Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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patients with GSD IV. Each case was classified into one of the seven GSD IV subtypes described above. GBE1 genotypes were analyzed and updated according to the HGVS nomenclature. Chart review of our previously reported case was performed for clinical updates.

**Results:** One hundred sixty-eight cases from 99 publications were selected, which reported 132 variants in the GBE1 gene. The literature included all subtypes, with 33 cases of Classic Hepatic, 20 cases of Non-progressive Hepatic, 54 cases of Fetal/Neonatal Neuromuscular, 7 cases of Congenital Neuromuscular, 16 cases of Childhood Neuromuscular, 26 cases of APBD, and 1 case of Isolated Cardiomyopathy. All patients with the Classic Hepatic subtype with known genotype had one severe variant (splice-site, non-sense, frameshift) in compound heterozygosity with a missense variant.

Genotypes characteristic to either hepatic subtype (i.e. Classic or Non-progressive) were not identified. Non-sense and splice variants were seen in both subtypes in compound heterozygosity with a missense variant. Large exonic variants were not found in either Hepatic subtype. Variants found in both subtypes are similarly distributed across the gene with no specific common hot spots. The p.Asn541Asp variant seen in our case was seen in a patient with classic hepatic subtype along with c.263G > A (p.Cys88Tyr) (Derks et al. 2021), as well as in a patient with APBD along with c.1543C > G(p.Arg515Gly) (Carvalho et al. 2021). The p.Pro552Leu variant has been seen in a patient with fetal perinatal neuromuscular subtype in a homozygous state. After 2-year follow-up, our patient's liver function remains stable, consistent with the predicted Non-progressive Hepatic phenotype. Her pre-prandial labs showed a normal glucose level but elevated beta-hydroxybutyrate. She was started on high protein diet, cornstarch therapy and avoidance of simple sugars. Interestingly, she has suffered from hemorrhagic gastritis and massive gastric distension (her initial clinical presentation), and later an episode of gastric ulcers and gastric perforation.

**Conclusion:** Our work adds to the previous reviews on GSD IV genotypes (Li et al. 2010, Iijima 2018, Souza et al. 2021). The association of gastric perforation and GSDIV in our case remains unknown.

**Poster # 88**

**IMPACT OF HYPERAMMONEMIA IN UREA CYCLE DISORDERS (UCD) ON DOWNSTREAM MARKERS OF IMPAIRED NEUROCOGNITION: USING NONINVASIVE IMAGING TO DELINEATE STRUCTURAL, METABOLIC AND FUNCTIONAL CONSEQUENCES**

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**Background:** Ornithine transcarbamylase deficiency (OTC) is associated with impairment of waste nitrogen removal in the form of ammonia. Although hyperammonemia originates from impaired ureagenesis in the liver, brain is the only organ known to be damaged by hyperammonemia. Exposure of the brain to HA can lead to a wide range of effects in the short and long term. Episodes of hyperammonemia (HA) with acute elevations of ammonia causing substantial injury to the brain’s white matter and subsequent downstream cognitive disruption. Routine T1/T2 MRI may be initially normal. Work as part of the UCDC has demonstrated the utility of multimodal imaging to capture early biomarkers useful for diagnosis, disease monitoring and prognosis.

**Methods:** 40 subjects with OTC and age matched controls underwent a multimodal MRI: DTI, MRS and fNIRs and cognitive testing.

**Results:** OTC is associated with an altered neurochemical and neurocognitive profile in an array of subdomains based in the prefrontal cortex (PFC), such as working memory, executive cognition and attention. Such deficits contribute significantly to disabilities despite normal global IQ in many patients and may be seen (albeit to lesser degrees) in female carriers of OTC. Clinical management focuses on neuroprotection from HA, as well as neurotoxicity from other known and yet unclassified metabolites.

**Conclusions:** Here we characterize the neurocognitive impact of HA on subjects with OTC and compare with brain volumetric, biochemistry and functional downstream effects using noninvasive measures and demonstrate the use of multimodal imaging and how it can be tailored to the clinical setting.

**Poster # 89**

**SARS-CO-V2 ANTIBODY STATUS IN CHILDREN WITH MITOCHONDRIAL DISEASE**

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**Introduction:** The impact of the COVID19 pandemic on pediatric neurodevelopmental disorders like mitochondrial disease (MtD) has not been well characterized. Viral infection is a major cause of morbidity in children with MtD. Historically, pediatric patients with MtD experience neurologic decline and metabolic decompensation if exposed to viral infection and families practice strict risk mitigation behavior to avoid infection. As many caregivers of children with MtD are essential workers, the household serves as a transmission risk factor. To better understand SARS-CoV-2 infection in children with MtD, we conducted a serologic study of MtD households.

**Methods:** Families with a child with MtD were shipped a Neoteryx Blood Collection kit. Patient samples came from fifteen states across the United States as well as two European countries. All household individuals provided a dried blood sample which was shipped back for analysis of SARS-CoV-2 antibodies against both the nucelocapsid and the spike protein. Online questionnaires were also distributed to each family to
THE MECHANISM OF CREATINE MEDIATED DOWNREGULATION OF AGAT EXPRESSION

Michael Tropak1, Alex Lee1,2, Ilona Tkachyova1, Andreas Schulze1,2,3
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The rate limiting step in creatine biosynthesis is carried out by the enzyme arginine:glycine amidino transferase (AGAT). Walker in the late 1950's demonstrated end-product inhibition of dietary creatine in rats by repression of AGAT activity in a non-enzyme kinetic manner. Not until the mid 1980's did Van Pilsum provide evidence that creatine acts at the pre-translational level to control AGAT expression. We used different cell models to further delineate the mechanism of creatine mediated downregulation of AGAT expression.

Following 24 h treatment of HeLa, HepaRG, RH30, and HAP1 cells with 50 mM creatine, a two- to three-fold decrease in AGAT mRNA and protein levels is observed using qPCR and Western blotting. Ethynyl-Uridine labelled endogenous nascent AGAT RNA levels in HepaRG cells in pulse-chase experiments directly showed that the stability of AGAT mRNA is decreased 50% by 50 mM creatine. We have generated AGAT-c-terminat Nanoluc Luciferase reporter HAP1 cell line by CRISPR that continues to respond to CT. Treatment with actinomycin D (ActD), a

assess exposure risks, MtD severity, and viral symptomatology. These data will allow us to define the status of proximate contacts of children with MtD, as well as symptomatology and asymptomatic infection.

Results: Twenty families enrolled with N = 83 samples collected. All 20 families had at least one member with a positive nucleocapsid antibody test. Of the 21 patients with mitochondrial disease, 18 were positive for antibodies against the nucleocapsid antibody. However, of the 14 MtD patients who reported community testing prior to sampling, only one patient with MtD had known a positive test in the community. Of those with positive nucleocapsid antibodies, 29% had a known exposure to someone with COVID-19 infection. Symptomatology analysis concluded that between March of 2020 and the sampling date, 6 patients experienced fever or chills, 2 experienced a new or worsening cough, 1 experienced shortness of breath, 2 experienced pneumonia and 1 presented with muscle or body aches.

Conclusion: There is serologic evidence that the majority of families affected by mitochondrial disease have been exposed to COVID19 despite strict risk mitigation behaviors. Of the patients exposed to COVID19, almost all had another family member also exposed, indicating the household as a possible transmission factor. None of these patients experienced hospitalization, neurologic decline, or metabolic decompensation. This implies that patients with mitochondrial disease may be capable of having asymptomatic COVID19 infections and may be able to tolerate this disease without acute decompensation. This may have implications about mitochondrial function in the immune response to COVID19. Future directions for this study include a network scale up model which will aid in making broader generalizations about this disease community through exposure levels.

Poster # 90
EFFECT OF CREATINE SUPPLEMENTATION ON AGAT EXPRESSION AND METABOLIC INTERMEDIATES IN GAMT-DEFICIENT MICE
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We investigated the effect of creatine supplementation on the expression of AGAT as well as creatine metabolites in a creatine-deficient mouse model. Wildtype and GAMT-deficient, 12-weeks old mice were fed with creatine-free or creatine-enriched (2% or 4%) mouse chow for 10 weeks. Urine was collected weekly. Brain, kidney, liver, heart, and skeletal muscle were harvested after 10 weeks.

In urine, HPLC analysis demonstrated increase of creatine from 1.600 to 4.370 and 14.500 μmol/mol creatinine in wildtype and from zero to 8000 and 6500 in mutant mice treated with 2% and 4% creatine, respectively. Guanidinoacetate (GAA) decreased from 200 to 40 (2%) and 30 (4%) μmol/mol creatinine in wildtype and from 6900 to 800 (2%) and 400 (4%) in mutants.

In selected tissues, LC-MSMS analysis demonstrated varied effect of creatine supplementation on creatine- and GAA levels. In kidneys, creatine increased from 600 to 2000 (2%) and 3000 (4%) in wildtype and from 20 to 2000 (2%) and 4% in mutant mice. In liver, creatine increased from 175 to 2600 (2%) and 7900 (4%) in wildtype and from 3 to 3900 (2%) and 5200 (4%) in mutants. There was no creatine change in wildtype brain and wildtype muscle; however, both tissues showed increase of creatine in mutants. For mutant brain, creatine increased from 1000 to 7500 (2% and 4%) and for mutant muscle creatine increased from 300 to 21,000 (2% and 4%). There was a slight decrease in creatine in wildtype heart; creatine dropped from 10,400 to 8000 (2%) and 6500 (4%); in mutant heart, creatine increased from 140 to 8000 (2%) and 5800 (4%). In kidneys, GAA decreased from 200 to 100 (2%) and 80 (4%) in wildtype and from 1000 to 400 (2% and 4%) in mutants. In liver, GAA decreased from 45 to 2.5 (2% and 4%) in wildtype, but unexpectedly increased from 1350 to 1820 (2%) and 2170 (4%) in mutants. In heart, GAA decreased from 6 to 3.5 (2%) and 2.5 (4%) in wildtype and from 6500 to 43 (2%) and 35 (4%) in mutants. In brain, GAA decreased from 75 to 5 (2% and 4%) in wildtype and from 2800 to 350 (2%) and 230 (4%) in mutants. There was no GAA change in wildtype muscle but decrease from 11,800 to 40 (2%) and 4% in mutants.

Quantitative PCR (qPCR) and Western blot analysis revealed marked decrease in AGAT gene and protein expression by ~50% (2% and 4%) in wildtype and mutant mice.

In summary, creatine metabolite analysis in urine and organ homogenates validates the GAMT-deficient model and confirms the efficacy of creatine supplementation through marked increases of creatine and persistent reductions in GAA (except liver) in both wildtype and mutant mice. The effect on GAA is likely caused by the creatine mediated suppression of AGAT.

Poster # 91
THE MECHANISM OF CREATINE MEDIATED DOWNREGULATION OF AGAT EXPRESSION

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The rate limiting step in creatine biosynthesis is carried out by the enzyme arginine:glycine amidino transferase (AGAT). Walker in the late 1950's demonstrated end-product inhibition of dietary creatine in rats by repression of AGAT activity in a non-enzyme kinetic manner. Not until the mid 1980's did Van Pilsun provide evidence that creatine acts at the pre-translational level to control AGAT expression. We used different cell models to further delineate the mechanism of creatine mediated downregulation of AGAT expression.

Following 24 h treatment of HeLa, HepaRG, RH30, and HAP1 cells with 50 mM creatine, a two- to three-fold decrease in AGAT mRNA and protein levels is observed using qPCR and Western blotting. Ethynyl-Uridine labelled endogenous nascent AGAT RNA levels in HepaRG cells in pulse-chase experiments directly showed that the stability of AGAT mRNA is decreased 50% by 50 mM creatine. We have generated AGAT-c-terminal Nanoluc Luciferase reporter HAP1 cell line by CRISPR that continues to respond to CT. Treatment with actinomycin D (ActD), a