P-202

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Homocysteine Is Negatively Correlated With Cognition In Homocystinuria Due To Cystathionine Beta-synthase Deficiency

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Background

Cystathionine beta-synthase deficient homocystinuria (HCU) is a rare autosomal recessive disorder caused by mutations in the cystathionine beta-synthase (CBS) gene leading to defects in methionine metabolism. The metabolic defect results in increased plasma levels of homocysteine (Hcy) and methionine (Met) and decreased levels of cysteine (Cys) and cystathionine. Clinical manifestations of HCU include involvement of the eye, skeletal system, vascular system (thromboembolism), and neuropsychiatric abnormalities, including learning difficulties, developmental delay, and intellectual disability (Morris et al. 2017, Mudd et al. 1985). Treatment consists of supplementation with B-vitamins (vitamins B6, B12, folate) and/or betaine, and/or restriction of the intake of the essential amino acid Met through a diet that is very low in natural protein to reduce the precursor load on the transsulfuration pathway. For patients on dietary treatment, supplementation with a Met-free L-amino acid mixture is also advised (Morris et al. 2017).

Previous research has demonstrated associations between lifetime total Hcy (tHcy) as a key predictor of intellectual functioning in HCU (Al-Dewik et al. 2019; Yap et al. 2001). Missing from the current literature is a description of profiles of cognitive strengths or deficits as well as exploration of whether proximal biomarkers of HCU and cognitive ability are associated.

Executive functions refer to a set of top-down mental processes that are effortful and needed for attention and concentration (Diamond 2013). Executive functioning is particularly sensitive to changes in physical health and is a good candidate to evaluate associations with biomarkers of HCU severity. Unlike overall intelligence, executive functioning can be improved through intervention (Diamond 2013).

Methods

Study CBS-HCY-NHS-01 is a multicenter (8 sites), international, observational, prospective, natural history study of HCU that enrolled 55 pediatric and adult patients to characterize the clinical course of HCU in patients under current clinical management practices over 3 years. It explored the range of plasma concentrations of tHcy and related sulfur metabolites and the variability of the clinical sequelae of the disease. Because Study CBS-HCY-NHS-01 is ongoing, this interim analysis was performed using a data cut-off date of 05 July 2019.Patients' characteristics and skeletal abnormalities were also assessed, and these data are reported in separate posters (0868 and 0874, respectively).

Cognitive function was assessed at baseline and every 6 months using the age-normalized NIH Toolbox Cognition Battery (NIHCB), which assesses language, working memory, episodic memory, processing speed, set shifting, and inhibitory control (Weintraub 2013a/b). The analyses used the median scores from the visits. Patient data from 1 to 5 visits were available. tHcy levels were measured in plasma. Correlations between cognitive function and tHcy, Cys and Met were calculated using the Pearson's correlation coefficient (r).

Results

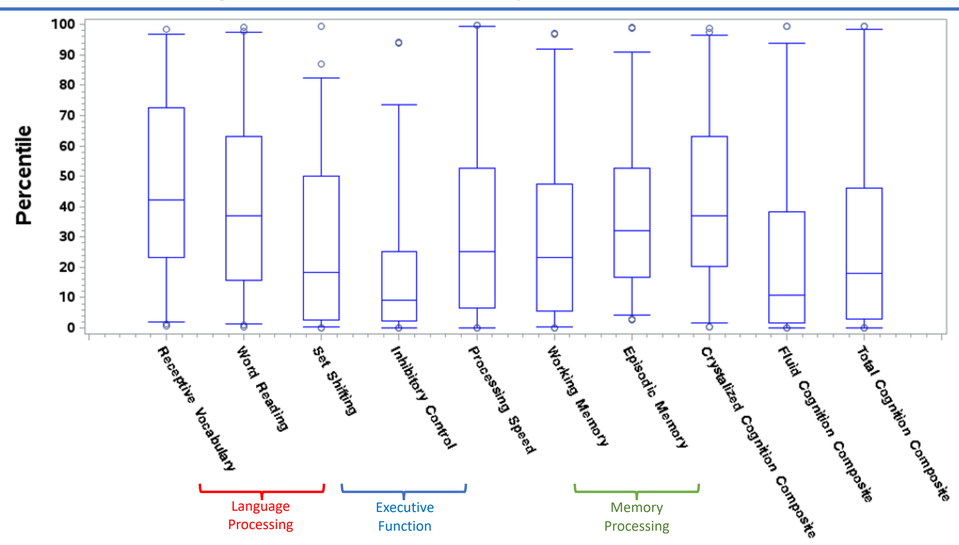
Patient Characteristics: 55 patients were enrolled in the study:

- 45%/55% females/males; most (84%) were white, non-Hispanic.
- Median (range) age at enrollment was 21 (5–53) years.
- Median time on study was 12.2 months.
- Half of the patients (51%) were diagnosed in their first year of life.
- The median plasma tHcy level was 95 µM (74 µM for pediatric patients; 104 µM for adult patients).
- 95% of pediatric patients had tHcy greater than the upper limit of normal (ULN), and 82% had tHcy >50 µM. The tHcy levels of almost half (45%) of the pediatric patients were >100 µM.
- All (100%) adult patients had tHcy greater than the ULN, 93% had tHcy levels >50 µM, and 77% had tHcy levels >100 µM.
- Median BMI was in the normal range (21.5 kg/m^2).
- Additional patient characteristics are reported in Poster P-204.

Cognitive Function Results (Fig. 1):

- Cognitive function data were available for 51 patients.
  - The overall cognitive function of HCU patients was severely affected (median *Total Cognition Composite* at 20th percentile; 21th percentile for adult and 14th percentile for pediatric patients).
- Areas of cognition that were impacted included:
  - **Fluid Cognition Composite**: summary score of memory, executive functioning, and processing speed. It includes the capacity for new learning and information processing (median *Fluid Cognition Composite* at 10th percentile).
  - **Executive function:** inhibition of automatic response tendencies and capacity to switch behavior based on task demands. It includes *Set Shifting* and *Inhibitory Control* (median at 18th percentile and 9th percentile, respectively). Working Memory is reported under Memory (below).
  - **Memory:** capacity to hold information in a short-term buffer and manipulate the information as well as ability to acquire, store, and retrieve information. It includes *Working Memory* and *Episodic Memory* (median at 24th and 32th percentiles, respectively).
  - **Processing Speed:** mental efficiency for taking in information (median at 24th percentile).
- Language processing function (*Receptive Vocabulary* and *Word Reading*) and areas of cognition that reflect past learning and knowledge (*Crystallized Cognition Composite*) were within normal range.
- NIH Toolbox results were consistent from visit to visit (CV<10% for the majority of patients). Intraclass correlations (ICC) ranged from 0.73 (*Inhibitory Control*) to 0.89 (*Total Cognition Composite*), with the exception of *Episodic Memory* with an ICC of 0.64. The original validation of the NIH Toolbox considered ICCs of 0.4 to 0.74 to be adequate and above 0.75 to be excellent (Weintraub et al. 2013a/b).

Figure 1. NIH Toolbox median and quartile score for each domain



Box-plot: the box encompasses the 25th percentile to the 75th percentile of the data, with the median value represented as the horizontal line in the box. Whiskers represent the data minimum and maximum.
Crystalized Cognition Composite = area of cognition that reflects past learning and knowledge.
Fluid Cognition Composite = area of cognition that reflects the ability to learn, solve novel problems, and use memory.

Correlations Between Cognition and Other Parameters:

- Hcy levels were negatively correlated with overall cognition (*Total Cognition Composite*) (Fig. 2; *r* = -0.32; p = 0.023; Table 1); ie, the higher the tHcy levels, the lower the cognition score. *Inhibitory Control* was the domain most impacted by tHcy levels (Fig. 3; r = -0.33; p = 0.019).

Figure 2. Correlation between tHcy levels and Total Cognition Composite

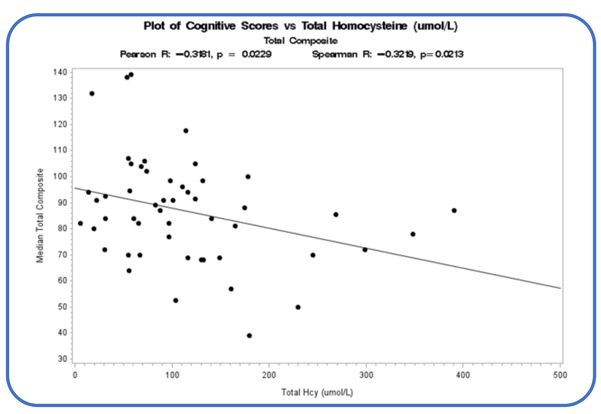


Figure 3. Correlation between tHcy levels and Inhibitory Control

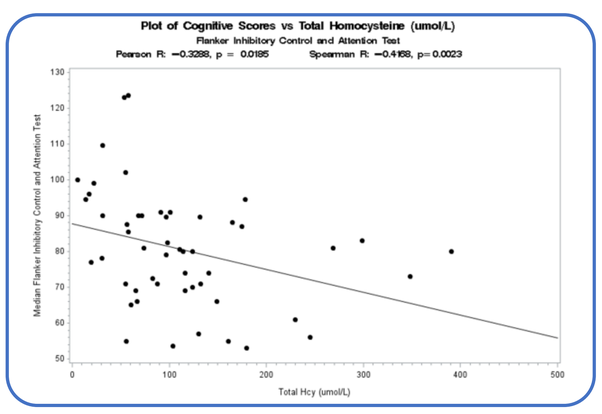


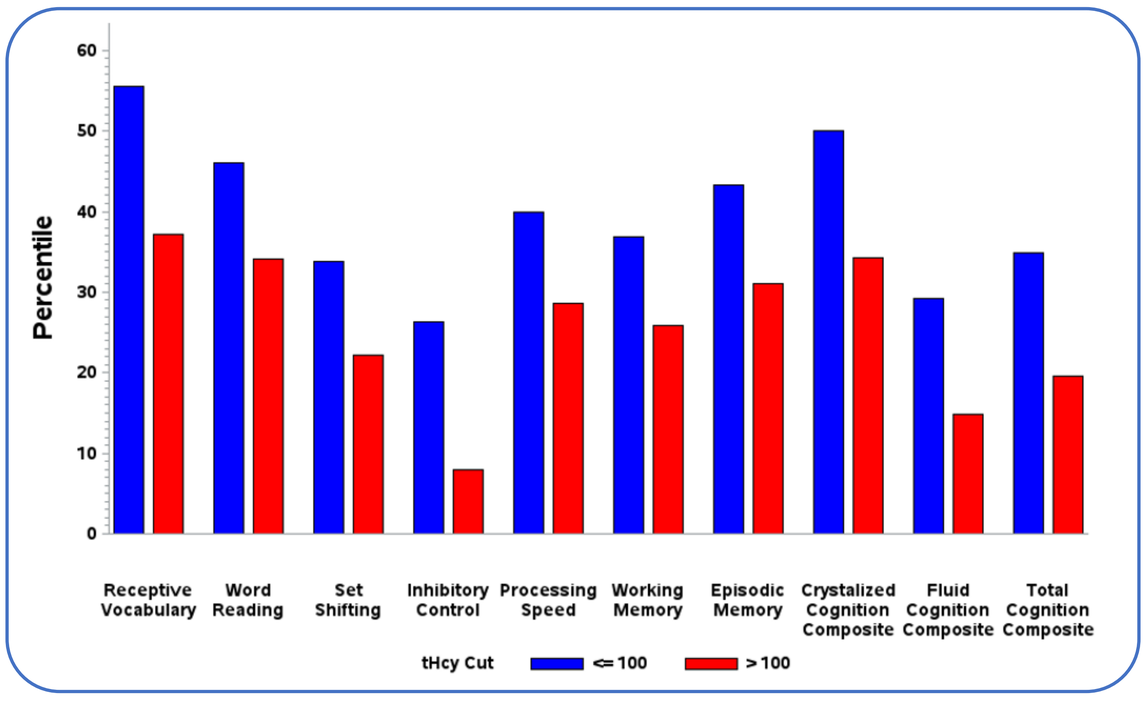
Table 1. Correlation between cognition and other parameters

Cognition areas	Pearson's parameters	Plasma tHcy	Plasma Cys	Plasma Met
Set Shifting	r	-0.2787	0.1547	-0.2001
	p	0.0476	0.2783	0.1591
	n	51	51	51
Inhibitory Control	r	-0.3288	0.2223	-0.1987
	p	0.0185	0.117	0.1622
	n	51	51	51
Processing Speed Test	r	-0.1526	0.0565	0.0620
	p	0.2852	0.6939	0.6659
	n	51	51	51
Episodic Memory	r	-0.1372	0.3245	-0.3374
	p	0.337	0.0202	0.0155
	n	51	51	51
Fluid Cognitive Composite	r	-0.28554	0.24182	-0.23209
	p	0.042	0.087	0.101
	n	51	51	51
Total Cognitive Composite	r	-0.3181	0.36741	-0.27767
	p	0.0229	0.008	0.0485
	n	51	51	51

Red: p ≤ 0.05

- Although the overall cognitive function of HCU patients was generally severely affected (*r* = -0.32; p = 0.023; Table 1), the impairment increased with increasing tHcy levels. Patients with tHcy levels >100 µM had overall much poorer cognition than those with tHcy ≤100 µM in all cognition areas. When comparing patients with tHcy ≤100 µM to patients with tHcy>100 µM, the domains for *Inhibitory Control* and *Receptive Vocabulary* showed the most statistically significant differences (Fig. 4).
- In contrast, plasma Met levels were negatively correlated with overall cognition (*r* = -0.28, p = 0.049; Table 1), suggesting that both tHcy and Met levels should be kept as close to normal as possible.
- Cys levels were positively correlated with overall cognition (*r* = 0.37; p = 0.008; Table 1).

Figure 4. Effect of tHcy levels on cognitive function



Discussion

- This study highlights the overall cognitive impairment in many HCU patients, confirming past studies (Mudd et al. 1985).
- Patients with lower plasma tHcy levels performed better on measures of executive functioning, extending prior studies showing that controlling tHcy levels is essential for maintaining intellectual functioning within average range (Walter et al.1998; Yap et al. 2001, Al-Dewik et al. 2019).
- As expected, lower Met levels, which reflect a better control of sulfur-amino acid metabolism, are associated with better cognition.
- The NIH Toolbox is a reliable instrument that has demonstrated potential value for assessing cognitive functioning over time in patients with HCU, including tracking response to intervention.
- The results of this study have practical implications for the management of HCU. Neuropsychological evaluations should be considered an important component of medical care for HCU patients, and assessment of executive functioning (including response inhibition) should be included as part of those evaluations. For children with HCU, supports similar to those for children with other executive functioning problems, such as ADHD, should be considered.
- Identification of specific cognitive deficits in HCU provides clues for future studies focused on neural systems impacted by HCU. Dorsal anterior cingulate cortex activation is associated with monitoring conflicting information, a central element of response inhibition on flanker tasks (Botvinick et al.2004).

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