Glutaric aciduria type 1 (GA1) arises from an enzymatic block in the common degradation pathway for lysine and tryptophan. It is a cause of crippling striatal necrosis during infancy (Strauss et al., 2003). Clinical experience teaches us two things about GA1. First, predicting precisely when and if basal ganglia injury will occur in an individual is presently difficult, if not impossible. Second, when such injuries ensue, we have no therapeutic instruments to stop them. Thus, to prevent injuries we need prediction, and there is ample clinical evidence that plasma and urine organic acid measurements are inadequate for this purpose (Strauss et al., 2003).

Real progress in the treatment of GA1 requires a deeper understanding of the premorbid state—the set of physiological adaptations entrained by abnormal organic acid metabolism in the brain. For this knowledge to be applied physiological changes that precede the catastrophic event must be defined, so that anatomical or biochemical abnormalities causatively linked to brain injury can be monitored in the clinical setting. Such a picture does not readily emerge from in vitro experiments, which generally use isolated single cell types from a variety of non-human species assayed under non-physiological conditions (see Köinker et al., 2004, for review), cannot be reproduced consistently (Freudenberg et al., 2004), and are difficult to reconcile with the complex conditions that prevail in a living patient.

Careful post-mortem studies are an invaluable tool for understanding physiological derangements that occur in life. In this issue of Brain, Dr Funk and colleagues report on six post-mortem brains from aboriginal Ojibway–Cree GA1 patients of Northern Canada to, in their words, ‘offer additional insight into the pathogenesis of the disorder . . . [to] help us develop an intervention strategy that could prevent the episode associated with acute striatal injury and thus minimize the devastating neurological sequelae seen in our affected patients’ (italics mine). The ‘episode’—a term used to underscore their central thesis that GA1, while a systemic and lifelong disorder of organic acid metabolism, causes an age-dependent paroxysm: a sudden, destructive, and anatomically restricted injury to the brain occurring within a particular developmental period.

Using quantitative neuron counts and cell-specific stains, the authors broaden our knowledge about the basal ganglia lesions associated with GA1. They show that striatal large cholinergic interneurons are lost in addition to medium spiny neurons, challenging the notion that the medium spiny neurons are uniquely vulnerable in GA1. In addition they demonstrate an activation/proliferation of microglia in the post-injury period that regresses over time. Together, these observations raise the possibility that acute striatal necrosis in GA1 is a form of pan-coagulative necrosis, as occurs in genuine cerebral ischaemia (Auer and Sutherland, 2002). In such injuries, the whole brain or large subregions may be affected by a common insult, but selective vulnerability arises due to regional particulars of blood supply and/or cell type. Thus, while medium spiny neurons may be more vulnerable to injury (Calabresi et al., 2000) they are not uniquely so, and neuronal necrosis in GA1 may not be so ‘selective’ as previously assumed (Strauss and Morton, 2003).

At a gross level, the authors try to address an important paradox: despite the fact that MR images of affected neonates and infants suggest atrophy of specific cortical regions and the axonal intermediate zone, these same brains are consistently heavy at post-mortem (Fig. 1). This implies that the MRI appearance cannot simply reflect brain atrophy, and casts doubt on the term ‘frontotemporal hypoplasia’ to describe the young GA1 brain (Strauss et al., 2003). While physical distortion of the frontal and temporal cortex is often noted post-mortem (Kimura et al., 1992; Soffer et al., 1994), histological evidence of cortical atrophy is never found.

Increased brain weight may reflect cerebral hypercellularity or, more likely, a poorly understood abnormality of intracranial fluid dynamics. If the material accounting for increased brain weight is water, where is it located, what is its source, and how does it communicate with other intracranial fluid compartments? These simple questions are difficult to answer. Finding correct solutions may be the key to explaining the puzzling constellation of hydrodynamic abnormalities seen in young GA1 brains: congenital ventriculomegaly and communicating hydrocephalus, middle cranial fossa arachnoid cysts, subdural collections of cerebrospinal fluid and/or blood, and T2- and diffusion-weighted signal enhancement in certain subcortical white matter regions (Strauss et al., 2003).

Perhaps the most important contribution of the paper is to corroborate the finding of previous studies (Goodman et al., 1977; Köinker et al., 2003) that brain glutaric acid (GA) is very high in patients with GA1, and exceeds plasma and CSF levels by one to two orders of magnitude. At the whole-organ level, only two scenarios could account for this. Either
circulating free glutaric acid is taken up and retained via a high-affinity concentrative mechanism of the blood–brain barrier, or the bulk of brain organic acids are produced within the brain itself, which may have a limited capacity to extrude them. For the first time, the authors identified abundant glutaryl-CoA dehydrogenase transcripts in human cerebral tissue, providing direct evidence that the human brain indeed has the capacity for de novo production of glutaric acid.

The potential for brain GA production could be large (Fig. 2). From birth to age 1 year, the typical infant brain grows from 335 to 852 g (Kinney and Armstrong, 2002). Approximately 10% of this weight is protein (Williams, 2003), of which about 9% by weight is lysine (molecular weight 146). Thus, the growing infant brain must accrete about 0.2–0.4 μmol of lysine per gram of brain tissue per day during its growth spurt. This is much lower than the
measured unidirectional influx of lysine into brain tissue, which is not known precisely in humans, but estimated to be 10–15 μmol/g tissue per day (Stoll et al., 1993). Even if net lysine uptake by the brain is considerably lower (e.g. due to free lysine efflux across the blood–brain barrier), it still greatly exceeds the demand for protein synthesis. Thus, in theory the young brain could produce as much as 5000–12 000 mol of GA per day from lysine alone. This is sufficient to account for the high brain GA concentrations found in the Ojibway–Cree cohort and would produce a large brain-to-blood flow of GA; it has important implications for the role of lysine restriction in dietary therapy for GA1 (Muller and Kölker, 2004).

Finally, it is important to note that these extraordinary brain concentrations of GA were found in a genetically homogeneous GA1 isolate known to suffer severe brain injury early in life while excreting very low levels of GA in urine. For the first time, Funk and colleagues provide a framework for understanding the anecdotal clinical observation that neurological outcomes tend to be worse in patient groups identified as ‘low excretors’. It may be that such patients retain more GA in brain and other tissues. In other words, if the net flow of GA is from brain to blood, the risk of brain injury may be inversely related to the efficiency of tissue organic acid clearance. This raises several questions for further study: What are the physicochemical consequences of intracerebral GA production? Are organic acids concentrated within mitochondria or cytoplasm, or are they present primarily in the interstitial and perivascular spaces of the brain, moving convectively toward cervical lymphatics (Weller et al., 1992)? How does the brain cope with the increased acid burden, and how do divergent dicarboxylate anions (i.e. glutarate and 3-hydroxyglutarate) leave the brain? Does the passage of GA out of brain alter production of interstitial or cerebrospinal fluid?

In summary, the observations in the present report encourage a more holistic approach to the pathophysiology of GA1. They distract attention away from models of extracellular organic acid toxicity, and encourage us to think carefully about inter-organ substrate transport, abnormal chemical events within brain cells, and the physiological adaptations entailed by them. As we move ahead with GA1 research, these concepts can form a framework for new experiments in the gchd−/− mouse (Koeller et al., 2002) and carefully designed clinical studies. The ultimate goals are prediction and prevention of striatal necrosis. Real progress will be measured by elimination of disability within this vulnerable patient population.

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