Journal of the Neurological Sciences 362 (2016) 309–313

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

FDG-PET study of patients with Leigh syndrome

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ARTICLE INFO

Article history:
Received 8 May 2015
Received in revised form 1 February 2016
Accepted 3 February 2016
Available online 4 February 2016

Keywords:
FDG-PET
Leigh syndrome
neuroimaging
positron emission tomography
mitochondrial disease
PET

ABSTRACT

We conducted a [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) study in five patients (median age 11 (range 4–13) years) with Leigh syndrome to evaluate its usefulness for understanding the functional brain dysfunction in this disease and in future drug trials. Four patients were found to have reported mitochondrial DNA gene mutations. The brain T2-weighted magnetic resonance imaging (MRI) showed high-intensity areas in the putamen bilaterally in five patients, caudate bilaterally in four, thalamus bilaterally in two, and brainstem in one. Cerebellar atrophy was observed in older two patients. For disease control, seven age-matched epilepsy patients who had normal MRI and FDG-PET studies were selected. For semiquantitative analysis of the lesions with decreased ^{18}F-FDG uptake, the mean standard uptake value (SUV) was calculated in regions of interest (ROIs) placed in each brain structure. We compared the SUV of nine segments (the frontal, temporal, parietal, and occipital lobes, thalami, basal ganglia, mid-brain, pons, and cerebellum) between patients with Leigh syndrome and controls. The glucose uptake was decreased significantly in the cerebellum and basal ganglia, which could explain the ataxia and dystonia in patients with Leigh syndrome. Although this study had some limitations, FDG-PET might be useful for evaluating the brain dysfunction and treatment efficacy of new drugs in patients with Leigh syndrome. Further study with more patients using advanced methods to quantify glucose uptake is needed before drawing a conclusion.

1. Introduction

Leigh syndrome is one of the most common mitochondrial disorders in children. An estimated *pre*-school incidence in western Sweden is 1 per 34,000 births [1]. It is characterized by neuropathological findings that include bilateral symmetrical lesions in the basal ganglia, thalamus, and brainstem [2–4]. These lesions appear hypodense on computed tomography and show hyperintense signal on T2-weighted and hypointense signal on T1-weighted magnetic resonance imaging (MRI) [2–4]. A comprehensive multicenter study showed that the median age of disease onset is 7 months [5]. The most common clinical features are abnormal motor findings such as hypotonia, dystonia, spasticity and ataxia, followed by abnormal ocular findings, feeding difficulties, epileptic seizures, respiratory dysfunction and mental retardation [5]. Increased level of lactate in the cerebrospinal fluid is significantly correlated to a more severe disease course [5]. 39% of patients had died by the age of 21 years, at a median age of 2.4 years [5]. Recent advances in genetic research have shown that this devastating disorder is caused by mitochondrial and nuclear DNA mutations [5]. Nevertheless, the genetic cause remains unidentified in 40% of patients, in whom discovery of the cause is left for future whole exome sequencing studies [5].

Changes in the basal ganglia, thalamus, and brainstem detected using MRI have long been thought of as one of landmarks for a clinical diagnosis of Leigh syndrome [4], while the role of functional neuroimaging, including single photon emission computed tomography (SPECT) and positron emission tomography (PET), is not clear in patients with Leigh syndrome [6–9]. Hexamethylpropylene amine oxime (HMPAO)-SPECT showed decreased brain perfusion, especially in the cerebellum

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http://dx.doi.org/10.1016/j.jns.2016.02.008
0022-510X/

Table 1
Clinical summary and results of gene analysis of five patients with Leigh syndrome

Patient no.	Sex	Onset	Age at FDG-PET	Initial symptoms	Gene analysis	Clinical symptoms at FDG-PET study	MRI findings at FDG-PET study	FDG-PET findings	Drugs at FDG-PET study
1	M	1 y	4 y	Tremor	Not done	Intellectual disability, truncal ataxia, tremor	Nodular high intensity lesions in the bilateral caudate, putamina and thalami on T2WI	Decreased metabolism in bilateral thalami, basal ganglia, temporal lobes and cerebellum	Vitamin *B*1, biotin, levodopa/carbidopa
2	M	6 y	7 y	Ophthalmoplegia, ptosis, squint	m.T10191C	Epilepsy, ophthalmoplegia, ataxic gait, intellectual disability	Punctate and sparse high intensity lesions in the bilateral putamina and thalami on T2WI, diffuse high intensity lesion in the mid brain on T2WI	Decreased metabolism in bilateral basal ganglia	Vitamin *B*1,biotin, anticonvulsants, levodopa/carbidopa
3	M	3 y	11 y	Ataxic-dystonic gait	m.T14887C	Intellectual disability, truncal ataxia, dystonia, ptosis, ophthalmoplegia, slurred speech	Diffuse high intensity lesions in the bilateral caudate and putamina on T2WI	Decreased metabolism in bilateral basal ganglia, thalami, temporal lobes and mid brain	Vitamin *B*1,biotin, coenzyme Q, dichloroacetate
4	F	1.5 y	12 y	Developmental delay	m.T8993G	Intellectual disability, truncal ataxia, ophthalmoplegia, slurred speech, bed ridden at febrile disorder	Diffuse high intensity lesions in the bilateral caudate and putamina on T2WI, cerebellar atrophy	Decreased metabolism in bilateral basal ganglia, thalami, temporal lobes and cerebellum	Vitamin *B*1, vitamin C, coenzyme Q, vitamin B12
5	M	2 y	13 y	Ataxic gait	m.T8993G	Intellectual disability, truncal ataxia, dystonia, spasticity of the legs, hyperactivity, regression with febrile disorder	Punctate high intensity lesions in the bilateral caudate and putamina on T2WI, cerebellar atrophy	Decreased metabolism in left frontal lobe, bilateral basal ganglia and cerebellum	Vitamin *B*1,vitamin C, biotin, coenzyme Q, arginine

and other structures[7–9]. [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) performed in one patient showed decreased glucose uptake in the putamen and caudate [6]. A recent study used HMPAO-SPECT to evaluate new therapeutic agents for mitochondrial disease, including Leigh syndrome [8–9]. We studied five patients with Leigh syndrome using FDG-PET to evaluate its usefulness for understanding the functional brain dysfunction in this disease and in future drug trials.

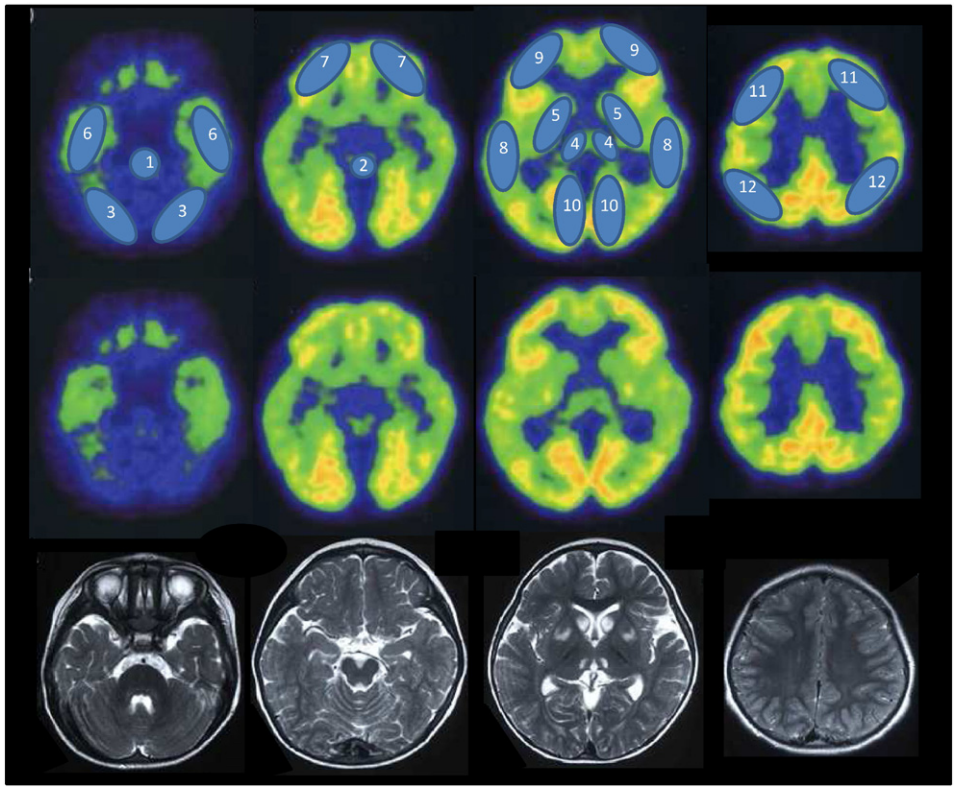

Fig. 1. Layout of the ROIs and the brain MRI (T2WI) in patient 1. ROIs were placed manually in the pons (1), mid brain (2), and bilateral cerebellar hemisphere (3) (at the slice level with the maximum cerebellar hemisphere), thalami (4), basal ganglia (5), and lower temporal (6), lower frontal (7), mid temporal (8), mid frontal (9), occipital (10), upper frontal (11), and parietal cortices (12). The MRI showed nodular high intensity lesions in the bilateral caudate, putamina and thalami on T2WI.