Value of Neuroimaging in Metabolic Diseases Affecting the CNS

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Neuroimaging has become an indispensable tool in understanding the regions of susceptibility, progression of disease, and therapeutic effectiveness for the management of neurologic diseases in humans. Metabolic diseases are recognized more frequently now as the biochemical basis is understood better. In addition, and as illustrated in this issue of the AJNR [1-3], clinicians can benefit immensely from the technologic advancements in neuroradiology.

Glutaric acidemia type I (GA I) and methylmalonic acidemia are autosomal recessively inherited organic acidemias, resulting from a deficiency of mitochondrial proteins [4, 5]. The vital role of mitochondria in energy metabolism is well known. Abnormalities in the function of these organelles affect regions in which increased energy demands occur. In the infant's brain, the basal ganglia appear to be especially susceptible to such insults. Glutaryl coenzyme A (CoA) dehydrogenase is involved in an important intermediate step in the degradation of lysine and tryptophan [4, 6-8]. Methylmalonic acidemia (MMA) is associated with a deficiency of methylmalonyl CoA mutase, with mutations occurring at different genetic sites [5]. Marked clinical heterogeneity occurs in both disorders, and the enzyme deficiency is not always associated with serious clinical consequences. Both disorders cause progressive neurologic deterioration that is primarily extrapyramidal, with acute episodic vomiting and lethargy [4, 5, 9-11]. Neonatal or infantile onset is common to both disorders [3, 12]. However, specific neuroradiologic findings can be used to help in the differentiation of the two conditions. In GA I, CT scans have shown significant frontotemporal atrophy in both symptomatic and asymptomatic patients with white matter abnormalities that are considered pathognomonic of this disorder [13, 14]. Symptomatic patients—more than those who are asymptomatic—show severe neuroradiologic involvement. MR highlights the abnormalities of the caudate and the white matter changes [15]. Despite prominent choreoathetosis, radiologic involvement of the basal ganglia may be minimal, suggesting that neuronal function could be altered before cell death. Severe involvement of the globus pallidus occurs in MMA. This change is seen both in those with acute decompensation and in those without such episodes [10, 16]. It is thought to be due to cytotoxic injury from the accumulated metabolites, which specifically target the globus pallidus [17]. In addition, tissue- and age-specific high energy requirements may not be met by malfunctioning mitochondria. Cytochrome c oxidase, a mitochondrial respiratory chain enzyme, is reported to be reduced secondarily in patients with methylmalonic or propionic acidemia during acute decompensation [18].

Pathologic reports in cases of GA I document the extensive loss of neurons in the caudate and putamen and spongiform changes in the white matter with sparing of U fibers [8]. The increased cell loss, particularly in the caudate and putamen, accounts for reduced levels of γ-aminobutyric acid (GABA) in the brain and spinal fluid [7, 15]. The reason for the progressive atrophy of these nuclei with age is not well understood but may result from accumulation of glutaric acid, which has been shown to be toxic to striatal cells in culture [19]. The involvement of the basal ganglia in neonates and infants with GA I and MMA is of great importance to developmental neurology. The reduction of GABA as reported in GA I and the energy depletion brought about by mitochondrial involvement in both conditions could result in neuronal injury from a relative...
excess or an increased sensitivity to endogenous excitatory amino acids. Several lines of investigation suggest the existence of a unique ontogenetic profile of susceptibility of the brain to excessive activation of excitatory amino acid receptor subtypes. The globus pallidus shows a transient increase in binding sites for glutamate (excitotoxin) during the perinatal period. Specific neuronal populations such as the striatum, hippocampus, and golgi cells of the cerebellum show an age-specific vulnerability to excitatory amino acids [20, 21].

Megalencephaly in the newborn period and infancy appears to be a frequent concomitant of GA I and could reflect metabolically induced cytotoxic edema seen as white matter abnormalities on CT scans and MR images [9, 14, 22]. The degree of frontotemporal atrophy seen as early as 3 weeks of life by lafolla and Kahler [22] suggests that the metabolic defect has a significant impact on the developing brain, with increased vulnerability of the frontal lobes and their projections. The striatum is associated intimately with frontal lobe structures. Although the exact cause of the brain injury in GA I is unknown, it is postulated that a potent neurotoxin, quinolinic acid, is increased in this disorder. It has been suggested that when the enzyme glutaryl CoA dehydrogenase is deficient, quinolinic acid, derived from tryptophan, is produced in excess and accounts for the seizures and neuropsychiatric changes of this disorder [23]. Amir et al. [13] proposed that the frontotemporal atrophy in GA I is not congenital and that the extent of atrophy correlates with the severity of the disorder because asymptomatic patients with the metabolic abnormality show only minimal atrophy of the frontotemporal region. It is surprising that microcephaly does not develop in these symptomatic patients, even when atrophy is progressive; instead, head circumferences are maintained in the higher percentiles. This raises the possibility that the frontotemporal changes occur in utero in the symptomatic patients. The changes may be masked by the cytotoxic edema related to metabolic interference during a rapid phase of myelination, synapse formation, and high energy demand. This in turn may cause megalencephaly in infancy followed by slow, progressive atrophy without reduction in head size.

The overall prevalence of arachnoid cysts is estimated to be five per 1000 autopsies [24]. Rengachary and Watanabe [25] found that the sylvian fissures had the highest rate (49%) of arachnoid cysts in 280 reported cases. Embryologists consider that the arachnoid and pia develop from primitive mesenchyme that separates into endo- and exo-mesenchymal. The exo-mesenchymal forms the dura, and the endo-mesenchymal differentiates into the arachnoid and pia. The subarachnoid space is independent on the pulsatile flow of CSF through it. An aberration in the flow leads to anomalous splitting of the arachnoid and formation of a blind pocket, which becomes the arachnoid cyst. In the early stages, the cysts communicate with the subarachnoid space and are referred to as communicating arachnoid cysts. When they are sealed off, they are termed arachnoid cysts or noncommunicating arachnoid cysts. It is proposed that these arachnoid cysts result from anomalous development of subarachnoid cisterns [25, 26]. The occurrence of rapid and severe frontotemporal atrophy in symptomatic patients with GA I would lead to alterations in CSF flow in the subarachnoid spaces and fluid accumulation as in a communicating arachnoid cyst. Alternatively, if the changes do occur in the fetus during the process of complex folding of the primitive neural tube and formation of normal subarachnoid cisterns, these changes could lead to anomalous splitting of the arachnoid membranes and formation of true arachnoid cysts. This could account for the fluid collections described by Hald et al. [2] in this issue of the AJNR. Venous anomalies are said to be present in nearly every case of arachnoid cyst. Subdural or intracystic hemorrhages complicate the issue, as was noted in two of the five patients of Giudicelli et al. [27]. The diagnosis of arachnoid cysts in the article by Hald et al. is based on radiologic evidence alone and lacks pathologic confirmation.

Patients with GA I and its typical neuroradiologic changes may not be easily recognized biochemically as these patients may have normal urinary organic acids. This results from a disparity between the residual liver enzyme activity compared with brain enzyme activity. The normal urinary organic acids occasionally seen in these patients may be due to rapid conjugation of glutaryl CoA with carnitine, which is excreted as glutaryl carnitine in the urine [9]. Therefore, in the presence of clinical symptoms and a radiologic pattern of partial uncou­ering of the insula with bilateral fluid collections resembling arachnoid cysts in the middle cranial fossa, enzymatic assay for glutaryl CoA dehydrogenase in skin fibroblasts is warranted even when urinary organic acid analysis is normal.

The MR changes in phenylketonuria (PKU) reported by Shaw et al. [1] in this issue of the AJNR warns us of the importance of continued dietary treatment in this disorder and the devastating consequences of noncompliance or early termination. The white matter is particularly vulnerable in PKU [28]. The autopsied brain of untreated PKU patients shows pallor of the white matter, and biochemical investigations have shown slower accumulation of myelin, with increased water and reduced lipid content. The reduction in myelin is not the result of neuronal loss, as it is not a frequent histologic finding. Proteolipid protein, an important component of myelin, is reduced markedly but has a normal amino acid composition. High levels of one or more amino acid can restrict the uptake of other essential amino acids, with subsequent reduction of protein synthesis, and account for the reduced levels of proteolipid protein [29]. Crome et al. [30] showed that the brain of their oldest patient with PKU had an increase in cholesterol esters, indicating active demyelination. Malamud [31] noted that frank demyelination occurs in adult patients with PKU, superimposed on the sponge changes, indicating that progressive alterations of myelin occur with age, corre­ponding to the clinical progression seen in later life. He therefore advocated the introduction of diet therapy at any stage of the disorder, as this condition was not stationary. Michaels et al. [32] showed that intelligence test scores were related to phenylalanine levels between 3% and 5% years of age and found a significant relationship between blood levels of phenylalanine and cognitive outcome variables at ages 6 to 10 years. Schuett et al. [33] noted that 60 patients with PKU who discontinued the diet between 3 and 20 years of age had it reinstituted because of poor school performance.
and mood or behavioral changes. Improvement was correlated with the length of time on the diet the second time, suggesting that the elevated levels of phenylalanine and its metabolites are neurotoxic and have detrimental effects on behavior and learning in older children and adolescents. These observations underscore the importance of dietary regulation even in older patients. It has important implications for pregnant women and their fetuses, as the diet needs to begin before conception and be maintained throughout pregnancy to protect the fetus maximally [34, 35]. In a double-blind crossover study, Berry et al. [36] administered valine, leucine, and isoleucine to adolescents and young adults with PKU who were off the diet or had poor dietary control. This study was based on the recognition that phenylalanine and other large neutral amino acids compete for receptor sites in the transport system of the blood-brain barrier [37 and 38]. It was hypothesized that the uptake of phenylalanine could be reduced by administering large neutral amino acids to patients with PKU, thereby reducing the toxic effects of phenylalanine on the CNS. The addition of valine, leucine, and isoleucine to the PKU-inducing diet of pregnant rats prevented the reduction in fetal brain weight and reduced the phenylalanine concentration by 35% compared with findings in fetal rats whose mothers were given only the PKU-inducing diet. Berry et al. [36, 39] noted that patients who received branched-chain amino acid supplements showed improved attention and faster mental processing without change in the serum levels of phenylalanine and had no toxic side effects. Patients who discontinue the diet have considerable difficulty returning to it. For them, and for those with poor compliance, such newer treatment approaches could prevent the neurotoxic effects of phenylalanine and prevent serious neurobehavioral changes. MR imaging will be a valuable tool in assessing the efficacy of dietary treatment and patient compliance.

Continued interaction between clinicians, neuroradiologists, and neuroscientists promises to result in improved understanding and delineation of various disorders and their phenotypes. This in turn, should lead to earlier recognition and more effective therapeutic intervention.

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