Clinical Neurology and Neurosurgery 180 (2019) 18–24

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Neurosurgical contribution within a complex NF1 supraregional service

H. Raffalli-Ebezant[a,*], K.J. George[a], E. Burkitt-Wright[b,c], F. Roncaroli[d,e], G. Evans[b,c], C. Soh[f], J. Ealing[b], G. Vassallo[b], J.E. Elloo[b], K. Karabatsou[a,e]

[a] Department of Neurosurgery, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester Academic Health Sciences Centre, Salford, Greater Manchester, UK
[b] Complex NF1 Service, Manchester Centre for Genomic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[c] Division of Evolution and Genomic Sciences, School of Biological Sciences, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK
[d] Neuropathology Unit, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester Academic Health Sciences Centre, Salford, Greater Manchester, UK
[e] Division of Neuroscience & Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[f] Department of Neuroradiology, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester Academic Health Sciences Centre, Salford, Greater Manchester, UK

ARTICLE INFO

Keywords:
Complex NF1
Neurofibromatosis

ABSTRACT

Objectives: The goal of this study was to review and present neurosurgical related activity within a multidisciplinary nationally commissioned specialty neurofibromatosis type I (NF1) center.
Patients & methods: We reviewed all NF1 Neurosurgical MDTs, NF1 Neurosurgical clinics and all neurosurgical procedures carried out in NF1 patients over an 8-year period.
Results: Since the inception of the service in 2009, 1505 cases were discussed at our NF-1 multidisciplinary meeting, 171 clinic appointments in complex NF1 patients with neurosurgical pathologies and 43(cranial and spinal) operations were performed.
Conclusions: The formation of a supraregional multidisciplinary team allows for a better understanding of the disease, a comprehensive evaluation of neuroimaging findings and a steep learning curve in the management of NF1 surgical conditions.
We provide holistic treatment for these patients via direct care, specialist advice and liaison with local units.

1. Introduction

Neurofibromatosis type 1 (NF1) is an inherited neurocutaneous tumor predisposition syndrome characterized by the development of benign and malignant nervous system neoplasms [10]. Adults with the condition have been estimated to carry at least a five-fold increased risk of developing high-grade gliomas [15,8]. NF1 presents with a diverse spectrum of clinical manifestations that, along with peripheral and central nervous system tumors, includes cutaneous and skeletal abnormalities as well as learning difficulties [6].

NF1 is dominantly inherited and is caused by a pathological variant in the tumor suppressor gene located on chromosome *17q11.2* [17,19]. This gene encodes neurofibromin, the loss of which results in increased Ras proto-oncogene pathway activity [7]. It is a relatively common disorder, with a birth incidence of between 1:2000 and 1:3000 [11,5], with approximately half of cases having no family history and arising from *de novo* mutations [10].

Friedrich von Recklinghausen first coined the term 'neurofibroma' in 1882 to describe the benign peripheral nerve sheath tumors that are characteristic of the condition [18] but it wasn't until 1988 that formal diagnostic criteria were established by the National Institute of Health consensus [13]. These criteria are sufficient to confirm the diagnosis in the large majority of affected patients, but are in the process of revision to take into account the molecular diagnosis.

2. Complex NF1 service

Within the population of patients affected by NF1, a small proportion will develop complex phenotypes or complications of the disease that can be associated with significant morbidity and mortality [4]. From a neurosurgical perspective, these manifestations include: brain and spinal cord glioma; spinal cord compression from cervical neurofibroma; complex neurovascular disease; refractory epilepsy due to structural lesions; symptomatic optic pathway gliomas (OPG) and

* Corresponding author at: Helen Raffalli-Ebezant, Salford Royal Foundation Trust, Stott Lane, Salford, M8 6HD, UK.
E-mail address: Helent84@doctors.org.uk (H. Raffalli-Ebezant).

https://doi.org/10.1016/j.clineuro.2019.03.002
Received 12 January 2019; Received in revised form 25 February 2019; Accepted 3 March 2019
Available online 04 March 2019
0303-8467/

Table 1
Complex NF1 manifestations.

Complex NF1 manifestations [4]
Intra-spinal cervical neurofibroma
Brain and spine glioma
Symptomatic optic pathway gliomas
Cerebrovascular disease
Extensive/complex plexiform neurofibromas
Refractory epilepsy secondary to structural lesion
Sphenoid wing dysplasia
Multiple sclerosis
Neurofibromatous neuropathy
Atypical neurofibroma and malignant peripheral nerve sheath tumours
Pseudarthrosis of longbones
Atypical phenotypes

sphenoid wing dysplasia. Table 1 summarizes these, along with the other complex manifestations of NF1 [4].

In 2009, the national specialized commissioning team developed specifications for a nationally designated "complex NF1″ service based at two NHS Trusts: Guys and St Thomas' NHS Foundation Trust and Department of Neurogenetics, Manchester Centre for Genomic Medicine, St Mary's Hospital. The view was to establish a cohesive national service, addressing the more complex manifestations of the disease and allowing for widespread access to specialist care. The aims of this service are to provide:

- Specialist workup of NF1 patients with complex complications and unusual phenotypes
- Co-ordinated care via a multi-specialist MDT
- Monitoring of patients at risk of NF1 related malignancy
- Long term follow up/monitoring of patients to evaluate need for surgery [14]

In Greater Manchester, the service is run by a team of NF1 specialist neurologists, neurosurgeons, neuroradiologists, sarcoma surgeons, plastic surgeons, orthopedic surgeons and ophthalmologists, along with geneticists, clinical nurse specialists and psychologists. The members liaise via NF1 sub-specialty designated multidisciplinary teams (MDTs). There are regular joint clinics and liaison with local units via the NF1 specialist nurses. Regional genetics clinics and satellite clinics across the North of England are also held and we have regular communication with the Guys and St Thomas' site via video conferencing and face-to-face meetings.

Patients have the opportunity to attend the Manchester complex NF-1 clinic where all the aspects of their care can be addressed or at least their local scans to be reviewed at NF-1 MDT for specialist advice. Patients with complex NF-1 indicators can be offered surgery at the Supraregional centre should they prefer, alternatively they can still be

Table 2
Neurosurgical operative interventions for complex NF1 patients since 2010.

Patient	M/F	Age	Complex NF indicator	Surgical intervention
1	M	23	Cord compression	Cervical laminectomy and resection of neurofibroma
2	M	56	Cord compression	Cervical laminectomy and resection of neurofibroma
3	F	24	Cord compression	1. Foramen magnum decompression, cervical laminectomy and resection of neurofibroma
		29		2. 4 level ACDF with plating and correction of kyphotic deformity
4	F	21	Cord compression	1. Thoracic laminectomy and resection of neurofibroma
		23		2. Resection of residual/recurrent neurofibroma and thoraco-lumbar stabilization
5	F	25	Cord compression	1. Cervical laminectomy and resection of neurofibroma with posterior stabilization
		28	Ventriculomegally	2. ICP monitoring and VP shunt insertion
6	M	37	Cord compression	1. C2-4 posterior fixation
		39		2. Manubriotomy for anterior thoracic fixation (T2-T4)
		39		3. Revision posterior cervicothoracic fixation C2-T8
7	F	21	Cord compression	1. Cervical laminoplasty and resection of neurofibroma
		23		2. C4-T1 ACDF and plating
		23		3. L2 spinous process osteotomy for resection of intradural nerve sheath tumour
8	M	19	Cord compression	1. Cervical and thoracic laminoplasty for resection of neurofibroma plus T12-L1 stabilisation
		19		2. Wound debridement and repair of duro-cutaneous fistula
9	F	21	Non cervical intraspinal tumours	Lumbar laminectomy and resection of intradural tumour
10	M	31	Extensive cervical neurofibroma	Left Posterior cervical triangle debulking of large neurofibroma
11	F	34	Brain glioma	1. Right parietal craniotomy for tumour resection
		35		2. Wound washout & cranioplasty
12	F	26	Brain glioma	Left frontal craniotomy for tumour resection
13	M	24	Brain glioma	Posterior fossa craniotomy for cerebellar tumour
14	F	24	Brain glioma	Craniotomy for occipital tumour
15	F	22	Brain glioma	1. ETV and biopsy of 3rd ventricular tumour
		22		2. Insertion of VP shunt
		25		3. Infratentorial supracerebellar approach for debulking of posterior third ventricular tumour
16	F	53	Brain glioma	1. Biopsy of right temporal tumour
		53		2. Debulking of right temporal tumour
17	F	17	Brain glioma	1. Posterior fossa craniotomy for cerebellar tumour
				2. Right parietal craniotomy for callosal tumour
18	M	24	Brain glioma	Stereotactic biopsy of left parietal tumour
19	F	59	Non glial CNS tumour	1. R parasagittal craniotomy for resection of meningioma
		59		2. Wound washout and bone flap removal
20	M	24	Chiari malformation	Foramen magnum decompression and VP shunt insertion
21	M	42	Chiari malformation	Foramen magnum decompression
22	F	35	Chiari malformation & scoliosis with syrinx	1. Syringo-subarachnoid shunt
		37		2. Syringo-peritoneal shunt
23	F	35	Ventriculomegally	VP shunt insertion
24	M	73	Ventriculomegally	VP shunt insertion
25	F	32	Extensive plexiform neurofibroma	1. Biopsy of suboccipital tumour
		32		2. Resection of suboccipital neurofibroma
26	M	21	Extensive plexiform neurofibroma	Insertion of cranioplasty
27	M	27	Epilepsy	Right temporal lobectomy with amygdalohippocampectomy

treated by Neurosurgeons, plastic surgeons etc. locally if more convenient for them.

This paper reviews the neurosurgical related activity that has arisen from the service to share the experience accumulated since the inception of the service.

3. Patients & methods

We have conducted a retrospective review of the adult neurosurgical activity related to the complex NF1 service in Manchester from 2009 to 2017 (since becoming a nationally designated service) including all NF1 Neurosurgical MDTs, NF1 Neurosurgical clinics and all neurosurgical procedures carried out in NF1 patients.

4. Results

4.1. Neuro-NF1 MDTs

From July 2009 to July 2017, 1505 cases have been discussed at the monthly neuro-NF1 MDT.

4.2. Neurosurgical NF1 clinics

The neurosurgical NF1 clinics are held on a monthly basis with a dedicated complex NF1 neurosurgeon and a specialist nurse. From October 2010 to July 2017, there have been 171 clinic appointments and 64 new patients have been seen, aged 18-71yrs, mean age 36 years (median: 34 years).

4.3. Neurosurgical operations

Since 2010, there have been a total of 43 operations on 27 (11 males and 16 females) of our complex NF1 patients. Table 2 lists these interventions. The median age at time of operation was 27 years.

The most frequent neurosurgical interventions for our cohort of NF1 patients are resection of intraspinal neurofibromas and central nervous system tumors.

4.3.1. Spinal operations

A total of 15 spinal operations were performed on 9 patients, with 4 patients undergoing two or more separate procedures (see Table 3).

The majority of the patients underwent resection of spinal tumors, predominantly neurofibromas, with all but two patients harboring multiple level lesions. Three cases also underwent spinal fixation at the time of tumor resection.

In all but two cases, the decision to operate was based primarily on the evidence of progressive neurological symptoms; of the remaining 2 patients, one had imaging suggestive of MPNST and the other asymptomatic increase in a previously operated residual tumor. The most common presenting symptoms were: myelopathy in five cases (three quadriparesis, one paraparesis, and one monoparesis with urinary symptoms); back pain and radicular pain in two cases and one case of neck pain.

Histology was in keeping with neurofibroma in 6 patients, MPNST in one and schwannoma in the remaining patient.

The follow-up period ranged between 3–60 months. All patients demonstrated symptom improvement or resolution after surgery with no subsequent deterioration at follow up. One patient showed progression of the residual tumor at 24 months and subsequently underwent a further operation with compete resection of the lesion plus spinal fixation. Progressive kyphotic deformity was observed in two patients at follow up (see below).

The remaining spinal operations were fixations. One patient presented with C2/C3 subluxation (following previous resection of multiple cervical neurofibromas with Hartshill frame fixation 20 years ago) and he underwent posterior upper cervical fixation. Twelve months

Table 3
Indication and outcome for spinal operations since 2010.

Patient	Surgical intervention	Indication	Length of f/u	Outcome
1	Cervical laminectomy & resection	Worsening myelopathy (paraparesis)	36 months	Improvement in weakness, no progression of residual tumour
2	Cervical laminectomy & resection	Worsening myelopathy (quadraparesis)	36months	Improvement in weakness, no progression of residual tumour
3	1 Cervical laminectomy & resection	1 Worsening myelopathy (quadraparesis)	60 months	1 Improvement in UL weakness, static LL, progressive kyphotic deformity
	2 Anterior Spinal Fixation	2 Progressive kyphotic deformity	24 months	2 Good correction, no progression
4	1 Thoracic laminectomy & resection	1 Backpain, left leg pain and weakness	24months	1 Resolution of pain and weakness, progression of residual tumour
	2 Thoracic laminectomy, resection & posterior spinal fixation	2 Increase in size of residual	12months	2 Complete resection
5	Cervical laminectomy, resection & posterior spinal fixation	Neck pain, concern of malignancy	12months	Resolution of pain, complete resection
6	1 Posterior Spinal fixation	1 Progressive subluxation	12months	1 No progression of deformity
	2 Anterior Spinal fixation	2 Fixation site fracture following fall	3 months	2 Further fracture through site of previous posterior fixation
	3 Revision posterior cervicothoracic fixation C2-T8	3 Further insufficiency fracture, failed hartshill frame	4 months	3 Good alignment
7	1 Cervical laminoplasty & resection	1 Worsening myelopathy (quadraparesis)	24months	1 Improvement in weakness, progressive kyphotic deformity
	2 Anterior Spinal fixation	2 Progressive kyphotic deformity	6 months	2 Good cervical alignment, increase in size of lumbar neurofibromas
	3 Lumbar osteotomy & resection	3 Foor drop, urinary urgency	Awaited	
8	Cervical and thoracic laminoplasty, resection & posterior spinal fixation	Urinary symptoms, LL monoparesis	12months	Resolution of urinary symptoms and weakness, no progression of residual
9	Lumbar laminectomy & resection	Back pain and sciatica	24months	Resolution of symptoms, no recurrence of tumour

Table 4
Indication and outcome for CNS tumour operations since 2010.

Patient	Surgical Intervention	Indication	Histology	Length of f/u	Outcome
11	Craniotomy & tumour resection	Headaches, mass effect	Anaplastic glioma undetermined WHO III	64months	No recurrence, resolution of symptoms
12	Craniotomy & tumour resection	Headaches, mass effect	Oligodendroglioma WHO III	36months	Small recurrence at 3yrs, undergoing further medical treatment
13	Craniotomy & tumour resection	Steady increase in size of lesion	Pilocytic astrocytoma WHO I	24months	No recurrence
14	Craniotomy & tumour resection	Steady increase in size of lesion	Pilocytic astrocytoma WHO I	24months	No recurrence
15	1. Tumour biopsy & ETV	Obstructive hydrocephalus	Pilocytic astrocytoma WHO I	30months	Increase in size of lesion at 30 months
	2. Craniotomy & tumour resection	Increase in size of lesion	Pilocytic astrocytoma WHO I		a/w follow up
16	1. Tumour biopsy	Complex partial seizures	1. Low grade glioma	3months	Tumour progression with high grade features
	2. Craniotomy & tumour resection	High grade features	2. Glioblastoma WHO IV	24months	Patient died
17	1. Craniotomy & tumour resection	Obstructive hydrocephalus	Pilocytic astrocytoma WHO I	20months	No recurrence
	2. Craniotomy & tumour resection	Increase in size of lesion	Pilocytic astrocytoma WHO I	a/w	a/w follow up
18	Stereotactic biopsy	Increase in size of lesion	Ganglioglioma WHO I	a/w	a/w follow up
19	Craniotomy & tumour resection	Increase in size of lesion	Transitional meningioma WHO I	12months	No recurrence

later he fell and suffered a fracture at the site of his previous Hartshill frame fixation. This was managed with anterior fixation at this level. Progressive kyphotic deformity and a further insufficiency fracture at the level of his Hartshill frame was found during follow-up that was treated with revision/extension of his posterior fixation and removal of the Hartshill frame. The other two operations were anterior fixations for correction of progressive kyphotic deformities that occurred in two out of nine laminectomy patients. These kyphotic deformities developed at 24 months and 60 months after initial surgery.

4.3.2. Brain tumor operations

Since 2010, 11 brain tumor operations have been carried out on 9 NF1 patients: 3 biopsies and 8 craniotomies for tumor resection (see Table 4).

4.3.2.1. Pilocytic astrocytomas. We have operated on five patients with suspected pilocytic astrocytomas (one had 2 separate lesions).

Two presented with obstructive hydrocephalus, one from a cerebellar and the other from a posterior third ventricular lesion; the former was also noted to have an enlarging callosal tumor on subsequent surveillance imaging.

A third patient presented with significant mass effect from the tumor and the remaining two patients had lesions that were steadily growing over a surveillance period of 3 and 5 years respectively.

We performed four gross total resections (2 supratentorial and 2 infratentorial), one subtotal debulking (callosal lesion) and one biopsy and subsequent debulking of the 3rd ventricular pilocytic astrocytoma

After revision of the original slides for this study, the diagnosis of pilocytic astrocytoma was confirmed in four tumors; the remaining two lesions had features of a glioma of undetermined type. One these two latter tumors showed low-grade features and the other showed anaplastic features consistent with a WHO grade III glioma. Immunoreaction for IDH1R132H was negative in both tumors. ATRX expression was preserved and there was no p53 expression.

All of the patients who underwent gross total excision (including the anaplastic glioma, who also received adjuvant radiotherapy) have to date remained recurrence free at follow up.

The patient with the 3rd ventricular tumor has now been referred for chemotherapy for enlarging residuum. Finally the patient with the subtotal resection of callosal lesion remains radiologically stable with no further growth to date.

4.3.2.2. Other cases. One patient presented with headaches and neuroimaging features suggestive of a low-grade glioma (see Fig. 1). She under went a gross total excision that histologically confirmed a WHO grade III, IDH1R132H mutant and 1p19q co-deleted oligodendroglioma (Fig. 2). She developed a small recurrence after 3 years requiring further treatment.

Another patient presented with complex partial seizures. Pre-operative MRI suggested a glioblastoma, which was confirmed histologically. The lesion was IDH1 wild type. ATRX was retained. She underwent further treatment with radiotherapy and temozolamide chemotherapy and died 2 years later.

One young male presented with an increasing enhancing callosal abnormality and underwent stereotactic biopsy. Pathological features were consistent with ganglioglioma.

The final tumor case was that of a female patient with headaches that had a craniotomy for a convexity WHO grade I transitional meningioma that had been increasing in size on serial imaging.

4.3.3. Other surgical procedures

Three patients presented with symptomatic Chiari malformations and underwent foramen magnum decompression with one of them requiring further surgery for syringoperitoneal shunt for progressive symptomatic syrinx.

Three patients developed symptomatic ventriculomegaly and

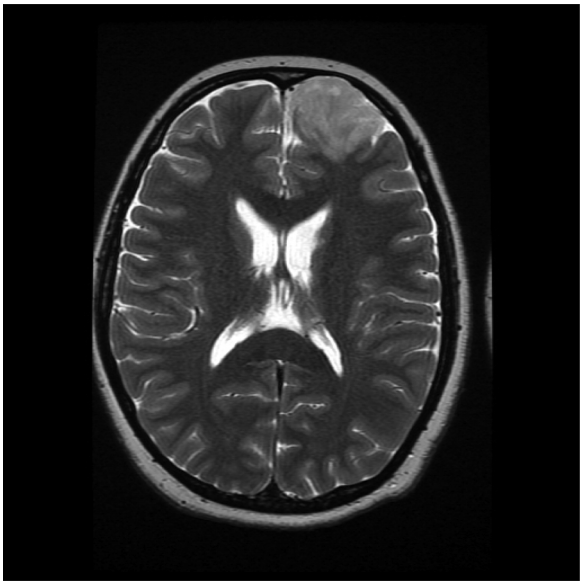

Fig. 1. Axial T2 MRI shows an intra-axial mass in the left frontal pole involving both grey and white matter with some gyral expansion. The lesion is scalloping the inner table of the left frontal bone indicating it is longstanding (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

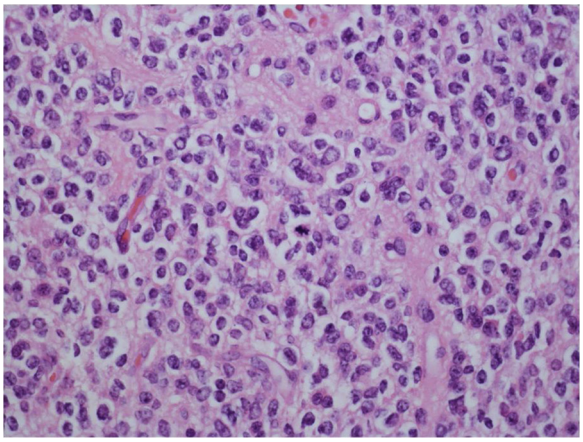

Fig. 2. H&E staining demonstrating WHO grade III, IDH1R132H mutant, 1p19q deleted oligodendroglioma.

underwent shunt insertion (the anatomy was not favorable for endoscopic third ventriculostomy).

Two patients underwent resection of enlarging diffuse neurofibromas of the scalp with the collaboration of plastic surgeons; one required simultaneous cranioplasty to cover a large skull defect from chronic bone scalloping.

One patient presented with intractable epilepsy having been on a number of anticonvulsants and Video EEG captured seizures arising from the right temporal lobe. He underwent a right temporal lobectomy and amygdalo-hippocampectomy, with histology in-keeping with mesial sclerosis. He remained seizure free 60 months following his surgery.

5. Discussion

Patients with Neurofibromatosis can exhibit a wide range of complications that can involve any systems. It is thought that one or several neurological manifestations can be observed in up to 55% of patients however only 1–2 % of patients with NF1 will require a neurosurgical intervention during their lifetime versus 6% requiring plastic surgery [3].

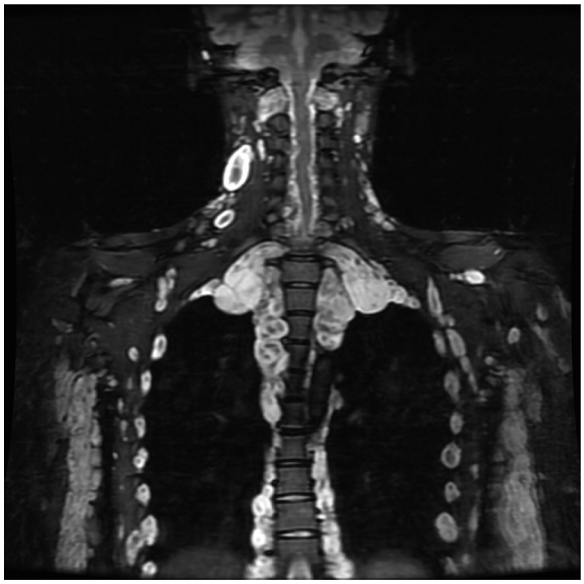

Fig. 3. Coronal STIR MRI of the neck shows undulation of the cervical cord due to intradural extension of the segmental neurofibromas. Extensive internal tumour burden is evident in this spinal variant.

We have presented an overview of the specialist, tertiary referring NF-1 service in our institution and summarized the neurosurgical activity.

5.1. Spinal surgery

In our series, most of the neurofibromas requiring intervention seem to be in patients with multiple spinal lesions (see Figs. 3 and 4). Similar to Leonard et al. [12] the worse level of compression occurred at the C2 level. C2 neurofibromas had significantly higher rates of intraspinal extension, bilateral location, intradural invasion and radiological cord compression than lesions at other levels of the spine.

All our patients experienced symptom improvement or resolution after surgical intervention. The correct indication for surgery is key to

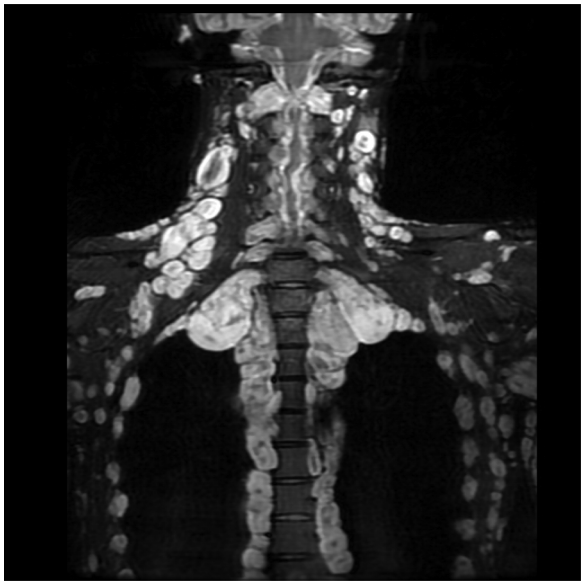

Fig. 4. Coronal STIR MRI of the neck 42 months later showed more pronounced side-to-side cord compression by progressive enlargement of the intradural components of the segmental tumours.

successful outcome; in our unit we reserve surgery for patients with progressive symptoms rather than radiological evidence of progression. The importance of a comprehensive neurorehabilitation service cannot be underestimated to achieve a speedier postoperative recovery.

Spinal surgery in the setting of NF1 is complicated by difficulty in achieving bony union, neuromuscular weakness, dural ectasia and osteopenic bones and sometimes very thin pedicles that make instrumented fixation difficult.

If surgery is performed for neurological compromise, in patients with multiple intracanalicular tumors, our preference is to concentrate on the tumors causing the greatest degree of cord compression. Surgery is performed with laminoplasty that makes it easier for revision surgery at a later date.

If surgery is performed for deformity or instability, an anterior column buttressing instrumentation is preferred with or without posterior stabilization.

5.2. Cranial tumors

It is well established that patients with NF1 have a predisposition for CNS tumors. In a large cohort of 100 NF1 patients with histologically proven gliomas that included autopsies and both adults and children, 49% were pilocytic astrocytomas, followed by infiltrating astrocytomas (27%) and indeterminate astrocytomas (19%) [16].

Data from the London NF1 National center, including both pediatric and adult tumors, from 100 patients with non-OPG gliomas suggested that the majority were scanned for non-glioma related reasons and 40% eventually required surgery [2].

Overall the pattern of genetic and epigenetic alterations for gliomas occurring in NF1 patients is not fully understood as well as their comparability to sporadic gliomas. NF1 pilocytic astrocytomas have different oncogenic molecular mechanisms such as differential activation of various signaling pathways, including the MAPK- and mTOR-pathways [9]. Other important factors in gliomagenesis in NF1 may be found in the tumor microenvironment and include angiogenesis and the production of growth factors by stromal cells.

Our service has a significant number of NF1 patients (approximately 140 recorded in our database) with a radiologically presumed pilocytic astrocytoma. In our experience over the years NF1 patients, pilocytic astrocytomas appear to show different localization patterns and a more indolent course than sporadic cases; therefore we can reassure and counsel our patients accordingly

OPGs are under-reported in the adult NF1 population, but some bulkiness in the optic nerve is commonly observed, which may represent the asymptomatic optic pathway gliomas that persist throughout the lifespan.

There is currently no recommended cranial MRI screening protocol for patients with NF1, whether or not they have non-optic pathway gliomas. Our current protocol offers annual monitoring scans to patients with asymptomatic gliomas for the first years; afterwards and once stable, we can usually relax our radiological surveillance. In our NF1 Neuro service, we employ specific imaging protocols, as discussed in the neuroimaging section.

5.3. Hydrocephalus

Hydrocephalus may be caused by intrinsic tectal mass, retrochiasmatic progression of OPGs and focal proliferation of periaqueductal subependymal glial cells [1]· In our series, two cases were associated with Chiari malformation; one with posterior third ventricular tumor and one had a picture of normal pressure hydrocephalus. The slow spread of OPGs, the favorable outcome of brainstem intrinsic tumors in patients with NF1, the extremely low rate of growth and the non-progressive behavior of the periaqueductal subependymal glial tumors[1] suggest that a close systematic radiological follow-up is probably unnecessary in adults with hydrocephalus.

5.3.1. Neuroimaging in NF1

Neuroimaging is divided into brain and spine, using our modified protocols that are specifically designed to provide economical but comprehensive assessment for the recognized NF1 related findings. They are performed separately from whole body MRI scans which is employed for different indications, including surveillance of plexiform neurofibromas or other large internal lesions. Brain imaging incorporates the assessment of the anterior visual pathways, whilst spinal imaging includes coronal sequences to assess the brachial and lumbosacral plexuses

In the last nine years, the experience accrued from local and external scan reviews has significantly increased our knowledge of imaging findings. The changes over time on serial imaging, or the lack of these, have also given us confidence in making clinical decisions. New diagnoses of NF1, including segmental NF1, have been correctly made based on recognition of NF1 associated features and the integration of them into the diagnostic process, particularly for patients in whom skin or other externally visible features were scant or absent.

Thorough assessment of scans often revealed multiple unexpected findings, most of which may be clinically asymptomatic and can be missed in a non-specialist setting. Occasionally, serious pathologies such as unexpected extra-CNS neoplastic lesions were identified.

All the imaging from external referrals for discussion at our NF1 MDT is formally imported into local PACS, reviewed and reported. These reports are returned to the referrer, constituting a second opinion.

5.3.2. Genetic basis of disease in the NF1 neurosurgery cohort

Of the 27 patients, results of mutation testing were available for analysis for 19. Two of these 19 patients had negative NF1 mutation testing, one of whom (patient 25) had clinically mosaic disease, with a plexiform neurofibroma and no more generalized features of NF1, consistent with the lack of a mutation in her blood. The other patient with no identifiable germ line mutation in blood (patient 1) is undergoing further investigation. The proportions of different types of mutations in the neurosurgery cohort appeared similar to those observed in the total NF1 population tested in the Manchester laboratory and those reported elsewhere: 9 frameshift mutations (47% of total), 5 mutations affecting splicing (26%), and one nonsense, one promotor region variant and one likely pathogenic missense variant (5% each) were identified. 12 patients had a parent affected with NF1, 12 had a *de novo* presentation consistent with generalized NF1 and the two remaining patients were clinically mosaic (patients 25 and 26), again comparable to the situation observed in the wider population of patients diagnosed with NF1.

5.3.3. Neuro NF1 MDT and clinics: outcomes of discussions

Monthly neurology/neurosurgery specific MDT meetings have been held since October 2009 and are attended by a geneticist, neurologist, neurosurgeons (with special interest in complex spine and neurooncology), neuroradiologist, clinical nurse specialists and a service coordinator. Patients are referred for discussion about diagnosis, assessment of NF1 and related neurological complications. Families appreciate the benefit of discussion of their management at this level as it provides them with additional reassurance.

Following our now 10-year experience we believe this model offers a patient-centered approach to individuals with this rare condition that can address all their needs “under one roof”. The experience accumulated can be applied in offering the best possible outcome while avoiding important aspects of their condition being missed or overlooked

Reviewing the outcomes of the MDT discussions from the past 8 years emphasizes some of the benefits of the dedicated complex NF1 service for neurosurgical patients. Neuroimaging discussions and outcomes include:

- Review of images arranged by local teams for neurological symptoms in patients without a prior NF1 diagnosis in whom the local team suspect NF1. The specialist neuro-NF1 MDT has been able to substantiate the likely diagnosis and arrange appropriate geneticist follow up or provide reassurance on cases where the imaging findings are not suggestive of NF1.
- Review of images referred by family doctors or local hospital teams for patients with new or worsening neurological symptoms. Advice is offered as to whether the radiological findings are likely to explain the symptoms.
- Reassurance to GPs, local hospital teams and patients about common non-sinister NF1 related imaging findings.
- Regular monitoring of potentially progressive lesions and tumors with advice on timing of follow up imaging.

Neurosurgical specific outcomes include:

- Arranging specialist clinic reviews for patients with NF1-related neurological complications such as CNS tumors and cervical cord compression, as well as for patients referred with probable incidental NF1-related findings (such as likely arrested hydrocephalus); usually these patients are reviewed at the multidisciplinary clinics (after been triaged) therefore they avoid multiple hospital visits. Follow-up appointments may remain with geneticists once neurosurgical condition is dealt with or remain under the joint clinics, if required.
- Advice to local teams on medical alternatives to surgical intervention, on indications for surgical intervention and to arrange transfer of care to the NF1 team to facilitate surgery and/or discuss NF1 specific outcomes of surgical intervention with patients.

6. Conclusion

Our specialist NF1 service may represent a model to adopt in other institutions as it offers a combined expertise of highly specialized team members with experience and knowledge of the natural history of NF1.Timely and appropriate interpretation of signs and symptoms of the disease and the choice of the right set of investigations in this complex group of patients is fostered by the MDT approach, enabling reassurance whenever possible and suggesting appropriate intervention when necessary.

A holistic service like ours offers coordinated care and expedites referrals of patients to relevant specialists. This enables early recognition and appropriate management of life threatening conditions, such as MPNSTs and pheochromocytomas. In addition the service, through its resources is able to keep track, direct and intervene if necessary in the co-ordination of multiple problems in complex cases.

The close collaboration with specialist geneticists enables signposting of atypical cases who may require more complex genetic evaluation. The service offers appropriate genetic counselling to all affected families.

The service offers regular study days with dissemination of up to date clinical information. The concentrated population of large numbers of affected individuals with NF1 within a nationwide, comprehensive health service offers unique opportunities for research and innovation.

Systematic multicenter longitudinal studies and a national database of patients would be valuable in the further evaluation of NF1-associated complications and the natural history of these.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] W.R. Boydston, R.A. Sanford, M.S. Muhlbauer, L.E. Kun, E. Kirk, F.C. Dohau Jret al., Gliomas of the tectum and periaqueductal region of the mesencephalon, Pediatr. Neurosurg. 17 (1992) 234–238.
[2] S. Byrne, S. Connor, K. Lascelles, A. Siddiqui, D. Hargrave, E. Rosalie, R.E. Ferner, Clinical presentation and prognostic indicators in 100 adults and children with neurofibromatosis 1 associated non-optic pathway brain gliomas, J. Neurooncol. 133 (3) (2017) 609–614.
[3] A. Creange, J. Zeller, S. Rostaing-Rigattieri, P. Brugieres, J.D. Degos, J. Reyuz, et al., Neurological complications of neurofibromatosis type 1 in adulthood, Brain 122 (1999) 473–481.
[4] R.E. Ferner, S.M. Huson, Management and treatment of “Complex neurofibromatosis 1”, in: M. Upadhyaya, D. Cooper (Eds.), Neurofibromatosis Type 1, Springer, Berlin, Heidelberg, 2012, pp. 31–45.
[5] R.E. Ferner, S.M. Huson, N. Thomas, C. Moss, H. Willshaw, D.G. Evans, et al., Guidelines for the diagnosis and management of individuals with neurofibromatosis 1, J. Med. Genet. 44 (2) (2007) 81–88.
[6] J.M. Friedman, et al., Neurofibromatosis 1, 2016, in: R.A. Pagon, M.P. Adam, H.H. Ardinger (Eds.), Gene Reviews, University of Washington., Seattle, 1993.
[7] D.H. Gutmann, L.F. Parada, A.J. Silva, N. Ratner, Neurofibromatosis type 1: modeling CNS dysfunction, J. Neurosci. 32 (2012) 14087–14093.
[8] D.H. Gutmann, S.A. Rasmussen, P. Wolkenstein, M.M. MacCollin, A. Guba, P.D. Inskip, et al., Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1), Neurology 59 (2002) 759–761.
[9] J. Helfferich, R. Nijmeijer, O.F. Brouwer, M. Boon, A. Fock, E.W. Hoving, et al., Neurofibromatosis type 1 associated low grade gliomas: a comparison with sporadic low grade gliomas, Crit. Rev. Oncol. Haematol. 104 (2016) 30–41.
[10] A.C. Hirbe, Gutmann, DH. Neurofibromatosis type 1: a multidisciplinary approach to care, Lancet Neurol. 13 (2014) 834–843.
[11] S.M. Huson, D.A.S. Compston, P. Clark, P.S. Harper, A genetic study of von Recklinghausen neurofibromatosis in south east Wales. 1. Prevalence, fitness, mutation rate, and effect of parental transmission on severity, J. Med. Genet. (1989) 704–711.
[12] J.R. Leonard, R.E. Ferner, N. Thomas, D.H. Gutmann, Cervical cord compression from plexiform neurofibromas in neurofibromatosis 1, J. Neurol. Neurosurg. Psychiatry 78 (2007) 1404–1406.
[13] National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis, Arch. Neurol. Chicago 45 (1988) 575–578.
[14] NHS England. 2013/14 NHS Standard contract for complex neurofibromatosis type I service (all ages), (2019) [ONLINE] Available at:18th Aug 2018 https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-comp-neurofib-1.pdf.
[15] S.A. Rasmussen, Q. Yang, J.M. Friedman, Mortality in neurofibromatosis 1: an analysis using US death certificates, Am. J. Hum. Genet. 68 (2001) 1110–1118.
[16] F.J. Rodriguez, A. Perry, D.H. Gutmann, B.P. O’Neill, J. Leonard, S. Bryant, et al., Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients, J. Neuropathol. Exp. Neurol. 67 (3) (2008) 240–249.
[17] D. Viskochil, A.N. Buchberg, G. Xu, R.M. Cawthon, J. Stevens, R.K. Wolff, et al., Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus, Cell 62 (1990) 1887–1892.
[18] F.D. von Recklinghausen, U¨ber die Multiplen Fibrome der Haut und Ihre Beziehung zu den Multiplen Neuromen, Hirschwald A, Berlin, 1882.
[19] M.R. Wallace, D.A. Marchuk, L.B. Anderson, R. Letcher, H.M. Odeh, A.M. Saulino, et al., Type 1 neurofibromatosis gene; identification of a larger transcript disrupted in three NF1 patients, Science 24 (1990) 181–186.