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Research Report

Cerebral glucose metabolism in adults with neurofibromatosis type 1

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ARTICLE INFO

Article history:
Accepted 21 August 2015
Available online 1 September 2015

Keywords:
Neurofibromatosis type 1
Cerebral glucose metabolism
FDG PET
Thalamus
Amygdala

ABSTRACT

Previous studies with positron emission tomography (PET) and the glucose analog F-18-fluorodeoxyglucose (FDG) in patients with neurofibromatosis type 1 (NF1) suggest reduced cerebral glucose metabolism in NF1 specifically in the thalamus. The latter is distinguished by extensive neural circuitry connections which makes thalamic hypoactivity in NF1 an interesting finding. Yet it is not very well confirmed, since previous studies were limited by small sample size and/or poorly matched control groups. Primary aim of the present study therefore was to compare brain FDG PET between a large sample of NF1 patients and a well-matched control group. Secondary aim was to test for an NF1-associated FDG effect in the amygdala, as increased blood flow in the amygdala has recently been detected in a mouse model of NF1. Fifty adult NF1 patients and 50 gender- and age-matched control subjects were included retrospectively. Voxel-wise comparison of brain FDG uptake was performed using the statistical parametric mapping (SPM8). Additional region-of-interest (ROI) analysis was performed using standard ROI templates. Voxel-based testing revealed a single 11.2 ml cluster of reduced FDG uptake in the thalamus of NF1 patients. There was no further significant cluster throughout the whole brain including the amygdala, neither hypo nor hyper. ROI-analysis confirmed reduction of thalamic FDG uptake in the NF1 group

Abbreviations: AAL, automated anatomical labeling; CNS, central nervous system; FDG, F-18-fluorodeoxyglucose; GABA, gamma-butyric acid; NF1, neurofibromatosis type 1; NPT, neuropsychological testing; PET, positron emission tomography; PNST, peripheral nerve sheet tumors; ROI, region of interest; SPECT, single photon emission computed tomography; SPM, statistical parametric mapping; TOVA, test of variables of attention

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http://dx.doi.org/10.1016/j.brainres.2015.08.025

($p<0.0005$) with a magnitude of 7.6%. In conclusion, adults with NF1 show reduced brain activity specifically in thalamus. There is no indication of abnormal brain activity in the amygdala in humans with NF1.

1. Introduction

Neurofibromatosis type 1 (NF1), an autosomal dominant inherited disorder, is associated with neurological symptoms such as cognitive impairment and motor deficits, but the underlying mechanisms are not well understood (Gutmann et al., 2012). In an attempt to contribute to improved understanding of the mechanisms, previous positron emission tomography (PET) studies with the glucose analog F-18-fluorodeoxyglucose (FDG) have provided indication of reduced glucose metabolism in NF1, specifically in the thalamus (Balestri et al., 1994; Buchert et al., 2008; Kaplan et al., 1997). However, these studies are limited by small sample size and/or poorly matched control groups. In a review on structural and functional brain alterations in NF1, Payne and coworkers reported on numerous magnetic resonance imaging (MRI) morphometric and functional studies, but found brain FDG PET studies in NF1 to be very scarce and pointed out that 'thalamic hypometabolism in both paediatric and adult NF1 cohorts is intriguing and worthy of further study' (Payne et al., 2010).

In addition, a recent study of our group (Apostolova et al., 2015), using cerebral perfusion single photon computed tomography (SPECT) to provide a surrogate for the spatial pattern of synaptic activity (Apostolova et al., 2012), demonstrated increased activity in the amygdala in an NF1 mouse model that exhibits cognitive abnormalities strongly resembling those in humans with NF1 (Costa and Silva, 2003). Further experimental data showed that the amygdala is a key region for neurological impairment in NF1. For example, a MRI study found significant reduction of T2 values in the amygdala of NF1 mice which was correlated with reduction in motor performance (Robinson et al., 2010). Molosh et al. (2014) found disruption in the regulation of classical Mapk pathways in the amygdala of NF1 mice as well as aberrant glutamate and GABA neurotransmission resulting in functional changes in amygdala networks. However, to the best of our knowledge, no previous study has specifically tested for altered brain activity as measured by FDG PET in the amygdala of NF1 patients.

The primary aim of the present study was to confirm altered thalamic glucose metabolism in a large, independent sample of NF1 patients compared to an appropriate age- and gender-matched control group. The secondary aim was to test for altered FDG uptake in the amygdala of NF1 patients.

2. Results

Visual comparison of group mean images revealed reduction of FDG uptake in the thalamus (Fig. 1A and B) but not in the amygdala of the NF1 patients compared to the control subjects. This was confirmed by voxel-based statistical testing which detected a single 11.2 ml cluster of reduced FDG uptake in the NF1 subjects located in the thalamus (Fig. 1C). There were no further significant clusters throughout the whole brain, neither hypo nor hyper.

Correcting for age during voxel-based testing resulted in a very small increase of the cluster of significantly reduced FDG uptake in the thalamus of the NF1 subjects from 11.2 ml without age correction to 11.8 ml with age correction. Age correction did not reveal any further significant clusters throughout the whole brain.

Further confirmation was provided by the ROI analyses. There was a 7.6% reduction of scaled FDG uptake in the thalamus of the NF1 patients which was highly significant according to the homoscedastic t-test (Fig. 2; 87.6 ± 7.6 versus 94.9 ± 7.0 in NF1 patients and control subjects, respectively; Levene test for homogeneity of variance: $p=0.403$; t-test: $t=4.938$, df=98, $p<0.0005$). Univariate ANOVA with group as a fixed factor, gender as a random factor and age as covariate also showed a significant group effect on the thalamic FDG uptake ($p=0.036$). There was a tendency towards a gender effect, male subjects having slightly lower FDG uptake in the thalamus than female subjects similarly in both groups ($p=0.057$), i.e. there was no group*gender interaction ($p=0.783$). Thalamic FDG uptake was not associated with age in the covered age range ($p=0.475$). FDG uptake in the amygdala ROI did not differ between NF1 patients and control subjects (76.3 ± 6.2 and 77.3 ± 8.8 in NF1 patients and control subjects, respectively; t-test: $p=0.423$; ANOVA: $p=0.482$).

3. Discussion

The primary aim of the present study was to test the hypothesis of reduced glucose metabolism in the thalamus of NF1 patients in a large, independent patient sample ($n=50$ is the largest sample of NF1 patients for brain FDG PET reported in the literature). Three previous FDG PET studies have reported reduced cerebral glucose metabolism in the thalamus of NF1 patients. However, these studies comprised small patient samples and/or poorly matched control groups. Balestri and co-workers compared FDG PET in 3 children (9–15 years) and one young individual (20 years) with NF1 to a control group of 9 patients (10–20 years) who had been referred to FDG PET because of various neurological disturbances (Balestri et al., 1994). The 3 children showed widespread areas of hypometabolism localized in the frontal, parietal and occipital cortex as well as in thalamus. Kaplan et al. (1997), who investigated cerebral glucose metabolism by FDG PET in 10 children with NF1, found significant cortical heterogeneity in addition to thalamic hypometabolism. The control group consisted of 5 adults and 4 children, 3 of whom