Building a Natural History Study for Canavan Disease

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Canavan Disease

Ultra rare leukodystrophy
1000 patients globally, 1:100,000 births
Autosomal recessive
Mutations in the *ASPA* gene, coding for the aspartoacylase enzyme
Defect prevents normal myelin from forming
Symptoms become most prominent in the first 3 to 5 months of life
Early symptoms: severe hypotonia, head lag & macrocephaly, seizures, etc
Severe neurologic deterioration leading to profound developmental delay
Why is a natural history study needed?

Paucity of published data
No established endpoints in Canavan
No scales / measures that are consistently used

Goal: to identify clinically meaningful changes that can be used to establish the necessary endpoint(s) for a treatment trial AND to use the data as a historical control

Commitment: Aspa will make data available to researchers
Challenges with NH Studies

If the study was too burdensome, families would not join

If the study was too burdensome, they would withdraw

Creative approach to making it as easy as possible
   Family travel support to site visits

Inconsistency across medical records

Important to note that and our future treatment trial, while connected by data, are not linked
   a patient does not need to be enrolled in the natural history study to enroll in the treatment trial and vice versa
Unique Aspects of Our Study

Record retrieval

Data extraction

In home assessments (US only) for prospective visits
Established strong relationships with KOLs / PIs to learn about current management of patients with Canavan disease

Patients Advocacy Groups input at all stages

Conducted Parent Focus Groups / Interviews to determine what they feel is most important when dealing with Canavan disease
Efforts to Date: CANinform

Contracted with several vendors

- VERISTAT
- TELEGEniSYS
- VALIS BIOSCIENCE
- Evidera
- greenphire

Consulted with several experts working on similar rare pediatric diseases

- MASSACHUSETTS GENERAL HOSPITAL
- THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER
- Northwestern University
- cureSMA
- Children's Hospital of Philadelphia
- Johns Hopkins University
- Holland Bloorview Kids Rehabilitation Hospital
Retrospective Data: Record Collection

Challenges with record retrieval
Time consuming & costly
Most critical: first 3 years of life

Identified Telegenisys & wrote protocol
Received IRB approved

Record: Hyperlinked, bookmarked

Once family receives record, they will be asked to enroll in NH study

Upon signing consent, record is transferred to site

To date, 15 families have signed up from US & outside EU
Data Extraction

Challenges with making sense of data across records

Link between sign and point on a scale

Data Extraction Plan (DEP): defines the steps for extracting data
In Home Assessments / Rater Training

Extensive Rater training across US and GER raters
   In person and & on line training modules

No Rater will perform an assessment until they have been certified by all qualified trainers

US – identified 3 highly qualified Physical Therapists to perform in home assessments (TIMPSI, GMFM, Bayley, HINE2)
   Extensive support for US Raters as they travel to family homes has been put in place

Rater Relatability Testing
   All Raters begin at the required level

Ongoing QC to ensure across prospective data, we maintain high level of quality & consistency
Conclusions

Don’t under-estimate the effort required to build a natural history study

Be prepared for gaps in data – anticipate how you will work through

If retrospective, establish not only a solid record retrieval plan but also a plan for how to integrate this with prospective data collection

Develop robust plans to collect data in a rigorous way

A natural history study is a clinical study – treat it as such
Thank You

Key Opinion Leaders / PIs

Patient Advocates

Vendors

Consultants

Future Families