

Brain Glucose Metabolism in Rett Syndrome

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Rett syndrome is a progressive neurologic disorder affecting girls in early childhood with loss of achieved psychomotor abilities and mental retardation. Six sedated female patients (4 to 15 years of age) with a diagnosis of Rett syndrome were studied with [¹⁸F]fluorodeoxyglucose (FDG) and underwent positron emission tomography scanning of the brain. Relative tracer concentrations between different areas of the brain were assessed, and results were compared with 18 age-matched control subjects. Patients were divided into two age groups: 3 to 8 years of age and 9 to 15 years of age. A relative decrease in [¹⁸F]FDG uptake in the lateral occipital areas in relation with the whole brain and a relative increase in the cerebellum was evident in both age groups ($P < 0.001$, unpaired Student *t* test). A relative increase in frontal tracer uptake was observed in the younger group. Sensorimotor areas and relations between cortical and subcortical structures were preserved in all patients. Changes in glucose cerebral metabolism resemble the regional distribution of normal children less than 1 year of age, likely reflecting a maturational arrest. Changes in frontal areas parallel those in postmortem *N*-methyl-D-aspartate receptor densities and could correlate with different clinical stages of the disease. This pattern differs from those described in Down syndrome, autism, and Alzheimer's disease. © 2002 by Elsevier Science Inc. All rights reserved.

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Introduction

In 1966, Andreas Rett described a progressive neurologic disorder affecting girls only and characterized by loss of achieved psychomotor abilities, stereotyped hand movements, truncal and gait ataxia, development of autistic trait, seizures, and decelerated head growth with mental retardation [1]. It is thought of as an X-linked dominant disease manifesting as an apparent arrest of neural maturation during the early perinatal years, although many of the cases are sporadic [2,3].

Several attempts have been made in recent years to determine its pathogenesis, and these patients are frequently diagnosed as having infantile autism [4]. Recent approaches have identified mutations in the methyl-CpG binding protein 2 (MECP2) gene located on Xq28 in girls with Rett syndrome [3,5] and other phenotypes [6]. Other pathologic and biochemical findings were nonspecific [7,8]. Classical neuropathologic findings include reduced pigmentation of the substantia nigra, decreased brain weight with a generalized reduction of neuronal size involving the entire cortex, thalamus, basal ganglia, amygdala and hippocampus [9], and dendritic abnormalities [10,11]. Normal [12] to variable degrees of cortical atrophy [13], primarily in the frontal areas with overall reduction in brain volume also involving basal ganglia and midbrain, has been described with computed tomography (CT) and magnetic resonance studies [14,15].

Alterations in most of the neurotransmitter systems were also reported in Rett patients. Dopamine D₂ receptors were studied with positron emission tomography (PET) demonstrating low to normal dopamine receptor density in the basal ganglia [16] without alteration in the dopamine transporter [17]. Benzodiazepine receptors were also studied with single-photon emission tomography (SPECT) and were demonstrated to be globally decreased in Rett pa-

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tients [18]. Other neurotransmitter systems were revealed to be abnormal in postmortem studies of Rett patients such as *N*-methyl-D-aspartate, kainate, gamma-aminobutyric acid, glutamate, and the cholinergic system [19-21].

Functional brain imaging studies in Rett patients evaluating cerebral blood flow and oxygen metabolism with PET [22] and perfusion with SPECT [23-26] have consistently demonstrated global cerebral hypoperfusion with variable involvement of frontal, temporal, and parietal regions.

Positron emission tomography has been successfully used to evaluate glucose cerebral metabolism with [¹⁸F]fluorodeoxyglucose in normal brain development [27,28] and in pediatric patients with epilepsy [29,30], Down syndrome (DS) [31], autism [32], and Tourette syndrome [33], among others. The purpose of the present study was to evaluate glucose cerebral metabolism in Rett patients with [¹⁸F]FDG and PET and to relate the findings to those previously described in Alzheimer's disease, Down syndrome, and autism.

Materials and Methods

Human Patients

Six female patients ranging between 4 and 15 years of age (mean = 9 ± 5 years of age) were studied with [¹⁸F]FDG and PET in the Division of Nuclear Medicine at the Johns Hopkins Medical Institutions (Baltimore, MD). All of the patients met diagnosis criteria for Rett syndrome [34] as determined by an experienced pediatric neurologist (S.N.). The study protocol was approved by the Institutional Review Board and Radiation Research Committee of the Johns Hopkins Medical Institutions, and written informed consent was obtained from the patients' parents prior to the studies.

Because of ethical difficulties in recruiting age-matched normal subjects, we compared our data to that calculated from absolute glucose metabolic values from 18 age-matched individuals with history of transient neurologic events and subsequent normal neurologic development who had normal PET-FDG brain metabolism on follow-up [28] (individual raw data provided by Dr. H.T. Chugani). These studies were performed with techniques similar to those used in the present study.

Prescan

To align the patients in the PET scanner an individual thermoplastic mask was marked using a limited x-ray CT scan. To prevent movement during the PET acquisition all six patients were sedated with methohexital under the strict supervision of an anesthesiologist (M.Y.). Four of them were sedated during the injection and uptake phase, one was unsedated, and one patient was studied both under sedated and unsedated conditions. Heart rate, blood pressure, temperature, and pulse oximetry were continuously monitored during the studies. Blood oxygen saturation was always maintained above 85%.

Scanning Procedures

A Scanditronix AB RNP-16 biomedical cyclotron was used to produce ¹⁸F. [¹⁸F]fluorodeoxyglucose was synthesized as previously described [35]. Studies were performed with a NeuroEcat II PET scanner (CTI, Knoxville, TN). The tomograph was operated in the high-resolution mode, providing an in-plane spatial resolution of 8-mm full width half maximum and a 14.5-mm slice thickness.

The patients were comfortably positioned with the mask in place to align the PET scans with the CT images. Three to five mCi of ¹⁸F]FDG were injected IV, and scans began 45 minutes after the injection of the radiotracer. During this phase all sensory stimuli were kept to a minimum. Four sets of images 10-15 minutes each were obtained resulting in 12 contiguous planes parallel to the orbitomeatal line covering the whole brain. Images were reconstructed and corrected for decay and attenuation using standard procedures.

Image and Data Analysis

Images were analyzed by visual inspection by experienced observers to determine gross glucose metabolic pattern. Square regions of interest were placed on transaxial images in selected brain areas with the aid of a pre-established template based on an anatomical atlas.

Data were analyzed in terms of relative radioisotope concentrations weighed by number of pixels between different areas of the brain assuming no regional effects of the sedation and considering that by 40 minutes after [¹⁸F]FDG injection the concentration was proportional to regional rates of glucose utilization [36]. Relative radiotracer concentrations were calculated according to the following procedures:

(1) The relationship between one lobe with the mean value of the regions of interest representative of the entire brain (whole brain, WB) [37,38]:

$$\left[\text{ROI}_1 / \left(\sum \text{ROI} (n/n) \right) \right]$$

(2) The relationship between one hemisphere with the opposite one expressed as laterality percentage difference [39]:

$$[\text{Right} - \text{left}/(\text{right} + \text{left})/2] \times 100$$

(3) The relation between frontal and temporoparietal lobes expressed as anterior-posterior percentage difference and calculated as the difference between frontal and temporoparietal lobes divided by the mean of the two and multiplied by 100 [39]:

$$[\text{frontal} - \text{temporoparietal}/(\text{frontal} + \text{temporoparietal})/2] \times 100$$

(4) The ratio between cortical structures (frontal, parietal, temporal, sensorimotor, and occipital, excluding the primary visual cortex) and subcortical structures (thalamus and basal ganglia) [39].

Patients and control subjects were divided in two age groups, including a first group who were 3-8 years of age and a second group who were 9-15 years of age. This age group subdivision matches the one proposed by Chugani et al. [28] to account for physiologic differences in brain glucose metabolism distribution occurring during normal development, allowing more accurate comparison between patients and control subjects. The control group was comprised of six patients in the younger group and twelve in the older group, and three patients in each age group were studied in the Rett patients. Statistical analysis was made by unpaired Student *t* test and significance was defined at the level of *P* < 0.001.

Results

Images obtained by CT scanning of the brain did not reveal signs of cortical atrophy in any of the patients. Relative regional distributions of brain glucose uptake in control subjects and Rett patients for both age groups are presented in Tables 1 and 2.

A consistent decrease in the occipital visual association areas and relative increase in tracer uptake in the frontal and temporal regions when related to the whole brain was observed in the group of patients between 3 and 8 years of age (Fig 1). No differences in the parietal lobe were

Table 1. Relative brain FDG distribution (3-8-year-old group)

	Control Group* (n = 12) (mean ± SD)	Rett Patients (n = 3) (mean ± SD)	P†
ROI/WB			
Frontal	1.04 ± 0.02	1.10 ± 0.02	<0.001
Temporal	0.94 ± 0.03	1.00 ± 0.01	<0.005
Parietal	1.04 ± 0.04	1.08 ± 0.02	ns
Occipital	1.08 ± 0.03	0.82 ± 0.09	<0.001
Cerebellum	0.62 ± 0.10	0.86 ± 0.10	<0.003
Subcortical	0.95 ± 0.11	0.95 ± 0.08	ns
C/SC	1.05 ± 0.04	1.07 ± 0.08	ns
AP %	4.77 ± 3.71	3.30 ± 3.98	ns

* Results calculated from individual absolute glucose metabolic values provided by H.T. Chugani.

† Unpaired Student *t* test.

Abbreviations:

AP % = Anterior-posterior percentage difference

C = Cortical

ROI = Region of interest

SC = Subcortical

SD = Standard deviation

WB = Whole brain

detected when compared with age-matched control subjects. Increased cerebellar relative tracer concentrations were also evident, and the patient with the highest increase also presented the lowest relative uptake in the subcortical regions when related to the cortical areas. However, no group differences were observed in the relative glucose uptake in the cortical/subcortical ratios or anterior-posterior percentage differences when compared with the control group.

Table 2. Relative brain FDG distribution (9-15-year-old)

	Control Group* (n = 6) (mean ± SD)	Rett Patients (n = 3) (mean ± SD)	P†
ROI/WB			
Frontal	1.03 ± 0.03	1.05 ± 0.07	ns
Temporal	0.91 ± 0.04	0.95 ± 0.09	ns
Parietal	0.98 ± 0.05	1.00 ± 0.09	ns
Occipital	1.04 ± 0.03	0.83 ± 0.05	<0.001
Cerebellum	0.62 ± 0.01	0.79 ± 0.09	<0.006
Subcortical	1.04 ± 0.04	1.11 ± 0.13	ns
C/SC	0.94 ± 0.05	0.89 ± 0.14	ns
AP %	4.66 ± 3.42	7.00 ± 11.00	ns

* Results calculated from individual absolute glucose metabolic values provided by H.T. Chugani.

† Unpaired Student *t* test.

Abbreviations:

AP % = Anterior-posterior percentage difference

C = Cortical

ROI = Region of interest

SC = Subcortical

SD = Standard deviation

WB = Whole brain

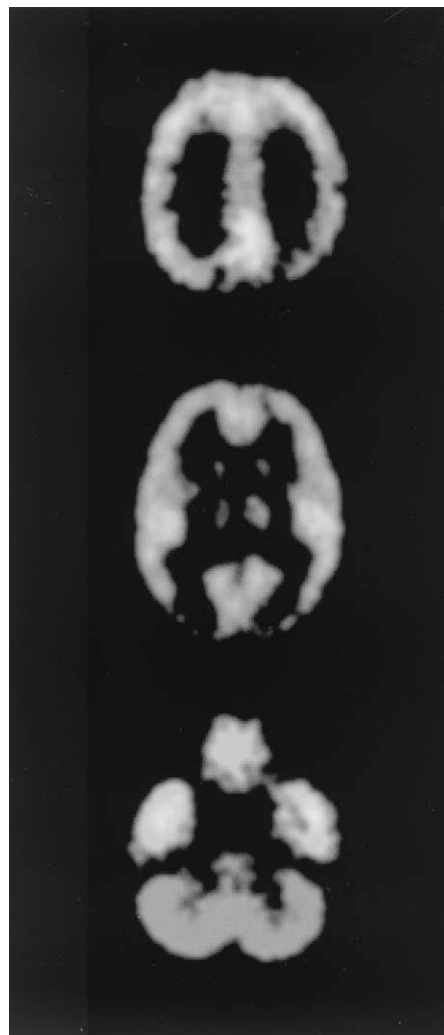


Figure 1. Representative images of a brain FDG-positron emission tomography study in an 8-year-old patient with diagnosis of Rett syndrome are presented. Relative increase in FDG uptake in the frontal lobes (top), decreased tracer uptake in the lateral occipital cortices (center), and increased cerebellar uptake (bottom) are observed.

Analysis of relative regional distribution of FDG in the group of patients between 9 and 15 years of age also demonstrated a significant decrease in the occipital visual association regions with sparing of the calcarine cortex but relatively preserved uptake in the frontal and temporoparietal regions. An increase in tracer uptake in the cerebellum was also evident, as found in the younger group of patients, although this relative increase was not as marked as that in the 3 to 8-year-old group. An apparent relative decrease in thalamus and basal ganglia was observed in relation to the cortical areas in two patients, but no significant statistical group differences were evident when compared with the control patients. No significant anterior-posterior percentage differences were detected either. Sensorimotor cortex was found to be preserved in both groups.

Relative differences in laterality percentages between hemispheres ranging from 4% to 9% and favoring the left were evident in some patients in both groups (mean

3-8-year-old group = $3.20\% \pm 2.49$; mean 9-15-year-old group = $3.39\% \pm 4.51$). Laterality data from normal control subjects was not available to establish the statistical significance of this observation.

Discussion

Cerebral metabolic rates of glucose present significant changes during normal brain development in children [28]. Regional distribution of cerebral metabolic rates of glucose are similar to adults by 1 year of age, but differences in rates of maturation and absolute values among structures are observed during development. Increased glucose metabolic rates of about twice the adult values are observed between 3 and 8 years of age, followed by a progressive decline to baseline adult values by 9 years of age. Based on these normal changes reported in cerebral glucose metabolism, we also divided our patient patients in two groups: one from 3 to 8 years of age and another one from 9 to 15 years of age.

One methodologic issue to consider in our studies is the use of sedatives. One patient that was studied under both sedated and nonsedated conditions during the uptake phase presented no significant differences in relative FDG uptake throughout the brain between the studies. This finding was consistent with previous observations both in humans and rodents indicating that the effects of barbiturates on brain glucose metabolism are generalized and nonregional [40,41]. In consequence, our results were expressed only in terms of relative tracer uptake.

A mild but significant increase in relative glucose utilization was observed in the frontal areas in the younger group of patients with relatively normal uptake in the older group. Autoradiographic studies from postmortem brain tissue of Rett patients demonstrated a significant increase in *N*-methyl-D-aspartate receptors (38%) in patients less than 8 years of age in the superior frontal gyrus but lower than normal receptor density in the older group, likely reflecting a persistent immature state. Adenosine monophosphate acid, kainate acid, and metabotropic types of glutamate receptors presented similar developmental profiles [20]. There is at present strong evidence to support a mechanistic relationship between the rate of glutamate/glutamine cycling and the rate of glucose cerebral metabolism in rat and human cortices [42,43]. It is therefore possible that the relative increase in frontal glucose utilization reflects these changes in excitatory neurotransmitters and could be associated with the earlier active stages of younger patients [8]. Electroencephalographic frontal lobe abnormalities with rhythmical and paroxysmal theta spike activity were described in Rett syndrome [44] and could also correlate with these results. Globally decreased cerebral blood flow but more predominant in the frontal areas has been reported by some investigators with SPECT [24,26]. The presence of cortical atrophy could at least in part account for discrepancies with the present study. Yoshikawa et al. [22] demonstrated relatively preserved

global cerebral blood flow with largest decreases in the frontal areas, low oxygen metabolism and extraction fraction that tended to improve with advancing age. Uncoupling between brain glucose utilization and blood flow has been reported in mitochondrial diseases [45-48]. Although less likely, the possibility that a relative increase in glucose metabolism represents a compensatory mechanism for abnormal mitochondrial function with impaired oxidative metabolism cannot be completely excluded and could also explain the discrepancies between frontal hypoperfusion described by other investigators and the relative frontal glucose hypermetabolism observed in the present study.

A consistent finding in the two groups of patients was the lower relative glucose metabolism detected in the occipital visual association areas. This observation is similar to that reported by Nielsen et al. [23] in blood flow studies with SPECT and ^{133}Xe and correlates with the electroencephalographic progressive loss and late absence of the occipital dominant rhythm with progression of disease described in Rett syndrome [49]. Similar decreases in glucose metabolism in the occipital regions were reported in patients with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome [50]. This finding could therefore reflect a possible impairment of mitochondrial function in Rett syndrome, as previously suggested by abnormalities of intermediary carbohydrate metabolism [51-54].

A relative increase in cerebellar glucose metabolism in both age groups was also observed in these studies, although less markedly in the older group of patients. Nielsen et al. [23] reported abnormalities in absolute cerebellar blood flow with ^{133}Xe in brain SPECT studies of Rett patients. A trend indicating increased cerebellar glucose metabolism has also been reported in autistic patients with PET and FDG [55]. Cortical cerebellar atrophy and gliosis have been present in postmortem brain examination of Rett patients more than 20 years of age [56,57]. Although this is not a longitudinal study, an initial increase in glucose metabolism before signs of atrophy begin to appear could be a possible explanation for these findings. Mild asymmetry between both hemispheres was also observed although the lack of laterality data in control subjects prevented statistical analysis. Similar findings in blood flow were also evident in Rett patients studied with SPECT, with a shift also favoring the left hemisphere when compared with control subjects [23].

An interesting finding in the present study is that the relative alterations in glucose metabolism in the occipital and cerebellar areas, but with sparing of the sensorimotor cortex, resemble the regional distribution reported in normal children of less than 1 year of age. By this age, the cerebellum is the structure that has the highest and closest cerebral metabolic rates of glucose when compared with adult values, than any other region of the brain. Conversely, the occipital visual association areas present a slowest maturational increase of glucose metabolism than

other cortical regions when compared with adult values [28]. Furthermore, in the immature human brain the sensorimotor regions are the earliest cortical regions to mature, and this phylogenetically old structure was demonstrated to be preserved in the present study.

Finally, when comparing the results present in our Rett patients with the brain glucose metabolic patterns described in Alzheimer's disease, Down syndrome, and autism, some particular differences were observed. In our study, Rett patients presented lower relative glucose metabolism in occipital areas, increased in the cerebellum, mild hyperfrontality in the younger group, and probable left asymmetries. Patients with Alzheimer's disease typically present with decreased metabolism in the temporoparietal regions with nondirectional asymmetries [58,59]. Patients with Down syndrome presented normal global glucose metabolism [60] or low metabolism in the temporal regions with no asymmetries [31]. Positron emission tomography studies from autistic patients have revealed variable results, with predominant abnormalities in the frontotemporal regions and no asymmetries [61–63].

The preliminary results of the present study support the hypothesis that the brain glucose metabolism in Rett patients resembles that of younger normal children, likely reflecting a maturational arrest, with a pattern somehow different to that observed in other entities such as Alzheimer's disease, Down syndrome, and autism. Longitudinal PET studies in these patients would be useful to elucidate the progression of these metabolic alterations.

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