A Pilot Study of Association of Adverse Childhood Experiences, Resilience, and DNA Methylation Profiling in Pediatric Irritable Bowel Syndrome

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Background

- Irritable bowel syndrome (IBS) is a brain-gut axis disorder characterized by abdominal pain and altered bowel habits. It is a multifactorial, stress-sensitive disorder with evidence for familial clustering attributed to genetic or shared environmental factors
- Higher Adverse Childhood Experiences (ACE) have been reported in patients with chronic disease and the effects of ACE are likely from epigenetic programming. In pediatrics, parents/ guardians report ACE
- For children exposed to high ACE, a child's perceived resilience may mitigate a negative health outcome or development of chronic disease
- Epigenetic alterations including DNA methylation changes have been associated with several chronic diseases and can link gene-environment interactions to long-term behavioral development

Objectives

- To compare ACE in pediatric IBS patients and healthy children
- To assess the adolescent/ teen's ability to self-report ACE amongst other questionnaires
- To compare parent/guardian reported and child-reported ACE
- To compare genome-wide and selected IBS-associated genes' methylation profiles in peripheral blood mononuclear cells (PBMCs)

Aims

- To compare ACE and resilience in pediatric patients with IBS and healthy children in order to determine their association with symptom severity and health outcomes
- To assess whether adolescents/teens' self-reported ACE scores are the same as the parent/guardian reported ACE scores for their child
- To assess the precision of adolescents/ teens' abilities to complete their own health related questionnaires
- To compare genome-wide methylation profiles and methylation of selected IBS-associated genes in PBMCs in pediatric patients with IBS vs. healthy children and determine whether these differences in DNA methylation can be used in creating a diagnostic biomarker in pediatric patients with IBS

Methods

- 12 patients with IBS (75% female, mean age = 16 years) and 12 healthy patients (50% female, mean age = 15 years). Recruited between July 2020 and December 2020 from our pediatric clinics.
- All subjects completed questionnaires- CASI-18 (anxiety sensitivity), GAD-7 (anxiety screener), PHQ-9 (depression screener), CDRISC-10 (resilience), PEARLS (ACE).
- IBS subjects additionally completed GI symptoms questionnaires: Rome IV IBS, PedsQL GI symptoms, and API.

Results

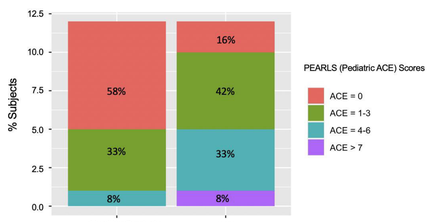
- Currently in data analysis phase
- Results thus far include:

- **Study Population Characteristics**:*(Table 1)*
  - Distribution of age, sex, and race were comparable between IBS and HC groups
  - Average BMI of IBS subjects were significantly lower that BMI of HC (p=0.02)
  - Average PHQ-A or depression score was higher in IBS subjects as compared to HC (p=0.0001)

Table 1. Characteristics of Study Population

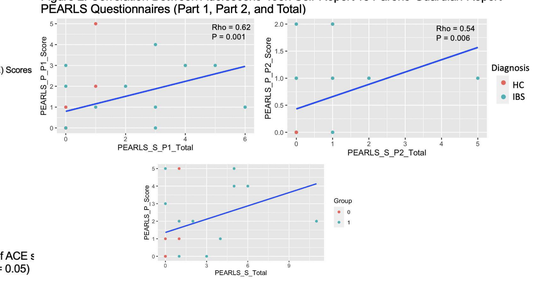
Characteristics- Means	IBS (N= 12)	HC (N = 12)	*P*
Age in years (SD)	16.08 (1.44)	15 (2.04)	0.15
Sex (% Female)	75%	50%	0.4
BMI percentile (SD)	56.62 (0.67)	79 (16.23)	0.02
Race (%)			0.57
White (European or Middle Eastern)	9 (75%)	9 (75%)	
Black (African American)	0 (0%)	2 (17%)	
Asian	0 (0%)	0 (0)	
American Indian, Alaskan Native, Native Hawaiian, or Pacific Islanders	0 (0%)	0 (0)	
(Other) Multi-racial	1 (0.8%)	1 (0.8%)	
Ethnicity			
Hispanic or Latino	3 (25%)	4 (33%)	
Not Hispanic or Latino	9 (75%)	8 (66%)	
CASI-18 Score (18-54) (SD)	25.08	29.25	
GAD-7 Score (0-21) (SD)	7.25 (5.14)	4.42 (5.2)	0.19
PHQ-A Score (0-27) (SD)	9.08 (4.25)	2.25 (2.49)	0.0001
CDRISC-10 Score (0-40) (SD)	27.67 (4.81)	25.25 (7.64)	0.37
IBS GI Symptoms			
Bowel Habit (%)			
IBS-C	5 (41.67%)	-	-
IBS-M	2 (16.67%)	-	-
IBS-D	5 (41.67%)	-	-
API Score (0-4) (SD)	2.26 (0.79)	-	-
Peds QLGI Total Score (0-100) (SD)	56.93 (11.66)	-	-

Figure 1: Distribution of ACE Scores in IBS vs HCs



Compared to an ACE Score = 0, the odds of having IBS increased with the number of ACE s of 1-3 (OR = 4.37, CI= 0.6 – 42.44, p = 0.16) and 4-6 (OR = 14, CI= 1.2 – 384.98, p = 0.05)

Figure 2. Correlation Between Adolescent/ Teen Self-Report vs Parent/ Guardian Report PEARLS Questionnaires (Part 1, Part 2, and Total)



- **ACE and IBS**: *(Figure 1)*
  - The odds of having IBS increased with
  - number of ACE
  - IBS patients had increased prevalence of ACE compared to HC, measured by PEARLS part 1 [OR (95% CI) =6 (1.11 – 41.11) and p=0.05]
  - The most common ACE reported in all subjects and in IBS subjects only was emotional abuse
  - IBS subjects compared to HC reported an increased prevalence of abuse related ACE (p=0.02)
  - Within IBS subjects, increased ACE score was not associated with increased abdominal symptoms reporting

- **PEARLS parent/guardian report vs self-report**: *(Figure 2)*
  - ACE question with the least concordance of 71% was parental related domestic violence

Conclusions

- Currently in data analysis phase
- Conclusions thus far include:
  - Average BMI of IBS subjects is likely lower to HC due to restricted diets with food avoidance. 100% of the IBS subjects interviewed avoided certain food categories such as sweets, meat, diary being the most common
  - IBS subjects reported higher depression and anxiety symptoms
  - In our group of subjects ACE score >1 is associated with an increased risk of IBS, supporting our hypothesis of ACE reported in childhood having a role in developing IBS in childhood, with emotional neglect being the most common ACE in IBS subjects
  - Parent/guardian report of ACE are different than adolescent/teen self-report of ACE. The most discordant category was parental related domestic violence

Significance

- Discussion thus far includes:
  - While an association between ACE and IBS prevalence has been previously reported in adults, we believe the current study provides novel information regarding pediatric patients with IBS and ACE
  - Our data supports that ACE screening and intervention for prevention of pediatric IBS, and likely other childhood pain disorders, is needed even earlier than adolescence
  - In relation to ACE interventions, we must also focus on other methods than only increasing self-perceived resilience
  - ACE of Emotional Abuse significantly differentiated IBS and HCs (58% in IBS vs. 8% in HC), consistent with adult data that shows a high correlation between abuse and IBS
  - We propose ACE screening of both pediatric patient and parent/ guardian when possible as biases and external to household experiences can cause under-reporting of ACE

References

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2. Thakur N, Hessler D, Kadiatou K, et al. Pediatric adverse childhood experiences and related life events screener (PEARLS) and health in a safety-net practice. Child Abuse & Neglect 108 (2020) 104685.

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