A Phase II Trial - Evaluation of [^{11}C]-Methionine PET in diagnosing Neurofibromatosis 1-malignant peripheral nerve sheath tumours

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Introduction

Neurofibromatosis 1 (NF1) is an inherited disorder that has a major effect on the skin, bone and nervous system. The hallmark lesion is the neurofibroma, a benign peripheral nerve sheath tumour. The complications involve many of the body systems and NF1 is associated with an increased risk of benign and malignant tumours. Malignant peripheral nerve sheath tumours are difficult to diagnose in people with NF1 and high grade tumours have a high morbidity and mortality.

We developed the method of early and late fluorodeoxyglucose (FDG) imaging in NF1 individuals and have found this to be successful in identifying patients likely to have malignant change. In a study of 105 NF1 individuals we demonstrated that FDG PET CT diagnoses MPNST with a sensitivity of 0.89 (95% confidence interval (CI) 0.76-0.96) and specificity of 0.95 (CI 0.88-0.98). The protocol uses both visual assessment and a cut off SUV (standard uptake value is a semi-quantitative measure reflecting the regional metabolic uptake of glucose). The drawback is that benign and malignant lesions are intermingled between SUV 2.5- 3.5 leading to false positive and negative scans.

[^{11}C]-methionine, an amino acid, closely reflects cell protein metabolism and is indirectly related to cell proliferation. This relationship to proliferation is stronger than that of FDG and therefore may have a greater ability to reflect malignant change than FDG.

Aims

The primary aim of our study was to evaluate whether [^{11}C]-methionine is more sensitive and specific than FDG PET CT in evaluating malignant transformation of plexiform neurofibromas in NF1 patients. The secondary aim was to evaluate the safety of [^{11}C]-methionine in patients with NF1 who are at risk of malignant transformation of plexiform neurofibromas to MPNST. We also wanted to compare the semi-quantitative uptake of methionine with genetic analysis of the NF1-MPNST, to identify individuals at risk for NF1- MPNST.

The aim was to recruit 55 participants from Guy's and St. Thomas' NHS Foundation Trust and from Central Manchester Universities Foundation Trust, as they are national neurofibromatosis services with about 800 NF1 patients attending each centre.

Termination of study on 31/12/2013

The study was terminated on December 31st 2013 and the anticipated end of study was May 10th 2014

- The premature termination was primarily due to technical problems with inadequate yield of [^{11}C]-Methionine. There had been previous problems with the IMP because of a flood involving the cyclotron.
- Strenuous efforts were made to recruit participants; people with symptomatic plexiform neurofibromas were given information sheets about the study and a summary of the proposed study was placed on Neuro Foundation website (lay organisation for neurofibromatosis). However, there were significant difficulties in recruiting patients with

this rare disease complication and with stringent inclusion criteria (age >16years and FDG PET CT SUV max delayed: 2 - 8).

- Ethical committee permission was granted on 10.01.2011. The start of the study was contingent on securing approval from the clinical trials office (where there was a high staff turnover) and the study started on 21.11.2011.
- There was difficulty in setting up the second clinical site for recruiting patients in Central Manchester.
- We were unable to look for genetic markers in the samples sent to Cardiff as there were no malignant tumours in the patients recruited.

Assessment of participants and reasons for exclusion

Twenty two individuals were assessed and did not undergo [^{11}C]-Methionine PET (see Table 1). Five patients signed consent and participated in the study.

Table 1

Reasons for not having MET PET	**N**
Too young <16 years	2
Did not consent or withdrew consent	4
FDG PET CT SUV delayed max too high (>8) for inclusion criteria	4
FDG PET CT SUV delayed max (<2) too low for inclusion criteria	4
Technical problems with MET (a) flood involving cyclotron; b) inadequate yield	3
Previous radiotherapy in region of symptomatic neurofibroma	1
Other - (erroneously thought to have had radiotherapy in region of symptomatic neurofibroma)	1
Symptoms not related to neurofibroma on PET	2
Did not complete full scan during initial FDG PET CT	1
Total	22

Recruitment of participants and sample collection for the study

We recruited 5 participants who underwent [^{11}C]-Methionine PET.

Five DNA blood samples were sent to Cardiff and 2 tumours samples were sent and DNA extracted from the tumours.

MET dose

On the day of the study participants 02, 03, 07, 08 received 800MBq (+/- 10%) of [^{11}C]-methionine as stated in the protocol. Participant 05 received 693.48 MBq which was a protocol deviation.

Results

Table 2: Evaluation of MET PET in diagnosing NF1-MPNST – Clinical and FDG PET CT. MET PET results and NF1 mutation analysis

Code	Gender	Age (yrs)	Site of plexiform neurofibroma	FDG PET delayed SUV max	MET SUV	Excision /biopsy	Histology	*NF1* mutation results
02	F	41	Knee	3.2	0.98	No	No	No mutation detected
03	F	29	Thigh	7.4	7.3	Yes	Benign	Nonsense in exon 5
05	F	28	Brachial plexus	5.7	3.02	Yes	Benign	Nonsense in exon 12a
07	M	42	paraspinal	2.8	0.98	Yes	Benign	Splicing mutation in intron 13
08	M	24	Thigh	7.1	3.69	No	No	Nonsense exon 16

DNA samples

The blood and tumour DNA cannot be analysed for tumour markers as there are no malignant tumours in the patients recruited. The samples have been banked in accordance with Cardiff HTA licence.

Table 3: **Evaluation of MET PET in diagnosing NF1-MPNST - length of follow-up, symptoms and other NF1 related problems in 5 NF1 individuals**

Code	Gender	Age yrs	Follow-up mths	symptoms	Other problems
02	F	41	20	None- main symptoms patella-femoral dysfunction	Atypical neurofibroma pelvis
03	F	29	18	More pain – awaiting assessment for excision	MPNST brachial plexus Optic pathway glioma
05	F	28	9	Neurological deficit	L2 MPNST
07	M	42	6	none	MPNST ; low vit D
08	M	24	2	Pain improved	-

Adverse events

No participant had any significant adverse events. Participant 03 had minimal short-lived discomfort in arm from a blood test.

Follow-up

On follow-up on 21/11/2013 participant 03 complained of recurrent pain in plexiform neurofibroma in thigh (biopsy benign). Assessment with a view to surgical excision has been arranged for January 2014.

All participants will remain under long-term care at the Guy's and St. Thomas' NHS Foundation Trust national neurofibromatosis service. They will also have access to our clinical nurse specialist advice line.

Conclusions

We have too few participants to determine whether MET PET is more sensitive and specific than FDG PET CT in diagnosing NF1 associated malignant peripheral nerve sheath tumours. The study has highlighted the difficulties in using MET in this group of patients.

Report

We will report the study outcome in our national neurofibromatosis meeting in 2014.