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Urea cycle defects and hyperammonemia: effects on functional imaging

Andrea L. Gropman,

Department of Neurology, Children's National Medical Center, George Washington University of the Health Sciences, 111 Michigan Avenue, N.W., Washington, DC 20010, USA, agropman@childrensnational.org

Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA

Morgan Prust,

Department of Neurology, Children's National Medical Center, George Washington University of the Health Sciences, 111 Michigan Avenue, N.W., Washington, DC 20010, USA

Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA

Andrew Breeden,

Department of Neurology, Children's National Medical Center, George Washington University of the Health Sciences, 111 Michigan Avenue, N.W., Washington, DC 20010, USA

Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA

Stanley Fricke, and

Department of Neurology, Children's National Medical Center, George Washington University of the Health Sciences, 111 Michigan Avenue, N.W., Washington, DC 20010, USA

Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA

John VanMeter

Department of Neurology, Children's National Medical Center, George Washington University of the Health Sciences, 111 Michigan Avenue, N.W., Washington, DC 20010, USA

Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA

Abstract

The urea-cycle disorders (UCDs) are a group of congenital enzyme and carrier deficiencies predisposing to hyperammonemia (HA). HA causes changes in the central nervous system (CNS) including alterations of neurotransmitter function, cell volume, and energy deprivation ultimately leading to cerebral edema. Neuropathological findings of UCDs primarily reflect changes in astrocyte morphology. Neurological features accompanying acute HA include changes in behavior and consciousness in the short term, and potential for impairments in memory and executive function as long-term effects. Plasma measures of ammonia and glutamine, although useful for clinical monitoring, prove poor markers of CNS function. Multimodal neuroimaging has potential to investigate impact on cognitive function by interrogating neural networks, connectivity and biochemistry. As neuroimaging methods become increasingly sophisticated, they will play a critical role in clinical monitoring and treatment of metabolic disease. We describe our findings in UCDs; with focus on Ornithine Transcarbamylase deficiency (OTCD) the only X linked UCD.

Keywords

Urea cycle disorders; Brain; MRI

Introduction

UCDs represent a group of rare inborn errors of metabolism leading to accumulation of ammonia, a toxic product of protein metabolism (Brusilow 1995). The symptoms of these disorders may present at any age. The major consequences are neurological of varying severity due to hyperammonemia, which depends in part on the particular disorder within UCD and age of onset. Studies of children with neonatal UCDs have shown variable intellectual outcomes, with a high percentage (~60 to 80 %) with mental retardation (Msall et al. 1984). UCD include deficiencies in any of six enzymes and two membrane transporters involved in urea biosynthesis (Table 1). All the UCD are autosomal recessive disorders, except the X linked condition, OTCD.

Neonatal onset UCD is associated with severe developmental and cognitive disabilities, childhood onset disorders present mild to severe mental and behavioral sequelae (Spada et al. 1994). Adults with UCD may be misdiagnosed as having psychiatric disorders and diagnosis may be delayed, if made at all (Choi et al. 2012).

HA is a significant cause of neurological damage in the proximal UCDs. HA is due to inability to scavenge nitrogen from protein breakdown. While HA can lead to severe consequences in the central nervous system (CNS), the pathophysiology remains unclear. Current theories have focused on: 1) glutamine accumulation leading to impaired cerebral osmoregulation, and 2) glutamate/NMDA receptor activation and excitotoxic injury (Llansola et al. 2007) and 3) energy deficit with impairment of energy metabolism, leading to both acute and long-term effects such as a failure of normal myelination and release of trophic hormones (Albrecht 1998; Bachmann 2002; Felipo and Butterworth 2002; Monfort et al. 2002, 2005; Ratnakumari et al. 1994; Braissant et al. 2002; Ahabrach et al. 2010; Skowro ska and Albrecht 2012). Neuropathological changes in UCD are similar to those in hepatic encephalopathy and hypoxic ischemic encephalopathy. UCD affect predominantly white matter (WM), reflecting astrocyte damage (Braissant 2010). The extent of WM injury depends upon the disease severity.

There are currently no specific treatments to protect the brain from the effects of HA in the UCDs. In clinical practice, the use of nitrogen scavengers has resulted in improved survival, but neurological outcome remains poor, especially in neonatal onset cases (Brusilow and Maestri 1996). Development of noninvasive measures to monitor early signs of injury and recovery are needed to understand the time course of damage and provide information regarding critical time periods for intervention as newer drugs are being developed for these conditions.

Cognitive deficits

Males with late-onset OTCD (defined as outside the new-born period) show deficits in executive function, motor planning, and working memory. A broad phenotype is observed in heterozygous females owing to varying degrees of X inactivation as well as allelic heterogeneity (Pridmore et al. 1995). Previous estimates predicted 85 % of heterozygous females with OTCD to be asymptomatic based on clinical history; the remainder show symptoms including behavioral and intellectual delay (ID), protein intolerance, cyclical vomiting, stroke like episodes and hyperammonemic coma (Batshaw et al. 1986; Smith et al. 2005) (Table 2). However, we have found evidence of executive dysfunction and working

memory deficits in these “asymptomatic” patients (Gropman et al. 2011). Additionally, we have shown with neuroimaging (¹H MRS, DTI, and fMRI) abnormalities in brain metabolism and function in patients with partial OTCD, reflecting cellular injury in otherwise normal appearing brain by conventional MRI (Gropman et al. 2010). Thus, multimodal imaging has shown “asymptomatic” OTCD is associated with altered neurocognitive profile in cognitive subdomains linked to the prefrontal cortex (PFC). These domains invoke working memory, executive cognition and attention. These deficits contribute significantly to disability and quality of life in these patients.

Methods

Subject recruitment Subjects were recruited as part of an NIH-funded Rare Diseases Clinical Research Center (Seminara et al. 2010; McCandless et al. 2010). The study included males with late-onset OTCD and asymptomatic and symptomatic females, with varying ages of diagnosis and metabolic control that had IQ scores above 80. The study was approved by the local institutional review board and all subjects gave informed consent for their participation.

Subjects

All patients were studied in the post absorptive state. All subjects consumed their normal diets and were not asked to restrict protein. The study was open to subjects who were at stable health. No subject had elevated ammonia, but several had baseline elevations of the glutamine (subjects), all controls had normal ammonia and glutamine. All subjects (subjects and controls) had normal liver function enzymes taken the day before or on the day of testing.

Cognitive testing

All patients underwent neurocognitive testing consisting of the comprehensive trail making test (CTMT), Part B, a pen and paper task that is norm-referenced and taps executive function and cognitive flexibility, as well as motor speed and visual search, all impaired in OTCD. They also completed a computerized version of the Stroop Color and Word Test, a test of shifting attention and executive function. We have previously found that performance on these tasks could discriminate individuals with OTCD from age-matched controls and that within the subset of subjects with late-onset OTCD, those with more substantial disease consistently perform worse on these tasks (unpublished results; Gyato et al. 2004).

Imaging

MRI was performed as we have described using a 3 T whole-body MRI scanner (Siemens MAGNETOM Trio, Erlangen, Germany). A three dimensional T1 weighted “anatomic MRI” was used to identify and segment CSF, gray (GM) and white matter (WM); evaluate GM and WM integrity and; to generate a high resolution template on which to align and map the MRS, DTI and fMRI data using a fully automated segmentation procedure as previously described (Gropman et al. 2008). ¹H MRS was acquired as previous described (Gropman et al. 2008). Quantification of metabolites was performed with LCModel (Provencher 1993). DTI Imaging and Data Acquisition and Fractional Anisotropy Calculation were performed as previously described (Gropman et al.). We also employed functional magnetic resonance imaging (fMRI), which is based on the principle that the recorded MRI signal changes with the magnetic properties of intravascular contents. The fMRI data was acquired as previously described by our group (Gropman et al. 2011).

fMRI task Methods

Our cohorts perform the N-back task that probes (dorsal lateral prefrontal lobe) association cortex function (Barbey et al. 2012). The task presents a sequence of individual uppercase letters, and the subject indicates when the current stimulus matched the one presented N steps earlier in the sequence. In controls, high load conditioning activates a region in the left prefrontal cortex, as well as right prefrontal and striatal regions, which activate during low load conditions.

Analysis

The groups were well matched and differed only in full scale IQ. The 13 point difference in IQ still falls within one standard deviation of IQ which is defined as 15 points. All subjects were instructed on the tasks prior to going into the scanner and acceptable understanding and performance was achieved in all prior to scanning. Additionally, a linear regressor for subjects' full scale IQ scores was also included to account for between group IQ differences. Linear contrasts were prepared by subtracting the 1-back beta image from the 2-back beta image for each subject. This was used to represent the individual increase in BOLD signal correlating to the increase in working memory load between the two conditions. These contrast images were then compared in a random-effects group analysis to create statistical parametric maps. Images were analyzed within groups using one-way t tests, and between groups using two-way t tests. In order to emphasize patterns of most robust neural activity, presentation of the one-way t test data was limited to a conservative threshold of $P < 0.01$, FWE corrected. A cluster size threshold of 160 mm³ was used to restrict the two-way between groups t test to a cluster level correction of $P < 0.05$. Finally, on the basis of extensive prior evidence of PFC involvement in executive cognition and Nback task performance, between-group second level analyses were restricted to the PFC (mask constructed in WFU Pickatlas using BA 9, 10, 32, 44, 45, 46, 47, dilated to 1) (Meyer-Lindenberg et al. 2008).

Results

Cognitive testing

There was no significant difference in FSIQ between controls and subjects (123 vs. 110). In measures of executive function, subjects with OTCD showed worse performance. Compared with controls, they demonstrated increased reaction time on the Stroop Color and Word Test and poorer performance on the CTMT ($P < .01$) which require a higher level of attention and cognitive flexibility. Symptomatic subjects consistently showed poorer performance than asymptomatic OTCD subjects on the CTMT.

Diffusion imaging in OTCD

Statistical parametric analysis of the FA data showed regions of decreased FA in the frontal white matter Fig. 1. We further examined the relationship between white matter integrity and neuropsychological function. Linear regression analysis showed positive correlations between FA in the frontal white matter and lower scores on the CTMT ($R = 0.6$), and longer reaction times recorded on Stroop ($R = 0.4$, Fig 5). This was not seen in controls.

¹H MRS in OTCD

We detected significant increases of gln levels ($p < 0.007$) in posterior cingulate gray matter (PCGM), parietal white matter (PWM), and frontal white matter (FWM) in subjects with OTCD (symptomatic and asymptomatic subjects). We found significant decrease in myoinositol in parietal and frontal white matter (PWM, FWM), thalamus and PCGM (Fig. 2). Degree of mI depletion was inversely correlated with gln level in subjects but not

controls (Fig. 2). Comparison of metabolite changes in OTCD individuals to age matched controls is shown in Fig. 3. A reduced level of mI in white matter of asymptomatic OTCD subjects suggests the possibility of unrecognized biochemical disturbances (such as edema and volume changes in astrocytes). The reduction of mI correlated with cognitive impairments in a pattern supporting the white matter injury model.

fMRI

Performance on the N-back task did not differ significantly for either 1-back or 2-back accuracy (1-back $p=0.859$, 2-back $p=0.854$) or reaction time (1-back $p=0.947$, 2-back $p=0.684$). Average accuracy decreased and average reaction time increased for the 2-back condition for each group (control group $p=0.0083$, OTCD group $p=0.0144$) with a non-significant increase in reaction time (control group $p=0.124$, OTCD group $p=0.193$).

However, what was important is that increased working memory load correlated with increased activation across groups in bilateral parietal and frontal areas, as well as bilateral cerebellum. Two-way between-group t-tests in OTCD subjects displayed significantly greater task-dependent BOLD signal in subjects versus controls at lower levels of cognitive load. In keeping with a model of cognitive inefficiency, we then saw decreased activation in right Broadman's areas 46 and 32 which house the dorsal lateral prefrontal cortex (DLPFC) and anterior cingulate (ACC).

Conclusions

These are the first multimodal imaging studies of patients with late onset OTCD, one of the UCDs. Contrary to previous assumptions, using neuroimaging we have found that patients previously believed to be asymptomatic show structural, biochemical and functional changes in the brain intermediate between symptomatic subjects and normal controls. Additionally, our findings overall demonstrate that ^1H MRS can be used to distinguish OTCD carriers from controls and aid in clinical diagnosis, as well as identify individuals who may be at risk for further brain injury (low mI level) due to reduced ureagenesis capacity. We hypothesize that low mI is a biomarker of a prior HA episode and represents a compensatory mechanism to correct astrocytic swelling due to high gln. Choline (Cho) was reduced in frontal white matter. As Cho-containing compounds relate to membrane turnover, membrane dysfunction preceding neuronal death is suggested to occur in the frontal cortex in OTCD heterozygotes. This dysfunction may be responsible for some of the neurocognitive deficits observed in this disorder; this disruption of the white matter is measurable by changes in DTI.

These data suggest that high gln and low mI and possibly their ratio are biomarkers of brain injury in OTCD. The role of the low Cho level in the frontal cortex is not clear at this point, but may contribute to the cognitive impairments specific to this disorder. Recent research suggests a role for the cholinergic system in working memory and executive function (Deiana et al. 2011; Newman et al. 2012; García-Ayllón et al. 2008), thus the role of choline in the UCDs should be explored further. These biomarkers may be used as endpoints for future therapeutic trials. Given the link between HA, and astrocyte swelling, and neuropathology data, we used diffusion tensor imaging (DTI) to evaluate white matter microstructural changes.

Diffusion tensor-derived parameters such as fractional anisotropy (FA) describe the micro architectural characteristics of brain tissue; which can be used to depict pathological changes. FA of the frontal white matter was significantly lower in patients than in controls indicating changes in white matter microstructure in this region. Fiber tracts in this region connect areas of brain that underlie executive function and working memory, DTI provides an objective means for determining the relationship to cognitive deficits in OTCD subjects

treated early or asymptomatic with abnormal findings on DTI images. When correlated with severity scores, there was an inverse relationship between FA and disease severity.

To date, no study has reported fMRI findings in patients with OTCD. We have used fMRI to compare task-dependent neural activation between OTCD patients and age-matched controls. We used an N-back working memory paradigm and the STROOP test which taps cognitive resources sub-served by the PFC. Our research has shown that even mild or “asymptomatic” OTCD is associated with an altered neurochemical profile with deficits in an array of cognitive subdomains based in the prefrontal cortex (PFC).

Working memory is affected in the domains of executive cognition and reaction speed. Working memory requires storage, manipulation and retrieval of information in conscious awareness over brief intervals and is a critical component of executive cognition. This ability is subserved by a number of brain regions with the dorsolateral prefrontal cortex (DLPFC) as the central component. DLPFC activation follows an inverted U-shaped curve in response to increases in cognitive load, first with peak neural activation as task demands maximally tap an individual’s cognitive capacity, and then with decreasing activation after capacity is breached. Furthermore, DLPFC activation is classified as “inefficient” when an individual reaches peak activation at low levels of cognitive demand, relative to the normal population. Significantly these areas with increased activation have hemispheric connections that overlap with our prior findings of reduced white matter integrity in the superior projections of the genu and rostrum of the corpus callosum.

There is combined value of both DTI and fMRI in understanding attentional networks. DTI studies allow evaluation of the structural integrity of the brain’s interconnections whereas fMRI provides insights into the *functional* integrity of such connections in terms of how spatially distinct regions work together to support complex cognitive processes. “Functional connectivity” reflects the degree of concordance in neural activity that is observed among networked regions. In our cohort, our data suggest that functional connectivity may be compromised even in the absence of overt structural damage on routine MRI.

Overall, our findings offer preliminary evidence that brain injury caused by biochemical dysregulation in OTCD may impact the functional neuroanatomy serving working memory processes. Our future research is aimed evaluating change in biomarkers during an episode of HA as well as during the acute and longer term phases of recovery.

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Fig. 1. Diffusion tensor imaging shows evidence of white matter injury in motor tracts that connect parts of the brain important in attention and memory

Fig. 2.

This figure shows significant increases of gln levels ($p < 0.007$) in posterior cingulate gray matter (PCGM), parietal white matter (PWM), and frontal white matter (FWM) in subjects with OTCD (symptomatic and asymptomatic subjects, as well as significant decrease in myoinositol in parietal and frontal white matter (PWM, FWM), thalamus and PCGM. The degree of mI depletion was inversely correlated with gln level in subjects but not controls. (Reprinted with permission from Gropman et al. Mol Genet Metab. 2008 95(1-2):21-30)

Fig. 3.

The spectra show a direct comparison of metabolite changes in an OTCD individual to an age matched control

Table 1

List of the urea cycle enzymes for which a clinical disease is possible

Gene name	Gene symbol	Protein	Chromosome
Carbamylphosphate	CPS1	Carbamoyl-phosphate synthetase I	2q25
Ornithine transcarbamylase	OTC	Ornithine carbamoylase transferase	Xp21.1
Argininosuccinate synthase	ASS	Argininosuccinate synthase	9q34
Argininosuccinate lyase	ASL	Argininosuccinate lyase	7cen-q11.2
Arginase	ARG1	Arginase 1	6q23
N-acetyl glutamate synthase	NAGS	N-acetyl glutamate synthase	17q21.3
N-acetyl glutamate synthase	NAGS	N-acetyl glutamate synthase	17q21.3
Ornithine transporter Mitochondrial 1	ORNT 1	Ornithine transporter Mitochondrial 1	13q14
Citrin 1	Citrin	Proposed hepatic mitochondrial aspartate transporter	7q21.3

Table 2

List of the clinical features seen in patients with early onset (neonatal) and later onset urea cycle disorders due to partial deficiency. Late onset disorders can present outside the new born period at any stage of life including adult onset

Features of early onset and late onset UCDs	
Clinical symptoms of UCDs	
Lethargy	Protein aversion
Unsteadiness/asterixis	Self injurious behavior
Seizures	Hyperactive behavior
Anorexia	Strokes
Vomiting	Encephalopathy
Hypothermia	Psychiatric disorders
Coma	Learning difficulties