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Possible Mechanisms in Infants for Selective Basal Ganglia Damage From Asphyxia, Kernicterus, or Mitochondrial Encephalopathies

Michael V. Johnston, MD; Alexander H. Hoon Jr, MD

ABSTRACT

Magnetic resonance imaging and neuropathologic studies have demonstrated remarkably selective patterns of injury to subregions of the basal ganglia in children. Examples are kernicterus and certain mitochondrial encephalopathies, which cause selective injury to the globus pallidus, and near-total perinatal asphyxia, which causes lesions in the putamen and thalamus. To explain the differential vulnerability of nuclei within millimeters of each other, we hypothesize that their locations within the neurotransmitter-specific circuitry of the basal ganglia motor loop are important. In severe hypoxic-ischemic encephalopathy, excitatory glutamatergic pathways into the putamen and thalamus are overactive, but the globus pallidus might be protected because its activity is silenced by inhibitory neuronal activity. In contrast, the relatively high resting neuronal activity in the globus pallidus might make it more vulnerable to less intense, subacute oxidative stresses from mitochondrial toxins such as bilirubin or from genetic mitochondrial disorders. This hypothesis has implications for designing neuroprotective therapies and for treating associated chronic movement disorders. (*J Child Neurol* 2000;15:588–591).

Brain magnetic resonance imaging (MRI) in children with neurologic disorders can demonstrate remarkably selective patterns of injury in the basal ganglia.¹ Recent reports have shown a pattern of selective damage in the putamen and thalamus following near-total peripartum asphyxia in term infants, sparing the globus pallidus, which lies directly medial to the putamen.^{2–6} In sharp contrast, kernicterus from hyperbilirubinemia or damage from cardiac surgery in children often targets the globus pallidus while sparing the putamen and thalamus.^{7,8} Other genetic metabolic disorders that target the basal ganglia in infants, such as mitochondrial encephalopathies, glutaric aciduria and propionic aciduria, can variably and selectively damage regions of the basal ganglia depending on the nature of the insult.^{9–11} These patterns of selective basal ganglia injury could provide insight into the mechanisms of injury as well as the pathophysiology of the movement disorders they cause.

We present three infants with selective basal ganglia lesions and consider the pathogenesis of their motor disability.

CASE REPORTS

Case 1: Globus Pallidus Injury Secondary to Pyruvate Dehydrogenase Deficiency

A 21-month-old boy was evaluated for episodic lethargy, choreo-athetosis, and weakness. His development was reportedly normal until 6 months of age, when he had delay in psychomotor milestones with episodic weakness associated with viral illness. Metabolic testing revealed lactic acidosis exacerbated by feedings and improved with fasting. Brain MRI showed selective, hyperintense signal abnormalities in the globus pallidus bilaterally (Figure 1A). The diagnosis of pyruvate dehydrogenase deficiency was established by enzymatic assay in cultured skin fibroblasts. This patient's MRI has been published previously.¹

Case 2: Kernicterus

An 8-month-old girl was referred for hypotonia and hearing loss. Following a pregnancy complicated by oligohydramnios, she was born by vaginal delivery at 36 weeks' gestation. Following discharge at 36 hours of life, she developed lethargy and poor feeding and was readmitted to the hospital with a total bilirubin level of 28 mg/dL and encephalopathy, including seizures, hypotonia, and poor suck. On examination at age 8 months, she had microcephaly,

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limitation of upgaze, tongue thrusting, and hypotonia. A T₂-weighted brain MRI showed hyperintense signal in the globus pallidus bilaterally and delayed myelination, but the thalamus and other basal ganglia structures were normal (Figure 1B). Evaluation included normal plasma amino acids and urine organic acids and brainstem auditory evoked responses consistent with an auditory neuropathy.

Case 3: Near-Total Asphyxia with Hypoxic-Ischemic Encephalopathy

Pregnancy was uncomplicated until an acute umbilical cord prolapse necessitated an emergency cesarean section delivery at term. The patient was resuscitated in the delivery room and taken to the neonatal intensive care unit, where seizures developed during the first 24 hours of life. On neurologic examination during the first week of life he was severely hypotonic with hypoactive reflexes and an absent gag reflex; assisted ventilation was required for 9 days. On day 6 of life, an MRI of the brain showed hyperintense signal in the caudate and putamen bilaterally on a T₁-weighted sequence. At 4 months of age, he had truncal hypotonia and dystonic posturing of his hands. At 1 year of age, an MRI showed that the enhanced signal on the T₁-weighted sequence had disappeared, but there was hyperintensity in the posterior segments of the putamen and in the thalami bilaterally (Figure 1C). The globi pallidi were normal. At 2 years of age he is severely disabled with extrapyramidal cerebral palsy manifested by axial hypotonia, rigidity, dystonic posturing of the arms and hands, and inability to vocalize or swallow.

DISCUSSION

These three cases, chosen from numerous others in our Movement Disorders Program, illustrate injury to specific basal ganglia nuclei in infants visualized using brain MRI. Similar patterns of injury have been documented in the literature and are seen clinically on a regular basis.¹⁻⁷ They

demonstrate that the pattern of basal ganglia injury in infants can be quite focal despite the fact that the entire brain is exposed to a metabolic disorder. They illustrate two sharply contrasting patterns of injury: selective pallidal injury associated with disorders such as kernicterus or certain mitochondrial disorders versus the putamen and thalamic injury pattern associated with severe asphyxia. It is noteworthy that the contrast between these two patterns of injury, which have been visualized only recently with MRI in living children, was previously described in neuropathologic material by Ahdab-Barmada and Moosy in 1984.¹²

Given the close proximity of these neuronal nuclei within the basal ganglia, it seems likely that their selective vulnerability is based on differences in their intrinsic vulnerability to metabolic stressors rather than to differences in blood flow or energy delivery. One factor that can strongly influence the vulnerability of neurons is their position within excitatory neuronal circuits.¹³ The relative positions of the putamen, globus pallidus, and thalamus in the circuitry of the basal ganglia are shown schematically in Figure 2. Current concepts of how the basal ganglia control movement focus on the flow of information through a multineuronal feedback loop from frontal cortex down to the putamen, inward through the globus pallidus to the thalamus, and back up to the cortex.¹⁴ The inhibitory influence of the globus pallidus on the thalamus and thalamocortical projections is thought to be a key step in controlling movement. The globus pallidus indirectly controls frontal cortical activity by influencing the activity of thalamocortical projections. If neuronal activity in the pallidal projections to the thalamus is high, movement will cease because frontal lobe activity directed by the thalamus is silenced. However, if pallidal inhibition is reduced, the thalamus is disinhibited and enhances frontal lobe activation of volitional movement. Although the cerebral cortex, putamen, globus pallidus

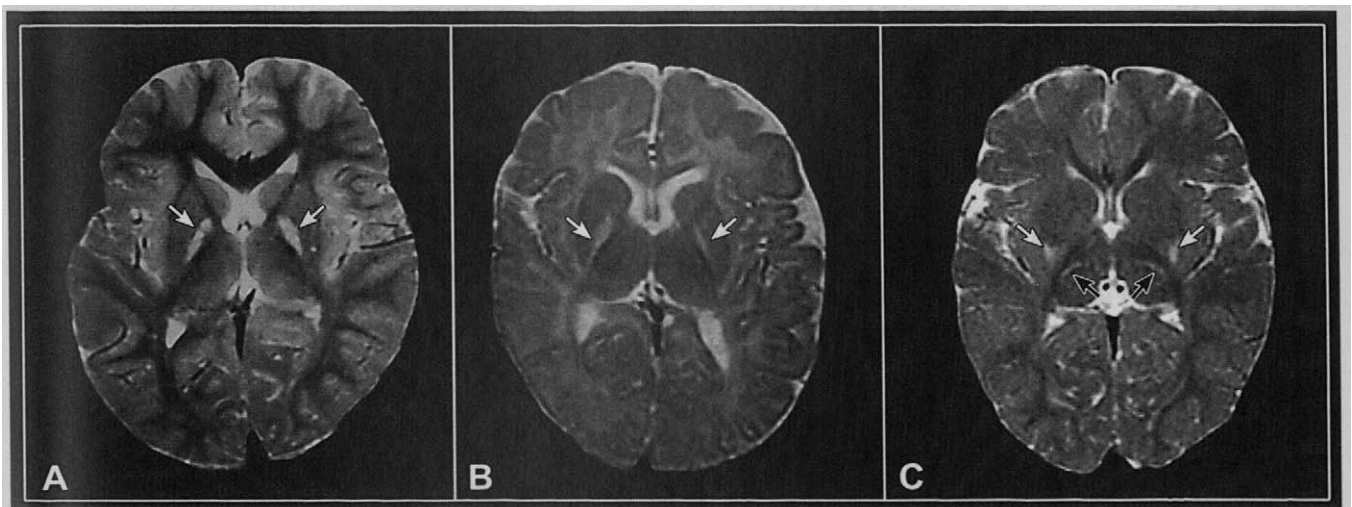


Figure 1. *A*, MRI from child with pyruvate dehydrogenase deficiency who had episodes of dystonia and athetosis. Note hyperintense lesions in globus pallidus bilaterally (arrows). Rest of basal ganglia and thalamus are normal. *B*, Child with kernicterus. Note increased signal in globus pallidus (arrows); rest of basal ganglia and thalamus is normal. There is also delayed myelination. *C*, Child following severe asphyxia. Note increased signal in thalamus and putamen bilaterally (arrows).

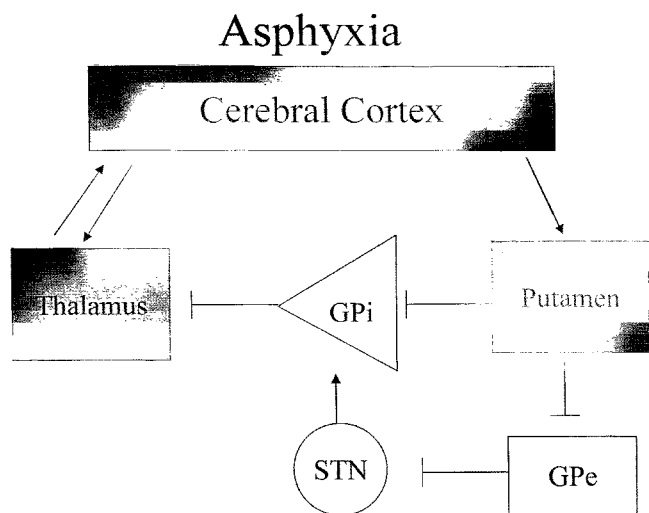


Figure 2. Diagram of normal basal ganglia motor control circuit and areas damaged by near-total asphyxia. Arrows indicate synapses with excitatory glutamate neurotransmitter; blunted lines indicate inhibitory γ -aminobutyric acid (GABAergic) inhibitory synapses. The loop connecting frontal cortex, putamen, globus pallidus interna (GPi), and thalamus is the direct pathway; globus pallidus externa (GPe) and subthalamic nucleus (STN) are in the indirect pathway. Movement is controlled by activity in the cortex. Neonatal globus pallidus also has transiently stronger innervation by glutamate fibers that is not prominent in the adult. Shaded areas indicate regions targeted by asphyxia. Each region receives strong excitatory glutamate innervation. Note that if these regions are firing rapidly, the effect on globus pallidus interna and globus pallidus externa is expected to be inhibitory because of inhibitory input from putamen. Residual effects of this damage include rigidity; paucity of movement, especially in upper extremities; and paucity of speech.

interna, and thalamus are linked together in a continuous multisynaptic loop, the synaptic neurotransmitter relationships distinguish the pallidum from the other three components¹⁴ (Figure 2). When the cortex, putamen, and thalamus are being activated by strong glutamate excitatory inputs, the pallidum is inhibited. In contrast, when the pallidum is active, the thalamus, motor cortex, and putamen are silenced by its γ -aminobutyric acid (GABA)-ergic inhibitory influences.

The reciprocal synaptic relationships among these regions under physiologic conditions could influence vulnerability of the pallidum versus the putamen and thalamus in pathologic circumstances. In asphyxia, brain regions that receive strong glutamate innervations are vulnerable to injury because of the accumulation of high levels of synaptic glutamate that occurs when reuptake pumps suffer energy failure^{15,16} (Figure 2). Accumulation of glutamate might be especially sensitive to failure of glycolysis, which is very important for powering glial glutamate reuptake pumps.¹⁷ Hypoxic-ischemic encephalopathy following severe asphyxia is characterized by seizures and electrical excitability seen on electroencephalography, suggesting that the corticothalamic, thalamocortical, and corticoputamin excitatory projections are active.¹⁸ Positron emission tomographic (PET) studies of human infants with hypoxic-ischemic encephalopathy after severe asphyxia have shown hypermetabolism in the basal ganglia and periorolandic cor-

tex, supporting this hypothesis.¹⁹ Hyperexcitability in these circuits could be directly related to excitotoxic lesions in thalamus and putamen seen on MRI following asphyxia.^{20,21} However, the position of the globus pallidus in the multisynaptic loop could reduce its vulnerability to injury. When seizure activity convulses the cortex and its projection sites, one would predict that the globus pallidus would be strongly inhibited and relatively protected¹⁴ (Figure 2).

A disorder of energy metabolism is also thought to mediate the damage from kernicterus and certain mitochondrial disorders, but the nature of the energy deficiency is likely to be different from that seen in near-total asphyxia²² (Figure 3). Kernicterus can result from the toxic effect of bilirubin disrupting mitochondrial metabolism.⁷ Both kernicterus and pyruvate dehydrogenase deficiency can injure neurons primarily by inhibiting mitochondrial maintenance of membrane potentials. In contrast to acute severe asphyxia, glycolysis is unimpaired in mitochondrial oxidative phosphorylation disorders and is usually markedly enhanced, as reflected by elevated lactate levels. In mitochondrial disorders, there is often a ready supply of glucose, which is not limited as it is in ischemia associated with severe asphyxia. Disorders of mitochondrial metabolism have been proposed to injure neurons through a process of subacute "passive excitotoxicity" when membrane depolarization leads to opening of postsynaptic voltage-dependent *N*-methyl-D-aspartate (NMDA) glutamate and sodium channels.²³ The relatively high baseline firing rate of pallidal neurons, which are disinhibited when the rest of the motor system is quiet, could predispose them to injury from mitochondrial failure.²⁴ Postmortem studies of human infants also indicate that the immature globus pallidus has a relatively high density of glutamate receptors that is lacking in adults.²⁵ Immature rodents also have been shown to have a transient glutamate

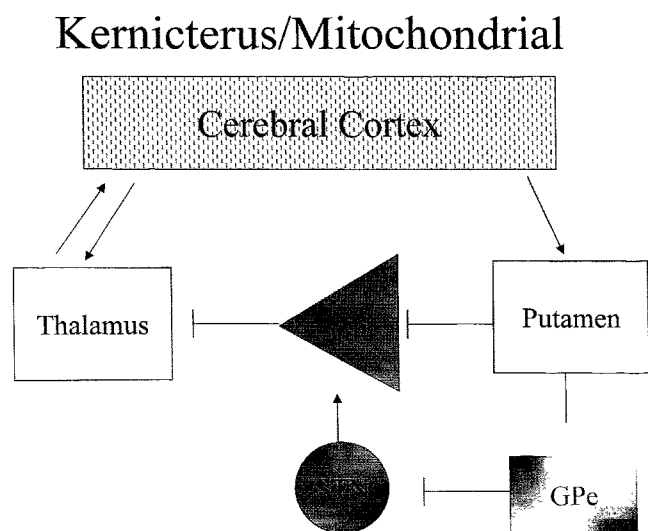


Figure 3. Pattern of injury with kernicterus and some mitochondrial disorders such as pyruvate dehydrogenase deficiency. Kernicterus targets globus pallidus and subthalamic nucleus. Net effect is to disinhibit thalamus, producing a hyperkinetic movement disorder. GPi = globus pallidus interna; STN = subthalamic nucleus; GPe = globus pallidus externa.

innervation in the globus pallidus that regresses in adults.²⁵ This novel excitatory circuitry in the infant basal ganglia, which could originate from the subthalamic nucleus, might contribute to the vulnerability of the globus pallidus to oxidative stress. As shown in Figures 2 and 3, the subthalamic nucleus is likely to be active at rest but silenced in asphyxia.

According to this hypothesis, the selective vulnerability of the globus pallidus versus the putamen, thalamus, and cortex is determined by their positions within the neuronal circuitry of the basal ganglia, their electrical activity, and their intrinsic vulnerability. A severe insult from asphyxia might spare the globus pallidus by silencing it. However, it remains relatively vulnerable to subacute energy failure of oxidative metabolism in mitochondrial disorders. Cases of combined energy failure, such as hypoglycemia superimposed on an oxidative phosphorylation disorder, might lead to the more severe combined putamenal and pallidal lesion that is sometimes seen clinically.

The neuronal circuit relationships in the basal ganglia also might help to explain the neurologic disability associated with each type of lesion. The putamenal/thalamocortical lesion following asphyxia disrupts integral components of the circuit involved in motor activation, producing a reduction in movements; rigidity, especially in the upper extremities; and reduced speech production later on.¹ Some of the bradykinesia in these patients could relate in part to enhanced activity in the relatively intact globus pallidus (Figure 2). In contrast, loss of neurons in the globus pallidus leads to disinhibition of the thalamocortical projections, leading to the hyperkinetic choreoathetoid movements typical of kernicterus. Dystonia can arise in either group of patients as a result of a disrupted pattern of pallidal activity²⁴ (Figure 3).

These observations in children with acquired basal ganglia injuries suggest that there is a plausible relationship between physiologic circuitry in the motor loop of the basal ganglia, mechanisms of injury, the location of selective lesions seen on MRI scanning, and neuropathology and the pattern of neurologic disability. New physiologic studies in experimental models indicate a strong link between activity of glutamate synapses, glucose metabolic rate determined through PET scanning, and activation of regional cerebral blood flow assessed by functional MRI.^{19,26} These techniques might be useful for testing these hypotheses in infants and children with syndromes that cause patterns of selective neuronal vulnerability in the basal ganglia.

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