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Pierre Wolkenstein, Yves Chaix, Natacha Entz Werle, Mona Amini-Adle, Sébastien Barbarot, Christine Boileau, Anissa Miled, Talha Rashid, Isabelle Aerts

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French cohort of children and adolescents with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas: CASSIOPEA study

Pierre Wolkenstein [a,*], Yves Chaix [b], Natacha Entz Werle [c], Mona Amini-Adle [d], Sébastien Barbarot [e], Christine Boileau [f], Anissa Miled [g], Talha Rashid [f], Isabelle Aerts [h]

[a] Department of Dermatology, Henri-Mondor Hospital, APHP, UPEC, Créteil, France
[b] Children's Hospital, Toulouse-Purpan University Hospital, Toulouse, France
[c] Pediatric Onco-Hematology Unit, University Hospital of Strasbourg, Strasbourg, France
[d] Department of Dermatology, CLCC Léon Bérard, Lyon, France
[e] Department of Dermatology, CHU Nantes, Nantes, France
[f] AstraZeneca, Paris, France
[g] Alexion, AstraZeneca Rare Disease, Paris, France
[h] Oncology Center SIREDO, Institut Curie, Paris, France

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ABSTRACT

Surgery is a treatment option for neurofibromatosis type 1 (NF1)-related plexiform neurofibromas (PN), but complete resection is often not feasible. Real-world studies are warranted to understand disease burden, progression, and need for medical treatment in patients with inoperable PN.

CASSIOPEA was a retrospective study of French pediatric patients (aged ≥3 to <18 years) presenting at a national multidisciplinary team (MDT) review with NF1 and ≥1 symptomatic, inoperable PN. Medical records were reviewed from the time of MDT review and over a follow-up period of up to 2 years. Primary objectives were to describe patient characteristics and target PN-associated therapy patterns. A secondary objective was evolution of target PN-related morbidities. Patients with prior, ongoing, or MDT recommendation of mitogen-activated protein kinase kinase (MEK) inhibitor treatment were excluded.

Overall, 78 target PN were identified in 76 patients. At MDT review, median age was 8.4 years, with approximately 30% of patients aged 3–6 years. Target PN were primarily internal (77.3%), and 43.2% were progressive. Target PN location was evenly distributed. 34 target PN had documented MDT recommendations; of these, a majority (76.5%) were for non-medication management, including surveillance. At least one follow-up visit was recorded for 74 target PN. Despite initially being considered inoperable, 12.3% of patients underwent surgery for target PN. At MDT review, most (98.7%) target PN were associated with ≥1 morbidity, primarily pain (61.5%) and deformity (24.4%); severe morbidities were identified in 10.3%. Of 74 target PN with follow-up data, 89.2% were associated with ≥1 morbidity, primarily pain (60.8%) and deformity (25.7%). Of 45 target PN associated with pain, pain improved in 26.7%, was stable in 44.4%, and deteriorated in 28.9%. Deformity improved in 15.8% and remained stable in 84.2% of 19 target PN associated with deformity. None deteriorated.

In this real-world study in France, NF1-PN disease burden was considerable, and a considerable proportion of patients were very young. Most patients received only supportive care without medication for target PN management. Target PN-related morbidities were frequent, heterogeneous, and generally did not improve during follow-up. These data highlight the importance of effective treatments that target PN progression and improve disease burden.

1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by germline mutations in the *NF1* tumor suppressor gene (17q11.2) resulting in dysregulation of the RAS/RAF/MEK/ERK pathway involved in cell proliferation and survival (Gutmann et al.,

* Corresponding author. Henri-Mondor Hospital, APHP, University Paris Est Créteil, 94010, Créteil Cedex, France.
E-mail address: pierre.wolkenstein@aphp.fr (P. Wolkenstein).

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2017; Yap et al., 2014). Although NF1 is considered a rare disease, it is one of the most common genetic disorders globally: NF1 prevalence ranges from approximately 1 in 3000–6000 people worldwide (Evans et al., 2010; Gutmann et al., 2017; Orraca et al., 2014; Uusitalo et al., 2015). NF1 is a progressive disease, which may lead to life-changing morbidities, impairment of health-related quality of life (QoL), an increased risk of cancer and cardiovascular disease, and a ~10–15-year lower life expectancy than the general population (Doser et al., 2020; Fjermestad et al., 2018; Friedman, 2002; Gutmann et al., 2017; Hamoy-Jimenez et al., 2020; Korf, 2000; Tonsgard, 2006; Uusitalo et al., 2015, 2016; Yang et al., 2022).

Plexiform neurofibromas (PN) are a common manifestation of NF1 (Tonsgard et al., 1998). PN are benign nerve sheath tumors that develop in up to 50% of patients with NF1, can grow rapidly, and may undergo malignant transformation in 8–15.8% of cases (Evans et al., 2002; Jett and Friedman, 2010; Mautner et al., 2008; Nguyen et al., 2012; Tonsgard et al., 1998; Uusitalo et al., 2016). PN may cause substantial complications, such as pain, airway obstruction, visual impairment, spinal cord compression, loss of mobility, sphincter/bladder dysfunction, hemorrhage, and disfigurement (Gross et al., 2020; Gutmann et al., 2017; Jett and Friedman, 2010; Prada et al., 2012).

PN may invade and surround nerves, blood vessels, and organs, which makes surgical resection challenging or impossible without risk of significant morbidity (Canavese and Krajbich, 2011; Mautner et al., 2006; Nguyen et al., 2013; Prada et al., 2012). Moreover, even for pediatric patients who are able to undergo challenging surgery, partially resected PN often regrow (43–44% of cases) and symptoms may not be relieved in about one-third of patients (Canavese and Krajbich, 2011; Needle et al., 1997; Nguyen et al., 2013; Prada et al., 2012). Until recently, supportive care (symptom management) and surgical resection were the only management strategies available for symptomatic PN (Gutmann et al., 2017). Thus, patients with NF1 and symptomatic, inoperable PN represent a substantial unmet medical need. Mitogen-activated protein kinase kinase (MEK) inhibitors have been used off-label to a limited extent in France since 2018, but it is only recently (EMA) that a MEK inhibitor (selumetinib; ARRY-142886, AZD6244) has been approved in the EU for pediatric patients (aged ≥3 years) with NF1-PN (2021). The approval of selumetinib was based on clinical trial evidence from the pivotal phase 2 SPRINT study conducted in the United States of America (USA) (Gross et al., 2020).

In France, the management of patients with rare diseases, such as NF1, is under the coordination of reference rare disease centers, and is guided by mandatory French clinical practice guidelines for rare diseases (Bergqvist et al., 2020; NEUROFIBROMATOSES, 2021). The care of clinically complex NF1 cases involves national multidisciplinary review meetings comprising a committee of experts (multidisciplinary team [MDT] review, known in France as Réunion de Concertation Pluridisciplinaire [RCP]) (NEUROFIBROMATOSES, 2021). The objective of the MDT review meetings is to discuss and identify the optimal individualized management strategy for each patient with NF1.

Real-world studies involving patients with NF1 are useful for assessing disease burden and progression with supportive care, and for understanding the need for medical treatment in routine clinical practice. Therefore, the retrospective CASSIOPEA study was conducted to describe the demographic and clinical characteristics and therapeutic patterns in a French cohort of pediatric patients with NF1 and symptomatic, inoperable PN in the absence of treatment by MEK inhibitors.

2. Materials and methods

2.1. Study design

This was a retrospective study of French children with NF1 and at least one symptomatic, inoperable PN, who were referred to a specialist NF1 center, or whose case underwent MDT review, between January 1, 2013, and December 31, 2019. Specialist NF1 centers were contacted via email and/or phone call. The national MDT review meeting could have included different specialties (e.g., neurologists, geneticists, pediatricians, surgeons, oncologists, radiologists, or neuroradiologists) depending on the individual NF1 case.

The primary objective of CASSIOPEA was to describe NF1 patient characteristics and treatment patterns in the absence of MEK inhibitors. Secondary objectives were to evaluate the number of pediatric patients with NF1 and inoperable and symptomatic PN at the time of national MDT review in France, to describe the evolution of morbidities related to target PN from initial MDT review and up to 2 years of follow-up, and the overall response rate of current standard of care in target PN.

2.2. Patients

Inclusion criteria were pediatric patients (aged ≥3 to <18 years) diagnosed with NF1 and with at least one measurable PN of at least 3 cm in one dimension who were referred to a specialist NF1 center or whose case underwent national MDT review, with confirmation that the symptomatic PN was inoperable. A key exclusion criterion was prior or ongoing treatment with a MEK inhibitor, or if it was recommended at the national MDT review that the patient start treatment with a MEK inhibitor (this would have constituted off-label use within the study timeframe), as CASSIOPEA aimed to provide information on natural history of NF1. Patients were also excluded if there was evidence of optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring chemotherapy or radiation therapy, or if they were opposed to data collection.

The study population comprised all patients who met the inclusion and exclusion criteria and for whom the treatment plan for the target PN was defined during national MDT review. Data were collected from when a patient underwent national MDT review (this corresponded to the date when the MDT reviewed a pediatric patient with NF1 presenting with a symptomatic PN) and, subsequently, up to 2 years of follow-up (at 6, 12, and 24 months, if available).

2.3. Data collection and analysis

Demographic, clinical, and imaging data (if available), including PN volume (if available), and the evolution of morbidities associated with the target PN from the time of national MDT review and over a follow-up period of 2 years were extracted from patient medical records. Patients were not required to attend any additional visits, nor undergo specific additional examination nor intervention. Data were collected into study-specific paper case report forms and were then entered into an electronic database.

The target PN was defined as the most clinically relevant PN; for example, the largest and/or most symptomatic at the time of the national MDT review. Selection of target PN was at the discretion of the investigator. Target PN response to treatment was planned to be evaluated using volumetric MRI imaging analysis and evolution of target PN-associated morbidities. Target PN was defined as progressive according to physician assessment, as described in patients' hospital records. To describe the evolution of target PN-associated morbidities, morbidities were rated on a three-point categorical scale (improvement, no change, or deterioration) at each follow-up visit and compared with initial national MDT review or the last available follow-up. Morbidities were considered PN-related according to physician assessment in hospital records, and improvement or worsening of these were defined by physician interpretation. Emergence of a new morbidity was considered to be deterioration.

2.4. Statistical analysis

No formal hypothesis testing was undertaken and hence no formal statistical tests were performed. For the descriptive statistics, analyses were performed using SAS® version 9.2 or higher (SAS Institute, Cary,

NC, USA). Descriptive statistics were either qualitatively or quantitatively summarized depending on the nature of the variables of interest. No imputation procedure of missing data was applied.

2.5. Ethics

As this was a retrospective and non-interventional study on secondary data, approval from an ethics committee was not required. The study was submitted to the Health Data Hub website (https://www.health-data-hub.fr/). However, the study was conducted in adherence with the ethical principles stated in the Declaration of Helsinki amended version (Fortaleza, Brazil, October 2013), and according to the ethics recommendations and Good Epidemiological Practices French version 2007 and applicable regulations.

Patients who were pre-identified by participating sites and were still alive at the time of study initiation were informed of the study and provided with a patient/legal representative information note. If the patient or their legal representative did not forbid the use of their personal data for research purposes within 3 weeks from the date of notification, data collection was performed on site by the International Clinical Trial Association's local study site coordinators or the centers' Clinical Research Associate under the responsibility of the site investigator. For patients who had died before the start of data collection, data were collected unless the patients or their family had expressed to the center their refusal for data collection before they died.

3. Results

3.1. Patients

Retrospective data were identified and collected between April 9 and June 23, 2021. A total of 37 centers in France were invited to participate; 25 centers accepted the invitation and 19 provided data for at least one patient (Supplementary Fig. 1). The earliest national MDT review identified in the records was March 19, 2013, and the most recent one was November 27, 2019. Medical records of 149 potentially eligible patients were screened, of which 76 patients (51%) met the inclusion criteria. Two patients underwent MDT review twice, at different times, for two PN and were included twice in the analysis in order to capture patient and target PN characteristics at each separate MDT review; thus, the study population was comprised of 78 patients. In the study population, 74 patients had available data from at least one follow-up visit.

3.2. Patient demographics and characteristics at MDT review

At national MDT review of the study population (N = 78), 50% of patients were female and the median age was 8.4 years (Table 1). The median age at diagnosis of NF1 was 3.7 years, and the median time between diagnosis and national MDT review was 3.4 years. Patients aged 3–6 years were the most represented age group at national MDT review (29.5%).

All patients met NF1 diagnostic criteria. Diagnosis criteria were retrieved from the medical records of 70 patients out of the 78 in the study population (89.7%) (at least two National Institutes of Health [NIH] criteria [1987] confirming diagnosis of NF1) (Neurofibromatosis, 1987). The most frequent NIH criteria were at least six café-au-lait macules (97.0%), at least two neurofibromas of any type or one PN (85.5%), and freckling in axillary or inguinal regions (63.2%). For the remaining patients (10.3%), NF1 diagnosis was confirmed by investigators, but NIH diagnosis criteria could not be retrieved from medical records.

At the time of national MDT review, 60 patients (76.9%) in the study population had morbidities related to NF1 overall, in addition to just those related to NF1-PN, the most common of which were pain (30/78, 38.5%), cognitive and behavioral deficits (25/78, 32.1%), scoliosis (14/78, 17.9%), and language disorders (3/78, 3.8%). In 11 patients (14.1%), these NF1-related morbidities not related to PN were severe (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3), including scoliosis in five patients (6.4%), pain in four patients (5.1%), cognitive and behavioral deficits in three patients (3.8%), fatigue in one patient, and syncope in one patient.

Table 1
Demographic and clinical characteristics of patients at the time of national MDT review (N = 78).[a]

Characteristic	Study population (N = 78)
Sex, n (%)	
Female	39 (50.0)
Male	39 (50.0)
Age at national MDT review, years, median (range)	8.4 (3.1–17.8)
Age at national MDT review, years, by category, n (%)	
3–<6	23 (29.5)
6–<9	18 (23.1)
9–<12	16 (20.5)
12–<15	13 (16.7)
15–<18	8 (10.3)
Age at NF1 diagnosis, years, median (range)	3.7 (0–15.7)
Time since NF1 diagnosis, years, median (range)	3.4 (0–15.8)
Patients with ≥2 NIH diagnostic criteria at the time of diagnosis,[b] n (%)	70 (89.7)
≥6 café-au-lait macules, %	97.0
≥2 neurofibromas or 1 PN, %	85.5
Freckling in axillary or inguinal regions, %	63.2
First-degree relative with PN, %	45.5
≥2 Lisch nodules, %	18.9
Optic glioma, %	13.3
Distinctive osseous lesion, %	10.2
Number of PN per patient,[c] n (%)	
1	67 (85.9)
2	8 (10.3)
≥3	3 (3.8)
Age at first PN appearance, years, median (range)	4.2 (0–16.9)
Time between target PN appearance and study inclusion, years, median (range)	2.4 (0–15.6)

MDT, multidisciplinary team; NF1, neurofibromatosis type 1; NIH, National Institutes of Health; PN, plexiform neurofibroma.

[a] Two patients underwent MDT review twice, at different times, for two PN and were included twice in the analysis in order to capture patient and target PN characteristics at each MDT review.

[b] NIH 1987 criteria.

[c] For the two patients who underwent MDT review twice for two different target PN at different times, individual data are not available to identify which category these patients were counted in.

3.3. Characteristics of PN at national MDT review (study inclusion)

The median age at appearance of the first PN was 4.2 years, and the median time between appearance of the first PN and national MDT review was 2.4 years (Table 1). At the time of national MDT review, each patient presented with a median of one PN (range one to four) (Table 1). Most patients (67/78, 85.9%) in the study population had one PN, eight patients (10.3%) had two PN, and three patients (3.8%) had three or more PN.

There were 78 documented target PN among 93 PN for the study population (N = 78) at national MDT review. The majority of target PN (58/78, 77.3%) were internal and their location was evenly distributed throughout the body (Table 2). Among the 78 target PN, 33 (42.3%) involved the trunk alone or with extension into the neck or extremity, 28 (35.9%) involved the extremities alone or with extension into the trunk, and 27 (34.6%) involved the head alone or with extension into the neck (Table 2).

Of 78 target PN, 76 (97.4%) were considered inoperable, and operable status of two (2.6%) target PN were unknown. Among 78 target PN, 32 (41.0%) had progressive growth, 29 (37.2%) were non-progressive, and there was insufficient data to categorize the remaining 13 PN

Table 2
Characteristics of target PN in the study population at the time of national MDT review.

Characteristic, n (%)	Target PN (N = 78)
PN type	
Internal	58 (77.3)
External	11 (14.7)
External and internal	6 (8.0)
Missing	3 (3.8)
PN location	
Extremity	18 (23.1)
Trunk	16 (20.5)
Head	15 (19.2)
Head-neck	12 (15.4)
Trunk-extremity	10 (12.8)
Neck-trunk	7 (9.0)
Inoperable	
Yes	76 (97.4)
No	0
Unknown	2 (2.6)
Progression status	
Progressive	32 (41.0)
Non-progressive	29 (37.2)
Unknown	13 (16.7)
Missing	4 (5.1)

MDT, multidisciplinary team; PN, plexiform neurofibroma.

(16.7%) (Table 2). One target PN had transformed into a malignant peripheral nerve sheath tumor, but did not require treatment with chemotherapy or radiotherapy, and so was not excluded from the study. Imaging data of target PN were available for 60 patients, but PN volume was quantified in only two patients at national MDT review (1.0 and 231.0 mL, respectively). Response rate to treatment could therefore not be evaluated as per one of the planned secondary endpoints of this study.

3.4. Management history prior to national MDT review

At the time of national MDT review, 51 patients (65.4%) in the study population had a documented history of at least one surgical procedure or medical treatment. A total of 14 patients (17.9%) had undergone curative complete surgical resection for a PN as part of their management history.

Medical treatments at the time of national MDT review included analgesics (11/78, 14.1%), mammalian target of rapamycin (mTOR) inhibitors (5/78, 6.4%), other medications (including anti-inflammatory, anti-rheumatic, and anti-epileptic treatments) (13/78, 16.7%), and non-medication therapies (including ophthalmologic therapy, physiotherapy, speech therapy, and orthopedic therapy (15/78, 19.2%) (Supplementary Table 1).

Prior to national MDT review, 12 patients (15.4%) had undergone at least one surgery for their target PN (range one to three times), with a median time between first surgery and national MDT review of 3.7 years (0.1–7.7 years). Prior to national MDT review, 11 patients (14.1%) were taking at least one medication to treat a target PN.

3.5. MDT recommendations and target PN management during follow-up

Management recommendations by the national MDT for target PN were documented in the medical records of 34 patients (43.6%). Among these, non-medication therapies were recommended for 26 patients (33.3%), mTOR inhibitors were recommended for six patients (7.7%), analgesics for one patient (1.3%), and another medication (not specified) for one patient (1.3%). Surveillance was the most commonly recommended non-medication approach (n = 17, 21.8%) (Supplementary Table 2).

Of 74 patients with available data from at least one follow-up visit after the national MDT review, over the 24-month follow-up period, nine patients (12.2%) had surgery to treat their target PN (eight partial resections and one complete resection), despite being initially deemed inoperable.

A total of 23 patients (31.1%) received drug therapy for management of target PN, including analgesics (13/23, 56.5%) and other drug therapies (18/23, 78.3%). These included immunosuppressants (6/18, 33.3%), psychoanaleptics (6/18, 33.3%), anti-inflammatory and anti-rheumatic agents (5/18, 27.8%), and anaesthetics (3/18, 16.7%) (Supplementary Table 3). No patient received radiotherapy or chemotherapy.

3.6. Evolution of morbidities related to target PN

All but one patient (n = 77, 98.7%) presented with morbidities related to target PN at national MDT review. The most common target PN-related morbidities were pain (61.5%), deformity (24.4%), and motor dysfunction (10.3%) (Table 3).

At the time of national MDT review, target PN-related morbidities were present at all ages, with considerable disease burden. The five most frequent target PN-related morbidities (pain, deformity, motor dysfunction, visual impairment, and respiratory disorder) were more common in patients over 12 years of age, notably pain (84.6% and 75.0% in patients aged 12–<15 and 15–<18 years, respectively, compared with <60% in other age groups) and motor dysfunction (23.1% and 25.0% in patients aged 12–<15 and 15–<18 years, respectively, compared with <10% in other age groups) (Fig. 1). Eight patients (10.3%) had at least one severe (CTCAE grade ≥3) morbidity related to target PN, including deformity (n = 4), pain (n = 4), and visual impairment (n = 2).

Follow-up data were available for target PN-related morbidities in 74 of the 78 target PN in the study population (Table 3). Of these, 89.2% of patients had at least one documented target PN-related morbidity during the 24-month follow-up period after national MDT review. The most frequently documented morbidities during follow-up were pain (45/74, 60.8%), deformity (19/74, 25.7%), motor dysfunction (9/74, 12.2%), visual impairment (5/74, 6.8%), and respiratory disorders (5/74, 6.8%).

Table 3
Morbidities related to target PN at national MDT review and during subsequent follow-up period.

PN-related morbidity, n (%)	At MDT review (N = 78)	Time post-MDT			
		0–6 months (n = 47)	6–12 months (n = 56)	12–24 months (n = 50)	Last available (n = 74)
≥1 target PN-related comorbidity	77 (98.7)	42 (89.4)	49 (89.1)	44 (88.0)	66 (89.2)
Pain	48 (61.5)	25 (53.2)	28 (50.9)	28 (56.0)	45 (60.8)
Deformity	19 (24.4)	11 (23.4)	14 (25.5)	13 (26.0)	19 (25.7)
Motor dysfunction	8 (10.3)	5 (10.6)	6 (10.9)	6 (12.0)	9 (12.2)
Visual impairment	5 (6.4)	4 (8.5)	6 (10.9)	4 (8.0)	5 (6.8)
Respiratory disorder	4 (5.1)	4 (8.5)	5 (9.1)	4 (8.0)	5 (6.8)
Ear canal stenosis	3 (3.8)	1 (2.1)	1 (1.8)	2 (4.0)	3 (4.1)
Limb asymmetry	3 (3.8)	1 (2.1)	2 (3.6)	2 (4.0)	2 (2.7)
Macroglossia	2 (2.6)	1 (2.1)	2 (3.6)	1 (2.0)	2 (2.7)
Scoliosis	2 (2.6)	1 (2.1)	2 (3.6)	2 (4.0)	2 (2.7)
Pruritis	2 (2.6)	–	–	–	–
Hypoacusis	0	1 (2.1)	0	2 (4.0)	2 (2.7)
Bladder disorder	0	1 (2.1)	0	2 (4.0)	2 (2.7)
Psychiatric disorder	0	1 (2.1)	2 (3.6)	1 (2.0)	2 (2.7)

MDT, multidisciplinary team; PN, plexiform neurofibroma.

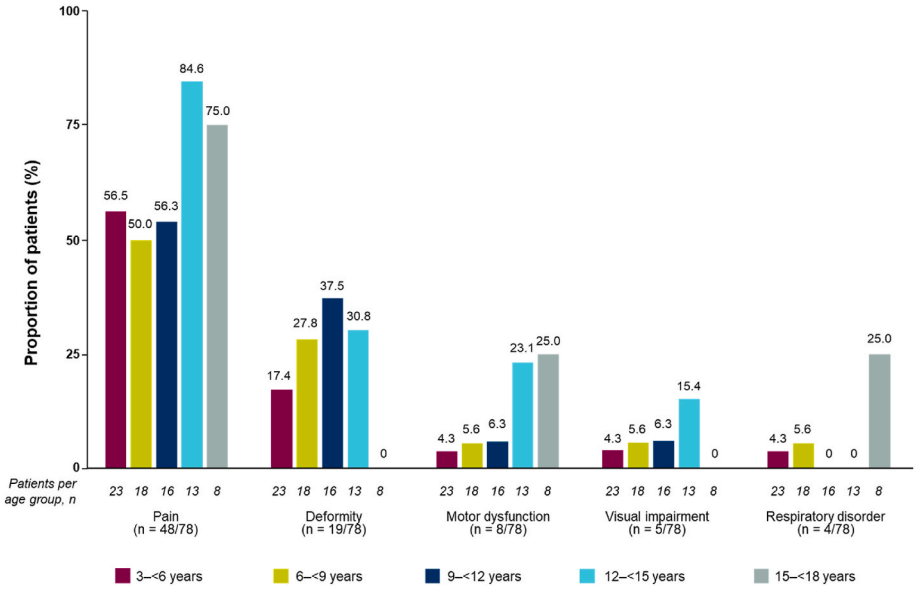

Fig. 1. Proportion of patients with target plexiform neurofibroma-related morbidities by age group at the time of inclusion (initial multidisciplinary review).

Evolution of morbidities during the 24-month follow-up period is depicted in Fig. 2. Of the 45 patients who experienced target PN-related pain, improvement was documented for 12 patients (26.7%), no change for 20 patients (44.4%) and deterioration for 13 patients (28.9%). Target PN-related pain was reported for 17 out of 23 target PN, which were managed with medications and four out of nine target PN which underwent surgery during follow-up. Improvement in pain was reported in six of 17 target PN managed with medications (35.3%) and two of four target PN managed with surgery.

Of the 19 patients who experienced target PN-related deformity during the follow-up period, improvement was documented for three patients (15.8%), all of whom underwent surgery for PN, and no change for 16 patients (84.2%). Target PN-related deformity was reported for two out of 23 target PN, which were managed with medications, and five out of nine target PN which underwent surgery during follow-up. All three target PN for which deformity improved had undergone surgery

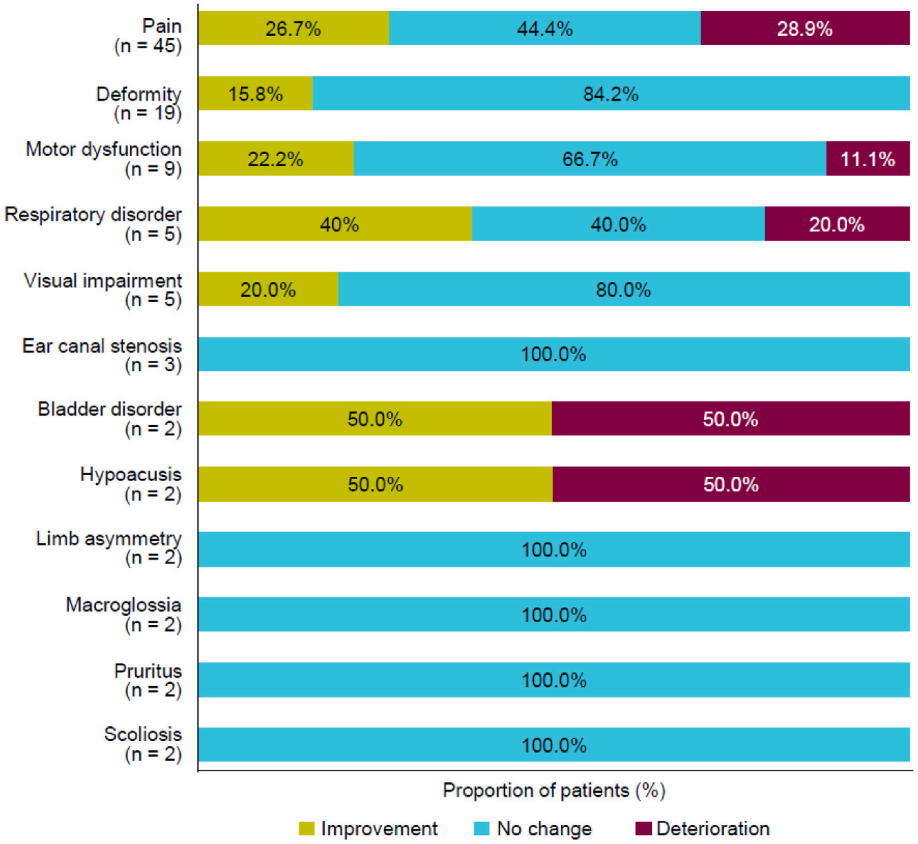

Fig. 2. Evolution of morbidities associated with target plexiform neurofibromas (PN) during follow-up (n = 74)[a]
[a] At least one follow-up visit was recorded for 74 target PN.

and improvement in deformity was not reported amongst target PN managed with medications.

4. Discussion

Real-world studies are warranted to assess disease burden and to understand the need for medical treatment in routine clinical practice in different parts of the world for patients with inoperable NF1-PN. Hence, our retrospective study aimed to describe real-world demographic and clinical characteristics, and therapeutic patterns of children and young adults with NF1 and symptomatic, inoperable PN, in France.

We found that NF1 imposed a substantial burden of disease on the patients. Over three-quarters of patients experienced morbidities associated with NF1 at the time of national MDT review, and all but one patient had morbidities associated with the target PN. Moreover, approximately 10% of morbidities were severe (CTCAE grade $\geq$3). Most patients had undergone at least one medical or surgical treatment for a PN and 14 individuals had previously had a PN that had been completely surgically resected.

As expected, morbidities were heterogeneous in nature. The most common target PN-related morbidities at national MDT review were pain (61.5%) and deformity (24.4%). Importantly, although some patients experienced improvement with respect to morbidities, most remained stable or deteriorated during follow-up. Notably, a proportion of PN-related pain improved following surgery, and all patients with improvement in deformity had undergone surgery. Similar data have been shown in two recent real-world studies from the United Kingdom (UK) and Denmark, where the most commonly reported morbidities amongst children with NF1-PN included pain, deformity/disfigurement, neurological deficits, and functional impairment (Collins-Sawaragi et al., 2022; Ejerskov et al., 2022). There were some slight differences between studies in relation to management of PN with surgery; we reported 12.2% of patients over the follow-up period underwent surgery, whilst these figures were higher in Denmark and the UK (38% and 28%, respectively) (Collins-Sawaragi et al., 2022; Ejerskov et al., 2022). However, surveillance was the most commonly recommended (non--medication) approach in our study, which was similar to the UK study where conservative management was most often applied (Collins-Sawaragi et al., 2022).

Over the period that the study data were collected, surgery was the only curative treatment available for PN (although complete resection was restricted to one patient), but this is not always feasible because of the anatomy and involvement of vital tissue. Treatment for inoperable, symptomatic NF1-PN documented in the present study was generally ineffective. Despite target PN initially being considered inoperable, a small number of patients underwent surgery, and in most cases (88.9%), this was only partial resection. Medications recommended by the national MDT were directed at symptoms rather than resolution of the target PN.

Our observations are also consistent with the NIH Natural History Study (Gross et al., 2018), in which the majority of PN were reported to be internal, and the most common morbidities also included pain and motor dysfunction. We also confirmed that PN typically do not spontaneously regress in the majority of cases, and primarily either remain stable or progress. In our study, it was challenging to correlate any improvement in pain with medications, as most of the available pain medications are available without a prescription, and so may not be noted in medical records. The small number of patients who experienced improvement in target PN-related morbidities highlights the importance of effective treatments that target PN. This medical need is reinforced by the higher mortality rate generally observed in patients with symptomatic NF1-PN than in patients without PN or with asymptomatic PN (Prada et al., 2012).

The study aimed to estimate PN volume and response to treatment; however, volumetric data were available for only two patients, which precluded conducting this analysis. PN are complex tumors and volume calculations are not routinely carried out in clinical practice.

Although our findings demonstrate high disease burden and medical need in children with NF1 and symptomatic, inoperable PN, this real-world study was not able to provide a reliable estimate for the size of the French NF1 pediatric patient population. We estimate that the real NF1 patient population in France is larger than the study population. Of 149 patients screened, just over half were subsequently included in our study, primarily due to patient eligibility criteria. The exclusion of patients with previous and concomitant use of MEK inhibitors may be a large contributing factor. Although only recently approved in France, MEK inhibitors have been used off-label for NF1-PN since 2018 (albeit to a limited extent). As use of MEK inhibitors was an exclusion criterion, data were not collected from patients who had received prior MEK inhibition. Therefore, the proportion of the patient population with NF1-PN who had received prior MEK inhibition in France was not a part of the results of this study and can be considered unknown. This is because this study was not intended to demonstrate the efficacy and safety of these treatments in a small patient population. The exclusion of patients who had received prior MEK inhibition introduced a recruitment bias to this study as inclusion of these patients will likely have impacted the study results.

Additionally, our study was subject to recruitment bias because of the limited number of sites that participated compared with the number invited, and the possible variation in the definition of “inoperable” and “symptomatic” when left to the physician’s discretion. Also, study sites may have selected patients who met the inclusion criteria while not recording those patients who did not in the non-inclusion log.

Due to the retrospective nature of the study, a large number of data were missing or unavailable, or were recorded in an inconsistent manner, and so this was an inherent limitation of the study. In addition, the proportion of patients receiving analgesics was low in proportion to the number of patients who experienced pain, perhaps because some analgesics may be purchased without a prescription, which may have resulted in informal, undocumented recommendations for analgesics in some cases. Finally, the national MDT recommendations were not clearly documented for each patient, perhaps because PN surveillance may not have been recorded as a treatment by some centers.

In conclusion, this study highlights that disease burden was considerable and target PN progressed in many patients in this cohort. A substantial proportion of patients were very young. Target PN-related morbidities were frequent and heterogeneous, and primarily deteriorated or remained stable during follow-up. These data emphasize the need for effective treatments that target PN progression and improve the burden of disease.

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Data sharing statement

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development.

CRediT authorship contribution statement

Pierre Wolkenstein: Conceptualization, Resources, Data curation, Formal analysis, Funding acquisition, Investigation, Validation, Visualization, Methodology, Supervision, Writing – review & editing. **Yves Chaix:** Resources, Data curation, Writing – review & editing. **Natacha Entz Werle:** Resources, Data curation, Investigation, Validation, Writing – review & editing. **Mona Amini-Adle:** Resources, Data curation, Investigation, Validation, Visualization, Supervision, Writing – review & editing. **Sébastien Barbarot:** Investigation, Validation, Visualization, Writing – review & editing. **Christine Boileau:** Conceptualization, Funding acquisition, Validation, Methodology, Supervision, Writing – review & editing. **Anissa Miled:** Conceptualization, Funding acquisition, Validation, Methodology, Supervision, Writing – review & editing. **Talha Rashid:** Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. **Isabelle Aerts:** Conceptualization, Resources, Formal analysis, Funding acquisition, Investigation, Validation, Visualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

PW received consultancy fees from AstraZeneca during the conduct of the study. YC's institution received fees from AstraZeneca during the conduct of the study. MAA has received grants or contracts from Bristol Myers Squibb and Pierre Fabre, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Bristol Myers Squibb, Pierre Fabre, and Sun Pharma, support for attending meetings and/or travel from Bristol Myers Squibb and Pierre Fabre, and has participated on a Data Safety Monitoring Board or Advisory Board for Sun Pharma. SB has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca, Almirall, Sanofi-Genzyme, AbbVie, Novartis, Janssen, LEO Pharma, Pfizer, Eli Lilly, UCB Pharma, and Chiesi and has also received support for attending meetings and travel from Almirall, Sanofi-Genzyme, AbbVie, and Eli Lilly. CB and TR both report employment at AstraZeneca. AM reports employment at AstraZeneca during the conduct of the study. NEW reports no conflicts of interest. IA has received consulting fees from AstraZeneca and has participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2023.104734.

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