



# Studying Neuropsychological Functioning in Rare Diseases:

Lessons learned from the Urea Cycle Disorders Consortium

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# Challenges to Studying Rare Disorders



1. Broad range of potential outcomes
2. Recruitment/Low incidence
3. Is this a “static” disorder or is their potential for decline over time?
4. Connecting neuropsychological functioning to biomarkers
5. The “Mild” cases: It’s not all about IQ!

# Urea Cycle Disorders Project



Title: Longitudinal Study of Urea Cycle Disorders

Study Objective: To conduct a longitudinal multidisciplinary investigation of the natural history, morbidity and mortality in people with UCD's

Time Course: Initial 5 year longitudinal study with recent extension for an additional 5 years

Funding: NIH/RDCRN (Rare Diseases Clinical Research Network) and Private Donors (O'Malley Foundation)

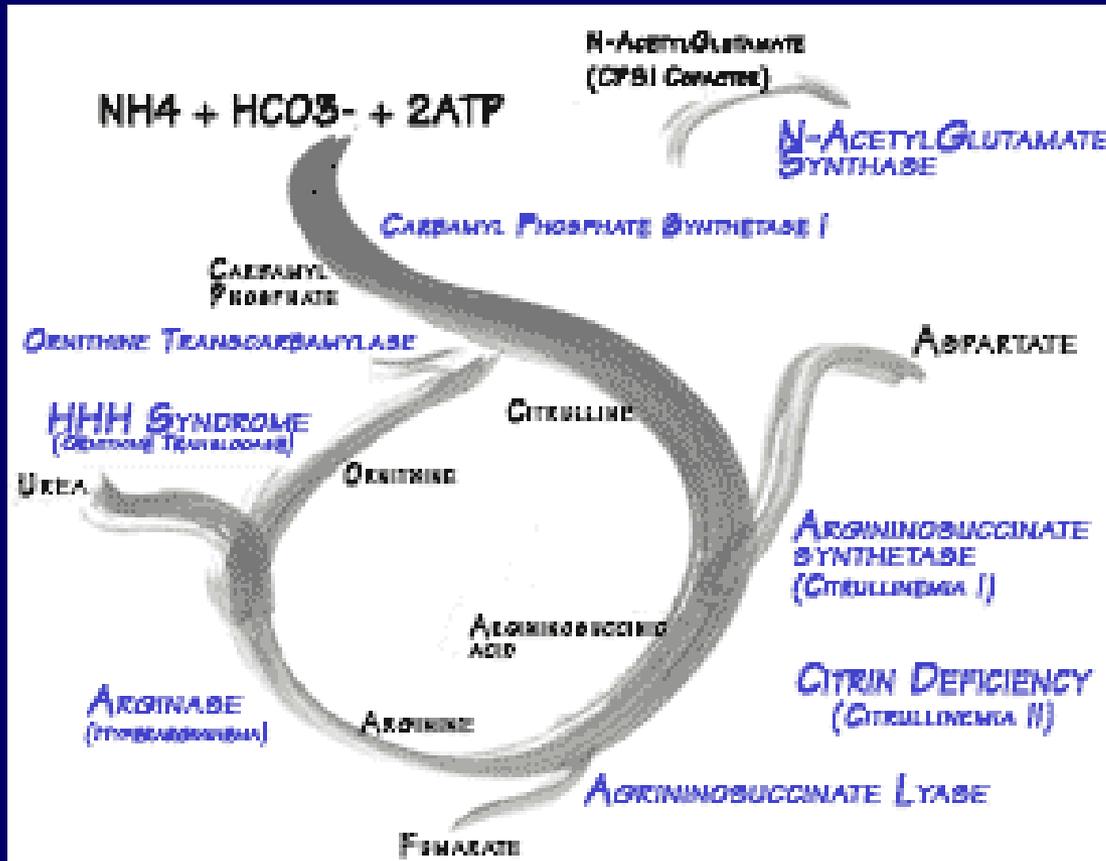
# Multi-Center Study



- **At study start: 8 US sites**

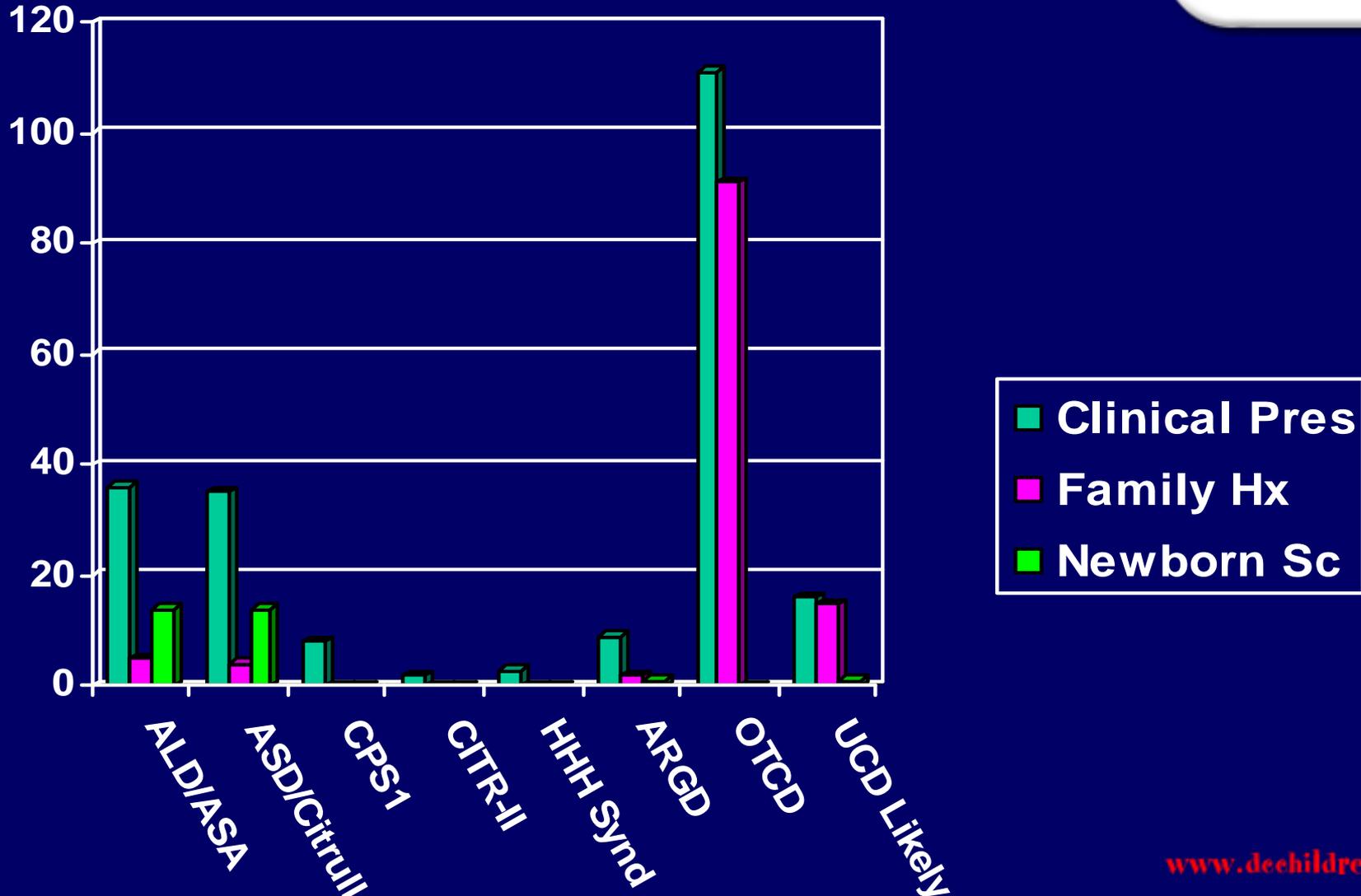
- (1) Children's National Medical Center, Washington, DC; (2) Baylor College of Medicine, Houston, TX (3) Vanderbilt University, Nashville, TN (4) Mt. Sinai School of Medicine, NY, NY (5) Yale University/Boston Childrens(6) UCLA, Los Angeles, CA (7) Case Western Reserve, Cleveland, OH (8) CHOP, Philadelphia, PA
- Added: 3 more US sites: (1) Denver Children's Hospital, (2) Oregon Health Sciences, (3) University of Washington, Seattle.
- Added 2 international sites: (1) Sick Kids Hospital, Toronto, Canada (2) University Children's Hospital, Zurich, Switzerland
- Potential to add more sites/travel clinics in Minnesota, New England

# Brief Overview:



1. NAGS Deficiency
2. CPS Deficiency
3. OTC Deficiency
4. AS Deficiency (Citrullinemia)
5. Citrullinemia II
6. AL Deficiency (ASA)
7. Arginase Deficiency (Hyperargininemia)
8. HHH Syndrome

# All UCD Subjects (N=369)



# Neuropsychological Component



- **Neuropsychological Testing included at distinct age time points:**
  - Enrollment (birth/6mo- adulthood)
  - Follow-up: 6 months, 18 months, 4 years, 8 years, 15 years, 18 years
  - Adults: Baseline and 3 months following severe hyperammonemic episode

# Challenge1 : Range of Functioning



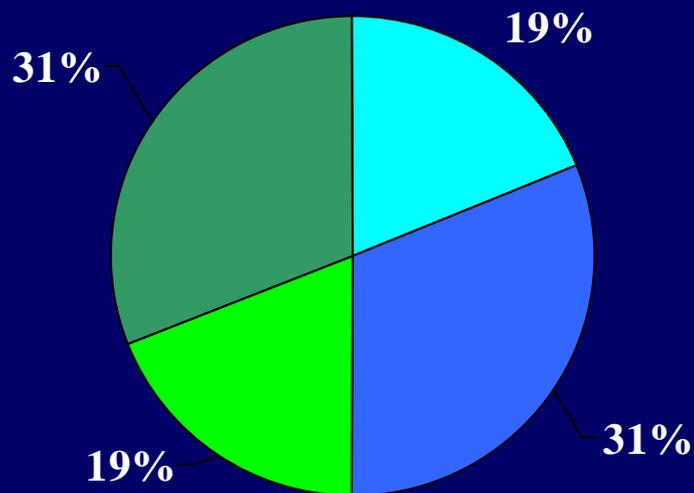
## - 3 separate batteries

- Very Low Functioning (i.e., cannot complete IQ testing with appropriate test for age).
- Low Functioning (i.e., IQ < 70, but able to complete testing).
- IQ 70 or above: Complete study battery (changes dependant on age) but to include:
  - (1) Intelligence/General Development, 2) Language, 3) Visual-Spatial Skills, 4) Verbal Memory, 5) Visual Memory 6) Simple Attention, 7) Executive Functions, 8) Basic Academic Skills, 9) Motor Skills, 10) Social/Emotional functioning, and 11) Adaptive Behavior.

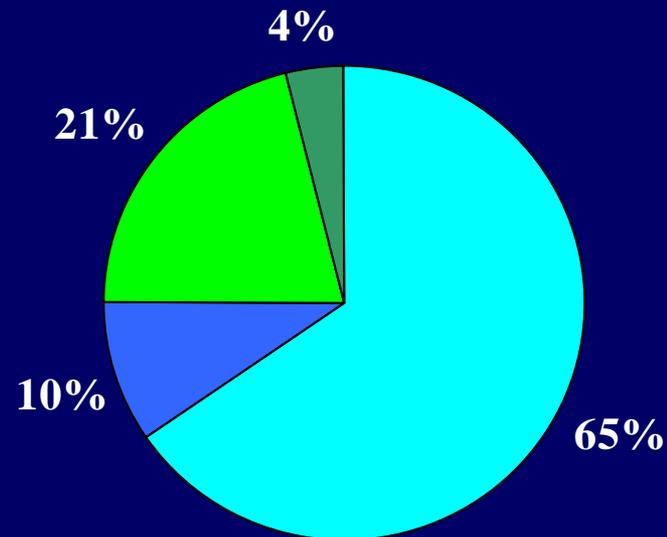
# Estimated Intellectual Functioning Neonatal vs. Late Onset (ages 3-16)



Neonatal Onset (N=16)



Late Onset (N=52)



- Average or above
- Borderline/Low Average
- Mild Intellectual Disability
- Severe Intellectual Disability

# Challenge 2: Low Incidence

## Broad Range of Ages



- **Must include a broad age range and combine data for analysis**
- **Poses challenges for developing a study battery**
- **For UCDC, age range is birth to Adulthood**
- **Test battery**
  - Combine tests into “domain scores” to compare across the ages (e.g., Language, Memory, etc)
  - Try to choose similar tests
    - Memory: CMS and WMS
    - Intelligence: WPPSI, WASI

# Challenge 2: Low Incidence Combining Disorders



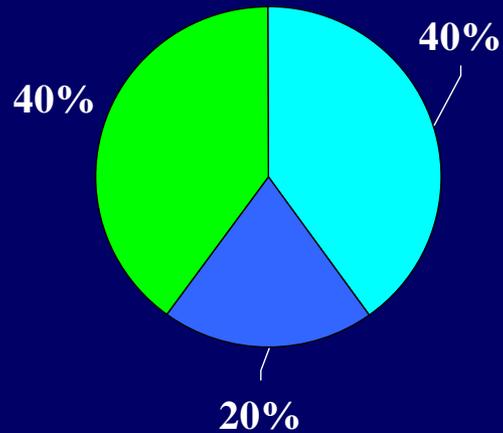
- Different disorders have often been combined to increase N
- UCDC
  - Although they are similar disorders, they involve different enzymes and have different metabolic abnormalities
  - Partial vs. full block of the Urea Cycle
  - Certain disorders appear to have poorer outcomes
  - Still difficult to study the most rare conditions

# Intelligence by Diagnosis

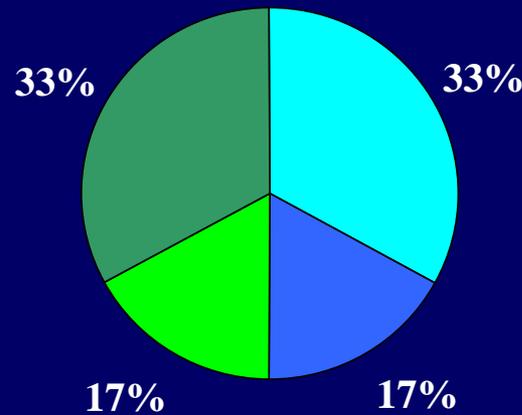
(ages 3-16)



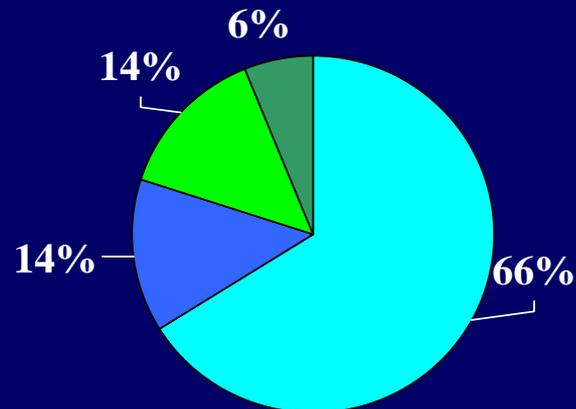
AL Deficiency (n=10)



AS Deficiency (n=12)



OTC Deficiency (N=36)



# Disorder Differences??



- Is this just because OTC group is more “mild” and has many “asymptomatic” carriers?
- No! even when we account for # of hyperammonemic episodes, the AS and AL Deficiency groups are about 1 SD lower in terms of overall IQ.
- There must be other factors beyond HA that contribute to disability in this population
- Lesson: disorders must be studied separately when possible

# Challenge 2: Low Incidence Non-English Speaking Subjects?



- **Language Issues:**
  - Several sites with large Hispanic Populations
  - Often the child spoke English, but parent did not
  - Solution: developed a non-English speaking battery, obtained parent questionnaires in Spanish

# Challenge 2: Low Incidence Non-English Speaking Subjects?



- **University Children's Hospital: Zurich, Switzerland**
  - Switzerland has 3 national languages: German, Italian, French
  - Focused on largest population around Zurich: German
  - Found local experts in pediatric neuropsychology
  - Developed an overlapping/unique battery covering same neuropsychological domain
  - Eliminated verbal tests without comparable German form
  - Got translated questionnaires

# Challenge: Low Incidence

## Possible Solution: Travel Clinics



- Travel clinic is set up at a site where there are a substantial number of patients to be recruited
- Group from UCDC travels to that site- local physician is the “PI” for that travel clinic
- First Travel clinic: Sick Kids Hospital: Toronto, Canada
  - Language barrier is minimal. No French-Canadians enrolled
  - US team of neuropsychologists travel to Toronto
    - Carry tests on the plane/borrow tests
    - Supervision/licensure issues: Get local supervision

# Challenge 3: Change Over Time

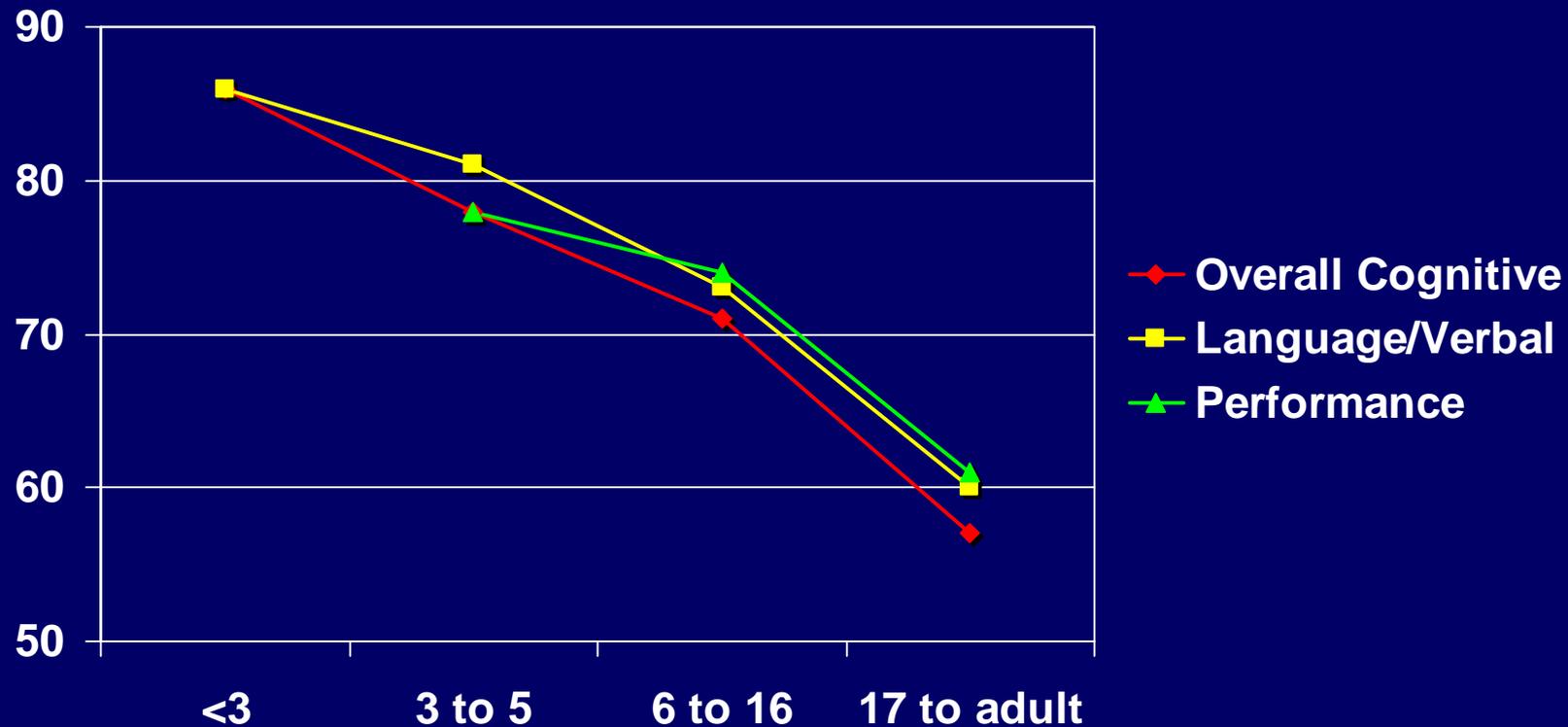


- Is there potential for change over time?
- How do you measure meaningful change?
- Even if they are metabolically stable, will they “grow into their deficits?”
- UCDC:
  - What is the impact of repeated HA episodes?
  - Is there evidence of decline over time?
  - Is the damage permanent- or is there potential for it to be reversible?
- Thus far we only have cross sectional data

# Challenge 3: Change over time?



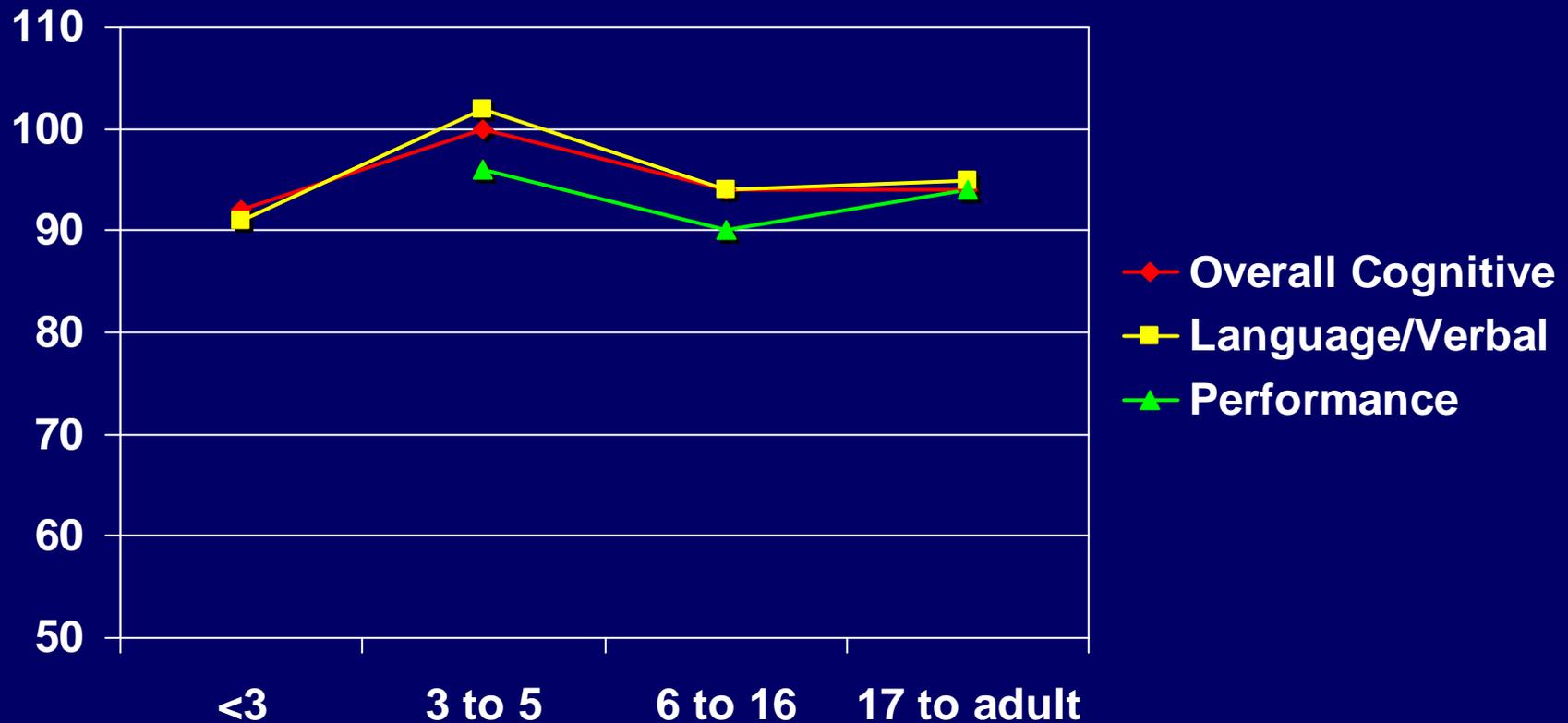
## Neonatal onset group



# Challenge 3: Change over time?



## Late onset group



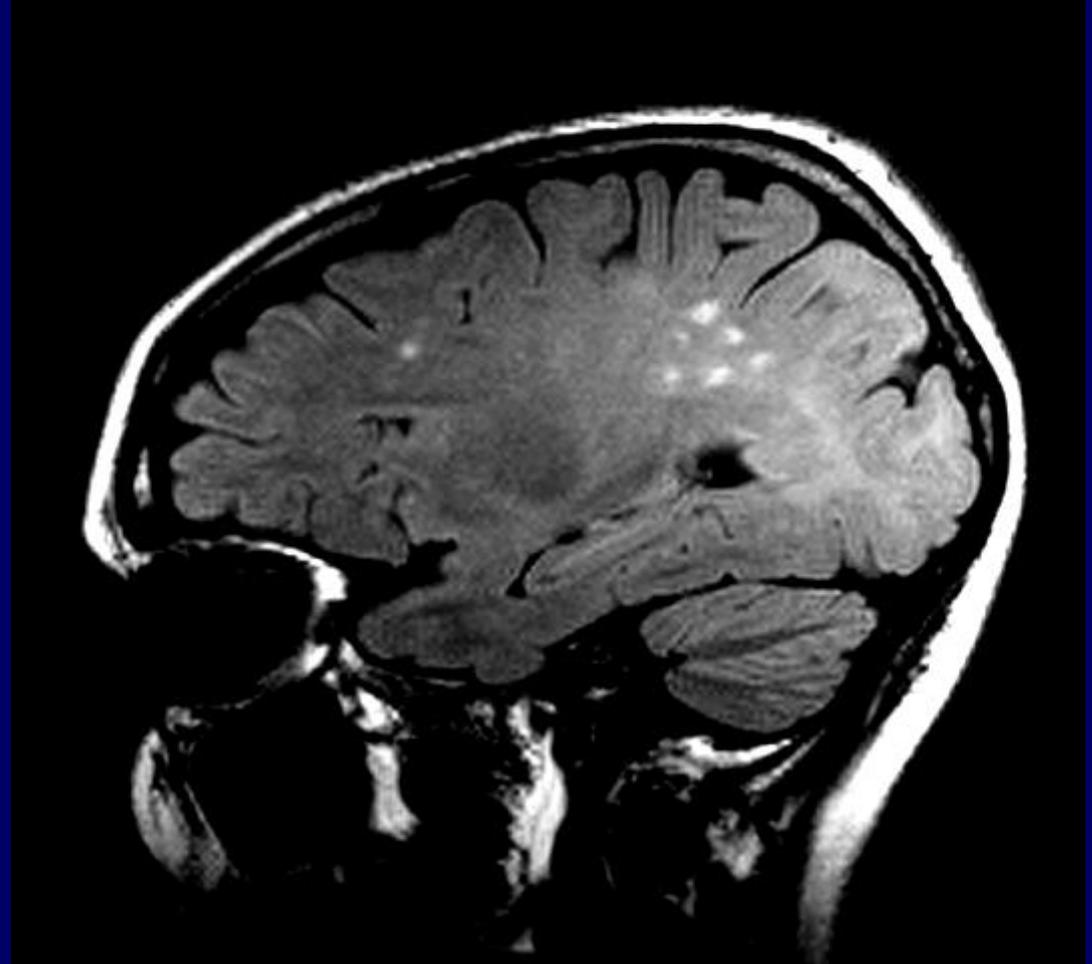
# Challenge 4: Biomarkers of Severity



- What are the important biomarkers for disease severity?
- How can they be linked to neurocognitive functioning?
- UCDC:
  - Genetic Mutation
  - Frequency and Severity of HA episodes
  - Other blood markers- HA is not the whole story
  - Neuroimaging data
    - White Matter Disease: Importance of techniques like DTI
    - Functional Imaging, MRS

# Biomarkers: MRI

T1 Weighted FLAIR image in a female with partial OTC showing abnormal white matter signal in the deep white matter of the centrum semiovale and motor association cortex. May be reversible and are felt to be markers of recent HA. There is also cortical atrophy with widened sulci. (courtesy of Dr. Andrea Gropman, CNMC, Washington, D.C.)



# Neonatal Onset



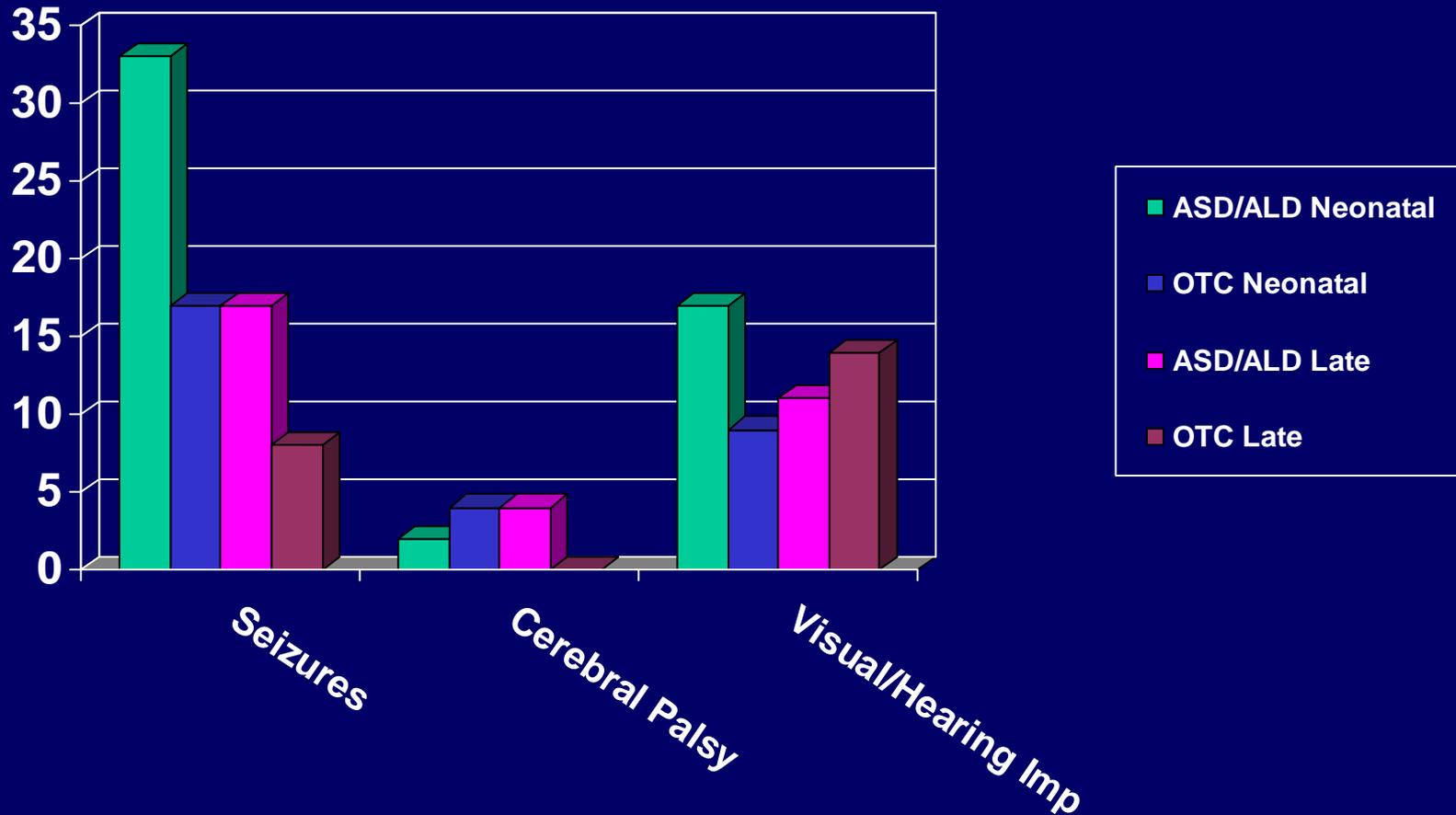
Subtype	Variable	N	Mean	STD	P-value
ASD or ALD	Bayley Cognitive Composite	12	87.917	18.520	0.2883
	wfullstd	23	59.609	20.834	0.0433
OTCD	Bayley Cognitive Composite	5	74	20.125	
	wfullstd	6	74.833	19.661	

# Late Onset

Subtype	Variable	N	Mean	STD	P-value
ASD or ALD	Bayley Cognitive Composite	11	97.273	11.909	0.7459
	wfullstd	24	73.5	22.790	0.0007
OTCD	Bayley Cognitive Composite	3	95	8.660	
	wfullstd	72	90.361	23.763	

# Percent Reported Disabilities

Medical/Physical



# One More Challenge!

What about the “Asymptomatic” or “Mild” groups



- Its not all about IQ!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
- Often there are “Carriers”, “Mildly Affected” or “Asymptomatic” individuals with these disorders
- Many if not all of these individuals are not followed by a physician
- Some naturally restrict their diets
  - E.g., protein restrictors

# Asymptomatic (ages 6 and up)



- **Strengths: (overall means in average range)**
  - Intellectual ability
  - Adaptive Skills
  - Basic Academic Skills
  - Language
  - Visual- Spatial skills (with NO motor demand)
  - Memory
- **Weaknesses (generally  $\frac{1}{2}$  to 1 standard deviation below average)**
  - Gross motor strength (Grip Strength)
  - Fine motor dexterity (Grooved Pegboard)
  - Visual Motor Integration (VMI-copying)
  - Complex planning/organization (Key Complex Figure)

# Thanks to all involved!



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  - Mark Batshaw
- **All site PI's & Coordinators**
- **NUCDF**
- **DTTC (data management center)**
  - HyeSeung Lee
- **CNMC Personnel:**
  - PI: Uta Lichter
  - Study Coordinator: Kara Lord
  - Psychometrist Support: Sybille Swanson
- **Neuropsychologists:**
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  - Linda Ashford
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