**A data-mining project to understand motor abnormalities in ASLD**

Individuals with ASLD can manifest with developmental delay, learning difficulties, intellectual and developmental disabilities, seizures, motor weakness, and behavioral abnormalities. Interestingly, some of these neurologic manifestations can be observed even in individuals without documented episodes of severe hyperammonemia and in individuals who clinically would be deemed to be in good metabolic control.1,2 Preclinical data have suggested that some of these neurological manifestations may be due to cell-autonomous loss of ASL. 3 We have recently shown that ASL regulates tyrosine hydroxylase in the nucleus locus coeruleus (LC); these findings imply that dopaminergic transmission may be impaired in ASLD. We thus propose to systematically evaluate the data collected by the UCDC to assess motor abnormalities in individuals with ASLD. We propose to conduct a data-mining project to answer the clinically relevant questions outlined in the following specific aims:

**Specific Aim 1: What is the prevalence of motor symptoms suggestive of an extrapyramidal disorder in ASLD as compared to individuals with ASS1D, males with OTCD, and females with OTCD females?**

We can collect information regarding the presence/absence (categorical variable) of motor symptoms suggestive of extrapyramidal motor from the following sources in the database:

**1) Medical and Developmental History Form**

Data point: **\***Nervous System and Development (include seizure disorder, mental retardation/developmental delay, cerebral palsy, ADHD, learning disability, autism spectrum disorder, communication disorder/delay)

* Please search free text for the following terms – parkinsons, parkinsonism, tremors, bradykinesia, rigidity
* Search SNOMED codes that map to the following ICD10 codes: (<https://icd10cmtool.cdc.gov/?fy=FY2019>):

1) Dementia

with Parkinson's disease G20

with Parkinsonism G31.83

2) Hemiparkinsonism G20

3) Parkinsonism (idiopathic) (primary) G20

4) Secondary Parkinsonism

G21 Secondary parkinsonism

G21.1 Other drug-induced secondary parkinsonism

G21.11 Neuroleptic induced parkinsonism

G21.19 Other drug induced secondary parkinsonism

G21.2 Secondary parkinsonism due to other external agents

G21.3 Postencephalitic parkinsonism

G21.4 Vascular parkinsonism

G21.8 Other secondary parkinsonism

G21.9 Secondary parkinsonism, unspecified

5) Tremor(s) R25.1

6) Bradykinesia R25.8

7) Sleep

disorder or disturbance G47.9

disorder or disturbance G47.9 child F51.9

disorder or disturbance G47.9 nonorganic origin F51.9

disorder or disturbance G47.9 specified NEC G47.8

8) Dystonia G24.9

***Also, please try to find these by SNOMED codes alone.***

**2) Physical and neurological examination forms**

Datapoints of interest:

\*Tone – normal/abnormal; search text for rigidity, hypertonia, SNOMED codes search for rigidity, hypertonia

\*Other neurological findings – search for terms rigidity, hypertonia, bradykinesia, gait abnormalities,

**3) Drug and other treatment form**

Data point of interest: \* Other Drugs Used

Search strategy will be by two methods

a) Search for the following drug names

* Selegiline OR rasagiline, OR safinamide
* Levodopa OR carbidopa
* trihexyphenidyl OR benztropine

b) Look at SNOMED codes for \*Other Drugs used and specifically search for the following ICD 10 mappable codes

* Tremor(s) R25.1
* Bradykinesia R25.8
* G21 Secondary parkinsonism
* Parkinsonism (idiopathic) (primary) G20

The criteria for defining the presence of motor symptoms suggestive of extrapyramidal motor symptoms will be met if TWO of the following are met:

* Presence of the same two datapoints of interest (1 through 6) from medical and developmental history form on two or more study visits (Note: Each patient would have had multiple study visits and if the data point is just present in one visit and not others, it may be a data entry issue.)
* Presence of same datapoint of interest on physical and neurological examination forms on two or more study visits
* Use of drugs to treat Parkinsons-related medications on two or more study visits

The overall aim would be to assess the proportion of individuals with ASLD who have presence of motor symptoms suggestive of extrapyramidal involvement as per above definition compared to individuals with ASS1D, males with OTC, and females with OTC.

A subaim would be to assess the proportion of individuals with ASLD WITHOUT hyperammonemia who have presence of motor symptoms suggestive of extrapyramidal involvement as per above definition compared to individuals with ASS1D, males with OTC, and females with OTC who also have had NO history of hyperammonemia. (Note: This would be relevant to dissect out the contribution of hyperammonemia in causing motor symptoms suggestive of extrapyramidal involvement).

**Specific Aim 2: What are the clinical characteristics of individuals with ASLD who have motor symptoms suggestive of an extrapyramidal disorder?**

In this descriptive aim,we will assess the number of hyperammonemic episodes, presence of two or more severe hyperammonemic episodes (defined by requirement for IV ammonia scavenger OR presence of coma OR requirement of dialysis), presence of absence of seizures, and the developmental outcome as assesses by standardized score from ABAS General Adaptive Composite score. This descriptive aim could answer whether the motor symptoms suggestive of an extrapyramidal disorder are restricted to those individuals with a severe phenotype or whether they can also be observed in individuals without hyperammonemia. This aim would be helpful to correlate with mechanistic studies in preclinical models.

References

1. Baruteau, J. *et al.* Argininosuccinic aciduria: Recent pathophysiological insights and therapeutic prospects. *J Inherit Metab Dis* **42**, 1147-1161 (2019).

2. Nagamani, S.C., Erez, A. & Lee, B. Argininosuccinate lyase deficiency. *Genet Med* **14**, 501-7 (2012).

3. Lerner, S. *et al.* ASL Metabolically Regulates Tyrosine Hydroxylase in the Nucleus Locus Coeruleus. *Cell Rep* **29**, 2144-2153 e7 (2019).