	0.756
SF-36 Role emotional	68.74 ± 8.17	66.74 ± 4.56	67.48 ± 5.67	0.879
SF-36 Mental health	60.6 ± 5.6	59.58 ± 3.13	66.18 ± 5.64	0.823
HGS (kg)	28.06 ± 2.43	27.89 ± 1.7	27.93 ± 1.94	0.963

Abbreviations: **BMI** = body mass index, **SPPB** = Short Physical Performance Battery; **SF-36** = 36-item Short Form Survey; **HGS** = handgrip strength.

Table III Dual-energy X-ray absorptiometry (DXA) scores (n=30 patients).

	TOTAL BODY BMD (g/cm²)	TOTAL BODY TS	TOTAL BODY ZS	L1-L4 BMD (g/cm²)	L1-L4 TS	L1-L4 ZS	I-FN BMD (g/cm²)	I-FN TS	I-FN ZS
Mean ± SD	1.04 ± 0.31	-.21 ± 1.03	0.19 ± 0.97	1.05 ± -.25	-.49 ± 1.08	-0.1 ± 1.11	0.88 ± 0.97	-1.03 ± 0.88	-.72 ± 0.77

Table III Dual-energy X-ray absorptiometry (DXA) scores (n=30 patients).

	TOTAL BODY BMD (g/cm²)	TOTAL BODY TS	TOTAL BODY ZS	L1-L4 BMD (g/cm²)	L1-L4 TS	L1-L4 ZS	I-FN BMD (g/cm²)	I-FN TS	I-FN ZS
Mean ± SD	1.04 ± 0.31	-.21 ± 1.03	0.19 ± 0.97	1.05 ± -.25	-.49 ± 1.08	-0.1 ± 1.11	0.88 ± 0.97	-1.03 ± 0.88	-.72 ± 0.77

Abbreviations: **BMD** = bone mineral density; **I-FN** = left femoral neck; **Ts** = T-score; **Zs** = Z-score; **L1-L4** = lumbar spine.

Table IV Densitometric and strength data of patients (n=30) stratified by physical activity.

PA LEVEL	AGE	HGS	TOTAL BODY BMD	TOTAL BODY TS	TOTAL BODY ZS	L1-L4 BMD	L1-L4 TS	L1-L4 ZS	I-FN BMD	I-FN TS	I-FN ZS
Group 0 (*n*=7)	41.63 ± 17.6	28.27 ± 9.3	1.04 ± 0.08	-0.96 ± 0.9	-0.14 ± 0.61	1.05 ± -1.23	-1.27 ± 0.07	-0.49 ± 0.53	0.82 ± 0.1	-1.60 ± 0.94	-1.03 ± 0.9
Group 1 (*n*=12)	39.56 ± 14.3	28.03 ± 10.3	1.08 ± 0.11	-0.17 ± 1.08	0.13 ± 1.19	1.05 ± 0.24	-0.4 ± 1.45	-0.06 ± 1.53	0.873 ± 0.08	-1.12 ± 0.67	-0.91 ± 0.81
Group 2 (*n*=11)	39.78 ± 12.99	27.78 ± 10.26	1.15 ± 0.099	0.23 ± 0.90	0.28 ± 1.05	1.19 ± 0.144	0.09 ± 1.25	0.22 ± 1.47	0.92 ± 0.09	- 0.62 ± 0.9	-0.53 ± 0.8
p-value	0.532	0.756	0.700	0.057	0.690	0.680	0.058	0.43	0.129	0.077	0.508

Abbreviations: **PA** = physical activity; **BMD** = bone mineral density; **HGS** = handgrip strength; **I-FN** = left femoral neck; **L1-L4** = lumbar spine.

Discussion

This study was focused on musculoskeletal impairment in a cohort of adult NF1 patients from southern Italy.

Data reported by Souza *et al*. showed that adults with NF1 had lower muscle strength than the general population [8,9]. Moreover, Cornet *et al*. showed that children with NF1 also have reduced muscle strength compared with healthy peers, suggesting that muscle weakness likely begins in the early stages of NF1 [10].

Murine models of NF1 highlight a direct role for neurofibromin in normal muscle development and function. Loss of this protein disrupts numerous metabolic pathways, leading to fat accumulation, increased triglyceride and fatty acid synthase activity, and mitochondrial dysfunction within muscle fibers, suggesting a primary myopathy within the NF1 clinical phenotype [10].

Muscle weakness may also be attributable to the intrinsic genetic and neurological impairment of neural-muscle cross-talk in NF1 in terms of both motor coordination and/or activation [7]. These deficits are often attributed to CNS dysfunction; however, we performed no clinical or instrumental examinations of the CNS in our sample. Finally, another potential cause of low muscle strength could be a sedentary lifestyle, commonly reported in this population. Sedentary behavior is understood as "any waking behavior characterized by an energy expenditure ≤1.5 METs" [11].

However, more than 50% of our patients were found to be sufficiently active or active/very active, with expenditure of more than 700 METs/day. Our findings contrast with those of Ferrara *et al*., who reported that both vigorous and moderate-intensity activities and walking appeared significantly reduced in young NF1 patients versus controls [12].

It is well established that PA positively impacts bone-muscle cross-talk in healthy populations. In our study, a statistically significant difference in muscle performance (SPPB scores) was observed between the low and high PA groups. Considering the early BMD deterioration frequently observed in NF1, promoting regular PA in this population could potentially improve overall muscle strength and function. Further research should explore the potential benefits of targeted exercise interventions for individuals with NF1.

The data from the DXA evaluation showed that 37% of the subjects had low BMD, consistent with the findings of Ferrara *et al*. who observed below age-matched reference values in 32/108 patients (29.6%) [12]. These data support the hypothesis of adynamic bone, based on observations in NF1 murine models, characterized by decreased bone formation and/or increased osteoclastic survival/activity [13,14].

In our study, although 11 out of 30 patients showed osteopenia/osteoporosis/low BMD values, only three were physically inactive. No statistically significant differences in densitometric values were found between the three levels of PA. Despite this, in our opinion, achievement of a good level of PA can influence performance and muscle strength and should be suggested in people with NF1, as exercise can stimulate bone formation and help counteract bone deterioration.

NF1 also presents social challenges, negatively affecting quality of life. The SF-36 overall and subgroup scores in our population were lower than those of the Italian normative sample for all subitems except "vitality" and (solely in the high-performance group) "mental health" [15]; this finding suggests that encouraging PA may help to improve these patients' mental health. Addressing health-related quality of life, taking into account both social and environmental support, should be a priority in managing the NF1 population.

Our findings emphasize the need for a healthy lifestyle in these patients, including appropriate PA and regular follow-up visits to evaluate bone health. After comparing our findings with NF1 studies in pediatric samples, it seems crucial to ensure proper interdisciplinary management during the transition period from adolescence to adulthood, in order to prevent worsening of muscle and bone health, and to promote exercise so as to maintain a good level of bone health, throughout life.

Limitations of our study were the small sample size, the lack of a control group, the cross-sectional design, and the absence of data on concomitant therapies. Further research in a larger sample may provide more conclusive results on the impact of PA on muscle and bone health in NF1 patients.

Conclusion

Our data provided a musculoskeletal characterization of a cohort of adults with NF1 in southern Italy. Although many patients were physically active, muscle strength remained below that of the general population, and bone health was compromised in one-third of the cohort. Promoting regular physical activity is crucial for improving musculoskeletal health in NF1 patients. Future research should focus on long-term effects of physical activity on bone strength in this population.

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