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Characteristics of patients with neurofibromatosis and patient and caregiver perspectives on the impact of the disease and its clinical management in Spain and Portugal

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Abstract

Background Neurofibromatosis (NF) is a genetic disorder of the nervous system that causes the growth of tumours on nerve tissues. There are three main types of NF: NF1, NF2-related schwannomatosis, and non-NF2-related schwannomatosis, each associated with distinct clinical characteristics and health complications. Although NF is primarily a non-malignant condition, it significantly impacts health-related quality of life (HRQoL) for both patients and their caregivers. Despite the growing availability of therapeutic options, including surgery and targeted therapies, NF remains a chronic condition requiring lifelong management.

Methods A cross-sectional, observational study conducted with patients diagnosed with NF across Spain and Portugal. Sociodemographic and clinical data were collected, and the impact of the disease on patients' and caregivers' quality of life was assessed through an online ad-hoc questionnaire.

Results The study revealed that NF has a multidimensional impact on both patients and caregivers. Patients reported significant physical, emotional, and social challenges, with symptoms such as chronic pain, tumor-related complications, and hearing loss as the most frequently reported, having the greatest impact on their QoL. Caregivers also experienced diminished HRQoL due to the demands of providing support. Despite the availability of surgical interventions and emerging targeted therapies, many patients indicated that they were not very satisfied with the management of the disease in the public health system.

Conclusions The findings highlight the need for more comprehensive management strategies that not only target the physical manifestations of NF but also provide greater psychosocial support for patients and caregivers in the context of Spain and Portugal. This region-specific insight would help to implement strategies to optimize the management, improve the quality of care, and, consequently, improve the quality of life of NF patients and their caregivers.

Keywords Neurofibromatosis, Schwannomatosis, Survey, Impact, Health-related quality of life

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Introduction

Neurofibromatosis (NF) is a genetic disorder of the nervous system characterized by the development of tumours on nerve tissues, including the brain, spinal cord, and peripheral nerves [1]. NF can be classified into NF1, NF2-related schwannomatosis and non-NF2-related schwannomatosis, formerly known as NF2 and schwannomatosis (SWN) [2]. NF1 is the most prevalent, accounting for 96% of the cases, whereas NF2-related and non-NF2-related SWN represent 3% and < 1% of all cases, respectively [3]. NF1 has a prevalence of one in 3000 births, NF2-related SWN one in 25,000, and non-NF2-related SWN one in 70,000 [4]. Each condition arises from different pathogenic gene variants associated with specific clinical characteristics [1].

NF1 typically leads to the development of cutaneous neurofibromas and other clinical manifestations such as plexiform neurofibromas, optic nerve gliomas, skeletal abnormalities, and neurocognitive impairment [5, 6]. The visible appearance of tumours associated with NF1 often results in increased self-consciousness and social isolation, which can negatively impact mental health [7, 8]. NF2-related SWN is primarily defined by the presence of vestibular nerve schwannomas, frequently resulting in progressive hearing loss [9]. Patients also experience balance difficulties, skin flaps, and muscle atrophy [1]. Tumours affecting the cochlear nerve can lead to dizziness, vertigo, ataxia, equilibrium disorders, headaches, tinnitus, and facial muscle dysfunction [10]. These symptoms significantly reduce HRQoL across physical, social, and mental domains [11, 12]. Non-NF2-related SWN is characterized by the presence of schwannomas and chronic neuropathic pain, often unrelated to tumour location [1, 5]. Furthermore, hearing impairment and persistent pain contribute to psychological distress, with disease severity being associated with increased depressive symptoms [5, 12, 13]. Overall, the primary concerns among patients with NF1, NF2-related SWN, and non-NF2-related SWN include impaired physical function, chronic pain, social limitations, and emotional distress [10, 14].

There is no cure for NF, although signs and symptoms can be managed through different therapeutic approaches [1, 5]. Surgery is the principal therapeutic option in patients with NF1 and NF2-related SWN to relieve symptoms caused by tumours compressing nearby tissue or damaging organs [3] or to help preserve hearing by using cochlear or brainstem implants [15, 16]. However, complete tumour excision is often not feasible, and some of these tumours are likely to regrow after partial resection [16, 17].

During the past decade, targeted therapies have been developed as a therapeutic alternative [18]. For example, Ras, MEK, and mTOR inhibitors have been tested in clinical trials for patients with NF1 and plexiform neurofibromas, showing encouraging results [19–21]. Targeted therapies in patients with NF2-related SWN are mainly based on using bevacizumab, a monoclonal antibody against the vascular endothelial growth factor [22, 23].

Pain is one of the critical symptoms impacting negatively HRQoL in NF1, leading many times to depression, anxiety, and cognitive problems [14]. Chronic pain in NF1 is heterogeneous, and its impact is exacerbated by itch, embarrassment, and fear of worsening skin disease [14]. Additionally, NF1-related neurofibromas significantly impact patients and caregivers, exacerbating pain and discomfort in patients, intensifying anxiety and depression, and reducing productivity in both patients and caregivers [24]. Thus, it becomes necessary to identify HRQoL predictors in this population to promote the well-being of patients and caregivers and develop targeted interventions [7].

Awareness and impact of NF vary across countries [25–28], highlighting the need for country-specific studies to better comprehend the characteristics of NF in different regions. In this context, a better understanding of the symptoms and complications related to the different types of NF and how these affect patients' and caregivers' on their daily lives within the geographic area of Iberia will allow to identify needs, and challenges and propose improvements in the disease management. Additionally, according to the higher prevalence of NF1, we aimed to provide a deeper comprehensive overview of the reality of N1 in the Iberian region (Spain and Portugal) to propose improvements based on the findings. Thus, the goal of the present study was to describe the sociodemographic and clinical characteristics of the NF population (NF1, NF2-related SWN and non-NF2-related SWN) in Spain and Portugal,. Additionally, the study sought to assess the impact of the disease on patients and caregivers, and to explore the current management of NF from the patients' perspective. Special attention was given to understand the role of specialists involved in the diagnosis and follow-up of NF patients, as well as their unmet needs and the availability of psychological support.

Methods

Study design and participants

This cross-sectional, observational study is based on an online ad-hoc questionnaire addressed to patients with NF or their caregivers who are part of the Spanish and Portuguese patient advocacy groups *Asociación de Afectados de Neurofibromatosis* (AANF) and *Associaçao Portuguesa de Neurofibromatose* (APNF), respectively. The study was approved by the Ethics Committee for Research with Medicines of the Germans Trias i Pujol

University Hospital (Barcelona) in Spain, and by the Ethics Committee of the IPOLFG (Instituto Português de Oncologia de Lisboa Francisco Gentil) in Portugal. Ethical approval ensured that the study methodology complied with current regulatory standards and that all participant data were handled anonymously and confidentially.

Given the number of patients belonging to the AANF (1800 members) and APNF (300 members), and considering that most of the survey responses would be measured as a proportion, the proportion estimation formula was applied to calculate the sample size assuming maximum indeterminacy, with a confidence interval of 95% and a precision error of 9% [29]. That resulted in a minimum sample size of 112 Spanish and 86 Portuguese participants to obtain a representative sample.

Participants were identified and invited to participate through the patients' advocacy groups. All participants were informed that their participation was voluntary, anonymous, and freely agreed to participate in the study. The questionnaire was available for 3 months, and participants could access the questionnaire via a link facilitated by the AANF and APNF. If the participant was a family member or caregiver, the questionnaire had to be answered from the patient's perspective, except for caregiver-specific questions.

Questionnaire

A custom-designed ad-hoc questionnaire was specifically developed for this study based on a comprehensive review of the literature concerning key issues in NF management [4, 30–38]. Additionally, input was gathered from a focus group consisting of AANF members affected by NF. This helped identify the aspects of greatest concern to patients, particularly regarding the disease's impact on their daily lives and its clinical management. Moreover, a steering committee consisting of a clinical geneticist (IB), a neurologist (JP) and a hospital pharmacist (JLV) expert on NF participated in developing the questionnaire. Members of the AANF and APNF reviewed the questionnaire to ensure its comprehensibility. The questionnaire was originally created in Spanish and subsequently translated into Portuguese by a professional translator. The same questionnaire was used in Spain and Portugal, adapted to the language and characteristics of the country.

The questionnaire included 43 items divided into four sections (Supplementary Material: Questionnaire): (1) sociodemographic variables: age, sex, region, and work/academic status; (2) clinical variables related to NF: type of NF, family history, age of symptom onset, age at diagnosis, initial and current signs and symptoms, and comorbidities; (3) impact of NF on daily life: a numerical rating scale (1 to 5) was used to assess the impact of NF signs and symptoms, disease burden, health-related quality of life (HRQoL) using the COOP/WONCA [39–41] questionnaire, which is a validated tool in Spain and Portugal [39–41], feelings/emotions about the disease, effects on work or academic life, need for caregiver support, and if applicable, the impact on the caregiver's life; (4) clinical management of NF: This section included questions about the medical specialty involved in diagnosis, healthcare professionals responsible for follow-up, and a 5-point Likert scale to evaluate the patient's current perspectives on the management of their disease.

Data analysis

The statistical analysis was performed using the software STATA version 14. A descriptive analysis of the study variables was performed. Relative and absolute frequencies were calculated for qualitative variables, while centrality (mean) and dispersion (standard deviation [SD], quartiles, minimum, maximum) measures were calculated for quantitative variables.

All the results obtained were calculated concerning the valid answers to each question, with the number of data (N) on which the calculations were made being reported in each case.

Results

A total of 340 Spanish and 58 Portuguese participants answered the questionnaire. Of the Spanish respondents, 54% were patients, and 46% were caregivers. Regarding the Portuguese participants, 57% and 43% were patients and caregivers, respectively.

Patients with neurofibromatosis

Demographic characteristics

Spanish patients had a mean age of 30.7 years, most were employed (39.4%) or students (38.2%). In addition, 36.5% of the patients had a disability certificate, with a mean degree of 49% (Table 1). Most of the patients (77.7%) did not have any family member with NF, while 13.8% were the child of an affected person, 8.8% had siblings, and 8.2% had children with NF (Supplementary Table S1).

Patients in Portugal had a mean age of 27.2 years, and almost 80% were active workers or students. Twenty-one patients (36.2%) had a certificate of disability, with a mean degree of 70% (Table 1).

Interestingly, in both Spain and Portugal, patients with NF1 had a lower mean age (26.0–29.7 years) compared to other participants with other types of NF.

Clinical characteristics

Overall, most (> 90.0%) patients presented NF1, while approximately 7.0% presented NF2-related SWN. Only a

Table 1 Patients' sociodemographic characteristics

	Spain	Portugal
Sex, *n* (%)		
Women	194 (57.1)	34 (58.6)
Men	146 (42.9)	24 (41.4)
Age (mean), years (SD)	30.7 (17.9)	27.2 (16.5)
NF1	29.7 (17.8)	26.0 (16.5)
NF2-related SWN	43.2 (15.9)	42.0 (6.6)
Non-NF2-related SWN	43.0 (1.0)	–
Employment situation, *n* (%)		
Employed	134 (39.4)	23 (39.7)
Student	130 (38.2)	22 (37.9)
Unemployed	21 (6.2)	4 (6.9)
Due to NF	8 (2.4)	1 (1.7)
Laboral inability	17 (5.0)	1 (1.7)
Due to NF	15 (4.4)	0 (0.0)
Not schooled	9 (2.7)	3 (5.2)
Early retired	7 (2.1)	1 (1.7)
Due to NF	5 (1.5)	1 (1.7)
Temporary sick leave	7 (2.1)	2 (3.5)
Due to NF	5 (1.5)	1 (1.7)
Homemaker	5 (1.5)	0 (0.0)
Other	10 (2.9)	2 (3.5)

NF neurofibromatosis SD standard deviation, *SWN* schwannomatosis

few Spanish patients (0.9%) presented non-NF2-related SWN. Symptoms onset and time of diagnosis differed depending on the type of NF. On average, diagnosis was delayed by 2.7 years in the three types of neurofibromatosis (Table 2).

Patients with NF1 Symptoms appeared in childhood, at a mean age of 4.9 years and 6.7 years in Spanish and Portuguese patients, respectively; and patients with NF1 showed the earliest onset in comparison to the other types of NF (Table 2). Café-au-lait spots were the most frequent (94.9%) initial sign in patients with NF1, either in Spain or Portugal Over time, clinical manifestations that were not so frequent initially, such as plexiform tumours or musculoskeletal features, appeared in both the Spanish and Portuguese populations (Table 3).

Patients with NF2-related SWN Symptoms developed in adulthood, at the mean age of 21.6 and 23.5 years in Spain and Portugal, respectively (Table 2). Bilateral vestibular schwannomas were the most frequent initial clinical manifestation, present in 60.9% and 75.0% of Spanish and Portuguese patients, respectively. Other clinical manifestations, such as schwannomas in cranial and spinal nerves and meningiomas, became more frequent as the disease progressed. Loss of balance was the most common symptom reported (65.2%) by Spanish patients (Table 4).

Patients with non-NF2-related SWN. Symptoms onset occurred in adolescence, at mean age of 16 years (Table 2). Only two of the three patients initially presented schwannomas in cranial, spinal, and peripheral nerves and disabling pain. However, over time, all of them presented schwannomas in cranial, spinal, and peripheral nerves, numbness or weakness in different parts of the body, and chronic pain (Table 5).

Impact of clinical manifestations on daily life

The impact of NF clinical manifestations on daily life was evaluated using a custom-designed ad-hoc questionnaire. A numerical rating scale (1 to 5) was employed to assess the perceived impact of NF signs and symptoms. Given the variability in clinical manifestations across the three of NF subtypes, the impact on daily activities was analyzed separately for each group.

Patients with NF1 Plexiform neurofibromas (3.7), defects in the vertebrae or scoliosis (3.4), and cutaneous neurofibromas (3.2) were the clinical manifestations that impacted the most on Spanish patients. However, other less frequent manifestations, such as disabling pain (4.4),

Table 2 Age of patients at symptoms onset and at diagnosis according to neurofibromatosis type

Neurofibromatosis	Spain			Portugal		
	Patients, *n* (%)	Age at symptoms onset (mean), years (SD)	Age at diagnosis (mean), years (SD)	Patients, *n* (%)	Age at symptoms onset (mean), years (SD)	Age at diagnosis (mean), years (SD)
NF1	314 (92.4)	4.9 (8.3)	7.6 (10.3)	54 (93.1)	6.7 (9.1)	10.3 (12.7)
NF2-related SWN	23 (6.8)	21.6 (11.9)	25.0 (11.7)	4 (6.9)	23.5 (4.4)	19.0 (12.0)
Non-NF2-related SWN	3 (0.9)	16.0 (3.5)	18.7 (3.1)	0 (0.0)	–	–
Total	340 (100)	6.2 (9.5)	8.8 (11.3)	58 (100)	7.8 (9.8)	10.9 (12.7)

NF neurofibromatosis, *SD* standard deviation, *SWN* schwannomatosis

Table 3 Initial and current signs and symptoms and their impact evaluation in patients with NF1

Symptoms and clinical manifestations	Spain						Portugal					
	Initial		Current		Impact		Initial		Current		Impact	
	n	%	*n*	%	Mean	SD	*n*	%	*n*	%	Mean	SD
Clinical manifestations												
Café-au-lait skin spots	298	**94.90**	309	**98.41**	1.90	1.25	52	**96.30**	53	**98.15**	2.00	1.29
Freckles in the groin or armpits	110	35.03	233	**74.20**	1.64	1.11	18	33.33	33	61.11	1.76	1.28
Cutaneous neurofibromas	82	26.11	229	**72.93**	**3.19**	1.35	13	24.07	32	59.26	2.84	1.02
Lisch nodules	66	21.02	171	54.46	1.58	1.06	–	–	16	29.63	1.81	1.05
Plexiform neurofibromas	41	13.06	136	**43.31**	**3.65**	1.27	6	11.11	15	27.78	3.13	1.41
Defects in the vertebrae or scoliosis	33	10.51	111	**35.35**	**3.41**	1.31	–	–	13	24.07	3.15	1.28
Optic glioma	33	10.51	63	20.06	3.30	1.52	–	–	10	18.52	2.80	1.48
Facial asymmetry	8	2.55	21	6.69	3.43	1.40	–	–	6	11.11	3.83	1.47
Macrocephaly	12	3.82	26	8.28	2.96	1.46	–	–	9	16.67	1.67	0.71
Bowlegs	11	3.50	21	6.69	3.10	1.70						
Pseudoarthrosis	10	3.18	21	6.69	**4.19**	1.12						
Attention deficit disorder (with or without hyperactivity)	52	16.56	63	20.06	**4.17**	1.06	6	11.11	13	24.07	**4.00**	0.91
Difficulty in learning and intellectual ability	43	13.69	53	16.88	**4.17**	1.03	6	11.11	9	16.67	**4.33**	0.87
Migraine	39	12.42	52	16.56	3.69	1.25	6	11.11	8	14.81	**4.13**	0.83
Low height	28	8.92	36	11.46	2.56	1.32	–	–	6	11.11	3.33	1.37
Brain glioma	13	4.14	20	6.37	3.75	1.59	2	3.70	5	9.26	3.00	1.41
Speech retardation	15	4.78	20	6.37	3.15	1.31	–	–	7	12.96	**4.00**	1.00
Thoracic deformation	13	4.14	19	6.05	2.58	1.26	1	1.85	1	1.85	1.00	–
Precocious puberty	14	4.46	19	6.05	2.84	1.50						
Autism spectrum disorder	11	3.50	12	3.82	**4.08**	1.31						
Others‡	26	8.29	44	14.02	–	–	3	5.55	7	12.96	–	–
Symptoms, sequelae, or consequences												
Abdominal pain or associated bowel symptoms	16	5.10	26	8.28	3.54	1.21	0	0.00	1	1.85	3.00	–
Vision loss	18	5.73	20	6.37	**4.25**	0.91	2	3.70	4	7.41	**4.75**	0.50
Associated arterial hypertension	8	2.55	14	4.46	3.00	1.47	2	3.70	2	3.70	3.50	0.71
Disabling pain	6	1.91	12	3.82	**4.42**	0.67	2	3.70	2	3.70	**4.50**	0.71
Epilepsy	6	1.91	7	2.23	**4.14**	0.90	2	3.70	2	3.70	**4.00**	0.00

SD standard deviation

‡Others (current n, average impact score; Spain [S], Portugal [P]): delayed puberty (S: 12, 3.08; P: 1, 5.00), hydrocephalus (S: 10, 3.60; P: 2, 2.50), juvenile xanthogranuloma (S: 8, 2.63; P: 2, 2.50), moyamoya syndrome (S: 3, 2.00; P: 1, 4.00), breast cancer (S: 3, 3.00; P: 1, 5.00)

vision loss (4.3), pseudoarthrosis (4.2), attention deficit (4.2), and learning difficulty (4.2), also had a great impact. Similarly, Portuguese patients with NF1 were highly affected by musculoskeletal features (3.2) and plexiform neurofibromas (3.1), as well as less common manifestations such as sight loss (4.8), disabling pain (4.5), and difficulty in learning and intellectual ability (4.17) (Table 3).

Patients with NF2-related SWN Hearing loss (4.4) and bilateral vestibular schwannomas (4.3–4.8) and schwannoma in cranial and spinal nerves (4.3) were the most frequent and impacting clinical manifestations. However, less frequent manifestations such as genital or sphincter problems (5.0), chronic pain (4.6), retinal hamartomas (4.5), and unilateral vestibular schwannoma (4.4) had the highest impact on Spanish patients'lives. Paresis (5.0), hearing loss (5.0), and ependymoma (4.0) showed a great impact on Portuguese patients with NF2-related SWN, although these were only present in one patient (Table 4).

Patients with non-NF2-related SWN Disabling pain (5.0) and unilateral vestibular schwannomas (5.0) were the main clinical manifestations causing the greatest impact, followed by the presence of schwannomas

Table 4 Initial and current signs and symptoms and their impact evaluation in patients with NF2-related SWN

Symptoms and clinical manifestations	Spain						Portugal					
	Initial		Current		Impact		Initial		Current		Impact	
	n	%	*n*	%	Mean	SD	*n*	%	*n*	%	Mean	SD
Clinical manifestations												
Bilateral vestibular schwannomas	14	**60.87**	14	**60.87**	**4.29**	1.14	3	**75.00**	**4**	**100.00**	**4.75**	0.50
Schwannoma in cranial and spinal nerves	5	21.74	13	56.52	3.69	1.03	0	0.00	**3**	**75.00**	**4.33**	1.15
Meningiomas	7	30.43	13	56.52	3.31	1.25	0	0.00	**2**	50.00	3.50	0.71
Hearing loss	7	30.43	12	52.17	**4.42**	0.90						
Unilateral vestibular schwannomas	4	17.39	5	21.74	**4.40**	1.34						
Schwannoma in optic and peripheral nerves	2	8.70	5	21.74	3.80	1.64	0	0.00	1	25.00	3.00	-
Ependymoma	0	0.00	3	13.04	2.67	1.15	0	0.00	1	25.00	**4.00**	-
Plaque-like lesions or skin lesions	10	43.48	12	52.17	1.50	1.17						
Paresis	4	17.39	7	30.43	3.14	1.77	0	0.00	1	25.00	**5.00**	-
Epilepsy	6	26.09	7	30.43	3.14	1.46						
Intracranial hypertension	4	17.39	5	21.74	2.20	0.84						
Cataracts	3	13.04	5	21.74	1.20	0.45						
Attention deficit with hyperactivity	2	8.70	3	13.04	3.00	2.00						
Peripheral nerve palsy	1	4.35	2	8.70	2.50	2.12						
Retinal problems or hamartomas	1	4.35	2	8.70	**4.50**	0.71						
Symptoms, sequelae, or consequences												
Loss of balance	9	39.13	15	**65.22**	3.80	1.47	0	0.00	1	25.00	3.00	-
Hearing loss	7	30.43	12	52.17	**4.42**	0.90	0	0.00	1	25.00	**5.00**	-
Dizziness	10	43.48	10	43.48	3.10	1.45						
Tinnitus	7	30.43	8	34.78	3.63	1.19						
Frequent headache	5	21.74	8	34.78	**4.38**	0.74						
Associated muscle mass loss	4	17.39	6	26.09	3.17	0.75						
Chronic pain	4	17.39	5	21.74	**4.60**	0.55						
Associated genital or sphincteric disorders	1	4.35	2	8.70	**5.00**	0.00						

SD standard deviation

Table 5 Initial and current signs and symptoms and their impact evaluation in patients with non-NF2-related SWN

Symptoms and clinical manifestations	Initial		Current		Impact	
	n	%	*n*	%	Mean	SD
Clinical manifestations						
Schwannomas in cranial, spinal and peripheral nerves	2	66.67	3	100.00	**4.00**	1.00
Numbness or weakness in different body parts	0	0.00	3	100.00	**4.00**	1.00
Unilateral vestibular schwannoma	0	0.00	1	33.33	**5.00**	–
Symptoms, complications or sequels						
Chronic pain	1	33.33	3	100.00	3.67	0.58
Disabling pain	2	66.67	2	66.67	**5.00**	0.00
Associated muscle mass loss	0	0.00	1	33.33	3.00	–
Delocalized pain	–	–	0	0.00	–	–

SD standard deviation

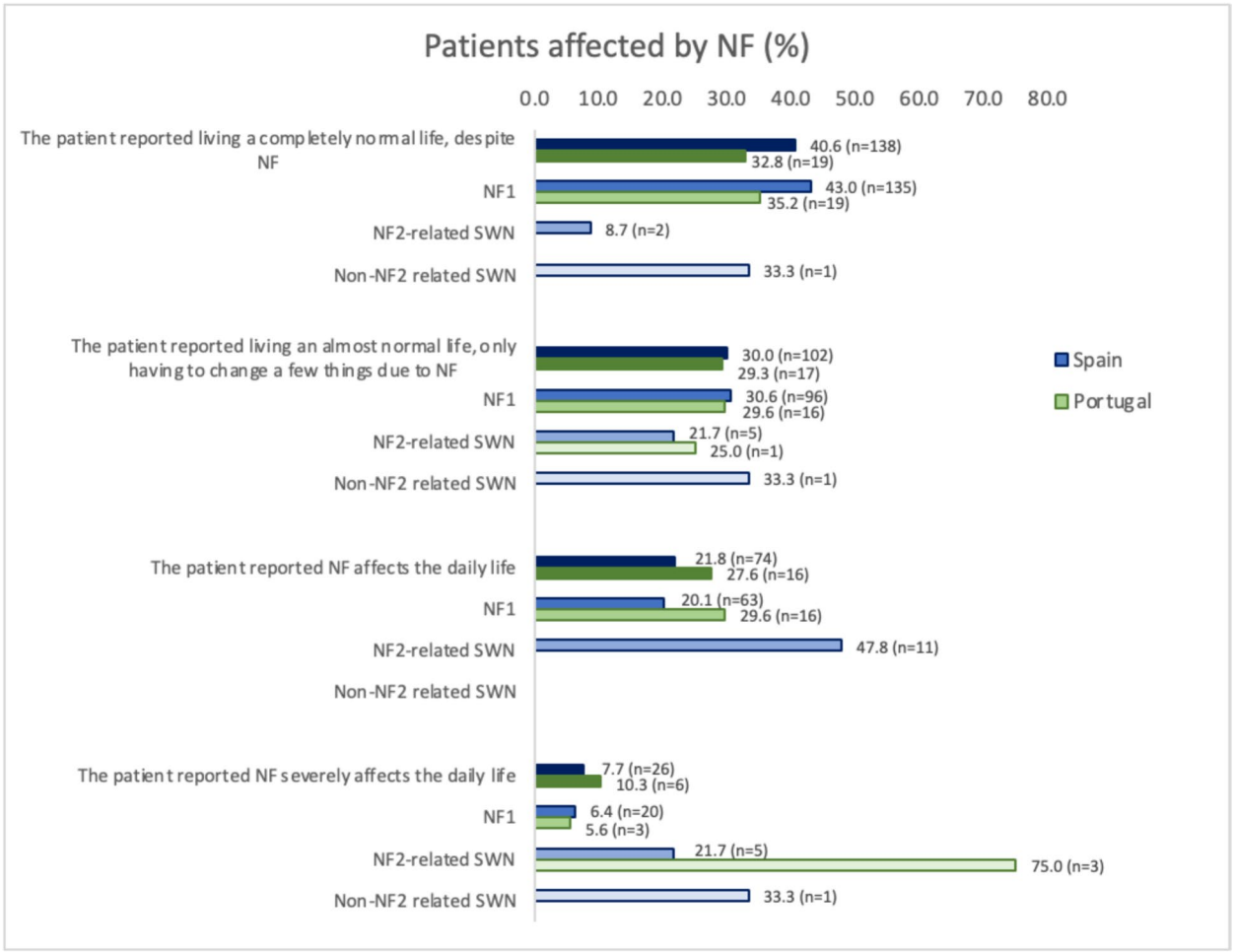

Fig. 1 Proportion of patients with NF with different degrees of impairment in their daily life due to the disease. NF: neurofibromatosis; SWN: schwannomatosis

in cranial, spinal, and peripheral nerves (4.0), weakness (4.0), chronic pain (3.7), and muscle mass loss (3.0) (Table 5).

Impact of the disease on daily activities

In general, 40.6% of Spanish patients and 32.8% of Portuguese patients reported living a normal or near-normal life despite NF (Fig. 1).

Patients with NF1 Over 40% of Spanish and over 35% of Portuguese patients with NF1 reported living a normal or almost normal life.

Patients with NF2-related SWN Nearly half of the Spanish patients (47.8%) reported that the disease affected their daily life, and 21.7% of Spanish and 75% Portuguese patients reported that their daily life was severely affected.

Patients withnon-NF2-related SWN The impact of the disease on regular activities was variable among the three Spanish patients with SWN, who reported a completely normal life (33.3%), almost a normal life (33.3%) and severely affected daily life (33.3%), respectively (Fig. 1).

Health-related quality of life

The overall score of the COOP/WONCA questionnaire was 17.04 for the Spanish patients and 17.24 for the Portuguese (7 = the best health status; 35 = the worst). Regarding questionnaire domains (1 = best; 5 = worst), the general health status was one of the most affected domains (Spain 2.91; Portugal 2.67), while daily activities were the less affected (Spain 1.84; Portugal 2.09) (Table 6).

Table 6 COOP/WONCA HRQoL scores in patients with NF

	Spain (*N* = 340)		Portugal (*N* = 58)	
Variable [range]	**Mean**	**SD**	**Mean**	**SD**
Index COOP/WONCA [7–35]	17.04	5.73	17.24	4.66
Health status	**2.91**	1.00	**2.67**	0.93
Health status change	2.87	0.66	2.95	0.63
Physical fitness	2.67	1.21	2.59	1.09
Feelings	2.52	1.27	2.74	1.26
Pain	2.21	1.34	2.12	1.08
Social activities	2.01	1.26	2.09	1.13
Daily activities	**1.84**	1.01	**2.09**	0.92
Type of neurofibromatosis				
NF1	16.59	5.59	17.00	4.54
NF2-related SWN	22.35	4.83	20.50	5.80
Non-NF2-related SWN	23.33	1.53	–	–

SD standard deviation, *SWN* schwannomatosis

The overall HRQoL score was 16.59 and 17.00 for Spanish and Portuguese patients with NF1, 22.35 and 20.50 for Spanish and Portuguese patients with NF2-related SWN, respectively, and 23.33 for patients with non-NF2-related SWN.

Emotional impact and feelings

Overall, 38.2% of the Spanish patients and 37.9% of the Portuguese reported needing psychological support. Of these, 77.7% and 86.4% received psychological support, with 43.4% and 42.1% had sought support on their own, respectively. Acceptance (36%) was the most frequent daily feeling among Spanish patients affected by NF, followed by uncertainty (29%), resignation (28%), and fear or worry (26%). In Portuguese patients, the most frequent feelings were fear or worry (45%) and acceptance (38%), followed by frustration (24%) and uncertainty (22%) (Supplementary Table S2).

Work or educational impact

Spanish and Portuguese patients with NF of working age reported difficulties accessing a job due to their disease (Spain 30.5%, Portugal 26.5%), while 39.9% and 35.3% had issues continuing their higher education studies, respectively. In addition, 25.9% among the Spanish and 24.1% Portuguese patients reported needing support from a social worker, and 77.3% and 71.4% received it (Supplementary Table S3).

Caregivers

Demographic characteristics

Spanish caregivers had a mean age of 40.1 years (74% women); almost all (96.2%) were the parents of the patients, and in most cases (94.2%) with no more than one patient in charge (Supplementary Table S4).

On the other hand, all Portuguese caregivers (mean age 44.2 years; 84.0% women) were the parents of the patients each responsible for a single patient (Supplementary Table S4).

Impact of neurofibromatosis on caregivers

Overall, 21.2% of Spanish and 27.6% of Portuguese patients reported depending on a family member or caregiver due to the NF symptoms.

Among the 154 Spanish caregivers who responded the questionnaire, 44.2% indicated the need for psychological care, and from those, 70.6% received it mostly from the private system (56.3%). Regarding the Portuguese caregivers, 36.0% indicated the need for psychological care, and 77.8% received it privately.

In addition, 12–17% and 4–8% of the Spanish and Portuguese caregivers, respectively, mentioned that they *always or almost always* felt that they had no time for themselves or their families, overburdened and limited in family activities (Supplementary Table S5). Moreover, 42.2% of the Spanish and 32.0% Portuguese caregivers stated that caring for the patient affected their work activity (Supplementary Table S6).

Disease management

Disease management in Spain

Use of healthcare resources

Patients with NF1. Among patients under 18 years of age, 34.22% were diagnosed with NF1 by paediatricians, whereas dermatology was the specialty that diagnosed the majority of NF1 cases in adults (Supplementary Fig. S1 A). The number of medical visits (same or different specialties) to reach the final NF1 diagnosis was 3.76 (SD 4.41). On average, participants reported attending their follow-up visits every 9.14 months (SD 6.65) (< 18 years old: every 6.82 months; ≥ 18 years old: every 10.56 months). The main specialties involved in the follow-up of NF1 patients were ophthalmology, dermatology, and paediatric neurology or neurology (Supplementary Fig. S2 A and Supplementary Table S7).

Patients with NF2-related SWN. Neurology was the speciality responsible for the diagnoses in both age ranges. followed by otorhinolaryngology and surgical specialities in the case of adult patients. Two paediatric patients were diagnosed by paediatric neurologists and oncologists (Supplementary Fig. S1B). For a final diagnosis, patients required an average of 3.74 (SD 2.60) visits. These patients attended their follow-up visits every 7.27 months (SD 5.15), which were mainly performed by otorhinolaryngology, neurology, surgery, and ophthalmology (Supplementary Fig. S2B and Supplementary Table S7).

Patients with non-NF2-related SWN. Two patients were diagnosed by a surgical speciality, while the third was diagnosed by neurology (Supplementary Fig. S3 C). The mean number of visits to obtain the final diagnosis was of 4.33 (SD 1.15). The follow-up visits of these patients were every 9.33 months (SD 3.06). Two patients were visited by internal medicine and surgery and the other by ophthalmology, primary care, and dermatology (Supplementary Fig. 2 C and Supplementary Table S7).

Therapeutical management of neurofibromatosis in Spain Approximately one-third (34.71%) of Spanish patients with NF had received pharmacological treatment since the onset of symptoms, while 25.59% were receiving treatment at the time of the study. Moreover, 63% of patients underwent surgery related to NF, with the mean number of surgeries per patient being 6.35 (SD 14.44). Concerning those patients with plexiform neurofibromas, 17.65% reported receiving specific drugs to treat symptoms or related complications, while 60.29% of the patients underwent surgery related to plexiform neurofibromas with a mean number of surgeries per patient of 3.18 (SD 2.68) (Supplementary Table S8).

Patient satisfaction with the healthcare system in Spain Most Spanish patients with NF (87.91%) were managed by the public health system. However, 38.8% occasionally used the private healthcare system to cover their needs.

Regarding the Spanish patients, the average satisfaction with the public healthcare system was > 3 points (1 = not at all satisfied; 5 = very satisfied) in all evaluated criteria except for psychological support (2.41) (Table 7).

Forty-nine percent (49%) stated that professionals managing them did *never or almost never* coordinate to schedule all follow-up visits on the same day, whereas 44% of the patients claimed that they were *always or almost always* informed about their disease and its treatment. Additionally, 46% of the patients reported that they *always or almost always* received guidelines on how to manage symptoms such pain and skin irritation (Supplementary Fig. S5 A).

Table 7 Satisfaction with Spanish and Portuguese healthcare

	Spain ($n = 340$)		Portugal ($n = 58$)	
Satisfaction	**Mean**	**SD**	**Mean**	**SD**
Diagnosis	3.56	1.36	4.34	0.93
Empathy from healthcare professionals	3.47	1.32	4.19	1.10
Disease follow-up	3.44	1.37	4.05	1.03
Referrals among medical specialities	3.42	1.34	3.97	1.15
Disease management, in general	3.27	1.32	3.88	1.17
Information received about NF and its treatment	3.13	1.41	3.83	1.39
Psychological support	2.41	1.44	3.47	1.39

NF neurofibromatosis, *SD* standard deviation

Disease management in Portugal

Use of healthcare resources

Patients with NF1. Similar to the situation in Spain, paediatricians diagnosed 38.5% of NF1 cases in patients under 18 years old, while dermatology was the specialty diagnosing most NF1 cases in adults (Supplementary Fig. S3 A). The mean number of medical visits for a final diagnosis was 2.43 (SD 1.79). These patients reported a mean frequency of follow-up medical visits of 6.80 months (SD 5.41) (< 18 years old: every 6.42 months; ≥ 18 years old: 7.15 months), and the main specialties involved were ophthalmology, neuropediatric and dermatology (patients aged < 18), while most of the patients over 18 years old were followed up by neurologists (69.0%) (Supplementary Fig. S4 A and Supplementary Table S7).

Patients with NF2-related SWN. One patient under 18 was diagnosed by neurology, while otolaryngologists, physicians and surgery specialties diagnosed the other adult patient, (Supplementary Fig. S3B). One (SD 0.00) visit was required to reach a final diagnosis. These patients were followed up every 2.00 months (SD 2.71) by otorhinolaryngologists and neurologists (Supplementary Fig. S4B and Supplementary Table S7).

Therapeutical management of neurofibromatosis in Portugal Regarding pharmacological treatment, 43.10% of Portuguese patients had received treatment since the onset of symptoms, while 34.48% were receiving it at the time of the study. In addition, 43.10% of the participants had undergone surgery, with a mean number of surgeries per patient of 3.32 (SD 2.76). Finally, 40.00% of the patients with plexiform neurofibromas received specific treatment, and 66.67% had plexiform neurofibroma-related surgery with a mean number of surgeries per patient of 2.00 (SD 0.00) (Supplementary Table S8).

Patient satisfaction with the healthcare system in Portugal Most Portuguese patients with NF (84.48%) were managed within the public healthcare system, although 46.94% of them had sought private healthcare services. The average satisfaction of Portuguese patients exceeded 3 points out of 5 in all areas of health care evaluated, with diagnosis being the main subject they were most satisfied with (4.34) and the psychological support, the least (3.47) (Table 7 and Supplementary Fig. S5).

Fifty-nine percent (59%) stated that professionals managing them did *always* or *almost always* coordinate to schedule all follow-up visits on the same day, and 71% of the patients claimed that they were *always or almost always* informed about their disease and its treatment. Moreover, 64% of the patients reported that they *always or almost always* received guidelines on how to manage symptoms such pain and skin irritation (Supplementary Fig. S5B).

In general, patients in Portugal were more satisfied with the healthcare system than in Spain.

Discussion

The existing literature provides valuable insights into the demographic and clinical characteristics of individuals affected by NF1, as well as the broad impact of the disease on both patients'physical and psychological well-being, and quality of life (QoL) of patients and their caregivers. However, there is a need for country-specific studies to gain a deeper understanding of regional variations in the manifestations and characteristics of NF1, healthcare system management as well as the unique needs of patients and their families. A recent study from India confirms that, similar to findings in Western countries, NF1 significantly affects patients' QoL due to changes in their appearance and the societal stigma associated with the condition. This study also highlights that even patients with relatively fewer lesions can experience a drastic decline in their QoL, emphasizing the importance of addressing mental health concerns for all patients, regardless of the extent of their lesions [25].

Moreover, other research suggests that the severity of NF1 and the associated disability may not always correlate with poor mental health outcomes [42]. In addition, deficits in social cognition have been observed in adults with NF1, potentially contributing to their social difficulties [26]. On the other hand, specialists in Germany and Austria, while advocating for guidelines to standardize clinical management for adults with NF1 through a multidisciplinary approach [43, 44], emphasize the need to strike a balance between providing meaningful diagnostic evaluations for certain patients and limiting extensive diagnostic efforts for others, depending on their specific needs. Thus, systematic surveillance efforts should be based on strong evidence, with careful consideration of their potential impact on both patients and the healthcare system. A similar focus on multidisciplinary surveillance and personalized care for NF1 patients has been highlighted in studies conducted in Gulf Cooperation Council countries [28]. Despite these efforts, NF1 continues to impose a significant economic burden, underscoring the ongoing need for more effective treatments [27].

Given the complexity of NF1, it is essential to further explore the diverse ways in which the disease impacts individuals on a daily basis, as well as the challenges faced by families providing care to NF1 patients across different countries and regions. The results of our study provide a comprehensive overview of NF management in Spain and Portugal. The data presented delineate the sociodemographic and clinical characteristics of people affected by NF, examining the disease impact on daily functioning and the challenges faced by caregivers. This enhances our understanding of the diverse manifestations of NF and provides a valuable resource for improving patient care and disease management strategies. The inclusion of people affected by NF from Spain and Portugal provides valuable insights into the idiosyncrasies and real-word experiences in both countries, enriching the existing evidence from other regions.

Overall, most participants had NF1, while NF2-related and non-related SWN were less represented, showing a similar distribution to that found in the literature [3]. Previous studies have reported fewer participants with NF1 compared to our results [45, 46], probably due to a more restrictive inclusion criteria. Only adult patients over 18 years of age participated in those studies, and the inclusion of caregivers was not considered, even though NF1 is often diagnosed during childhood.

Generally, a wide range of clinical manifestations differ depending on the NF type. According to the participants, the most frequent clinical manifestations of NF1 had less impact on their daily lives than those associated with NF2-related and non-related SWN. Patients with mild NF1 can have a reasonable life expectancy. However, patients with moderate to severe disease have a poor HRQoL, which is highly related to the visible and nonvisible symptoms that contribute to stigma, negatively affecting self-image, social interactions, employment, and intimate relationships, particularly among women [47, 48]. In fact, those with NF1 who suffer from pain, vision loss, pseudarthrosis, learning difficulties or consequences such as epilepsy have their daily life considerably affected, in line with what has been previously described in the literature [47]. On the other hand, genital or sphincter disorders reported by NF2-related SWN patients and schwannomas reported

by non-related NF2 SWN patients greatly impacted their daily lives. Furthermore, it has been recently published that patients with NF2-related SWN who present facial weakness, hearing loss, and imbalance showed significantly lower HRQoL, led mainly by increased levels of disease-related anxiety, personal and financial stress, and lack of social support [49].

It is worth noting that approximately 73% of Spanish and 59% of Portuguese participants with NF1 in our study presented cutaneous neurofibromas, a clinical manifestation that usually affects all patients with NF1 [50]. A previous European survey performed among a population with cutaneous neurofibromas confirmed that the visible stigma and appearance significantly impact patients' quality of life [51]. The difference observed between the Spanish and the Portuguese populations in our study could be attributed to the younger age of the participants, since cutaneous neurofibromas usually develop during adolescence and increase with age [52]. Given that this clinical manifestation scored highly in our study for its impact on daily life, its later onset may explain the variation observed between the populations of both countries.

In general, patients with NF present an impaired HRQoL, worse than the HRQoL observed in other pathologies, such as type 2 diabetes (18.7) [53] or those related to haemodialysis (18.89) [54]. Similarly, previous systematic reviews have shown that HRQoL, as assessed through other generic questionnaires, is worse in patients with NF compared to the general population [7, 10]. In our study, the assessment of HRQoL showed a higher score (worse quality of life) in the COOP/WONCA quality of life scale for Spanish and Portuguese patients with NF2-related (22.35 and 20.50) and non-related SWN (23.33) compared to the patients with NF1 (16.59 and 17.00) [40].

Despite the challenges faced by patients with NF in work and academic settings, the need for psychological support (38%), and the high proportion of patients who have undergone surgery (63% in Spain and 43% in Portugal), with an average of 6.35 surgeries in Spain and 4.5 in Portugal, 70% of Spanish and 60% of Portuguese participants reported living a "completely normal" or "almost normal" life, even in cases of NF1. This could be explained, at least in part, due to the early onset of the disease, especially for those affected by NF1, and the mean age of the participants at the time of the study (26–43 years old, depending on the type of NF). Patients had been living with the disease for over 20 years when responding to the questionnaire and probably had accepted their situation. Moreover, when participants were asked about the daily impact of NF regarding their feelings or emotions, acceptance, resignation and fear/worry were three of the most frequently described.

In our study, 21% and 28% of Spanish and Portuguese participants reported depending on a family member due to NF. In this context, it was observed that 42% and 32% of the Spanish and Portuguese caregivers consistently reported feeling overburdened, with little to no time for themselves or their families. Many expressed that their caregiving responsibilities significantly limited their participation in family activities. Furthermore, they indicated that providing care for the patient had a direct impact on their professional lives, often affecting their ability to maintain regular work activities. Despite this, most caregivers did not report excessive burden or limited family time, perhaps due to feelings of guilt or to prior adjustments, such as reducing their working hours. The data available in the literature on this matter is scarce. A previous interview study including patients with NF1 reported that the disease could be considered a "family thing", where patients find support in other family members, especially if they are also affected by this condition [55]. However, family functioning could be greatly impacted as the disease brings worry or guilt about the affected family members and future children [56]. These findings highlight the substantial emotional, social, and economic burden faced by caregivers and underscore the need for targeted support interventions to alleviate their strain.

Regarding NF management, the data from our study reveal that over 10 medical specialties were involved in diagnosing patients with NF in both countries. Neurology, ophthalmology, and dermatology diagnosed most adult patients and paediatrics for children. However, there are differences by type of neurofibromatosis and age (paediatric vs adult). That highlights the importance of a multidisciplinary approach for correctly diagnosing and managing NF as previously reported [57, 58]. Most patients were treated in the Spanish and Portuguese public health systems, although approximately 40% and 47% reported resorting to private care. A previous study showed that care needs increased with patients turning 18. Moreover, problems related to communication or organization of follow-up arose during the transition to adult health care [59]. That and the multidisciplinary approach required for NF could explain the necessity of seeking assistance in private care observed in our study. In fact, both Spanish and Portuguese patients showed satisfaction levels in different aspects of the healthcare slightly over 3, which manifests that they were not completely satisfied with the management of the disease in the public health system. Future research in NF should focus on developing individualized management strategies that address both tumour burden and overall quality of life [12]. Current treatment options are limited, with only one FDA-approved therapy for NF1 and none for NF2 or schwannomatosis, highlighting the need for novel therapies [18]. However,

given the complexity of NF signalling pathways, combination therapies may be required [18]. On the other hand, while surgery remains the standard for symptomatic tumours, non-surgical approaches, including pharmacological and MBTs, have shown potential benefits [14, 46, 60, 61]. MBTs have demonstrated improvements in physical, social, and environmental quality of life in NF patients and may serve as a complementary strategy for chronic NF management [14, 62, 63]. Additionally, multidisciplinary care, supported by programs like the Neurofibromatosis Therapeutics Program (NTP), is essential for comprehensive patient management [64]. Finally, further investigation into the tumour microenvironment, developmental risk periods, and factors influencing multiple tumour formation is crucial for advancing effective treatments, particularly for NF2 and schwannomatosis [18].

This study had limitations inherent to its cross-sectional, observational nature. We were not able to establish causality, and the study lacked temporality. Moreover, the differences between the Spanish and Portuguese health systems could significantly affect the management of patients with NF, particularly in terms of access to specialized care, financial burden, and coordination of services, impacting their satisfaction with the healthcare system. The results are based on an ad hoc questionnaire explicitly designed by a scientific committee but were not validated. The questions included were closed-ended, which may complicate the interpretation of participants' perceptions. Additionally, the COOP/WONCA questionnaire is not specific for patients with NF, and questions refer to the last 2 weeks. In this regard, using a different, more global questionnaire could result in different outcomes. The sample size was calculated for the entire population with NF, not for each pathology subgroup. Therefore, because our sample reflects the natural distribution of the pathology, only three Spanish patients with non-related-NF2 SWN and none from Portugal participated. Moreover, given that NF1 is a rare disease, as well as other forms of neurofibromatosis such as NF2-related SWN and non-NF2-related SWN, the expected number of subjects included in this study is limited; therefore, we do not anticipate having a sufficiently large sample size to detect significant differences among the different types of NF and only a descriptive analysis was conducted. However, the information provided on each type of NF can still be valuable for enhancing and expanding the understanding of these conditions.

In this context, it is important to mention that the required minimum sample size was not reached for the Portuguese population, and thus, conclusions should be taken with caution. However, despite this limitation, the overall results from the Portuguese participants are similar to those from the Spanish participants.

Regarding the study population, participants belonged to a patient advocacy group, which may differentiate their profile from that of the general population with NF. Their involvement in such organizations suggests that they may be more engaged in managing their condition and have greater access to support and coping resources. Thus, their perception of the impact on their quality of life might be biased. On the other hand, patients with less impairment may be overestimated, as those with more severe symptoms or cognitive impairment might not have participated. Finally, clinical data were not directly collected from the medical records but were patient-reported. Despite the state limitations, our sample included representation from all regions of Spain and Portugal. Thus, we believe that our findings accurately reflect the current situation of NF in both countries.

Conclusion

The results of the present study provide highly information to gain an overview of the NF patient's profile in Spain and Portugal and the impact of the disease not only on their daily life but also on those of their caregivers. Therefore, our study can aid in implementing strategies to optimize NF management, improve the quality of care, and, consequently, improve the quality of life of patients and their caregivers.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44162-025-00089-8.

Supplementary Material 1: Table S1. Relatives with NF of Spanish participants. Table S2. Patients' emotions and feelings concerning NF. Table S3. Work and educational impact of neurofibromatosis on Spanish and Portuguese participants. Table S4. Caregivers'socio-demographic characteristics. Table S5. Impact of NF on caregivers. Table S6. Caregivers' work impairment concerning NF. Table S7. Frequency of medical visits. Table S8. Clinical management of NF. Figure S1. Medical specialities involved in the diagnosis of Spanish patients with NF1 (A), NF2-related (B) and non-NF2 related SWN (C). NF: neurofibromatosis; SWN: schwannomatosis. Figure S2. Medical specialities involved during the follow-up of Spanish patients with NF1 (A), NF2-related (B) and non-NF2 related SWN (C). NF: neurofibromatosis; SWN: schwannomatosis. Figure S3. Medical specialities involved in diagnosing Portuguese patients with NF1 (A) and NF2-related SWN (B). NF: neurofibromatosis; SWN: schwannomatosis. Figure S4. Medical specialities involved during the follow-up of Portuguese patients with NF1 (A) and NF2-related SWN (B). NF: neurofibromatosis; SWN: schwannomatosis. Figure S5. The frequency (%) with which Spanish (A) and Portuguese (B) participants have identified different issues related to the management of NF.

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Authors' contributions

All the authors contributed equally to the work.

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Data availability
Data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted following the Declaration of Helsinki and is consistent with Good Pharmacoepidemiology Practices. The University Hospital Germans Trias i Pujol and Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG) Clinical Research Ethics Committees evaluated and approved the study. Written informed consent was obtained from all participants in the focus group and the study.

Consent for publication
Not applicable.

Competing interests
LG and AR are employees of AstraZeneca Rare Diseases Unit.
JLV, JP, AA, AEP, LBP and IB declare no conflicts of interest.

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