Cerebral glucose metabolism in neurofibromatosis type 1 assessed with [¹⁸F]-2-fluoro-2-deoxy-D-glucose and PET

P Balestri, G Lucignani, A Fois, L Magliani, L Calistri, C Grana, R M Di Bartolo, D Perani, F Fazio

Abstract

Cerebral PET with [¹⁸F]-2-fluoro-2-deoxy-D-glucose has been performed in four patients with neurofibromatosis type 1 (NF1) to assess the relation between cerebral metabolic activity, MRI, and the presence of neurological symptoms, including seizures, as well as mental and language retardation. Widespread hypometabolism occurred in three of the patients. The lesions on MRI, which were localised in the subcortical white matter and grey structures, had normal rates of glucose metabolism. This finding suggests that the abnormalities seen on MRI are not due to defective blood supply, localised oedema, or grey matter heterotopic foci as previously hypothesised. The presence of the hypometabolic areas seems to be inconsistently related to the occurrence of seizures and is not proportional to the degree of mental impairment. This study provides evidence of a widespread cerebral hypometabolism that is not related to the presence of MRI abnormalities; conversely normal metabolism was present in the areas with an abnormal MRI signal.

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Symptoms of cerebral involvement are often reported in neurofibromatosis type 1 (NF1). Seizures, sometimes drug resistant, are present in 3-8% of these patients,¹⁻⁴ mental retardation in 3-8%,^{1,5,6} and learning disabilities in 30-60%.^{1,4,6} The reason for a higher incidence of seizures and cognitive impairment in patients with NF1 than in the general population is largely unexplained. Disorders of cortical architecture and the presence of cerebral heterotopias have also been reported.⁷⁻⁹ The clinical relevance of these findings is still controversial, however, although it has been suggested that they might be related to the occurrence of mental retardation and epilepsy.^{2,8}

Imaging abnormalities of the CNS have been shown by x ray CT¹⁰ and by T2 weighted MRI studies^{10,11} in 34-62% of patients with NF1, and even in patients presenting without neurological symptoms. The lesions are usually oval or round and primarily localised in the basal ganglia, brainstem, and cerebellum. They are found more often in young patients and can disappear or reduce in size with time.^{10,12} Their nature is controver-

sial and the hypothesis has been raised that they might be hamartomatous areas, preneoplastic lesions, areas of free water content, or ischaemia, as well as foci of grey matter in deep white matter.^{10,11,13,14}

The presence of lesions, shown by x ray CT or MRI, in patients with NF1 does not always correlate with the occurrence of neurological deficits¹¹; moreover patients with NF1 may present with different combinations of neurological symptoms, including epilepsy, either with or without detectable morphological lesions.

Diffuse and focal metabolic abnormalities have been shown by PET in patients with epilepsy. Furthermore abnormalities in regional cerebral blood flow have been correlated with developmental cognitive disorders including dysphasia and dyslexia.^{15,16}

In epileptic patients focal PET abnormalities can correlate with paroxysmal activity in the EEG and may coincide with morphological lesions on x ray CT or MRI. In some epileptic patients the presence of areas of abnormal metabolism identified with PET has been attributed to cytoarchitectural disorders and biochemical abnormalities undetectable by conventional imaging techniques.¹⁷ Indeed the assessment of cerebral metabolism in patients with NF1 has the potential of showing focal cerebral abnormalities, characterised by metabolic changes, in regions that appear normal, as well as in those that are pathological in x ray CT or MRI studies. To our knowledge studies of cerebral metabolism with PET in patients with NF1 have not been reported. Thus we have evaluated the cerebral pattern of glucose utilisation in four patients presenting with NF1 to assess the relation between cerebral functional activity, morphological findings, and clinical presentation.

Patients and methods

PATIENTS

We examined four patients, in whom the diagnosis of NF1 was based on the criteria indicated by the Consensus Development Conference,¹⁸ and a control population of nine patients, age range 10-20 years. The nine control subjects were all examined by PET for diagnostic reasons and were all presenting with mild forms of various neurological disturbances; they were five epileptic patients, seizure free for at least six months, two with mild cognitive developmental disabilities, one with headache, and one with spinal amyotrophy; they were presenting either with normal MRI or with aspecific abnormalities on MRI

Institute of Paediatrics, University of Siena, Italy

P Balestri
A Fois
L Calistri
R M Di Bartolo

INB-CNR, University of Milan, Scientific Institute H S Raffaele, Milan, Italy
G Lucignani
L Magliani
C Grana
D Perani
F Fazio

Correspondence to: Dr P Balestri, Institute of Paediatrics, University of Siena, Via P A Mattioli, 10, I-53100 Siena, Italy.

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such as mild enlargement of the subarachnoid spaces or ventricles. Permission for the study was issued by the ethics committee of the Institute H S Raffaele where the PET studies were performed.

PET STUDIES

The synthesis and the quality control procedures for 2- ^{18}F fluoro-2-deoxy-D-glucose (^{18}F FDG) were carried out according to the method previously described.¹⁹ We used an ECAT 931/04-12 tomograph (CPS/Siemens, Knoxville, TN, USA) with an axial field of view of 5.4 cm. All subjects were studied in the resting state with eyes open and ears unplugged; the two patients presenting with epilepsy underwent EEG monitoring during the PET examination. Before each study a 20 gauge Teflon catheter was inserted under local anaesthesia into the radial artery; the patient was then positioned in the PET scanner and the head was restrained by a customised head holder. Scanning was performed parallel to the orbitomeatal line. Two 10 minute consecutive transmission scans, one for each bed position necessary to examine the whole brain, were performed with a $^{68}\text{Ge}/^{68}\text{Ga}$ source external to the subject to measure the coefficients to correct for attenuation of the emitted photons. At the end of the transmission scan each subject received an intravenous injection of about 250 MBq of ^{18}F FDG. Timed arterial blood samples were collected continuously for the first minute after the tracer injection and then at increasing intervals throughout the PET study, to assay the plasma concentration of glucose and ^{18}F . Emission scans were carried out between 45 and 70 minutes after intravenous ^{18}F FDG injection. Data were acquired from two sets of seven equally spaced transaxial planes (four direct and three cross planes; slice thickness 6.75 mm) parallel to the orbitomeatal line covering an axial field of view of 10.8 cm. Scans were reconstructed with a Hann filter with a cut off frequency of 0.5 cycles per pixel. Under these conditions, the spatial resolution in the image plane was 8 mm full width at half maximum. Each image was reconstructed on a 128×128 matrix with a pixel size of 1.56 mm. Correction for attenuation of the 512-keV γ rays by the tissue was performed with the coefficients obtained from the transmission scan. Average values of regional cerebral glucose utilisation (rCMRglc) were calculated in each region of interest based on the plasma glucose and ^{18}F assays. This was according to a model based on the three rate constants operational equation of Sokoloff *et al.*,²⁰ and used the kinetic constant and lumped constant reported by Reivich *et al.*²¹

DATA ANALYSIS

Reconstructed images were transferred to a SUN SPARC workstation for the analyses. Circular regions of interest, with a diameter of 9.6 mm—that is, 1.5 full width at half maximum—were drawn on 13 anatomical-functional cortical, subcortical, and cerebellar

structures, identified from the atlas of Damasio and Damasio.²² The data analysis was carried out on the mean rCMRglc values calculated, for each of the 13 regions, by averaging the rCMRglc values of the multiple regions of interest included in each anatomical region, for both controls and patients with NF1. Because of the progressive decline in normal values of rCMRglc during cerebral maturation,²³ the use of mean rCMRglc values between the ages of 9 and 20 as control values would have been incorrect. On the other hand due to the few available normal controls in this age range, different age matched control groups for each of the different patients examined could not be studied. To overcome this limitation, normal values of rCMRglc for each of the 13 anatomical-functional regions examined were defined by fitting a straight line to the values of rCMRglc determined for each region in the nine controls (age range 10–20; see fig 3). This procedure was adopted as a linear decrease in rCMRglc between 9 and 20 years of age has been reported previously.²³

CASE REPORTS

Case 1

The patient was a boy aged 9 years and 8 months with NF1. At the age of 5 years and 2 months he was referred for language delay. Magnetic resonance imaging showed an area, of about $1.5 \times 1 \times 1$ cm, with increased signal in the right globus pallidus and internal capsule on T2 weighted images. At the age of 8 years complex partial seizures resistant to medical treatment appeared. His IQ was 77 (performance 79; verbal 79), language was severely delayed, and learning disabilities were present. Echo Doppler of the carotid arteries was normal. At this age MRI indicated that the area of hyperintense signal in the right globus pallidus and internal capsule was unchanged (fig 1). Examination by PET at

Figure 1 MRI in patient 1 at the age of 8 years: an area of increased signal is present in the right globus pallidus and internal capsule on T2 weighted images.

Figure 2 Cerebral glucose metabolism using PET with [^{18}F] FDG in patient 1. Two tomographic levels parallel to the orbitomeatal line through the middle part of the brain are presented. The study shows pronounced reduction of metabolism in the temporal-medial-inferior cortex and in the thalamus, and more pronounced reduction in the occipital cortex. The basal ganglia appear well defined in both images. Note the preservation of metabolism in particular in the right globus pallidus in which an increased signal was present on T2 weighted MRI (fig 1).

the age of 8 years and 10 months showed a global cerebral hypometabolism with an involvement of the frontal, parietal, and temporal associative cortices, and the whole occipital lobe, including the calcarine cortex, bilaterally. The thalamus and cerebellar hemispheres were also hypometabolic (fig 2, fig 3). Conversely, normal rCMRglc was detected in the globus pallidus and internal capsule, in which an increased MRI signal was seen (fig 2). An EEG performed during the PET examination showed spikes, polyspikes, and slow waves bilaterally in the occipital areas. The child was being treated with carbamazepine and phenytoin.

Case 2

This patient was a boy aged 11 years and 3 months. The diagnosis of NF1 was made at the age of 2 years and 10 months. x Ray CT at the age of 4 years and 4 months showed a bilateral enlargement of the optic nerves. Areas of decreased density were present bilaterally in the capsulolenticular regions. At the age of 5 years and 9 months two areas, round shapes of hyperintense signal were seen in T2 weighted MRI images in the capsulolenticular regions—about 1.8 cm in diameter in the right hemisphere and 2.5 cm in the left hemisphere—in paravermian white matter, and in the pontomesencephalic regions. Their presence was confirmed by further MRI studies performed at the ages of 8 years and 5 months, 10 years, and 11 years and 3 months. Visual field examinations and EEGs were always normal. His IQ, evaluated at the age of 10 years, was 49 (performance 61; verbal 46), and there was also a severe language delay. Examination by PET at the age of 11 years and 3 months showed a slight metabolic reduction in the frontal regions, more evident on the left. The hypometabolism was also present bilaterally in the parietal cortex and in the thalamus; it was normal in the capsulolenticular regions with abnormal MRI signals (fig 3).

Case 3

This patient was a 15 year old girl. She was referred for evaluation at the age of 7 years.

Mental development was in the low normal range (IQ 89; performance 94, verbal 84). Cerebral x ray CT and EEG repeated at the age of 10 years were normal. At the age of 12 years an area, about $1 \times 0.8 \times 0.8$ cm, of increased signal was found in the right splenium by T2 weighted MRI; small areas of increased signal were also detected in the internal capsule and striatum bilaterally, pons, and cerebellar white matter. These areas were unchanged at the age of 13 years and 6 months and 14 years and 6 months. Echo Doppler of the carotid arteries was normal. A PET study on this 15 year old patient showed global cerebral and cerebellar hypometabolism. The whole frontal, temporal, parietal, and occipital cortex, including the calcarine cortex, was bilaterally involved. For the subcortical structures only the thalamus showed a profoundly reduced metabolism, whereas the basal ganglia were almost within normal range. A normal metabolic activity was present in the areas with hyperintense signal on MRI (fig 3).

Case 4

The patient was a 20 year old man. At the age of 2 years and 6 months he presented with a prolonged febrile seizure after a coma lasting 12 hours. The diagnosis of NF1, suspected at this time, was confirmed at the age of 17 years. His IQ was not assessed but a global psychological evaluation indicated a mental development in the low normal range. At the age of 9 years and 6 months simple and complex partial seizures appeared and were not responsive to medical treatment. An EEG showed paroxysmal activity in the bifrontal areas and subsequently a right temporal focus. A slight enlargement of the right cerebral ventricle was shown by x ray CT and confirmed by MRI at the age of 18. At the age of 20 years PET indicated the presence of normal cerebral metabolism. The metabolism in the cerebellar hemispheres was slightly reduced (fig 3). An EEG during PET examination indicated the presence of slow waves in the right temporal cortex. The patient was being treated with carbamazepine.

Figure 3 Values for rCMRglc determined in the right (○) and left (●) hemisphere, in 13 discrete brain regions, for four patients with NF1. Values for rCMRglc in nine controls are indicated by △ and a continuous line on each graph. Patients were numbered 1 to 4 according to age (patient 1 9 years and 8 months; patient 2 11 years and 3 months; patient 3 15 years; patient 4 20 years). Horizontal axis is age (y); vertical axis is rCMRglc (mg/100/min).

Discussion

This study of cerebral metabolism in four patients with NF1 showed the presence of reduced metabolic activity in numerous areas that appeared normal at MRI. Conversely normal metabolic activity was detected in areas with an abnormal MRI signal.

In case 1—who presented with drug resistant epilepsy and EEG abnormalities localised bilaterally in the occipital cortex—the areas of hypometabolism were more widespread than the EEG abnormalities. This finding is consistent with previous PET studies in patients with seizures indicating that epileptic areas are hypometabolic in the interictal periods.^{17,24} Phenytoin may affect brain metabolism,²⁵ but treatment with phenytoin is insufficient to explain the severity of hypometabolism in this case. It is also important to notice that no metabolic alterations were detected in patient 4, presenting with drug resistant epilepsy and EEG abnormalities in the temporal cortex, whereas diffuse reduced glucose utilisation was present in the two patients without history of seizures or EEG abnormalities (patients 2 and 3). Thus the hypometabolic

pattern found with PET in three out of four patients with NF1 seems to be inconsistently related to the presence of epilepsy.

The possibility of a relation between cerebral hypometabolism and cognitive impairment in this series of patients with NF1 should be considered. Patients 1 and 3, presenting with low to normal intelligence, showed a global hypometabolism; patient 1 also had a severe language delay. Patient 2 had moderate to severe mental retardation and a severe language delay; however, the reduction of cerebral metabolism in this case was less severe and widespread than in patients 1 and 3. Thus, cerebral hypometabolism does not seem to be reduced in proportion to the degree of mental impairment and language retardation. As selective neuropsychological testing was beyond the aim of this study, the relation between location of the hypometabolism and the presence of specific cognitive disabilities cannot be properly considered in the present series.

The pronounced hypometabolism of the calcarine cortex in patients 1 and 3 might be related to the frequent involvement of the

optic pathways and in particular of the optic nerve in NF1^{1,26}; however, a visual impairment was not found in these two patients, or in case 2 presenting with bilateral enlargement of the optic nerves.

It is possible that metabolic alterations are related to microscopic disorders of cortical architecture,²⁷ but this cannot be confirmed in our patients in the absence of a histopathological examination.

Metabolic activity was normal in the subcortical grey structures that appeared hyperintense on MRI T2 weighted images in all cases. As it has been reported that small lesions in the white matter do not produce detectable reductions in metabolism,²⁸ it cannot be excluded that the failure in detecting metabolic abnormalities in the small areas of abnormal MRI signal in case 3 is due to the location of only a few hyperintense areas in the white matter or to their size being smaller than the spatial PET resolution. The metabolic activity was also normal in the large areas with an MRI hyperintense signal in the basal ganglia in patients 1 and 2, and in the right splenium in patient 3. Therefore, the hypothesis that hyperintense T2 weighted images represent areas of defective blood supply or variations of intracellular or extracellular water content seems unlikely. The presence of foci of grey matter is not compatible with our results because in these situations glucose utilisation has been reported to be increased.²⁷ Studies by PET were not able to add further clarification concerning the possibilities that these images could have originated from tumours. On the other hand a stereotactic biopsy of the high signal intensity areas, performed in three cases to our knowledge, did not show evidence of neoplasm or cytoarchitectural disorganisation in one patient with NF1,²⁹ and in two other patients it was consistent with hyperplastic or dysplastic glial proliferation, supporting a malformative rather than a neoplastic nature of the lesions.³⁰ A follow up of these patients by MRI is advisable, in consideration of the fact that invasive diagnostic procedures (for example, brain biopsy) seem justified only when a relation exists between lesions and clinical symptoms.

In studies relating PET and MRI, the occurrence of abnormal metabolic patterns in areas remote from morphological lesions is a common finding, usually attributed to neuronal deafferentation after the interruption of neuronal pathways at the site of the morphological lesion. In our patients, however, the presence of hypometabolism does not seem related to the lesion of any specific neuronal pathway, including the areas of abnormal MRI signal.

In conclusion, the MRI abnormalities and the metabolic alterations in the brain appear as two distinctive features of NF1. Our results indicate that metabolic activity is normal in areas that appear abnormal with MRI or x ray CT. Moreover, this study provides evidence of a widespread metabolic involvement of the CNS in patients with NF1 that is not proportional to the degree of neuropsychological deficit. In patients with NF1 cerebral biopsy is not usually justified and histopathological

examination is possible only postmortem. Serial MRI and PET studies may help to understand the meaning of these findings.

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