Location, Symptoms and Management of Plexiform Neurofibromas in 127 children with Neurofibromatosis 1, attending the National Complex Neurofibromatosis 1 Service, 2018-2019.

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Conflict of Interest :

Professor Rosalie Ferner is a medical advisor for AstraZeneca. Professor Darren Hargrave is a consultant/advisor for AstraZeneca (selumetinib), Roche-Genetech (cobimetinib), Novartis (trametinib). INSPECT trial is an Investigator led trial (DH as Principal Investigator) funded by an Industry Grant from AstraZeneca (Grant code GOSH R&D number 15H1530).

Data Availability: Data available on request due to privacy/ ethical restrictions.

Abstract:

We report on the location, symptoms and management of plexiform neurofibroma (PN) in children with Neurofibromatosis Type 1 (NF1) attending the 2 National Complex Neurofibromatosis 1 Services at Guy's and St. Thomas' NHS Foundation Trust, London and St Mary's Hospital, Manchester. Retrospective data collection was performed from patient chart reviews from April 2018 to April 2019. There were 127 NF1 patients with PN, age range 0.8-17.0, mean age was 9.9 years (SD ±4.2 years). The main location of the PN was craniofacial in 35%, and limb in 19%. Disfigurement was present in 57%, pain in 28%, impairment of function in 23% and threat to function in 9% of children. 54% of patients were managed conservatively, 28% surgically and 19% are either taking or due to start a mitogen-activated protein kinase kinase (MEK) inhibitor (selumetinib or trametinib), either through a clinical trial or compassionate usage scheme. This national study provides a comprehensive overview of the management of children with PN in an era where new therapies (MEK inhibitors) are becoming more widely available. We anticipate that there will be a shift to more patients receiving MEK inhibitor therapy and combination therapy (surgery and MEK inhibitor) in the future.

Keywords:

Neurofibromatosis Type 1, Plexiform Neurofibroma, Location, Symptom, Management

Introduction

Neurofibromatosis Type 1 (NF1) is an autosomal dominant condition with a prevalence of at least 1/4560 (Evans et al., 2010). Mutation in the NF1 tumour suppressor gene leads to activation of the RAS pathway (Basu et al., 1992) and results in cell growth (Donovan, See, Bonifas, Stokoe, & Shannon, 2002; Johannessen et al., 2005; Dasgupta, Yi, Chen, Weber, & Gutmann, 2005) and proliferation (Anastasaki & Gutmann, 2014) leading to tumour formation.

Plexiform neurofibromas (PN) are peripheral nerve sheath tumours that occur frequently in NF1 with 32% of patients having clinically visible plexiform neurofibroma (Huson, Harper & Compston, 1988) while in over 50% of patients, internal plexiform neurofibroma can be detected on imaging (Mautner et al., 2008). There is an estimated 15.8% lifetime risk of these plexiform neurofibromas transforming into malignant peripheral nerve sheath tumours (MPNST) (Uusitalo et al, 2016) although this risk can be as low as 0.5% in childhood (Evans et al., 2017). Benign plexiform neurofibromas frequently cause pain, disfigurement, neurological deficit and impaired quality of life.

Management of plexiform neurofibromas can be broadly classified into three categories: conservative, surgical and medical therapies, currently MEK inhibitor therapy. Conservative management involves both clinical and radiological (MRI) surveillance with pain management and psychology input as required. Surgery is an option however complete excision is rarely achievable and there is a high re-growth rate especially in children (Kim et al., 2009). Other risks of the procedure include bleeding, nerve damage and scarring. Therefore, surgery is reserved for selected symptomatic cases such as large superficial lesions which may be amenable to complete excision. For deep seated lesions debulking surgery is appropriate when there is a threat to function from the plexiform neurofibroma which will not be further compromised through surgery (such as upper airway obstruction or spinal cord compression with radiological and clinical progression). Surgery is also performed for extensive lesions such as craniofacial lesions where surgery is often undertaken in stages, or when there is suspicion for or diagnosis of MPNST (rapid growth, change in texture from soft to firm, pain, neurological deficit).

The third option which should be reserved for inoperable, symptomatic PN is medical therapy with MEK (mitogen-activated protein kinase kinase) inhibitors in particular selumetinib. Selumetinib has been shown in paediatric phase 1 and 2 clinical trials to produce a radiological partial volume reduction (defined as 20% reduction) in 70% of patients as well as some reported clinical benefit in child and parent reported pain and functional outcome score measures (Dombi et al, 2016; Gross et al, 2020). Recently selumetinib has received FDA (Food and Drug

Administration) approval for paediatric inoperable plexiform neurofibroma. Although selumetinib is under orphan drug status by the European Medicines Agency (EMA), in the UK, MEK inhibitors are only available through clinical trials or through the compassionate usage scheme. The UK INSPECT trial (NCT03326388) is investigating the effectiveness and toxicity profile of an intermittent dosing schedule of selumetinib at a higher dose than the NCI trial with 1 cycle consisting of 5 days on medical treatment and 2 days off treatment for a total of 28 days. The NCT02124772 trial for trametinib is investigating dosing, toxicity profile and clinical effectiveness of trametinib in paediatric plexiform neurofibroma. Preliminary phase I/IIa data published suggests it is safe and associated with volumetric reduction of plexiform neurofibroma (McCowage et al., 2018). With the advent of novel therapies, it is very important to determine the clinical presentation of children with symptomatic PN, so that the most appropriate treatment can be given at an early stage.

Aim:

To characterise the location, symptoms and the management of NF1 plexiform neurofibromas in paediatric patients less than 17 years of age seen in the National Complex Neurofibromatosis 1 Service (comprising 2 centres: London and Manchester) in the UK over a 13 month period from 1 April 2018- 30 April 2019.

Method:

Retrospective data collection was undertaken by the clinical teams through review of the patient case records. All complex NF1 paediatric patients with a plexiform neurofibroma aged 16 years old or under seen between 1 April 2018 - 30 April 2019 in the National Complex Neurofibromatosis Service at Guy's and St. Thomas' NHS Foundation Trust, London, UK or St Mary's Hospital, Manchester, UK were included. The study has been registered by both hospitals and has been approved as a clinical evaluation study number 11499 and 9713.

The following were recorded: age; sex; location of plexiform neurofibroma (main site); symptoms from the PN including disfigurement (defined as change caused by the plexiform neurofibroma which was visible, caused distortion or asymmetry of anatomical features); pain (defined as a sensation expressed by the patient which may require analgesia and/or affect quality of life – note that pain scales have not been applied); impaired function; threat to function (defined as airway compromise or asymptomatic radiological cord compression); management: conservative; surgery; MEK inhibitor (name of inhibitor and how this was accessed (trial vs compassionate usage)). Data on the total number of patients and complex NF1

patients seen in clinic was also collected. Complex NF1 is defined as rare or potentially life-threatening complications of NF1 or manifestations that require management by expert, specialist clinical teams.

Chi squared testing was performed to test if association between treatment groups and symptom or PN location were present (Microsoft Excel) with a significance level set at $p<0.05$.

Results:

Between April 2018 and April 2019 there were 649 paediatric NF1 patients seen in the two National Complex Neurofibromatosis Service of which 43% (281/649) were complex NF1 patients. There were 127 children with plexiform neurofibroma which accounted for 20% of all paediatric NF1 patients and 45% of complex paediatric NF1 patients seen. Mean age and standard deviation for NF1 plexiform neurofibroma patients was 9.9 ± 4.2 years, age range 0.8 - 17.0 years. There were 62 males and 65 females.

Location

The location of the plexiform neurofibromas is shown in Figure 1. Craniofacial PN (45/127 = 35%) were most common followed by limb PN (24/127 = 19%) (with lower limb affected twice as commonly (16/24) as upper limbs (8/24)), spinal/paraspinal (20/127) and neck (19/127). Other locations include abdomen and pelvis (10/127), chest (7/127), and back (2/127) plexiform neurofibromas.

Symptoms

Symptoms of the plexiform neurofibroma are shown in Figure 2. Disfigurement was seen in 57% (72/127) of plexiform neurofibroma patients. Impairment of function was seen in 23% (29/127) and include motor difficulties, upper airway compression, spinal cord compression, bowel obstruction and visual impairment. In 9% (12/127) of patients the PN was classified as posing a threat to function in the light of radiological upper airway obstruction and/or cord compression. Upper airway obstruction was seen in 3/12 patients while asymptomatic radiological cord compression was seen in 9/12 patients (5 cervical spine, 2 thoracic spine, 2

lumbar spine). Pain as defined above was present in 28% (36/127) of patients and the most common site was in the lower limbs. 27% (34/127) of our complex NF1 PN patients had no symptoms while 31% (40/127) had more than one symptom.

Management

54% (68/127) of our patients were managed conservatively. Mean age ± SD of conservatively managed patients was 9.5 years ± 4.6 years, age range 0.8-17.0 years. Most common locations of plexiform neurofibroma for conservatively managed patients were craniofacial (20/68 =29%), limb (16/68 = 24%), spinal/paraspinal (12/68 = 18%) and neck (10/68 = 15%) (Figure 3).

35/127 (28%) of paediatric plexiform neurofibroma patients had had or were awaiting surgery. Mean age ± SD of surgically managed plexiform neurofibroma patients was 10.4 years ±3.5 years, age range 3.7-16.6 years. In order of frequency the locations were craniofacial (21/35 = 60%), limb (4/35 = 11%), other sites (4/35 = 11% chest, abdomen, pelvis, back), spinal/paraspinal (3/35 = 9%), and neck (3/35 = 9%) (Figure 3). The proportion of craniofacial PN was the highest in the surgical group in comparison to the other treatment groups. The proportion of patients with disfigurement from the PN (before surgery) was also the highest in the surgical group. All 21 craniofacial PN patients managed surgically had disfigurement from the PN (before surgery).

Indications for surgery were disfigurement in 23/35 patients, threat to function (brain herniation) in 1 patient, other symptoms from PN in 11 patients (symptomatic cord compression/myelomalacia in 2 patients; MPNST in 2 patients; pain, discomfort or enlargement in 5 patients; restricted neck movement in 1 patient, difficulty in defecation in 1 patient). Surgery performed was debulking in 28/35, total excision in 5/35, wide resection in 1/35 while 1 patient did not proceed to surgery. All disfigurement symptoms improved with surgery with good patient satisfaction and no complications although some patients have subsequently required repeat operations as expected for craniofacial PN surgery. 1 CNS infection was seen post neurosurgery for threat to function. The 11 patients undergoing surgery for symptoms of PN all improved with only 1 regrowth of PN due to MPNST.

24/127 (19%) were either on or about to receive a MEK inhibitor either as part of a clinical trial (INSPECT or NCT02124772 trial) or on compassionate basis. Mean age ± SD for these patients

was 10.3 years ± 4.1 years, age range: 3.2-15.3 years. 16 patients are enrolled to receive selumetinib as part of the INSPECT trial which started recruiting in September 2019 and 8 patients were on trametinib during the study period (2 trial and 6 on compassionate grounds). Location of these plexiform neurofibroma were neck (6/24 = 25%), spinal/paraspinal (5/24 = 21%), other (5/24 = 21% chest, abdomen, abdomen/buttock, pelvis/buttock and back), craniofacial (4/24 =17%) and limb (4/24 = 17%) (Figure 3). Patients in the MEK inhibitor group had the highest proportion of patients experiencing pain and threat to function.

All outcomes cannot be currently reported as the duration on MEK inhibitor for some patients is limited and final outcomes are awaited from the trials. However, since the study period 18 patients have started MEK inhibitor with 13/18 patients continuing and 5/18 stopping treatment. Reason to stop MEK inhibitor were due to side effects in 1 patient, lack of clinical benefit in 2 patients, and both side effects and lack of clinical benefit in 2 patients. Side effects were skin (8/18 mild, 5/18 moderate, 5/18 significant), gastrointestinal in 8/18 (2/18 mild, 2/18 moderate, 4/18 significant) and others (gross haematuria 1, weight gain 1). 10/15 patients had PN either decrease in size (6/10) or stabilise (4/10) while in 5/15 patients there was no benefit on PN size seen. Softening was seen in 12/15 but not in 3 patients. Pain improved in 5/11, function (threat to function or impairment in function) either stabilised or improved in 7/10 patients and disfigurement stabilised or improved in 3/9 patients.

Discussion:

We have presented results from a retrospective case note study of 127 children with plexiform neurofibroma seen in the National Complex Neurofibromatosis 1 Services in London and Manchester over a 13 month period from 1st April 2018 - 30th April 2019. We identified that 54% (68/127) of patients were managed conservatively, 28% (35/127) surgically and 19% (24/127) were being considered for or already taking a MEK inhibitor.

Children from the whole of England are referred to our National Neurofibromatosis 1 services in London and Manchester for management therefore we believe we have captured the data on the majority of symptomatic PN. As far as we are aware, this is the first descriptive national study of plexiform neurofibroma in children. Data that are available regarding plexiform location are typically from select groups, for example patients undergoing trials or surgical cohorts and therefore not comparable and representative of the NF population as a whole. The most common location of plexiform neurofibromas being in the craniofacial location is similar to surgically managed patients by Nguyen et al. (2013). However, Kim et al. (2009) and Gross

et al. (2020) found that in patients enrolled in clinic trials for plexiform neurofibromas, the most frequent location was mainly in the trunk region. This is unsurprising as frequently these lesions are not amenable to surgical intervention.

Overall, 28% of our patients experienced pain symptoms but in our MEK inhibitor group 67% of patients experienced pain which is the highest proportion of patients with pain when management groups are compared (22% conservative, 14% surgical). Uncontrolled pain is an indication for starting MEK inhibitor which explains this bias. The high proportion of patients with pain in the MEK inhibitor group accords with published studies such as 52% of plexiform neurofibromatosis patients with pain in the NCI selumetinib trial (Dombi et al., 2016).

Unsurprisingly, as inoperable PN is an indication for MEK inhibitor treatment, we found that the highest proportion of patients with 'threat to function' were in the MEK inhibitor group at 33% (in comparison to 4% in conservative, 3% surgical) while the highest proportion of patients with disfigurement and craniofacial PN was seen in the surgical group. There was no association between PN location in other areas and treatment group (Chi squared test).

This study has provided an overview of patients with PN seen in the complex NF1 clinic over a 1 year period. We have not collected longitudinal data to map out the patient's journey, but we would anticipate that as plexiform neurofibromas in children naturally progress, there will be some movement between the three treatment groups especially from the conservative group into the surgical or medical treatment group.

It is important to highlight that although selumetinib has been granted FDA approval in the USA, in the UK this is still under evaluation (NICE, 2019). We believe that our data are invaluable as part of the health technology appraisal process.

We anticipate that a carefully selected group of patients with extensive disfiguring plexiform neurofibromas with pain and or threat to function may benefit from MEK inhibitors either as monotherapy or in combination with surgery. This is seen in other centres, where MEK inhibitors are used to reduce tumour size to enable surgical excision to be performed (Vaasen, Dürr, Röhrig, Willing, & Rosenbaum, 2019). We are firmly of the view however that decisions regarding management of symptomatic PN should be made within the multidisciplinary specialist NF1 service.

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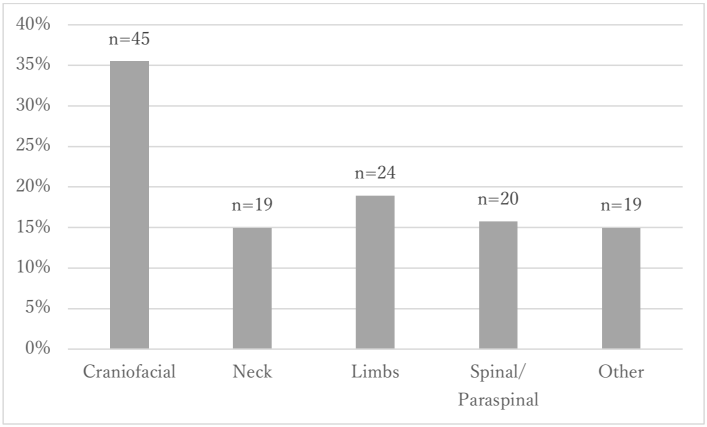

Figure 1: Plexiform Neurofibroma main location and percentage of plexiform neurofibroma NF1 patients for London and Manchester (n=127)

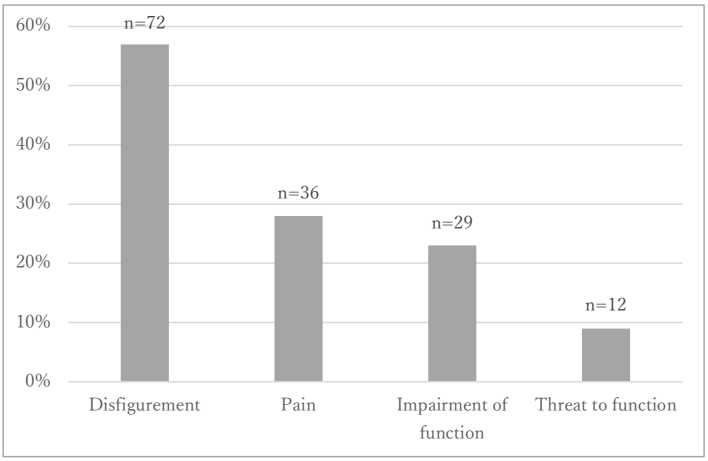

Figure 2: Symptoms caused by PN as a percentage of 127 NF1 PN patients for London and Manchester combined

	Conservative	Surgical	MEK inhibitor	TOTAL
Craniofacial	20	21	4	45
Neck	10	3	6	19
Limb	16	4	4	24
Spine/ Paraspinal	12	3	5	20
Other:	10	4	5	19
Chest	5	1	1	7
Abdomen/ Pelvis/ Buttock	5	2	3	10
Back	0	1	1	2
TOTAL	68	35	24	127

Figure 3: Table to show main location of the PN in 127 patients and the management category

Data Sharing: Data available on request due to privacy/ ethical restrictions.