Atypical Neonate Extra-axial CSF is Associated with Reduced Cognitive Development at Age 1 and 2

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INTRODUCTION

- Extra-axial cerebrospinal fluid (EA-CSF) is the cerebrospinal fluid (CSF) located in the subarachnoid space.
- Study by Shen et al. (2017) confirmed that elevated EA-CSF volumes, extracted from MRIs of 6-month infants who were at high risk for developing ASD, correlated with an ASD diagnosis at age 2.
  - Higher volumes of EA-CSF correlated with more severe symptoms of ASD in a child[2].
- **Goal**: Further study the role extra-axial CSF at infancy plays in a child's cognitive development in the first two years of life.

OBJECTIVES

We aim to assess if enlarged extra-axial cerebrospinal fluid (EA-CSF) volume at neonatal age is associated with a child's performance on the Mullen Scales of Early Learning (MSEL) at 12 and 24 months of age.

METHODS & MATERIALS

- 3T MRI scans acquired from 651 infants (300 females, 351 males) at neonate age (20.8+/-8.9 postnatal days) from:
  - Pregnant women recruited from UNC Hospitals and Duke University Medical Center
  - Enrolled in the Early Brain Development Study (PI Gilmore)
- EA-CSF and global tissue volumes computed via AutoEACSF[1]
- The MSEL was administered at 12 and 24 months measuring:
  - Gross motor ability
  - Cognitive composite score: fine motor, visual reception, receptive language, expressive language.
- General linear models to predict MSEL scores from EA-CSF volumes
  - Additional covariates: intracranial cavity volume, gestational age at birth, mother education, age at MRI, age at MSEL assessment, absolute time of MRI, and sex
- Hypotheses based on Shen et al (2017)
  - No major association for typical kids
  - Atypical EA-CSF enlargement leads to reduced cognition

Automatic Segmentation of Extra-Axial CSF:

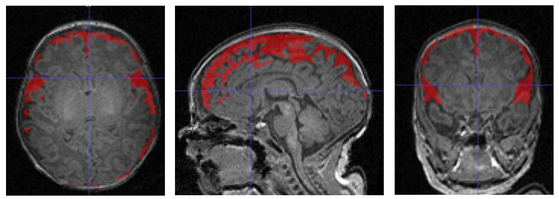

Figure 1. Quantification of extra-axial cerebrospinal fluid computed using a tool called AutoEACSF[1].

RESULTS

- No associations with any MSEL scores were found for the full set of subjects => focus on subjects with atypically enlarged EA-CSF

Analysis of subjects in top 5th percentile of EA-CSF at infancy

- Significant negative correlations between elevated EA-CSF at neonatal age and:
  - Expressive language score (p=0.001), 12mo
  - Cognitive composite score (p=0.016), 12mo
  - Receptive language score (p=0.002), 24mo

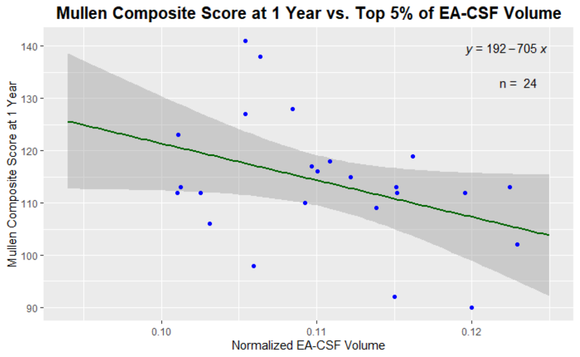

Figure 2. Linear regression between Mullen composite score at year 1 and normalized EACSF volumes for subjects in top 5th percentile of EA-CSF at infancy.

Analysis of subjects in top 10th percentile of EA-CSF at infancy

- Significant negative correlations between elevated EA-CSF at neonatal age and:
  - Fine motoric score (p=0.016), 12mo
  - Cognitive composite score (p=0.010), 12mo
  - No significant associations at 24mo

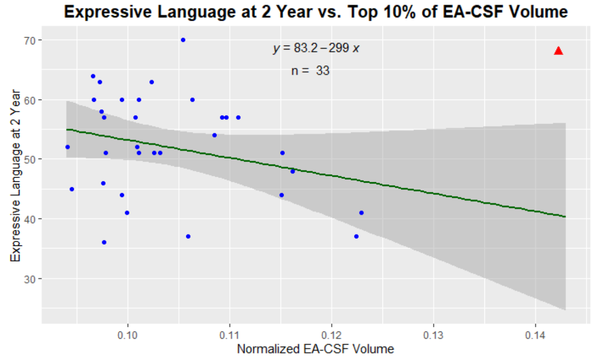

Figure 3. Linear regression between Mullen composite score at year 2 and normalized EACSF volumes for subjects in top 10th percentile of EA-CSF at infancy after removing one outlier case (red triangle).

Top 5th percentile of EA-CSF at infancy

MSEL	YEAR 1 (n = 26)	YEAR 2 (n = 17)
General Motor	P = 0.754 r^2 = 0.24 (-)	P = 0.758 r^2 = 0.48 (-)
Fine Motor	P = 0.161 r^2 = 0.36 (-)	P = 0.333 r^2 = 0.44 (-)
Expressive Language	P = 0.021* r^2 = 0.47 (-)	P = 0.121 r^2 = 0.57 (-)
Receptive Language	P = 0.340 r^2 = 0.43 (-)	P = 0.002** r^2 = 0.72 (-)
Visual Response	P = 0.097 r^2 = 0.46 (-)	P = 0.120 r^2 = 0.56 (-)
Mullen Cognitive Composite	P = 0.029* r^2 = 0.55 (-)	P = 0.069 r^2 = 0.55 (-)

Top 10th percentile of EA-CSF at infancy

MSEL	YEAR 1 (n = 44)	YEAR 2 (n = 34)
General Motor	P = 0.330 r^2 = 0.10 (+)	P = 0.884 r^2 = 0.17 (+)
Fine Motor	P = 0.016* r^2 = 0.35 (-)	P =0.174 r^2 = 0.17 (-)
Expressive Language	P = 0.087 r^2 = 0.20 (-)	P = 0.060 r^2 = 0.19 (-)
Receptive Language	P =0.111 r^2 = 0.19 (-)	P = 0.173 r^2 = 0.34 (-)
Visual Response	P =0.203 r^2 = 0.14 (-)	P =0.442 r^2 = 0.20 (-)
Mullen Cognitive Composite	P = 0.010** r^2 = 0.33 (-)	P = 0.067 r^2 = 0.22 (-)

Tables 1 & 2. Results of generalized linear model to predict MSEL scores with EA-CSF volumes of subjects whose EA-CSF volumes measured in the top 5th (left) and top 10th (right) percentile at infancy. Covariates include intracranial cavity volume, gestational age at birth, mother education, age at MRI, age at MSEL, absolute time of MRI and sex. p-value: *** ≤0.001, ** ≤0.01, * ≤0.05; (-): Negative Association

DISCUSSION & CONCLUSION

- Missing association in general/typically developing kids confirms Shen et al. : EA-CSF at infancy does not appear to be a biomarker characterizing typical brain development
- Atypically high levels of EA-CSF volume shortly after birth are significantly associated with lower expressive language, fine motor and overall cognitive ability at 12 months of age
- Similar patter is shown for receptive language ability at 24 months
- General pattern of early fine motor association and later language association in brain development reported in literature
- Atypical EA-CSF enlargement seems to be a be indicating atypical brain development or an increased risk for atypical brain development
- May be a pathological threshold of high EA-CSF volume
  - Could serve as an early biomarker of a child's reduced cognitive ability at 12 and 24 months
- Limitations:
  - low sample size: high risk recruitment needed
  - Single EA-CSF volume measure whereas EA-CSF pattern is non-uniform (see Figure 4)
- Next steps
  - Analysis of verbal vs non-verbal Mullen quotient
  - Follow up: potential diagnoses at later stage
  - Follow up: normalization of brain development
  - Analysis of local EA-CSF

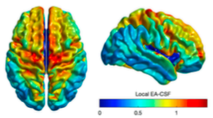

Figure 4. Average local EA-CSF at 12 month

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[2] Shen MD *et al.*, "Increased Extra-axial Cerebrospinal Fluid in High-Risk Infants Who Later Develop Autism," *Biol. Psychiatry*, vol. 82, no. 3, pp. 186–193, Aug. 2017, doi: 10.1016/j.biopsych.2017.02.1095.

ACKNOWLEDGMENTS

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