Cerebral Glucose Hypermetabolism in Friedreich's Ataxia Detected with Positron Emission Tomography

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Local cerebral metabolic rate for glucose was studied with ^{18}F-2-fluoro-2-deoxy-D-glucose and positron emission tomography (PET) in 22 patients with Friedreich's ataxia and 23 age-matched normal control subjects. The diagnosis of Friedreich's ataxia was established by the history and physical findings and by excluding other diseases through laboratory investigations. PET studies revealed a statistically significant widespread increase of local cerebral metabolic rate for glucose in the brains of patients with Friedreich's ataxia who were still ambulatory, in comparison with normal control subjects. Nonambulatory patients with Friedreich's ataxia, in comparison with normal control subjects, had significantly increased local cerebral metabolic rates for glucose in the caudate and lenticular nuclei, but not in the other structures studied. The rate was significantly greater in ambulatory patients with Friedreich's ataxia than in nonambulatory patients in all structures studied except the caudate and lenticular nuclei. The data suggest that early in the course of Friedreich's ataxia, the local cerebral metabolic rate for glucose is increased extensively in the central nervous system, and as the disease progresses, it decreases in a regionally specific manner.

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Friedreich's ataxia (FA) is a chronic progressive neurological disorder inherited as an autosomal recessive trait with the abnormal gene located on chromosome 9 [1–6]. The disorder usually begins before puberty with progressive ataxia of gait and muscle weakness. As these symptoms worsen, other disturbances appear and include: limb ataxia; dysarthria; scoliosis; pes cavus; loss of position sense, vibration sense, and light touch sensation of the limbs; loss of the deep tendon reflexes; and the appearance of extensor plantar responses [1–4]. Nearly all patients eventually require a wheelchair because of progressive weakness and ataxia of the legs. A cardiomyopathy occurs and usually accounts for death by middle age [7]. Some patients with FA develop diabetes mellitus [5].

The principal neuropathological changes in FA involve the peripheral nerves and the spinal cord [1, 4, 8–11]. Degeneration occurs in peripheral sensory nerves, dorsal root ganglia, and dorsal roots. Within the spinal cord, there is degeneration of posterior columns, lateral corticospinal tracts, and dorsal and ventral spinocerebellar tracts. The cerebellum and brainstem have been described as normal [11], but in some patients there is shrinkage of the pons and medulla [9, 10]. Occasional patients show patchy atrophy of the Purkinje cells, and in many there is degeneration of neurons in the dentate nuclei [10]. Degenerative changes may also occur in the reticular and vestibular nuclei of the brainstem [9, 10].

Many biochemical abnormalities have been reported in fibroblasts, leukocytes, or muscle tissue from patients with FA, but some of these findings are controversial. Deficiencies in activity of the pyruvate dehydrogenase complex and alpha ketoglutarate dehydrogenase complex have been described [12, 13]. Other abnormalities reported include deficiency of mitochondrial malic enzyme activity [14, 15] and of serum lipoprotein lipase [16] and abnormalities of erythrocyte membrane phospholipids, plasma catecholamines, and leukocyte glutamate dehydrogenase activity [5].

In most patients with FA, the characteristic history and physical findings make the diagnosis relatively straightforward [1–4]. In patients with progressive ataxia whose history and physical findings differ from those typical of FA, however, the diagnosis is often

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difficult and requires extensive laboratory testing. The differential diagnosis of these patients includes malformations, degenerations, demyelinative diseases, neoplasms, remote effects of neoplasms, vascular diseases, and metabolic abnormalities [1, 17].

Positron emission tomography (PET) with ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been used to study local cerebral metabolic rate for glucose (lCMRglc) in the central nervous system of patients with olivopontocerebellar atrophy, another degenerative disease causing ataxia [18–20]. A distinctive pattern of hypometabolism was found in the brainstem and cerebellum without involvement of the cerebral cortex, basal ganglia, or thalamus. The present study was undertaken to determine whether a unique pattern might be found in patients with FA as well. Degeneration of spinocerebellar afferents, which terminate in the granule cell layer of the vermis [1], might be expected to result in cerebellar hypometabolism principally within vermal regions. In addition, degeneration of second-order sensory neurons originating in the gracile and cuneate nuclei as well as transynaptic effects from degeneration of first-order sensory neurons [9, 11] might be expected to result in loss of synapses and hypometabolism in the thalamus. Surprisingly, the results of this study demonstrated widespread cerebral hypermetabolism in patients with FA who were still ambulatory, with metabolic rates close to normal control levels in patients with FA who were no longer ambulatory. Preliminary descriptions of this work have been published [21–24].

Materials and Methods

We studied 22 patients with FA and 23 normal control subjects (Table 1). The studies were approved by the institutional review board, and informed consent was obtained from all subjects. Among the patients with FA, the duration of illness averaged 18 ± 7 years and ranged from 6 to 30 years. Ten patients had one or more affected siblings, 11 had no affected relatives, and 1 patient had a cousin who may have FA. The normal control subjects had no history of neurological disease and no significant abnormalities on neurological and general physical examination. The patients and normal control subjects were taking no medication known to affect central nervous system (CNS) function or to cause CNS side effects and subjects with a history of alcoholism were excluded.

The diagnosis of FA was made on the basis of the history, physical examination, neurological examination, and laboratory tests to exclude other diseases. Required findings included ataxia of limb movements and of gait if the patients were still ambulatory; weakness of the lower extremities; ataxic dysarthria; decreased or absent muscle stretch reflexes in the lower extremities; extensor plantar reflexes; and decreased position and vibration sense in the lower extremities. The diagnosis was supported by the findings of scoliosis, pes cavus, decreased pinprick and light touch sensation in the distal parts of the extremities, and atrophy of the distal limb muscles. All patients met the diagnostic criteria of Harding [2]. All patients also met the criteria of Geoffroy and colleagues [25] except one whose age at onset (23 years) is above their limit of 20 years; elimination of this patient from the analysis did not substantially alter the findings of this study. Patients with an atypical history or examination were excluded from the study before their data were analyzed. The patients excluded were a 28-year-old man who had preserved position sense and vibration sense in the legs, a 49-year-old man who had intact deep tendon reflexes in the legs, and a 30-year-old woman who did not have dysarthria. Analyses of duration of illness excluded 6 patients who were not the first member of their family diagnosed with FA, to avoid the bias that may be introduced in determining disease onset when another family member has been previously diagnosed with FA.

Table 1. Average Ages of the Subjects Studied

	Control Subjects		Patients with Friedreich's Ataxia	
	n	Age (yr) (± SD)	n	Age (yr) (± SD)
Male	13	28 ± 5	9	30 ± 7
Female	10	34 ± 9	13	31 ± 7
All subjects	23	30 ± 8	22	30 ± 7

PET studies of normal control subjects and patients with FA were performed with the subjects lying supine, awake, immobile, not speaking, and blindfolded in a quiet room. They were maintained under these conditions from 5 minutes before injection until completion of the scan. ^{18}F-FDG was synthesized by an adaptation of the method of Shiue and associates [26] or of Hamacher and coworkers [27]. Radiochemical purity was greater than 95%. Scans were performed 30 to 75 minutes after intravenous injection of 5 to 10 mCi of ^{18}F-FDG and lasted for 8 to 12 minutes. Each subject was placed in a headholder that maintained the head immobile throughout the study. The head was aligned along the orbitomeatal line with a laser. PET scans were performed with a TCC PCT 4600A tomograph having an inplane resolution of 11-mm full width at half maximum (FWHM) and a Z-axis resolution of 9.5-mm FWHM. Five planes with 11.5-mm center-to-center separation were imaged simultaneously. Four sets of scans were taken per patient, including two interleaved sets through lower brain levels and two interleaved sets through higher brain levels for a total of 20 slices, each separated by 5.75 mm. Attenuation correction was calculated by fitting ellipses to the contour of the scalp outline and modified to account for attenuation from the headholder and skull. Blood samples were collected from one radial artery. lCMRglc was calculated with a three compartment model and single-scan approximation, with gray matter kinetic constants derived from normals.

Regions of interest (ROIs) were studied in the cerebral cortex, basal ganglia, thalamus, cerebellar hemispheres, cerebellar vermis, mesencephalon, and pons. Data from the cerebral cortex were obtained by measuring lCMRglc in the cortical rim from six consecutive slices beginning with the

Table 2. Local Cerebral Metabolic Rate for Glucose (in mg/100 gm/min) in All Subjects[a]

Structure	Control Subjects (n = 23)	Patients with Friedreich's Ataxia (n = 22)	*p* Value
Cerebral cortex	5.80 ± 1.07	6.64 ± 1.30	0.02
Caudate nucleus	6.20 ± 1.32	7.91 ± 1.56	0.0003
Lenticular nucleus	6.82 ± 1.44	8.10 ± 1.64	0.008
Thalamus	6.81 ± 1.46	7.29 ± 1.87	NS
Cerebellar vermis	5.10 ± 1.05	5.55 ± 1.33	NS
Left cerebellar hemisphere	5.59 ± 1.20	6.04 ± 1.61	NS
Right cerebellar hemisphere	5.47 ± 1.18	6.10 ± 1.66	NS
Mesencephalon	5.06 ± 1.02	5.54 ± 1.21	NS
Pons	4.10 ± 0.79	4.46 ± 1.05	NS

[a]Values given are the mean ± SD; statistical test, Student's *t* test.
NS = not significant; $p > 0.10$.

lowest slice containing the basal ganglia. This was accomplished with an algorithm that detects the outer edge of the cortical rim on images that have been passed through a contrast-enhancing filter. The algorithm then identifies a cortical strip on the original image that extends inward from this edge until either the metabolic rate drops below the value on the outer edge of the rim or the strip reaches a width of 15 mm. The mean metabolic rate was computed for each of the ROIs and the final value was a weighted mean of the values from the six individual slices. The ROIs for the basal ganglia consisted of an 11 × 11-mm square on each side of the caudate nucleus and an 11 × 15-mm parallelogram on each side of the lenticular nucleus (putamen and globus pallidus). The other ROIs consisted of an 11 × 11-mm square on each side of the thalamus, a 22 × 11-mm parallelogram on each cerebellar hemisphere, and an 11 × 18-mm rectangle on the cerebellar vermis. For analysis of the mesencephalon and pons, a three-dimensional image set consisting of planes spaced at 3.75 mm intervals in the rostrocaudal direction was generated by interpolation of the two-dimensional images. A midsagittal image, 11 mm in thickness, was derived from this image set. The resulting volume of interest for the mesencephalon was an 11 × 11 × 7.5-mm right parallelepiped, while that for the pons was a 15 × 11 × 15-mm right parallelepiped. The ROIs were centered over a local peak in lCMRglc. For reference, an individual image element (pixel) is 3.75 × 3.75 mm in size. Data were obtained from two slices containing the cerebellum and brainstem, from one slice containing the thalamus, and from one slice containing the basal ganglia. ROIs from the cerebellar vermis were posterior to the fourth ventricle, as determined by direct visualization of the ventricle.

An index of brain volume was developed to compare the patients with FA and the control subjects. The mean cross-sectional area of the brain from the two largest adjacent PET slices was measured, and this value was raised to the 3/2 power.

Statistical analysis was performed with two-tailed Student's *t* tests, analysis of variance, the Newman-Keuls test, and Spearman rank correlation analysis. A *p* value of 0.05 or less was taken as significant.

Table 3. Comparison of Ambulatory and Nonambulatory Patients with Friedreich's Ataxia[a]

	Ambulatory	Nonambulatory	*p* Value
Age[b]	30 ± 7	30 ± 7	NS
Age of onset (yr)[c]	17 ± 4	10 ± 4	0.007
Duration (yr)[c]	15 ± 5	21 ± 5	0.08

[a]Values given are the mean ± SD; statistical test, Student's *t* test.
[b]n = 8 ambulatory, 14 nonambulatory patients.
[c]n = 5 ambulatory, 11 nonambulatory patients (only first patients affected in a family are included).
NS = not significant; $p = 0.95$.

Results

Mean lCMRglc for the entire FA group was 7% to 28% greater than that of the control group for the structures analyzed. Statistical testing revealed significantly increased lCMRglc in the patients with FA, compared with the control subjects, in the cerebral cortex, caudate nucleus, and lenticular nucleus, but not in the thalamus, cerebellar vermis, cerebellar hemispheres, or brainstem (Table 2).

To examine the relationship between the severity of the neurological disorder and lCMRglc, we divided the patients into two groups, ambulatory and nonambulatory. The two groups were equal in age at the time of the study, but the ambulatory patients had a significantly later age of onset than did the nonambulatory patients (Table 3). Mean lCMRglc for the ambulatory group was 23% to 34% greater than that of the control group for the structures analyzed (Table 4, Fig 1). lCMRglc in the ambulatory group was significantly increased, compared with the normal control subjects, in all structures studied except the pons. In contrast, mean lCMRglc for the nonambulatory group ranged

Table 4. Local Cerebral Metabolic Rate for Glucose (in mg/100 gm/min) in Control Subjects and Ambulatory and Nonambulatory Patients with Friedreich's Ataxia (FA)[a]

Structure	Control Subjects (n = 23)	Ambulatory Patients with FA (n = 8)	*p* Value[b]	Nonambulatory Patients with FA (n = 14)	*p* Value[c]	*p* Value[d]
Cerebral cortex	5.80 ± 1.07	7.24 ± 0.80	0.01	6.29 ± 1.42	NS	0.07
Caudate nucleus	6.20 ± 1.32	8.30 ± 1.23	0.002	7.68 ± 1.72	0.005	NS
Lenticular nucleus	6.82 ± 1.44	8.51 ± 1.53	0.03	7.86 ± 1.71	0.03	NS
Thalamus	6.81 ± 1.46	8.58 ± 1.43	0.007	6.55 ± 1.71	NS	0.01
Cerebellar vermis	5.10 ± 1.05	6.28 ± 0.79	0.04	5.13 ± 1.41	NS	0.03
Left cerebellar hemisphere	5.59 ± 1.20	7.09 ± 1.03	0.007	5.45 ± 1.61	NS	0.02
Right cerebellar hemisphere	5.47 ± 1.18	7.17 ± 1.02	0.008	5.49 ± 1.67	NS	0.006
Mesencephalon	5.06 ± 1.02	6.22 ± 0.93	0.03	5.15 ± 1.20	NS	0.03
Pons	4.10 ± 0.79	5.09 ± 0.67	0.07	4.10 ± 1.07	NS	0.03

[a]Values given are the mean ± SD; statistical test, Newman-Keuls.
[b]Comparison of normal control subjects with ambulatory patients with FA.
[c]Comparison of normal control subjects with nonambulatory patients with FA.
[d]Comparison of ambulatory with nonambulatory patients with FA.

NS = not significant; $p > 0.20$.

from 4% less to 24% greater than that of the normal control group for the structures analyzed. lCMRglc was significantly higher in nonambulatory patients than in normal controls for the basal ganglia, but not for the other structures (see Table 4). lCMRglc was significantly greater in the ambulatory patients than in the nonambulatory group in all structures studied except for the cerebral cortex, where the difference approached significance, and in the basal ganglia (see Table 4). The differences between control, ambulatory, and nonambulatory groups are portrayed in Figure 2, in which the data in the two FA groups are normalized to the values of the control group.

To determine whether differences in lCMRglc between the sexes contributed to the observed differences between groups, we compared lCMRglc in patients with FA and normal control subjects using analysis of variance with sex and disease group as factors (Table 5). The results revealed that sex was not a significant factor for any region. Disease group was a significant factor for the cerebral cortex, caudate nucleus, and lenticular nucleus, but not for the thalamus, cerebellum, or brainstem. There was no significant interaction between disease group and sex for lCMRglc values from any region.

Since FA is a progressive disorder, we examined lCMRglc as a function of age and duration of symptoms. lCMRglc declined significantly with increasing age in the caudate nucleus (Spearman rank correlation coefficient $r_s = -0.46$, $p = 0.03$) and lenticular nucleus ($r_s = -0.48$, $p = 0.02$), but lCMRglc did not correlate significantly with age for the other brain regions analyzed ($r_s = -0.29$ to -0.08, $p > 0.20$). lCMRglc did not correlate with duration of symptoms for any region ($r_s = -0.33$ to $+0.06$, $p > 0.20$) in the 16 patients who were the first in the family to develop the disease.

Patients with FA are thought to have an increased incidence of diabetes mellitus [5], and elevation of the plasma glucose level could influence measurements of lCMRglc in the CNS. Only 1 patient, who was nonambulatory, had diabetes mellitus, and his fasting blood glucose was elevated (326 mg/100 dl). His lCMRglc values averaged approximately one standard deviation (SD) above the mean of the nonambulatory group. If this patient's results were eliminated, the data presented in Tables 2 and 4 would change little, and all significant results in these tables would remain significant. Mean fasting blood glucose levels were 87 ± 8 mg/dl (mean ± SD) in the normal control group and 86 ± 8 mg/dl in the FA group, excluding the diabetic patient.

The brain volumes of the patients with FA were compared with those of the normal control subjects. In the patients with FA (n = 22), the mean volume index was 2,080 ± 157 cm^3, whereas in the normal controls (n = 23), the mean volume index was 2,269 ± 230 cm^3. These values are significantly different ($t = 3.22$, $p < 0.003$). This difference was found in both males and females (male FA: n = 9, 2,176 ± 159 cm^3, versus male control subjects: n = 13, 2,390 ± 210 cm^3, $t = 2.59$, $p = 0.02$; female FA: n = 13, 2,013 ± 118 cm^3, versus female control subjects: n = 10, 2,111 ± 146 cm^3, $t = 1.78$, $p = 0.09$). The mean volume index for the ambulatory patients with FA (n = 8, 2,081 ± 175 cm^3) was not significantly differ-

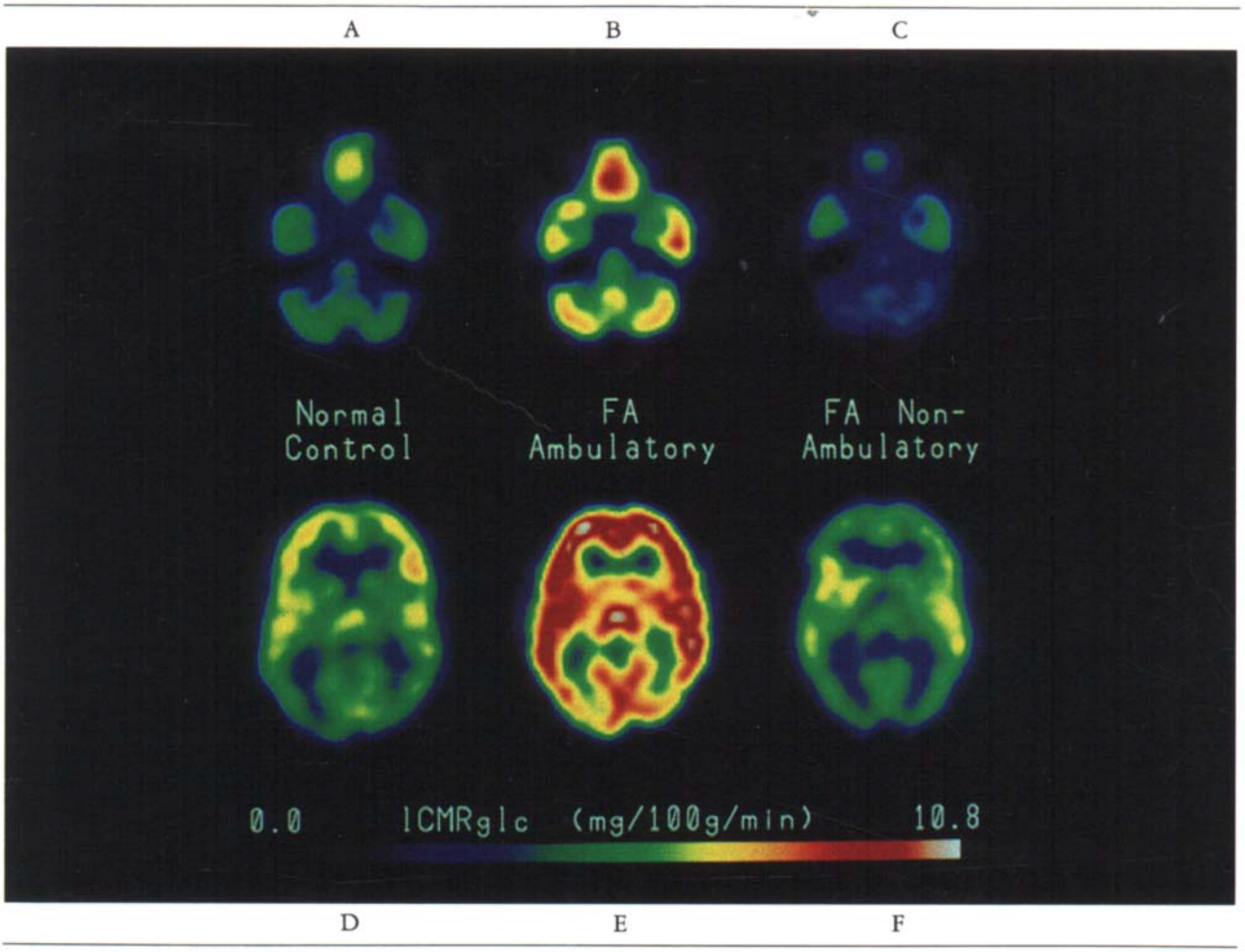

Fig 1. PET scans showing cerebral glucose utilization as detected with ^{18}F-2-fluoro-2-deoxy-D-glucose. Scans in A, B, and C show a horizontal section at the level of the cerebellum and the base of the temporal and frontal lobes. Scans in D, E, and F show the level of the basal ganglia and thalamus. Color bars indicate the rate of glucose utilization (mg/100 gm/min). (A and D) Control subject, female, age 24 years. (B and E) Ambulatory patient with Friedreich's ataxia, female, age 25 years. (C and F) Nonambulatory patient with Friedreich's ataxia, female, age 29 years. Note the glucose hypermetabolism in the ambulatory patient with Friedreich's ataxia compared with the control subject and the nonambulatory patient with Friedreich's ataxia.

ent from the mean volume index for the nonambulatory patients with FA (n = 14, 2,079 ± 151 cm^3, t = 0.02, $p > 0.5$).

Discussion

This study provided evidence of cerebral glucose hypermetabolism extensively in the CNS of patients with FA who are still ambulatory in comparison with age- and sex-matched normal control subjects. Significantly increased lCMRglc also was found in nonambulatory patients with FA in comparison with normal control subjects, but only within the basal ganglia. Ambulatory

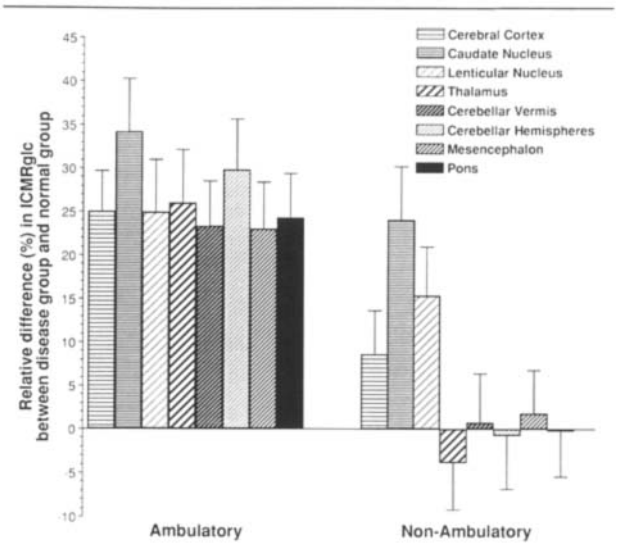

Fig 2. Mean local cerebral metabolic rate for glucose (lCMRglc) relative to the values of the normal control subjects for ambulatory and nonambulatory patients with Friedreich's ataxia. Error bars represent the standard error of the mean.

Table 5. Local Cerebral Metabolic Rate for Glucose (in mg/100 gm/min) in Males and Females[a]

Structure	Male Control Subjects[b] (n = 13)	Female Control Subjects[b] (n = 10)	Male Patients with FA[b] (n = 9)	Female Patients with FA[b] (n = 13)	*p* Value[c]
Cerebral cortex	5.54 ± 0.92	6.14 ± 1.21	6.42 ± 1.07	6.79 ± 1.45	0.04
Caudate nucleus	5.92 ± 1.17	6.56 ± 1.47	7.60 ± 1.40	8.12 ± 1.68	0.0006
Lenticular nucleus	6.50 ± 1.24	7.23 ± 1.64	7.95 ± 1.42	8.20 ± 1.83	0.014
Thalamus	6.24 ± 1.03	7.54 ± 1.67	6.90 ± 1.45	7.55 ± 2.12	NS
Cerebellar vermis	4.75 ± 0.87	5.56 ± 1.13	5.37 ± 1.06	5.67 ± 1.51	NS
Left cerebellar hemisphere	5.26 ± 1.08	6.01 ± 1.27	5.66 ± 1.11	6.31 ± 1.88	NS
Right cerebellar hemisphere	5.13 ± 1.08	5.91 ± 1.20	5.67 ± 1.17	6.40 ± 1.91	NS
Mesencephalon	4.63 ± 0.72	5.62 ± 1.10	5.37 ± 1.09	5.65 ± 1.31	NS
Pons	3.88 ± 0.69	4.39 ± 0.86	4.28 ± 0.97	4.58 ± 1.12	NS

[a]Values given are the mean ± SD; statistical test, analysis of variance with disease group and sex as factors.
[b]Sex is not a significant factor for any region.
[c]*p* Value: disease as factor (comparison of disease group for male and female normal control subjects versus male and female patients with FA).
FA = Friedreich's ataxia; NS = not significant, $p > 0.20$.

patients had significantly higher lCMRglc than nonambulatory patients for all structures except the basal ganglia. Neither the sexes nor the ages of the patients was a significant factor in the findings.

The age of onset of symptoms was significantly greater in patients who were ambulatory at the time of the study than in the nonambulatory patients. This difference is most likely explained on the basis of selection bias. Age 18 was the minimum age at which normal control subjects and patients were eligible for our study in accordance with institutional policy regarding studies with radionuclides in children. In a slowly progressive disease such as FA, patients who remain ambulatory over the age of 18 are likely to be those with a late age of onset. It may also be that our ambulatory patients had intrinsically milder disease or slower progression of disease than our nonambulatory patients. We cannot exclude the possibility that our group of ambulatory patients represents, in part, a different phenotype from the nonambulatory group. Variations in phenotype are known to occur even in kindreds that inherit the same abnormal gene [8, 25, 28, 29].

Our findings may indicate that, early in the course of FA, glucose metabolic rate is increased broadly in the CNS, and as the disease progresses, metabolic rate decreases. The decrease is nonuniform, with the basal ganglia maintaining a higher metabolic rate with disease progression than the other structures studied. The increased metabolism may reflect a fundamental biochemical defect in FA, while the decline in metabolic rate with disease progression may be due to loss of neurons and synaptic terminals. This would explain the finding of more substantially increased metabolic rate in ambulatory than in nonambulatory patients, since typically with disease progression, FA patients lose the ability to walk.

The possibility that the finding of glucose hypermetabolism is artifactual must be considered. The major potential sources of error are FA-specific alterations in ^{18}F-FDG rate constants between subject groups, and smaller brain size in patients with FA than in normal control subjects. The possibility that FA-specific alterations in the rate constants affected our data seems unlikely, since changes in rate constants that cause major errors in the single-scan approximation used to evaluate lCMRglc have not been found in any progressive degenerative neurological disease. We found that patients with FA have smaller brain volumes than normal control subjects; however, this finding is not likely to account for the glucose hypermetabolism. Hatazawa and colleagues [30] found in normal subjects that lCMRglc is inversely proportional to brain volume. Since the small brain volume in patients with FA presumably results from their disease process, it is questionable whether the same relationship applies to them. This relationship clearly does not apply to patients with Alzheimer's disease, who have a decreased volume associated with hypometabolism. Even if this relationship were to apply to patients with FA, the 7% decrease in brain volume compared to normal subjects would account for only a 7% increase in lCMRglc, yet we observed a 23% to 34% increase in lCMRglc in ambulatory patients with FA, compared with normal subjects.

The demonstration of CNS glucose hypermetabolism in patients with FA might be explained by abnormalities of carbohydrate metabolism in this disease [31]. Many patients with FA have been found to have difficulty with the metabolism of pyruvate [32–34]. Following a glucose load, patients with FA typically have elevated blood pyruvate levels [13], and pyruvate clearance is delayed [34]. The precise defect in FA

responsible for abnormalities of carbohydrate metabolism is controversial. Deficiencies of the pyruvate dehydrogenase complex, alpha ketoglutarate, and mitochondrial malic enzyme in FA have been found in some laboratories [12, 15, 35–37] but not in others [32, 38–40]. Perhaps some of the discrepancies in findings relate to the stage of the disease in which the patients' tissues are examined or to different phenotypes of the disease.

Blass and associates [31] suggested that the characteristic biochemical abnormality in FA and related conditions results from damage to mitochondria rather than deficiency of a specific mitochondrial enzyme. Damaged mitochondria may explain some of the controversial biochemical findings [31, 41]. Mitochondrial abnormalities have been invoked to explain much of the pathophysiology of this disease [30, 33] and a mitochondrial disorder could explain the findings in the present study. Glucose hypermetabolism may reflect a needed increase in glycolytic rate because of difficulty in the oxidation of pyruvate to enter the Krebs tricarboxylic acid cycle. Future studies of the mitochondrial abnormalities in FA should take into account the stage of the disease process or the phenotypic expression of the disease since our study suggests that the abnormalities may change with progression of the disease.

We cannot exclude the possibility that an increased value for the lumped constant for fluorodeoxyglucose in FA could partially or completely account for our finding of increased lCMRglc values, which were calculated assuming a normal value for the lumped constant (0.51). An increase in the lumped constant for 2-deoxyglucose has been described in hypoglycemia [42, 43] and is thought to be due to a shift in the rate-limiting step from phosphorylation to transport. Conceivably, an increased value of the lumped constant in FA could share the same mechanism. Alterations in the lumped constant could influence our findings in either of two possible ways. First, the lumped constant could be increased in patients with early disease and could then decline with disease progression. This possibility is unlikely because changes that may occur with disease progression, such as loss of neurons and synaptic connections, would not be expected to reverse the change in the lumped constant substantially. Second, the lumped constant could be increased in all patients with FA, and the decrease in lCMRglc values in nonambulatory patients compared with ambulatory patients could represent a true decline in glucose metabolism associated with loss of neuronal elements.

The difference in metabolism between ambulatory and nonambulatory patients may be due to loss of neuronal connections as the disease progresses. Study of the degree of atrophy in ambulatory as compared with nonambulatory patients in anatomical scans would perhaps clarify this issue. The findings of glucose hypermetabolism within certain structures in ambulatory but not in nonambulatory patients resulted from examining a cross-section of patients. Our speculation that glucose metabolism decreases with progression of FA may be strengthened by longitudinal follow-up of individual patients with repeated testing. We have not studied patients with FA early in the disease process because our PET studies are limited to patients and normal subjects age 18 and older. From our present results, we cannot determine whether patients early in the course of FA have a greater degree or a lesser degree of hypermetabolism than our ambulatory group, most of whom are at an intermediate stage of the disease with a moderate level of disability. Similarly, our data do not make clear whether metabolism declines to a level below that of normal subjects. Examination of patients with FA toward the end of their disease process would be necessary to establish this.

In previous PET studies, the finding of glucose hypermetabolism in steady state is unusual. Increased glucose metabolism has been reported in Down's syndrome [44, 45], anorexia nervosa [46], and autism [47], but in a recent report no definitive evidence of increased metabolism was found in autism [48], and the finding in Down's syndrome is now thought to be artifactual [49]. Thus, FA is one of only a few conditions demonstrated through PET to involve hypermetabolism in steady state.

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