Postnatal Choline Supplementation in Children with Prenatal Alcohol Exposure

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Study Rationale

- Choline is an essential nutrient (IOM, 1991)
  - Critical to cell membranes, lipid metabolism, etc.
  - Precursor to acetylcholine
  - Cells die by apoptosis without it
- Animal studies demonstrate impact on brain development
  - Brain fatty acids and hippocampal structure are affected
  - Choline deficiency leads to neural tube disorders, cognitive impairment
  - Peri-natal supplementation enhances structure and function
    - Larger cell bodies; increased dendritic arborization, decreased apoptosis
    - Increased acetylcholine levels
- Pre- & post-natal supplementation effects shown in FASD rats
  - Spatial learning, delayed discrimination, etc. (Thomas et al.)

University of Minnesota Post-natal Choline Trial

- Age range: 2.5 to 5 years
  - Translation from rats to human childhood is not exact
  - Hippocampal synaptogenesis and hippocampal-dependent learning develops into years 4 & 5
- Patient characteristics:
  - Heavy prenatal alcohol exposure
  - Mild, moderate, or severe facial features
  - Full range of cognitive impairment
- Resources engaged:
  - UMN FASD Clinic (est. 1978; sees 250-300 children per year)
  - UMN International Adoption Clinic
  - Center for Neurobehavioral Development
  - Investigational Drug Services pharmacy
  - University of North Carolina Nutrition Research Institute

Domain Neurodevelopmental Measure Dependent Measures

Primary Measures

- General Cognitive Function:
  - Mullen Scales of Early Learning
    - Gross Motor Score
    - Visual Reception Score
    - Fine Motor Score
    - Expressive Language Score
    - Receptive Language Score
    - Composite Score
- Memory:
  - Elicited Imitation (EI) – Immediate memory
    - Number of actions reproduced
    - Number of correct sequences
  - Elicited Imitation (EI) – Delayed memory
    - Number of actions reproduced
    - Number of correct sequences
- Executive Functioning:
  - Elicited Imitation (IE) – Interleaved / Working Memory
    - Number of actions reproduced
    - Number of correct sequences
- Processing Speed:
  - Visually-evoked potentials (VEP)
    - P100 latency (in milliseconds)

Elicited Imitation (EI) Paradigm (Pat Bauer et al.)

- Playground (Arbitrary):
  - Researcher modeled playing in a sandbox, riding a bike, walking a dog, playing ball, flying a kite, feeding a goose, spinning a merry-go-round, pushing a swing, and sliding down a slide.
- Farm (Arbitrary):
  - Researcher modeled making a horse jump, putting a cow in the barn, putting eggs in a basket, working in the field, planting seeds, hooking up a tractor, stacking hay, putting a carrot in a bin, and chopping wood.

University of Minnesota Post-natal Choline Trial

- Treatment
  - 500 mg. choline vs. placebo per day
    - Randomization is critical
    - Supplement dose based on adequate intake of 200-250 mg. per day
  - Fruit-flavored drink mix
  - Nine month duration
  - FDA Investigational Drug exemption in place

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Scalp EEG measures: 1. Event Related Potentials (ERP) measure examining the brain’s response to familiar objects from the Elicited Imitation task vs. unfamiliar objects; 2. Visual-evoked potentials (VEP) measuring the brain’s basic processing speed, a reflection of brain development including myelination status.

Recruitment pool #1
FASD Clinic:
Recruitment pool #2
Int. Adoption Clinic:
Screening, Baseline, & Randomization (n=20)
Placebo: (n = 10)
Choline: (n = 10)

Evaluation:
Recruitment and consenting procedures
How accessible is the population? How can participation be maximized?
How can compliance be maximized?
What are the barriers to completion?
Is a 9 month study feasible?

6 month follow-up evaluation
9 month follow-up evaluation

Will parents accept randomization?
What are the barriers & solutions?
What are the side effect rates?

R21 Phase: Years 1 & 2

Monitoring
• Diet – periodic 24 hour recalls
• Choline levels in blood
• Betaine, Phosphatidylcholine, Sphingomyelin
• Regular checks with our study pediatrician
• Phone visits with symptom checklists
• Review by an un-blinded statistician
• Review by an independent Data Safety Monitoring Board
• Additional regular review by a University IRB
• Additional review by the FDA as part of the IND process

Barriers / Challenges
• Guardianship often in flux at this age
• Social workers / adoption workers hesitant to allow participation in a trial
• Placebo arm is a concern for some parents
• Multiple children in same adoptive family
• Some families need extensive assistance – transport, phone, frequent reminders, etc.

Status of the study
• 18 out of 20 participants enrolled
• Only 1 drop-out
• No side effects have emerged
• Tolerance appears to be very good

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