Extra-Axial Cerebrospinal Fluid as a Potential Biomarker in Infants Who Develop ASD and Insights into the Role of Early Behavior

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Initial Report of Extra-Axial CSF

2013: Published initial finding at UC Davis MIND Institute

BRAIN
A JOURNAL OF NEUROLOGY

Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder

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Total sample: **N=55 (ASD=10)**

Shen et al., 2013
Extra-Axial CSF from 6-24 months

Low-Risk Infant with Normal MRI; **ASD-negative**

High-Risk Infant with Increased Extra-Axial CSF; **Diagnosed with ASD**

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(Shen et al., 2013, *Brain*)
Infant Brain Imaging Study (IBIS) Network

- MRI Scans at 6, 12, 24 months; Diagnosis at 24M
- 4 clinical data collection sites
- N=343 infants (804 total scans)

Automatic Segmentation of Extra-Axial CSF:

(Shen et al., 2017, Biol Psych)
HR infants later diagnosed with ASD had increased Extra-Axial CSF by 6 months, persistently elevated through 24 months

\[60\] 70 80 90

Age

Extra-Axial Fluid (cm³)

- High Risk-ASD
- High Risk-Negative
- Low Risk-Negative

\[N=47\]
\[N=174\]
\[N=122\]

Tot = 343

\[18\%\] \((d=.54)\)
\[-13\%\] \((d=.48)\)
\[10\%\] \((d=.46)\)

%diff vs. HR-negaBve (Cohen’s d effect size)

Covariates: Age, Sex, Site, Total Cerebral Volume

*p<0.005 vs. LR-neg, HR-neg (Shen et al., 2017, Biol Psych)

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Large ASD group (n=47)

... 

Examine subgroups based on symptom severity

(Gotham & Lord, 2007)
**More pronounced increase of Extra-axial CSF in more severe ASD subgroup**

Covariates: Age, Sex, Site, Total Cerebral Volume

**p<0.05 vs. all other groups  
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(Shen et al., 2017, Biol Psych)
Extra-axial CSF as a single brain measure at 6 months has modest prediction accuracy of ASD diagnosis at 24 months

25-fold cross-validation
Logistic regression (ROC curve)

IBIS 2017 sample:
- Overall accuracy = 69%
- Sensitivity at 6 months = 66%
- Specificity at 6 months = 68%

Externally validated in MIND 2013 sample:
- Overall accuracy = 72%
- Sensitivity at 6 months = 80%
- Specificity at 6 months = 67%

1. Observable, reliable brain anomaly
2. Detectable w/ any structural MRI
3. Replication is rare

(Shen et al., 2017, Biol Psych)
CSF: Filtration System of Brain

- Continuously produced
- Continuously absorbed
- Turns over every 6 hours
- Delivers growth factors to developing brain
- Removes inflammatory cytokines, metabolites (Aβ)

Neuroinflammation?
Cytokine accumulation?

Xie, 2013 (Science)
Iliff, 2012 (Science Transl Med)
Louveau, 2015 (Nature)

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video: medical/animations.com
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Current follow-up studies
(unpublished)

1) **What is the specificity?**
   - Is it present in monogenic subtypes of ASD?
     Or in other neurodevelopmental disorders?

2) **What is the pathogenic mechanism?**
   - Using mouse models to test hypothesized mechanism of neuroinflammation

3) **Are there genetic variants associated with extra-axial CSF?**
   - DNA in family quads (infant, parents, older ASD sibling)
   - Genome-wide SNP genotyping, Whole-exome sequencing, Polygenic risk scores

4) **Combined with other brain/behavioral measures to improve prediction?**

(Collaborators: David Amaral, Joseph Buxbaum, Dani Fallin, Patrick Sullivan, John Gilmore, Ben Philpot)

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Integrating behavior & early language environment
(Meghan Swanson et al., 2017)

Brain development doesn’t occur in a vacuum

LENA recorder = “Language Pedometer”
- Whole-day recordings @ 9 months
- NaturalisBc, home environment

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20% of HR infants were “hyper-vocal” at 9 mos.

- Parents of high- and low-risk infants provided equally rich language environments

- Hyper-vocalizers had lower social babbling (AOSI)

- Early stereotyped behavior?

To be continued… 24 month diagnosis?
Example of the added value of behavior:

*Hyper-vocalization as an early marker for heterogeneous outcomes?*

- Moving beyond dichotomous outcomes (ASD, not ASD) to understanding an early trajectory of heterogeneous outcomes
  - More/less social, language delay

- Benefits:
  - Scalable, high-throughput, quantifiable, and objective
    - Attributes that are critical for a potential early marker

- Cost-effective:
  - Easily implemented by sending recorders in mail
  - Data is automated
Multidimensional Approach to Early Markers of Autism

Brain surface area/volume:
- Increased proliferation of progenitor cells

Extra-axial CSF Accumulation
- Inflammatory cytokines

1. Improve prediction in infancy
2. Develop personalized treatments

- Molecular gene 1cs
- Early language/psychological environment

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