Clinic for Leukodystrophies, Department of Pediatrics

A Multi-Center, Multi-National Retrospective and Prospective Natural History Study of Canavan Disease

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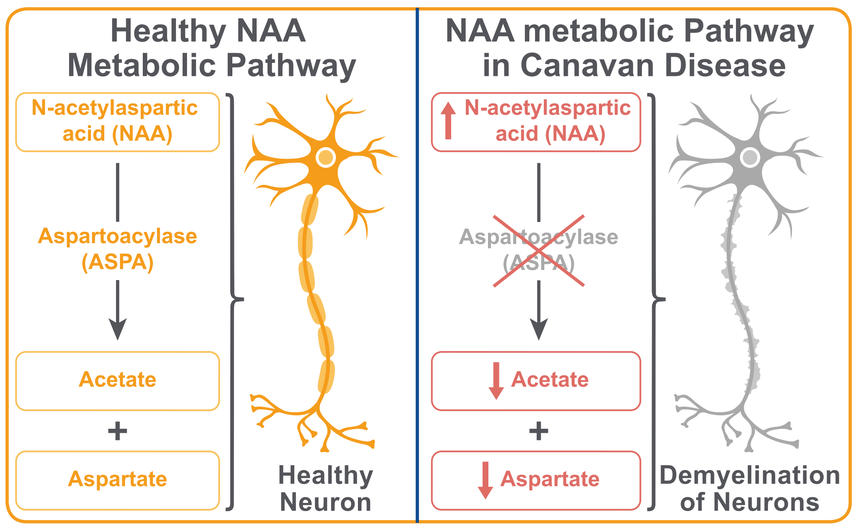
Canavan Disease

Canavan Disease (CD) is a serious and ultra-rare (1:100,000 births each year in the United States and European Union[1]) progressive, neurodegenerative disorder that belongs to a group of genetic disorders known as the leukodystrophies.[2-5] In patients with CD, a genetic mutation on chromosome-17 results in a deficiency in aspartoacylase (ASPA enzyme), the metabolic regulator of N-acetylaspartic acid (NAA).[6] The accumulation of NAA interferes with growth of the myelin sheath of the nerve fibers of the brain. CD is characterized by degeneration of myelin, resulting in disruption of the phospholipid layer insulating the axon of a neuron.

Natural History

The limited available published data in CD support the idea that progression of the disease can be most pronounced in the earliest months of life. However, there is a paucity of published longitudinal data on the progression of CD, and no approved therapies exist. Advancing the understanding of CD and facilitating the development of therapeutic options requires a comprehensive, precise delineation of CD natural history. Therefore, a collaboration between established Canavan patient treatment sites in Germany and the United States will be supported by Aspa Therapeutics as the sponsor of a natural history study of patients with CD. The objective of the study is to rigorously collect natural history data from CD patients and caregivers, define endpoints for interventional trials, and identify gaps in disease management across ranges of ages and disease severity.



ASPA Enzyme Deficiency and NAA Accumulation Leads to Demyelination in Canavan Disease

Natural History Study

This multi-center natural history study will be conducted in Germany and the United States to enroll CD patients for prospective, longitudinal collection of clinical data using standardized instruments and intervals on an observational basis and for retrospective collection of medical record data.

ELIGIBILITY

- Clinical diagnosis of CD
- Biochemical diagnosis of CD
- Available medical records since birth that permit:
  - documentation of disease characteristics
  - developmental milestones

ASSESSMENT OF DISEASE PROGRESSION

Motor and Cognitive Development	Biochemical and Laboratory
Assess every 2-4 months for patients ≤ 3 years; every 6-12 months for patients > 3 years	Assess every 6-12 months for all patients
Neurological, Diagnostic, and Imaging	**Parent/Caregiver**

3 Years

Study Endpoint and Assessment Selection

No instruments for data collection or disease assessment are validated for CD. Therefore, in addition to review of available published data on neurodevelopment in CD, critical input for selection of assessments was also sought by the study sponsor from three sources. First, expert neurologists at treatment centers in Germany and the United States provided advice and guidance. These experts diagnose and treat patients with CD and counsel families with children affected by CD. The German experts had experience conducting a natural history study in CD. Second, parents and caregivers of patients with CD participated in focus groups and provided details of their experiences of living and caring for a child with CD. Finally, patient advocacy groups, members of which are parents of children with CD or of children who have died from complications of CD, provided valuable perspective and advice.

Motor and Cognitive Development Assessments

The available data show that the hallmark characteristics of CD involve delays in gross and fine motor function, poor head control, and cognitive and language impairment, each or all of which can manifest at different times during the early months and years of the patient's life. Instruments for assessment during the natural history study will include:

- **Test of Infant Motor Performance Screening Items (TIMPSI) [motor]:** Measures postural and selective control of movement needed for functional motor performance in early infancy
- **Gross Motor Function Measure (GMFM) [motor]:** Measures gross motor function in children between 5 months and 16 years
- **Bayley Scales of Infant Development (BSID)-III [motor, cognitive, language]:** Measures gross motor and fine motor developmental functioning as well as expressive and receptive communication and cognition development in children between 1 and 42 months
- **Hammersmith Infant Neurological Examination (HINE)-2 [motor]:** Measures head control, sitting, voluntary grasp, ability to kick in a supine position, rolling, crawling or bottom shuffling, standing, and walking between 2 and 24 months
- **Canavan Disease Assessments:** Measures disability/ability in several common and important domains in CD based on analyses of the previous natural history study in CD (Hamburg leukodystrophy-database in cooperation with Canavan centers in the United States)

Biochemical and Laboratory Assessments

- **Urinary NAA Levels:** NAA is the direct substrate for the ASPA enzyme, and NAA levels accumulate to pathologically elevated levels in CD
- **Biomarker and Genetic Mutation Analysis:** Measurement of ASPA enzyme levels in blood cells and characterization of genetic mutations and variability among patients with CD may contextually frame genotype, pathophysiology, and disease severity
- **Routine Laboratory Tests:** Measurements may reveal other trends in patients' physiology

Neurological, Diagnostic, and Imaging Assessments

In addition to standard physical examination parameters, assessments during the natural history study will focus on functional decline unique to CD, including aspects of neurological exams, diagnostic tests, and historical standard of care tests whose results are extracted from the patients' medical records:

- **Neurological Exams:** Level of consciousness, expression/reception of language; temperament; ocular function; truncal and appendicular tone (including active/passive, and gross/fine motor function, reflexes [including deep tendon reflexes], plantar response, presence of clonus, primitive reflexes; withdrawal to touch, presence of adventitious movements, ability to bear weight, and gait, if ambulatory); muscle bulk; and presence of contractures
- **Diagnostic Tests:** Nerve conduction velocities; visual evoked potential
- **Standard of Care (Historical Records):** Imaging (MRI), hearing, and neural conduction assessments

Parent/Caregiver Assessments

The impact of CD on the patient's quality of life and the impact on the family of a child with CD are important for understanding the emotional and social aspects of living with the disease. The patient's parent(s), legal guardian(s), and/or caregiver(s) will be asked to provide responses. Instruments that may be used during the natural history study include:

- **Pediatric Quality of Life Inventory (Family Impact Module) (PedsQL-FIM):** Measures parent self-reported physical, emotional, social, and cognitive functioning; communication; and worry
- **Vineland Adaptive Behavior Scale:** Measures the level of a patient's personal and social skills required for everyday living, including communication, daily living skill, socialization, motor skills, and maladaptive behavior
- **Canavan Disease Questionnaire:** Measures aspects of life and functioning specifically in patients with CD

Summary

- **This multi-center, multi-national retrospective and prospective natural history study will collect and assess data of disease characteristics that are caused by the neurodegenerative disorder of CD**
- **Clinical sites are in the final stages of initiation, and enrollment is expected to open in September 2019**
- **The study is expected to continue for 3 years with no maximum on enrollment so that sufficient data can be collected to characterize the natural history of CD**
- **The natural history database will be available to physicians and scientists for meaningful research towards treatment of CD**

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References: 1) Orphanet 2019 **2)** Hoshino 2014 *Pediatr Int* **3)** Gordon 2001 *Eur J Paediatr Neurol* **4)** Pastores 2010 *Dementia* **5)** Surendran 2003 *J Child Neurol* **6)** Matalon 2018 *NCBI Bookshelf*

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