Utilization of NIH Toolbox Cognition Battery in a Rare Disease Conference Setting

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Congenital Central Hypoventilation Syndrome (CCHS) Overview

• Approximately 1,200 cases worldwide

• Characterized by:
  – Hypoventilation asleep and in severe cases awake and asleep
  – Autonomic nervous system (the system that functions automatically to keep us alive) dysregulation
  – ↑ risk for neurocognitive deficits
Etiology of CCHS

- **PHOX2B** is the disease-defining gene for CCHS
- It is expressed early in the embryology of the ANS
- There are 2 types of CCHS-related **PHOX2B** mutations:
  - **Polyalanine repeat expansion mutation (PARM):** expansion of normal 20 alanine repeat region to 24-33 repeats on one allele (90-92% of CCHS cases); genotypes 20/24 to 20/33
  - **Non-polyalanine repeat mutation (NPARM):** missense, nonsense, frameshift, & stop codon mutations (8-10% of CCHS cases)
**PHOX2B Genotype/CCHS Phenotype Association**

- In general, patients with NPARMs and longer PARMs have a more severe CCHS phenotype
  - Need for 24 hour/day artificial ventilation
  - Hirschsprung disease
  - Risk of a tumor of neural crest origin
Endogenous Daily Exposures in CCHS

Repeated exposure to hypoxemia & hypercarbia

- Impaired regional oxygenation in the brain

- Negative effects on neurocognitive outcome?
Prior CCHS Neurocognitive Research

• School age CCHS patients have mean FSIQ values one SD below the norm, with a broad range of neurocognitive outcomes (Zelko et al., 2010)

• Preschool age CCHS patients with the PHOX2B 20/25 genotype have normal mean FSIQ, but longer PARMs have reduced FSIQ as in school age patients (Charnay et al., 2016)

• Need for larger cohorts to better understand factors that impact neurocognitive outcome

• Given the rarity of CCHS, large cohorts are challenging to evaluate in a narrow testing window
How did we evaluate cognition?

- NIH Toolbox Cognition Battery (NTCB)

**Types of Cognition**

- **Fluid**
  - Learn & process new information in novel situations

- **Crystallized**
  - Depends on past learning experiences & is influenced by education

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<tr>
<th>Cognitive Abilities</th>
<th>NTCB Tests</th>
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<tbody>
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<td>Working Memory</td>
<td>List Sorting Working Memory</td>
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<tr>
<td>Episodic Memory</td>
<td>Picture Sequence Memory</td>
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<td>Processing Speed</td>
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<td>Executive Function &amp; Attention</td>
<td>Flanker Inhibitory Control and Attention, Dimensional Change Cards Sort</td>
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<td>Dimensional Change Cards Sort</td>
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<th>Cognitive Abilities</th>
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<tr>
<td>Language</td>
<td>Picture Vocabulary, Oral Reading Recognition</td>
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Prior Clinical Implementation of NTCB

• NIH Toolbox Cognition Battery (NTCB) has been administered in 38 CCHS patients over a 3 year period at Lurie Children’s Hospital (n=35) and Seattle Children’s Hospital (n=3)

• Previously administered in a traditional, clinical setting:
  – A controlled environment
  – Quiet
  – Limited distractions
  – Private testing room
2018 CCHS Family Network Meeting

• Offered an opportunity to collect a larger CCHS cohort in short time frame
• This cohort represented a diverse range of management and compliance with ATS recommendations for CCHS
2018 CCHS Family Network Meeting

• But…..a non-traditional testing environment
  – Network meeting conducted in hotel conference setting, with no access to private individual rooms for research
Research Objectives

1. Evaluate the ability to capture valid neurocognitive performance data using NTCB testing with a protocol modified to accommodate environmental limitations in non-traditional testing setting.

2. Collect neurocognitive performance data from a large cohort of CCHS patients representing patients not followed by the largest and most comprehensive center for CCHS in the world (Lurie Children’s).
Hypothesis

- We hypothesized that NTCB can be used to assess neurocognition in CCHS patients in a non-traditional setting (hotel conference center) and that performance results of this cohort will not be significantly different than the cohort collected in the more traditional, controlled clinical setting.
Methods
Recruitment & Consent Process

• Research team members on site (n=7)

• Eight-hour window for testing
  – consented participants
  – administered NTCB assessments
  – Completed REDCap ANS dysregulation questionnaire specific to CCHS phenotype for each consented participant
Methods

Room Set-up

CONSENT & REDCap Questionnaire Station

PARTITION DIVIDING ONE ROOM INTO TWO
Methods

Environmental Limitations & Adjustments

- A single room
- Noise and distractions from other participants and hallway
- Recruitment constraints by conference organizers
Methods
Statistical Analyses

• Age-corrected scores for clinic vs. conference groups tested with unpaired t-tests

• Fluid vs. crystallized composite scores tested with paired t-tests

• Age-corrected scores were tested against the population mean of 100 with Student's t-tests
Results
Comparison of Clinic & Conference Cohorts

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<tr>
<th>NTCB Collection Site</th>
<th>Clinic</th>
<th>Conference</th>
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</thead>
<tbody>
<tr>
<td>Age Range</td>
<td>5-35 years</td>
<td>5-37 years</td>
</tr>
<tr>
<td>Mean Age</td>
<td>15.5 years</td>
<td>18.3 years</td>
</tr>
<tr>
<td>Number of Participants</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>Duration of Data Collection</td>
<td>3 years</td>
<td>&lt;1 day</td>
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Neurocognition was assessed in 29 unique patients in EIGHT hours!
CCHS NTCB age-corrected scores were not significantly different when stratified by testing environment (p>0.05 for all scores)
Results

Summary of Conference CCHS Findings

• Normal composite
• Above average crystallized scores
• Below average fluid cognition scores

• All major findings replicate findings previously identified in our clinical cohort
Conclusions

- Our results support the validity of using the NTCB to collect neurocognitive data using a modified protocol in a non-traditional setting.

- The NTCB data replicate previous findings that crystallized cognition scores are higher than fluid scores in CCHS.

- The NTCB is a robust tool because it allowed us to effectively nearly double our CCHS NTCB number of tested subjects in 8 hours at a bustling rare disease conference compared to the tightly regulated clinic cohort collected over three years.

- The NTCB is easy to implement, yet a powerful tool to assess neurocognition, especially in a rare disease population.
Future Directions

• Our results
  • support the use of a modified NTCB protocol in future studies to overcome environmental limitations of a non-traditional testing environment
  • support the power of NTCB for increasing study cohort sizes in rare diseases, with testing at rare disease conferences
Thank you!

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References
