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ORIGINAL RESEARCH

Clinical Characteristics and Management of Children and Adults with Neurofibromatosis Type 1 and Plexiform Neurofibromas in Denmark: A Nationwide Study

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ABSTRACT

Introduction: Plexiform neurofibromas (PN) are benign nerve sheath tumours that are a frequent and potentially debilitating complication in patients with neurofibromatosis type 1 (NF1). The objective of this study was to describe the natural history of PN in children, adolescents and adults with NF1.

Methods: This was a nationwide, longitudinal cohort study of patients with NF1 under observation at the two national centres of NF1 expertise in Denmark between 2000 and 2020. Patient and clinical characteristics were documented from individual medical records.

Results: A total of 1099 patients with NF1 were included. Overall, 12% (35/296) of paediatric patients and 21% (172/803) of adult patients had ≥ 1 large PN (≥ 3 cm). Approximately half of patients with a large PN had ≥ 1 symptomatic PN. The most frequent symptoms were pain, neurological deficits, cosmetic issues, disfigurement, compression, increased psychosocial burden and vision loss. Clinical evaluations of PN size were available for 40 PN in 34 paediatric patients and 191 PN in 159 adult patients with large PN. Surgery (complete resection or debulking) was performed in 38% (15/40) of PN in paediatric patients and 45% (86/191) in adult patients. In addition, 35% of PN in paediatric patients and 33% in adult patients were inoperable. In a subgroup analysis, the overall PN size increased 1.06-fold per year. Malignant peripheral nerve sheath tumours (MPNST) were diagnosed in 21 patients (two paediatric and 19 adult patients).

Conclusions: This study shows that PN are common, their size and prevalence increase with age, many are often inoperable and pain and other symptoms are frequently associated. The results highlight the severe sequelae and unmet need for alternatives to analgesia and surgery in patients with PN.

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Keywords: Epidemiology; Malignant peripheral nerve sheath tumour; Neurofibromatosis type 1; Plexiform neurofibromas

Key Summary Points

Real-world studies of the disease burden of patients with neurofibromatosis type 1 (NF1) and plexiform neurofibromas (PN) are limited and data on the natural history of the disease are scarce; therefore, there is a pressing need to better understand the impact of PN in patients with NF1.

This comprehensive database study showed that PN are common amongst patients with NF1 and that their size and prevalence increase with age.

Moreover, many PN were associated with pain and other symptoms, with approximately one third deemed inoperable—with surgery as a standard treatment option for PN, these data highlight the unmet need for alternatives to surgery and symptom management with analgesics for these patients.

In light of this, further natural history studies in NF1-PN are clearly warranted.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder involving the *NF1* gene and can lead to a dysregulation of RAS activity [1]. With a prevalence of one case per 3000–6000 individuals (birth incidence approximately one per 2500–3333) worldwide, NF1 is relatively common compared with other rare diseases [2–5]. Patients with NF1 have impaired health-related quality of life (QoL), are at an increased risk of cancer and have lower life expectancy when compared with the general population [3, 6–9].

Plexiform neurofibromas (PN) are benign nerve sheath tumours that grow along the length of a nerve and are a frequent and potentially debilitating complication in patients with NF1 [10, 11]. It is estimated that approximately 30–50% of patients with NF1 develop PN [1, 12, 13]. Until recently, surgery has been the only standard therapy for patients with NF1 and PN [4, 10, 11]; however, full surgical resection of PN is often challenging due to their invasive nature, location and size [4, 10, 11, 14]. Moreover, PN frequently re-grow after surgical removal and may also transform into malignant peripheral nerve sheath tumours (MPNST) [10, 14, 15]. MPNSTs typically occur at a younger age in patients with NF1 compared with the general population and are associated with a poorer prognosis [15, 16]. The cumulative lifetime risk for MPNST is 8–13% in patients with NF1 [16].

Real-world studies of the disease burden of patients with NF1 and PN are limited. Moreover, data on the natural history of these patients are scarce and there is a need to better understand the impact of PN in patients with NF1 [14, 17, 18]. Denmark is a country with a population of approximately 5.8 million, where all residents have equal access to publicly financed healthcare. Follow-up of NF1 patients is centralised at two national NF1 expert centres: The Centre for Rare Diseases at Aarhus University Hospital (CRD-AUH) and at Rigshospitalet Copenhagen (CRD-CPH).

The primary objectives of this study were to identify and describe the demographics, clinical characteristics, treatment patterns and natural history of large PN in children, adolescents and adults with NF1 in Denmark. Further exploratory objectives were to describe symptoms, PN size, surgery including inoperable PN and minor debulking, PN growth, cumulative incidence of PN and MPNST, with a focus on patients with large PN.

Table 1 Baseline characteristics of patients with NF1 and PN with active records

Characteristic	All paediatric patients with NF1, *n* = 278[a]			All adult patients with NF1, *n* = 711[a]		
	Paediatric patients with PN			Adult patients with PN		
	Small PN (< 3 cm), *n* = 74	Large PN (≥ 3 cm), *n* = 32	All, *n* = 106	Small PN (< 3 cm), *n* = 310	Large PN (≥ 3 cm), *n* = 151	All, *n* = 461
Sex, *n* (%)						
Female	34 (46)	20 (63)	54 (51)	186 (60)	86 (57)	272 (59)
Male	40 (54)	12 (38)	52 (49)	124 (40)	65 (43)	189 (41)
Duration of follow-up, median (range), years	9.6 (1.6–15.9)	9.3 (1.6–16.5)	9.5 (1.6–16.5)	12.1 (0.6–33.0)	13.7 (1.0–27.3)	12.7 (0.6–33.0)
Age at NF1 diagnosis, median (range), years	2.3 (0.2–11.9)	4.0 (0.4–13.0)	2.8 (0.2–13.0)	25.9 (0.2–72.7)	20.0 (0.4–70.8)	24.7 (0.2–72.7)
Age at diagnosis of first PN, mean ± SD (range), years[b]	—	6.3 ± 3.7 (0.1–15.2)	–	–	24.3 ± 16.4 (0–75.7)	–
Age at diagnosis of first PN, years, *n* (%)[b]						
0–1	–	3 (9)	–	–	6 (4)	–
2–5	–	13 (41)	–	–	11 (7)	–
6–10	–	10 (31)	–	–	15 (10)	–
11–17	–	6 (19)	–	–	28 (19)	–
18–29	–	–	–	–	34 (23)	–
30–39	–	–	–	–	18 (12)	–
40–49	–	–	–	–	13 (9)	–
50–59	–	–	–	–	8 (5)	–
60–69	–	–	–	–	3 (2)	–
70–79	–	–	–	–	1 (< 1)	–
Number of large PN/patient, mean ± SD	–	1.2 ± 0.4	–	–	1.2 ± 0.5	–

Table 1 continued

Characteristic	All paediatric patients with NF1, *n* = 278[a]			All adult patients with NF1, *n* = 711[a]		
	Paediatric patients with PN			Adult patients with PN		
	Small PN (< 3 cm), *n* = 74	Large PN (≥ 3 cm), *n* = 32	All, *n* = 106	Small PN (< 3 cm), *n* = 310	Large PN (≥ 3 cm), *n* = 151	All, *n* = 461
Number of large PN/patient, *n* (%)						
1	–	26 (81)	–	–	117 (78)	–
2	–	6 (19)	–	–	22 (15)	–
3	–	0	–	–	3 (2)	–
4	–	0	–	–	1 (< 1)	–

Includes patients in the NF1 cohort with active records only at data cut-off

NF1 neurofibromatosis type 1, *PN* plexiform neurofibromas, *SD* standard deviation

[a]At the data cut-off (1 July 2020), median age range was 11.1 (range 1.7–17.9) years in paediatric patients and 35.6 (range 18.0–91.7) years in adult patients

[b]Data on age at first diagnosis of first PN are missing for 14 adults. Date of PN diagnosis was very uncertain/not available for small PN. Therefore, age at PN diagnosis is not presented for small PN

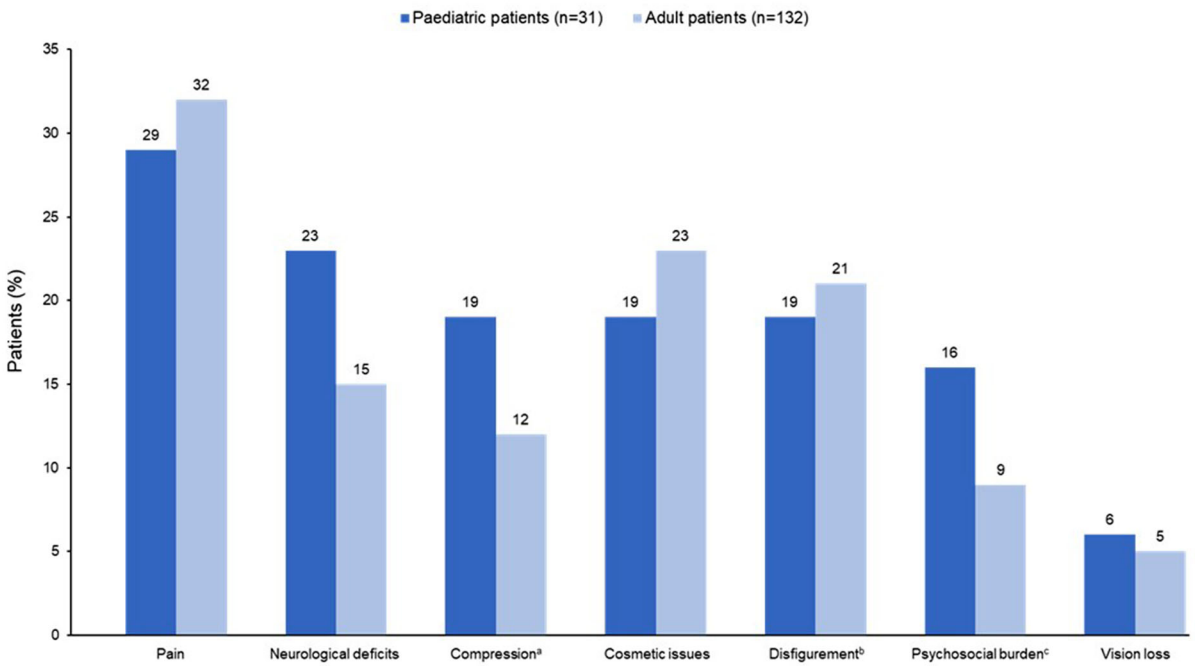

Fig. 1 Symptoms in patients with large PN. Included patients with active and closed (who had no follow-up visit in 5 years, died and/or transferred or emigrated elsewhere) records at data cut-off; data were available for 31 of 35 paediatric patients and 132 of 172 adult patients with large PN; patients may have reported > 1 symptom and therefore values will not add to 100%. *PN* plexiform neurofibromas. [a]Includes compression of the bladder, intestine, trachea, nerve and other. [b]As per physician's evaluation. [c]Self-reported patient burden noted in the medical records included stress due to pain, functional disability, potential future health burden, family and relationship burden and cosmetic burden

METHODS

Study Design and Patients

This nationwide, longitudinal cohort study involved a review of the medical charts of all Danish patients with NF1, with or without PN, who were under observation at the two national centres of NF1 expertise (CRD-AUH and CRD-CPH). All patients with NF1 in Denmark, regardless of disease severity or socioeconomic status, are offered the opportunity to be followed-up throughout their lifetime at these two centres.

Data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted by the Department of Clinical Medicine, Aarhus University. REDCap is a web-based platform designed for safe handling of data captured for research and has automated data export functions [19, 20]. Patients were included if they had a confirmed clinical diagnosis of NF1, according to their electronic medical record, and were followed-up between 1 January 2000 and 1 July 2020. Baseline characteristics and National Institutes of Health (NIH) diagnostic criteria were collected for all patients. In addition, data on PN symptoms, pain medication, PN treatment and functional impairment were collected. Inoperable PN were defined as PN where surgical intervention was not possible or could not be fully resected; hence minor debulking surgery could be performed.

Patients were categorised as to their follow-up status (active or closed [patients who had no follow-up visit in the previous 5 years, had died and/or transferred or emigrated elsewhere]) at the cut-off date (1 July 2020) and as paediatric patients aged ≤ 17 years or as adult patients aged ≥ 18 years. Patients were further stratified

Table 2 Clinical characteristics of large PN

Characteristics of PN	Paediatric patients with large PN (*n* = 34)	Adult patients with large PN (*n* = 159)
PN, *n*	40	191
Location at diagnosis, *n* (%)		
Trunk	12 (30)	50 (26)
Leg	9 (23)	56 (29)
Head/neck	7 (18)	47 (25)
Arm	7 (18)	20 (11)
Pelvis	4 (10)	16 (8)
Paravertebral	4 (10)	13 (7)
Abdomen	2 (5)	11 (6)
Thorax	1 (3)	5 (3)
Superficial PN diameter, mean ± SD (range), cm		
Initial radiological evaluation	*n* = 27	*n* = 100
	4.5 ± 2.5	6.4 ± 5.0
	(0.5–10.0)	(1.0–40.0)
Follow-up radiological evaluation	*n* = 24	*n* = 84
	7.4 ± 4.9	8.5 ± 5.6
	(3–20)	(3–30)
Internal PN diameter, mean ± SD (range), cm		
Initial radiological evaluation	*n* = 15	*n* = 32
	6.3 ± 3.1	8.7 ± 3.6
	(2.5–14.5)	(3.4–16.0)
Follow-up radiological evaluation	*n* = 14	*n* = 25
	7.7 ± 4.2	9.0 ± 3.8
	(2.5–14.5)	(3.4–16.0)

Includes patients in the NF1 cohort with active and closed records at data cut-off

NF1 neurofibromatosis type 1, *PN* plexiform neurofibroma, *SD* standard deviation

Table 3 Surgical interventions in patients with large PN

Requirement for surgery	Paediatric patients with large PN (*n* = 34)	Adult patients with large PN (*n* = 159)
PN, *n*	40	191
PN that underwent surgery, *n* (%)	15 (38)	86 (45)
PN with no surgery in the medical record, *n* (%)	25 (62)	105 (55)
Surgeries per patient, *n* (%)		
1	9 (69)	36 (49)
2	2 (15)	19 (26)
3	0	9 (12)
4	2 (15)	1 (1)
≥ 5	0	1 (1)[b]
Surgeries per PN, *n* (%)		
1	12 (80)	54 (63)
2	1 (7)	15 (17)
3	1 (7)	9 (11)
4	1 (7)	1 (1)
≥ 5	0	4 (5)
Unknown	0	3 (4)
Type of surgery per PN, *n*/*N* (%)		
Full resection	7/15 (47)	34/86 (40)
Debulking	8/15 (53)	52/86 (60)
Inoperable PN, *n*/*N* (%)[a]		
Minor debulking	6/14 (43)	35/62 (56)
No surgery	8/14 (57)	27/62 (44)

Includes patients in the NF1 cohort with active and closed records at data cut-off

NF1 neurofibromatosis type 1, *PN* plexiform neurofibroma

[a]Surgical intervention not possible or the PN was not fully resectable and minor debulking may be performed

[b]One patient had 15 surgeries for one PN

into three cohorts by PN size: no PN, small PN (< 3 cm) and large PN (≥ 3 cm). Additional data on NF1 characteristics and clinical and imaging data in patients with large PN were collected, where available. In Denmark, regular imaging of PN is not performed; imaging is performed for a clinical indication, such as uncertainty of diagnosis (PN or not), growth, discomfort, as well as pre-surgical. Since the primary objective of the study was to investigate patients with large PN, data specific to small PN were not collected.

Tumour Growth Analysis

Tumour growth was analysed in a subset of patients with large PN followed-up at CRD-AUH on whom a minimum of two magnetic resonance imaging (MRI) scans had been performed during follow-up. Patients who had undergone surgery or experienced malignant transformation were censored at the date of surgery.

PN were measured using available MRI sequences (i.e. measurements were not limited to a particular target PN). Baseline and follow-up examinations were compared to ensure that the scans covered the same anatomic region. Since this was a retrospective study, all available MRI sequences containing a PN were used. In principle, only PN located deep within the muscle fascia were measured; however, if a PN extended into the subcutaneous tissue, it was considered to be one entity and the subcutaneous portion was included in volume measurements. Isolated superficial subcutaneous PN were not measured. The volume of PN was measured quantitatively using Multi-Modality Tumor Tracking (MMTT, Philips Healthcare, Intellispace Portal, Koninklijke Philips N.V., Amsterdam, Netherlands). The program uses signal thresholding and contour recognition. A detailed description of the methodology used to measure PN volume can be found in the electronic supplementary material.

Data Analysis

The data are presented using descriptive statistics, such as counts and proportions for categorical variables and medians and ranges for continuous variables. All analyses were performed separately on paediatric and adult patients. A test for two proportions was used to compare the distribution of baseline characteristics, such as sex and the binary outcome presence of PN (present or absent).

Tumour growth was analysed in patients with at least two measurements using a mixed model, taking into account multiple PN per patient and repeated measurements per PN as random effects. The time between measurement and the time of PN diagnosis (referred to as time since diagnosis) were included as random coefficients. The number of PN, time since diagnosis and the interaction between these two factors were included as fixed effects. The estimates were further adjusted using age and sex as covariates.

The study was approved by the ethics committee of the Central Denmark Region (journal no. 1-45-70-3-20, obtained on 18 August 2020).

RESULTS

Total Cohort – Baseline Characteristics and PN

The study identified 1099 patients with NF1 at the data cut-off (1 July 2020), including 989 patients with active records and 110 with closed records (see Fig. S3 in the electronic supplementary material). Of these, 1046 were alive and on this basis, the rate of NF1 in Denmark is estimated at one case per 5500 individuals in 2020.

Of the 989 patients with active records at the data cut-off, 278 were paediatric patients and 711 were adult patients. The median age was 11.1 (range 1.7–17.9) years for paediatric patients and 35.6 (range 18.0–91.7) years for adults, and 50% of paediatric patients (n = 139) and 57% of adults (n = 404) were female.

A total of 106 of 278 (38%) paediatric patients and 461 of 711 (65%) adult patients had at least one PN. The median follow-up time for paediatric patients (n = 106) was 9.5 years (range 1.6–16.5) and for adults (n = 461) 12.7 years (range 0.6–33.0) The baseline characteristics of these individuals are presented in

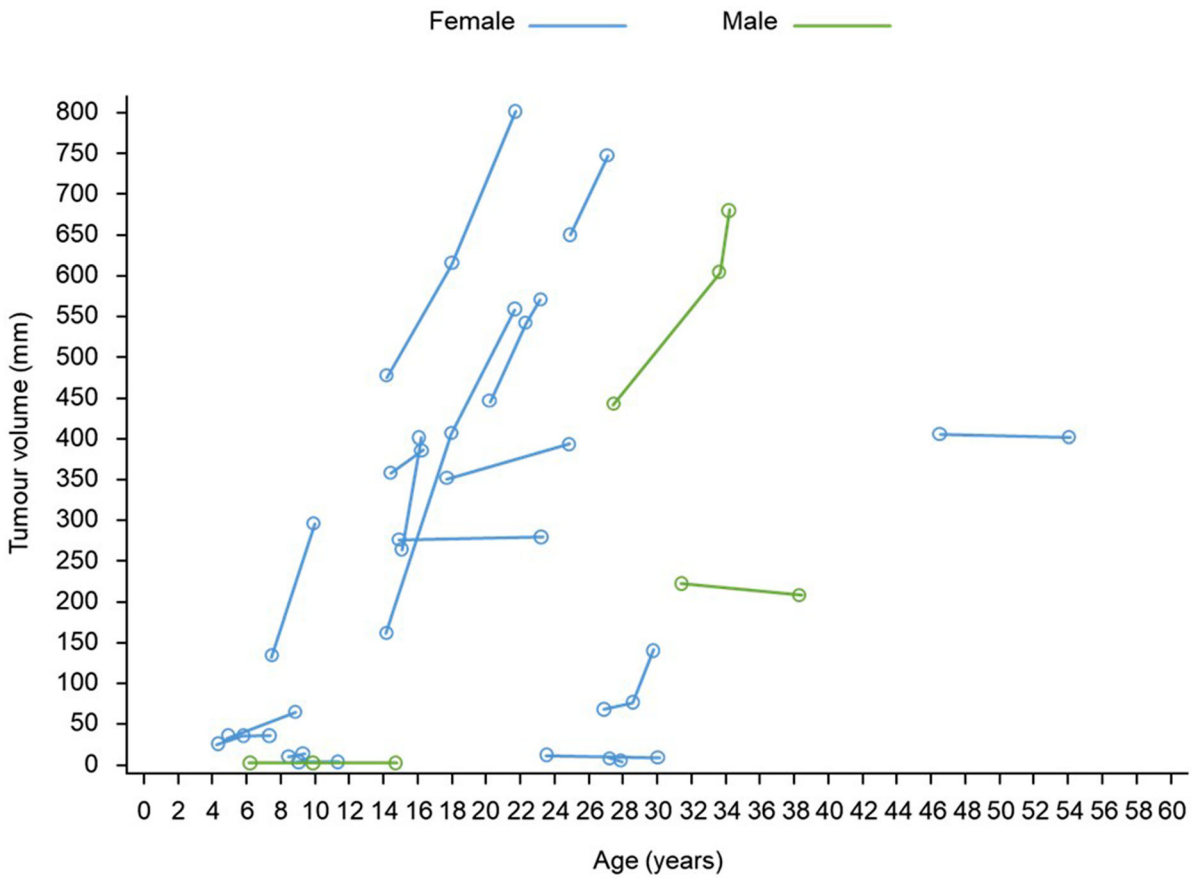

Fig. 2 Tumour growth over time by attained age (years) in 22 patients with large plexiform neurofibromas (≥ 3 cm)

Table 1 according to PN size. Among all paediatric patients, 12% (32/278) had large PN (≥ 3 cm), 27% (74/278) had small PN (< 3 cm) and 62% (172/278) had no known PN, and among all adult patients, 21% (151/711) had large PN (≥ 3 cm), 44% (310/711) had small PN (< 3 cm) and 35% (250/711) had no known PN.

Of the 110 patients with closed records prior to the cut-off date, 18 were paediatric patients and 92 were adult patients. Of these, 22% (24/110) had large PN (≥ 3 cm), 34% (37/110) had small PN (< 3 cm) and 45% (49/110) had no known PN. Among patients with large PN, three were paediatric patients and 21 were adult patients. Baseline characteristics and reason for closure of records of patients who had closed records at data cut-off are presented in Table S1 in the electronic supplementary material.

Large PN Cohort

Overall, including patients with both active and closed records, a total of 12% (35/296) of the paediatric patients and 21% (172/803) of the adult patients had at least one large PN. Large PN was defined as ≥ 3 cm either on clinical description or measurement by the physician, or on radiological evaluation (in some PN both were reported measures).

Symptoms

Among all patients with at least one large PN at their most recent examination (active and closed records), information on symptoms was noted in the records for 31 of 35 paediatric patients and 132 of 172 adult patients. Approximately half of the paediatric (n = 16, 52%) and adult patients (n = 69, 52%) had at least one symptomatic large PN. Pain was the

most frequently documented symptom among both paediatric (n = 9/31, 29%) and adult patients (n = 42/132, 32%) (Fig. 1). Of those who were recorded as experiencing pain, analgesia was used by three paediatric patients (n = 3/9, 33%) and 13 adult patients (n = 13/42, 31%); analgesia used varied from paracetamol only to other non-steroidal anti-inflammatory drugs, opioids, antiepileptic and tricyclic antidepressants, as well as different combinations of these.

Location and Evaluation of PN Size

The location of PN was available for a total of 40 PN in 34 paediatric patients and 191 PN in 159 adult patients with large PN (active and closed records; Table 2). Among paediatric patients, large PN most frequently occurred in the trunk (n = 12/40 PN, 30%), legs (n = 9/40 PN, 23%), head and neck (n = 7/40 PN, 18%) and arms (n = 7/40 PN, 18%), whereas in adult patients, large PN occurred most commonly in the legs (n = 56/191 PN, 29%), trunk (n = 50/191 PN, 26%) and head and neck (n = 47/191 PN, 25%).

Clinical and radiological evaluations of PN size were available for a reduced number of PN (active and closed records; Table 2). For the missing PN, the PN size was described anatomically and true clinical measure in centimetres was not documented in the medical chart. At the first clinical evaluation the mean diameter of superficial PN was 4.5 ± 2.5 cm in paediatric patients (n = 27 superficial PN documented) and 6.4 ± 5.0 cm in adult patients (n = 100 superficial PN documented, Table 2). At follow-up, the mean diameter of superficial PN was 7.4 ± 4.9 cm in paediatric patients (n = 24 PN documented) and 8.5 ± 5.6 cm in adult patients (n = 84 PN documented).

At the first radiological evaluation (all modalities) the mean diameter of internal PN was 6.3 ± 3.1 cm in paediatric patients (n = 15 PN evaluated) and 8.7 ± 3.6 cm in adult patients (n = 32 PN evaluated, Table 2). At follow-up, the mean diameter of internal PN was 7.7 ± 4.2 cm in paediatric patients (n = 14 PN evaluated) and 9.0 ± 3.8 cm in adult patients (n = 25 PN evaluated).

Surgery

A requirement for surgery was documented for 15 of 40 PN (38%) in the 34 paediatric patients and for 86 of 191 PN (45%) in the 159 adult patients with large PN (active and closed records; Table 3). Among the large PN that required surgery, most had required one procedure (12 of 15 PN [80%] in paediatric patients and 54 of 86 PN [62%] in adult patients) at the time of data cut-off. Procedures included complete resection (seven of 15 procedures [47%] in paediatric patients and 34 of 86 procedures [40%] in adult patients) and debulking (eight of 15 procedures [53%] in paediatric patients and 52 of 86 procedures [60%] in adult patients). A total 14 of 40 PN (35%) in 34 paediatric patients and 62 of 191 PN (32%) in 159 adult patients were reported as inoperable. In these patients, minor debulking was performed to relieve symptoms in six of the 14 inoperable PN (43%) in paediatric patients and in 35 of the 62 inoperable PN (56%) in adult patients, but the PN were not fully resectable.

Tumour Growth Analysis

Data for the PN growth analyses were obtained from patients followed up at CRD-AUH. Of 54 paediatric and adult patients evaluated, 22 patients with 24 PN were subsequently included in the analysis. Patients were excluded because images could not be retrieved (n = 10), the analysis could not be performed on available images (n = 6) or because of previous surgery on PN (n = 17). Of the 22 patients included in the analysis, six were aged ≤ 17 years (27%), the mean age was 24.4 years, 16 were female (73%) and 20 (91%) were under active follow-up as of the data cut-off. The two patients who were no longer being followed-up had died at age 24 and 30 years. The change in PN size by attained age in individual patients is shown in Fig. 2. Overall, PN size increased 1.06-fold per year (95% confidence interval [CI] 1.0–1.1).

Cumulative incidence of PN

Of the 1099 patients in the total cohort, cumulative incidence of large PN was calculated using data from 1053 patients with NF1. Fourteen patients with large PN were excluded

because crucial data from clinical examination, or medical records, were missing, including no date of large PN diagnosis, and 33 patients were excluded because PN was diagnosed prior to NF1.

The cumulative incidence of large PN increased with time since the diagnosis of NF1 and was estimated to be 15% (95% CI 13–18), 21% (95% CI 17–24) and 25% (95% CI 21–30) at 10, 15 and 20 years after NF1 diagnosis, respectively (Fig. S4 in the electronic supplementary material). Among patients with NF1 who developed PN, the median time from NF1 diagnosis to diagnosis of PN was 1.9 (95% CI 0.003–25.4) years.

Malignant Peripheral Nerve Sheath Tumours and Other Cancers

Among the entire cohort of 1099 patients with NF1, MPNST was documented in two paediatric patients (aged 12–14 years at the time MPNST was diagnosed), both of whom had large PN diagnosed prior to the diagnosis of MPNST, and in 19 adult patients (median age 31.8 [range 15.7–67.5] years at diagnosis), 15 of whom had large PN diagnosed prior to the diagnosis of MPNST. Both paediatric patients received chemotherapy, and debulking surgery, radiation therapy and proton beam therapy were performed in one patient each. One patient was deceased at data cut-off. Among the 19 adult patients, 11 underwent surgery (full resection in eight and debulking in three), five received chemotherapy, and 11 received radiation therapy. Eleven were deceased at data cut-off.

Two of 34 paediatric patients with large PN subsequently developed brain tumours (low-grade glioma and low-grade astrocytoma) during follow-up.

A wide range of tumours (in addition to MPNST) occurred in adult patients during follow-up. Seven patients were diagnosed with brain tumours; five patients were diagnosed with breast cancer; two patients were diagnosed with pheochromocytoma; and one patient was diagnosed with leukaemia.

DISCUSSION

This is the first nationwide, population-based study of PN in patients with NF1 in Denmark. On the basis of this analysis, we estimate that the rate of NF1 in Denmark is one in 5500 individuals as of 1 July 2020. This is consistent with previous estimates of the prevalence of NF1 in other populations (one in 2500 to one in 6000) [2, 3, 21].

Out of a population of 1099 individuals with confirmed NF1, more than one-third of children and adolescents (38%) and approximately two-thirds of adults (64%) had at least one PN of any size. The cumulative incidence of PN increased consistently throughout childhood and adolescence. Among all patients with at least one PN, approximately one-third had a large PN defined as $\geq$ 3 cm in diameter.

The presence of a large PN is clinically significant because of the association with symptoms and the need for surgery. Previous analyses have reported an association between PN size (volume) and symptoms with larger PN being associated with more frequent or severe symptoms [14, 22]. In the present analysis, the presence of at least one large PN was associated with a wide range of symptoms in both paediatric and adult patients. The presence of symptoms was documented in the medical records of approximately half of the patients with a large PN; however, this may be underestimated as only symptoms explicitly mentioned in medical records were included. The most prevalent symptom was pain, which was documented in approximately one-third of medical records of patients with a large PN. Analgesia used differed between over the counter to scheduled medication and were often used in combination, showing that management of pain in PN can be complicated. Pain was also the most common morbidity associated with PN in a recent registry study by Gross et al. [14] and use of pain medication increased over time as the size of PN increased in that analysis [14]. It should be noted that, in contrast to our study of unselected patients, the study by Gross et al. [14] is an ongoing natural history study that involves patients with more severe disease, and therefore

more likely to be symptomatic. In the present study, neurological deficits and phenomena related to tissue compression were slightly more frequently documented in the medical records of paediatric patients than adults. Concerns about cosmetic issues and disfigurement were documented in approximately 20% of medical records of both paediatric and adult patients.

An analysis of serial MRI sequences in a subset of patients ($n = 22$) allowed us to estimate that the PN volume increased by approximately 6% per year (median, 95% CI 2–10). There was a large variation in growth rate observed, with a median that was somewhat lower than the median growth rate of 16% reported in the recent study by Gross et al. [14]. This difference can be explained by the exclusion of stable PN, defined as $< 20\%$ change in volume from baseline, from calculations of growth rate in that study as well as the younger age of the patient cohort in their study (median, 13 vs 24 years of age) [14]. Previous studies have reported the most rapidly growing PN occur in young children [14, 18]. Young female patients were over-represented in our analysis as 19 of 22 patients included in the analysis were female and all but two patients were aged ≤ 30 years when the first PN measurement was obtained.

Surgery and pain management is a main treatment for PN, although it is not always possible to completely excise a PN [1, 10, 23]. Approximately one-third of PN in paediatric and adult patients were considered to be inoperable in our study, which means either that surgical intervention was not possible, or the PN was not fully resectable and that only limited debulking surgery could be considered.

The MEK inhibitor selumetinib was approved for use in the EU in 2021 as the first systemic therapy for paediatric patients (aged ≥ 3 years) with NF1 and symptomatic, inoperable PN [24]. The approval of selumetinib was based on the pivotal phase 2 SPRINT study which demonstrated clinically significant shrinkage in PN volume [25]. An early access programme was set up in Denmark but no patients included in the study had started treatment at the cut-off date.

Patients with NF1 are at increased risk of MPNST, which carries a poor prognosis [14–16, 22, 26]. The overall frequency of MPNST in our NF1 cohort was 2% (21 of 1099 patients) and all but four cases of MPNST were documented in patients with clinically evident large PN. This is consistent with previous literature that showed that MPNSTs usually arise from pre-existing PN [6, 16]. The frequency of MPNST in our cohort was lower than that reported by Evans et al. [16] in their registry study from northwest England. This discrepancy can be partially explained by the largely unselected population included in our cohort, which has a young average age and is a close representation of the true Danish prevalence. In the future, it would be interesting to investigate the prevalence of cancer, and MPNST in particular, by linking patients in the PN cohort with the Danish Sarcoma Database and nationwide cancer registry, which includes all cancers diagnosed in Denmark.

There is no standard method for measuring the size of PN. The tumour tracking software was fast and easy to use, enabling measurement of the entire volume of a PN, thereby proving useful in daily clinical practice. Semi-automated volumetric segmentation methods for PN monitoring have previously been described, but are used mainly for research purposes [27]. In daily clinical practice, the largest PN is usually chosen, and the length and width on one slice are used to monitor PN size over time. PN segmentation using MMTT is subjective and ultimately guided by the operator, but the process seems more objectively quantifiable than using the widest measurements on a single slice.

To our knowledge, this is the first nationwide population-based study of PN in patients with NF1. A strength of the study is the comprehensive nature of the database, which includes an unselected population of all patients with NF1, regardless of their socioeconomic status or ability to pay—all patients in Denmark have free and equal access to healthcare, including at their respective NF1 centres. However, this study also has certain limitations, most of which can be attributed to the nature of the observational study design. These include missing data, under-reporting of symptoms and incomplete MRI scan data and the subjective nature of PN segmentation using MMTT. MRI is

not routinely performed in patients with NF1 in Denmark and only when specific indications or symptoms from a PN are apparent; not only prior to surgery but also when there is uncertainty related to diagnosis (PN present or not), rapid growth, discomfort or disfigurement. In particular, the frequency of symptoms may have been underestimated as symptoms were not documented in a systematic fashion; only prominent symptoms would have been noted in the electronic medical record. In order to obtain a more reliable picture of NF1 symptoms, a study based on patient-reported outcomes would be required. In addition, although all patients with NF1 in Denmark are candidates for referral to CRD-AUH and CRD-CPH, it is possible that some individuals with very mild symptoms may not have been diagnosed or chose not to be followed for NF1 disease at these centres.

CONCLUSIONS

In conclusion, this nationwide analysis of medical records shows that PN are frequently reported in patients with NF1, with 19% of patients developing large PN and cumulative incidence increased over time. These PN are often deemed inoperable and are associated with a number of symptoms and morbidities, the most frequent of which was pain, highlighting that disease burden was considerable. Furthermore, a proportion of patients developed MPNST, not all of which arose from a known PN. Therefore, these results highlight the severe sequelae and unmet treatment need in patients with NF1-PN.

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Author Contributions. Cecilie Ejerskov conceptualised the study and was involved in resources, data curation, formal analysis, supervision, investigation, validation, visualisation, methodology, funding acquisition and project administration, and reviewed and revised the manuscript. Mette Møller Handrup participated in the conceptualisation, resources, data curation, supervision, investigation, validation, visualisation, methodology, funding acquisition and project administration for the study, and reviewed and revised the manuscript. Sofie de Fine Licht participated in the conceptualisation, formal analysis, supervision, validation, investigation methodology, funding acquisition and project administration for the study, and reviewed and revised the manuscript. Stense Farholt participated in the conceptualisation, resources, data curation, supervision, validation, investigation, and methodology of the study, provided software, and reviewed and revised the manuscript. Trude Ågesen participated in the conceptualisation, supervision, validation, investigation, methodology, funding acquisition and project administration for the study, and reviewed and revised the manuscript. Flemming Secher Kromann Nielsen participated in the conceptualisation, formal analysis, investigation, visualisation,

methodology of the trial, software provision and reviewed and revised the manuscript. Ingunn Berg and Stine Bogetofte Thomasen participated in the data curation, formal analysis, investigation, methodology of the study and reviewed and revised the manuscript. Aparna Udupi participated in the data curation, formal analysis of the study and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Disclosures. Cecilie Ejerskov, Stense Farholt, Flemming Secher Kromann Nielsen, Ingunn Berg, Stine Bogetofte Thomasen and Aparna Udupi report no conflict of interest. Trude Ågesen and Sofie de Fine Licht report employment with AstraZeneca. Mette Møller Handrup reports honoraria from AstraZeneca, support for attending meetings and/or travel from AstraZeneca and advisory board participation for AstraZeneca.

Compliance with Ethics Guidelines. The study was approved by the ethics committee of the Central Denmark Region and according to the General Data Protection Regulation, the study has been recorded in The Central Region internal database of research projects (journal no. 1-45-70-3-20, obtained on 18 August 2020). The study was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki and the applicable legislation on Non-Interventional Studies and/or Observational studies. As this study only includes secondary data from electronic medical records, it has been confirmed and approved by Region Midtjylland that no informed consent from patients is needed.

Data Availability. 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. Link to Data Request Form: https://alexion.com/contact-alexion/medical-information.

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