

Metabolic Recovery in Caudate Nucleus of Children Following Cerebral Hemispherectomy

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In 3 children who had undergone cerebral hemispherectomy (hemidecortication) between the ages of 1 year 5 months and 4 years for the alleviation of intractable epilepsy, cerebral glucose utilization was studied serially with positron emission tomography. Three to 7 months after hemispherectomy, glucose utilization in the caudate nuclei on the side of hemispherectomy had decreased to below preoperative values, presumably due to total deprivation of ipsilateral cortical input. One to 2.5 years after surgery, complete restoration of glucose metabolic activity to preoperative levels was seen in 2 patients and partial recovery was seen in 1 patient. These alterations of cerebral glucose utilization are believed to reflect microscopic anatomical reorganizational changes (e.g., collateral sprouting) that have been documented following similar lesions in several animal models. Our findings suggest that positron emission tomography may provide a sensitive measure of developmental brain plasticity *in vivo*.

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Immature vertebrates in many species can sustain damage to relatively large areas of the brain and yet show remarkably little functional deficit. This is generally attributed to the reorganizational potential of the developing brain [1, 2]. The greater plasticity of the developing brain over the adult state is known as the Kennard effect, although evidence supporting this principle had been presented long before Kennard (reviewed in [3]).

Children who have undergone neurosurgical procedures, such as multilobar resection or hemispherectomy for the alleviation of intractable epilepsy, pro-

vide a unique opportunity for studying developmental brain plasticity. These subjects manifest marked cognitive and motor sparing/recovery following surgical resection [4-7]. Skills such as language, visual processing, auditory-temporal processing, abstraction, and reasoning may be retained after hemispherectomy [8, 9]. Even the ability to perform complex tasks (e.g., interfield visual discrimination) has been reported in humans who underwent hemispherectomy during childhood [10].

We present here evidence of brain plasticity as indicated by alterations in the pattern of glucose consumption determined with 2[¹⁸F]fluoro-D-glucose (FDG) and positron emission tomography (PET) in 3 children who had undergone cerebral hemispherectomy in infancy or childhood.

Materials and Methods

The clinical features of the 3 patients included in this report and the circumstances leading to hemispherectomy are provided in the Table.

All studies were performed with informed consent and in accordance with the policies of the University of California at Los Angeles (UCLA) Human Subject Protection Committee. The FDG-PET procedure, as applied to infants and children, was discussed previously [11]. Briefly, the subjects were fasted for 4 hours prior to PET. A venous catheter was inserted into either a hand or a foot to administer FDG (0.143 mCi/kg). Just prior to, and for 30 minutes after FDG administration, sensory stimulation was minimized by dimming the lights and discouraging speech. Forty minutes after FDG injection, scanning of the brain was initiated using either the NeuroECAT positron tomograph (12 images, spatial resolution of 8.4 mm in plane of section, 12.4-mm slice thickness) or the CTI 831 positron tomograph (15 images, spatial resolution of 5.6 mm in plane of section, 6.3-mm slice thickness). A head holder was used to minimize movement during scanning, and all tomographic slices were obtained parallel to the canthomeatal plane. Absolute measurements of cerebral glucose metabolic rates were not obtained because of the increased invasiveness of this process, which requires arterial blood sampling in these children who had already benefited from surgery.

Preoperative and postoperative PET images were displayed on a computer monitor and analyzed initially by visual inspection. Subsequently, the concentrations of radioactivity in subcortical brain regions (basal ganglia and thalamus) spared by surgery were determined by drawing regions of interest, and expressed as ratios to the concentrations of the same brain regions in the contralateral (intact) cerebral hemisphere to yield indices of regional metabolic asymmetry for each PET study. An asymmetry index was chosen rather than normalization to the entire intact cerebral hemisphere (as is usually done in analyses of PET data) because glucose metabolic rates undergo complex and hitherto inadequately described changes during brain development [12], particularly in the cerebral cortex, thus precluding its use as a "stable" reference in longitudinal studies such as the present one.

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Summary of Patients' History and Positron Emission Tomography (PET) Results

Subject No./ Gender	Clinical Information	Age at Hemispherectomy and Outcome	Age at PET Scan	Thalamus ^a	Lenticular Nuclei ^a	Caudate ^a
1/M	Normal birth. Seizure onset at age of 8 hr; uncontrolled with medication 1 yr, 6 mo: developmental delay (3-4 mo level); no speech; normal visual tracking; diffuse hypotonia; R arm monoparesis; reached for objects with L hand	1 yr, 6 mo: L hemispherectomy. 6 yr: ambulatory; only occasional seizure associated with febrile illnesses; functions at about 3-yr-old level	Pre: 1 yr, 3 mo	0.86	0.88	0.84
			Post: 2 yr	0	0	0.66
			Post: 4 yr	0	0	0.86
2/M	R hemimegalencephaly. Intractable epilepsy from 2nd day of life 1 yr, 5 mo: no language; did not roll over; no visual regard; L hemiparesis	1 yr, 5 mo: R hemispherectomy. 3 yr, 5 mo: acquired receptive but not expressive language; points to body parts; babbles, plays with puzzles; L hemiparesis unchanged, no spasticity	Pre: 1 yr, 4 mo	0.92	0.94	1.13
			Post: 2 yr	0	0	0.53
			Post: 2 yr, 5 mo	0	0	0.69
3/F	Difficult and prolonged labor; perinatal anoxic-ischemic damage; seizure onset on 2nd, uncontrolled 4 yr: developmental delay; no speech; poor head control; did not crawl; R spastic hemiparesis	4 yr: L hemispherectomy 9 yr: ambulatory; seizure free; language function at about 6-7 yr; dysarthric; R visual field deficit; can squeeze with R hand, flex elbow, elevate shoulder, but no fine motor control of R hand	Pre: 3 yr, 11 mo	0.72	0.90	0.93
			Post: 4 yr, 3 mo	0	0	0.51
			Post: 6 yr, 1 mo	0	0	0.91

^aNormalized value represents structure ipsilateral to hemispherectomy/structure contralateral to hemispherectomy.

L = left; R = right.

Results

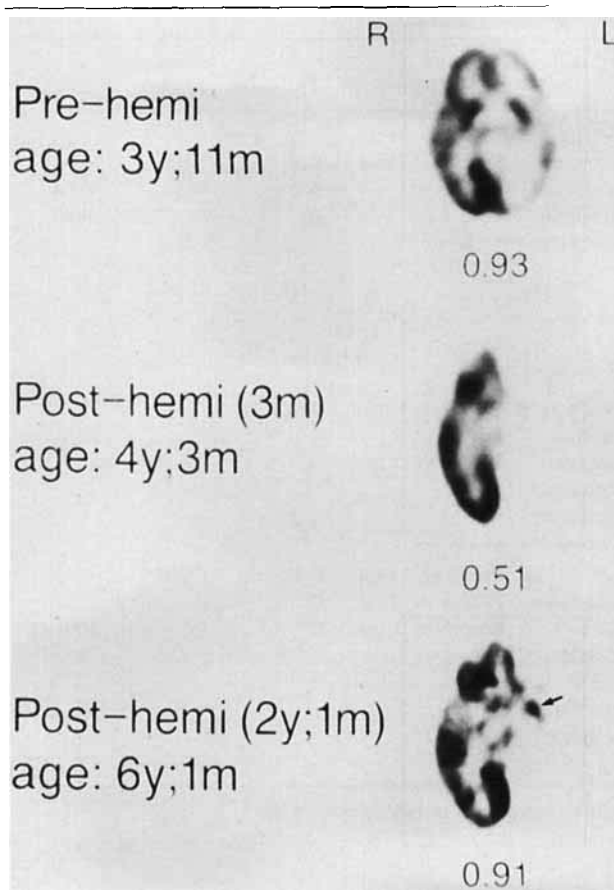
Ratios of metabolic asymmetry for the basal ganglia and thalamus are presented in the Table. In normally developing children, metabolic asymmetry is $\pm 8\%$ for cerebral cortical and cerebellar structures, and $\pm 5\%$ for basal ganglia and thalamus across subjects (unpublished data, 1987).

Metabolic changes suggestive of reorganization after hemispherectomy were seen in the caudate nucleus of all 3 patients. Three to 7 months after surgery, glucose utilization in the caudate ipsilateral to the hemispherectomy had decreased below preoperative values (see Table). Partial or complete restoration of glucose metabolic activity to preoperative levels in the affected caudate was observed in PET studies performed 1 to 2.5 years postoperatively. The recovery of caudate glucose utilization reached preoperative levels in Patients 1 and 3. In Patient 2, metabolic recovery in the caudate was less complete, possibly because this child's neurological condition (hemimegalencephaly) is believed to be associated with bilateral cerebral abnormalities [13], and hence, consists of neural substrate that cannot fully support reorganizational changes following surgery (see below). In contrast to findings in the caudate, the lenticular nuclei and the thalamus exhibited a total loss of glucose metabolic activity postoperatively, and no

measurable recovery in subsequent PET studies (see Table, Fig).

Discussion

The ability of various species to compensate in response to brain injury is dependent on the maturational state of the nervous system at the time of injury. Developmental brain plasticity has been particularly well studied in the cat [14], in which neonatal focal ablation (e.g., of sensorimotor cortex) or cerebral hemispherectomy is associated with far better functional recovery (e.g., of postural reflexes and locomotion) than is a comparable adult lesion. Several anatomical reorganizational processes have been observed: (i) The intact sensorimotor cortex of kittens sustaining contralateral sensorimotor ablation retains exuberant projections present in normal neonatal animals, resulting in bilateral corticothalamic and corticorubral projections [14]; (ii) the intact corticospinal pathway in cats that underwent hemispherectomy as neonates reinnervates the partially deafferented thalamic, brainstem, and spinal cord nuclei with new collateral fibers to a much greater extent than in cats with lesions made during adult years [15]; and (iii) following hemispherectomy, there is less retrograde neuronal degeneration in the thalamus and upper brainstem nuclei of



PET scan of cerebral glucose utilization in Patient 3. The numerical values are indices of asymmetry, and represent ratios of glucose metabolic rate in the caudate nucleus ipsilateral to hemispherectomy to the metabolic rate in the caudate contralateral to hemispherectomy. Metabolic recovery in the caudate nucleus post-operatively is indicated on the third PET image (arrow). The caudate with a ratio of 0.51 is not clearly visualized on the second PET image due to a scaling factor; that is, its metabolic rate is considerably less than the rates of several other structures seen on this plane.

kittens than adults [16]. Preliminary data on kittens after hemispherectomy from our laboratory [17] indicated that glucose utilization in brain regions (e.g., ventrolateral thalamus on hemispherectomy side) receiving collateral sprouting can be detected using a ^{14}C -2-deoxyglucose (2DG) autoradiography technique.

Our findings in humans are relevant in light of previous studies in several species documenting plasticity of the caudate nucleus following injury. For example, 2DG autoradiographic studies in adult macaque monkeys subjected to unilateral ablation of Brodmann's areas 4 and 6 demonstrated transient ipsilateral glucose hypometabolism in the caudate followed by a partial restoration of glucose utilization 8 weeks after ablation, presumably secondary to enhanced influence from un-ablated ipsilateral corticostriatal pathways [18].

This mechanism, however, cannot account for the metabolic recovery of the caudate in the present study (see Fig) because of the total disconnection of ipsilateral corticostriatal pathways. A more likely mechanism in these subjects is increased influence from crossed corticostriatal pathways. In the monkey, the caudate and putamen receive bilateral projections from motor cortex [19], and following neonatal bilateral frontal cortical lesions, the caudate assumes functions (e.g., delayed response) mediated by dorsolateral prefrontal cortex [20]. In the rat, the striatum receives bilateral projections from all major areas of cerebral cortex, although ipsilateral projections predominate [21]. With neonatal (but not adult) rat hemispherectomy, crossed corticostriatal projections increase [22]. Behaviorally, in rat [23], sparing of contralateral motor function following neonatal motor cortex ablation is markedly diminished if the caudate-putamen is also removed. This also appears to be the case in humans [4]. Interestingly, none of the subjects in the present study had a return of glucose metabolic activity in the ipsilateral thalamus, despite the fact that in the monkey the dorsal thalamus receives contralateral projections from frontal association cortex [24].

The alterations of glucose utilization in the human caudate nucleus described in the present study presumably reflect progressive changes of energy demand associated with anatomical reorganization, such as those described in kittens after hemispherectomy [14, 15, 17]. Further evidence to support this notion comes from Sharp and Evans [25], who demonstrated that electrical stimulation of remaining motor cortex in 90-day-old rats following unilateral sensorimotor cortex removal elicited an increase of glucose utilization in ipsilateral basal ganglia and thalamus, and contralateral cerebellum if the lesion was made at 30 days, but bilateral increases in animals with lesions made at the age of 1 day. In humans, hemispherectomy is not performed for lesions acquired in adulthood. Recovery of glucose consumption in the caudate nucleus of our patients possibly could have resulted from a compensatory increase in physiological activity by remaining neural processes within this structure, or less likely, from persistence of increased glial activity in the chronic state. Finally, because our data are presented as asymmetry ratios and not absolute glucose metabolic rates, which are more difficult to achieve in children than in adults, it remains possible that decreased metabolic activity in the contralateral caudate or bilateral changes in the caudate could have contributed to our findings. These issues are currently being addressed in our laboratory.

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Apolipoprotein E ε4 Allele Distribution in Alcoholic Dementia and in Alzheimer's Disease in Japan

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The apolipoprotein E ε4 allele has been associated with both familial and sporadic Alzheimer's disease (AD). Given its possible role in nerve repair and growth, it is plausible that apolipoprotein E may be a common denominator in the pathogenesis of several dementing diseases. Therefore, we investigated ε4 frequencies in demented and nondemented alcoholics, as well as in patients with sporadic AD and controls in Japan. No significant difference in allele frequencies was found between demented and nondemented alcoholics and controls, while a significant association was demonstrated between AD and the ε4 allele. These results support a specific role of ε4 in the pathogenesis of AD, rather than a more general role for ε4 in dementing illnesses.

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Since the first report by Strittmatter and colleagues [1], there have been several additional studies that have demonstrated an association between the apolipoprotein

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