Natural History Project

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Sponsored by the NINDS and ORDR-NCATS at NIH, PAG, Industry, Professional Societies, and/or other sources.
Natural History Project

**Goal:** Collect clinical and exam data to better understand:

- phenotypic spectrum of all dystonias
- how symptoms change over time
- if other family members are affected
- researchers to use data for research
Natural History Recruitment Goals
(isolated dystonia): 200 cases/year

New cases

Focal
Multifocal
Segmental
Generalized
Hemidystonia

Must have started in:
Face (Craniofacial/Blepharospasm/Oromandibular)
Larynx (Laryngeal)
Limbs (Limb dystonia)

Follow-up cases

Focal
Multifocal
Segmental
Generalized
Hemidystonia

Must have started in:
Neck (Cervical Dystonia)
Face (Craniofacial/Blepharospasm/Oromandibular)
Larynx (Laryngeal)
Limbs (Limb dystonia)
Natural History: To Date

➢ The Natural History Study began recruitment in 2010
  ➢ Natural History/Biorepository
  ➢ Natural History Early Stage/Late Stage, 2016
  ➢ DCP3, 2020 to present

➢ Minimal changes to data collection and video protocols
➢ No change for sample NINDS Coriell collection
  ➢ Biobank at WUSM (2020)
➢ Follow-up visits, determined by a sliding scale

<table>
<thead>
<tr>
<th>If onset of symptoms was</th>
<th>Subsequent follow-up visit should be</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt; 3 years ago</td>
<td>1 year from last visit</td>
</tr>
<tr>
<td>3 to &lt; 5 years ago</td>
<td>2 years from last visit</td>
</tr>
<tr>
<td>5 to &lt; 7 years ago</td>
<td>3 years from last visit</td>
</tr>
<tr>
<td>At least 7 years ago</td>
<td>4 years from last visit</td>
</tr>
</tbody>
</table>
Natural History Enrollment: 2010-2022

42 Sites recruited 3607 cases, 1396 follow-ups
# Distribution of Isolated Dystonia (March 2023)

The table below shows the distribution of isolated dystonias enrolled as of March 2023:

<table>
<thead>
<tr>
<th>Type</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal Dystonia</td>
<td>2563</td>
</tr>
<tr>
<td>Generalized</td>
<td>165</td>
</tr>
<tr>
<td>Hemidystonia</td>
<td>15</td>
</tr>
<tr>
<td>Multifocal</td>
<td>296</td>
</tr>
<tr>
<td>Segmental</td>
<td>858</td>
</tr>
</tbody>
</table>
## Distribution of Focal Dystonia Subtypes

<table>
<thead>
<tr>
<th>Body Site</th>
<th>Affected at onset of illness</th>
<th>Affected at time of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>123</td>
<td>207</td>
</tr>
<tr>
<td>Hand</td>
<td>527</td>
<td>836</td>
</tr>
<tr>
<td>Jaw</td>
<td>189</td>
<td>304</td>
</tr>
<tr>
<td>Larynx</td>
<td>406</td>
<td>645</td>
</tr>
<tr>
<td>Lower Face</td>
<td>316</td>
<td>729</td>
</tr>
<tr>
<td>Neck</td>
<td>2081</td>
<td>2460</td>
</tr>
<tr>
<td>Pelvis</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>Shoulder</td>
<td>199</td>
<td>740</td>
</tr>
<tr>
<td>Tongue</td>
<td>59</td>
<td>144</td>
</tr>
<tr>
<td>Trunk</td>
<td>62</td>
<td>227</td>
</tr>
<tr>
<td>Upper Arm</td>
<td>164</td>
<td>354</td>
</tr>
<tr>
<td>Upper Face</td>
<td>729</td>
<td>958</td>
</tr>
<tr>
<td>Upper Leg</td>
<td>56</td>
<td>97</td>
</tr>
</tbody>
</table>
Natural History Available Data

Completed by Neurologist
➢ Global Dystonia Rating Scale (GDRS)
➢ Burke-Fahn Marsden Dystonia Scale (BFM)

Completed by participant
➢ Short Form Health Survey 36 (SF-36)
➢ Beck Depression Inventory II (BDI-II)
➢ Hospital Anxiety and Depression Scale (HADS)
➢ Liebowitz Social Anxiety Scale (LSAS)
➢ Patient Health Questionnaire 9 (PHQ-9)
Natural History Available Data

Completed by Coordinator
- DCP Data Collection Form
  *demographic, medical history, medications, exam, family history*

- Neurological Exam Video
  *over 3,000 videos available*
Data Accessibility - Who

- Enrolling Sites
  - Access to site data and videos

- New Research Projects
  - IRB approval
  - Data Access Agreement form
  - Executive Committee approval
    - Data
    - Videos (restricted access)
    - Biospecimens

- REDCap Data Interface / Chiron Interface
  - Publically available non-PHI data
  - Full research data, de-identified
Data Accessibility - Where

- Washington University in St. Louis
  - REDCap
  - Video Repository
  - REDCap
    - Full data set for research

- NINDS Coriell Institute for Medical Research, New Jersey
  - DNA samples
  - De-identified data

- Data Management and Coordinating Center (DMCC),
  Cincinnati Children’s Hospital Medical Center
  - De-identified data for public (Chiron)
  - De-identified data for research (Chiron)
Data Sharing/Access

Public Access: Chiron (DMCC)

Full Data or Video Access

- Application
- Data access agreement
- IRB approval
- Executive Committee approval
- Only project specific data release
- Video: only streaming, not downloading
Investigator Responsibilities

➢ Use data for proposed studies only
➢ No secondary release
➢ No attempt to identify participants
➢ Adequate staff training
➢ Share findings with Dystonia Coalition and publish data
➢ Acknowledge source
Data Utilization

➢ Use data for proposed studies only
➢ No secondary release
➢ No attempt to identify participants
➢ Adequate staff training
➢ Share findings with Dystonia Coalition and publish data
➢ Acknowledge source
Blepharospasm Diagnostic Criteria:
(bleph: n =211; control: 166)

1* step
Self-administration of the blepharospasm screening questionnaire

2* step
Answering YES to questions 3 and/or 5 and/or 6

3* step
Neurologic examination by diagnostic algorithms

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Case-Patients</th>
<th>Control Subjects</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm 123 (combining spasms, sensory trick, and blink rate)</td>
<td>165</td>
<td>15</td>
<td>78% (165/211)</td>
<td>91% (151/166)</td>
</tr>
<tr>
<td>Algorithm 124 (combining spasms, sensory trick, and inability to voluntarily suppress the spasm)</td>
<td>164</td>
<td>15</td>
<td>78% (164/211)</td>
<td>91% (151/166)</td>
</tr>
<tr>
<td>Algorithm 1234 (combining spasms, sensory trick, blink rate, and inability to voluntarily suppress the spasm)</td>
<td>170</td>
<td>18</td>
<td>81% (170/211)</td>
<td>83% (138/166)</td>
</tr>
</tbody>
</table>

Prof Giovanni Defazio

Defazio G et al, Parkin Relat Dis, 2021
Blepharospasm: Clinical features

N = 884

Dark: focal bleph
Light: spread

Scorr LM et al, Dystonia 2022
CD: Non-motor phenotypic subgroups
(N = 183 (DC), 114 dystonia wales)

Wadon ME et al, Brain Behav 2021
CD: classification & Diagnosis:

Cases with CD

<table>
<thead>
<tr>
<th>Body region affected on exam</th>
<th>Cases with dystonia</th>
<th>Cases with tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>1245</td>
<td>720</td>
</tr>
<tr>
<td>Shoulder</td>
<td>226</td>
<td>8</td>
</tr>
<tr>
<td>Hand</td>
<td>69</td>
<td>157</td>
</tr>
<tr>
<td>Larynx</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Upper face</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Lower face</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Upper arm</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Trunk</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Jaw</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Foot</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Upper leg</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tongue</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 4  Recommendations for diagnosis of cervical dystonia according to body regions affected

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Body regions involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal cervical dystonia</td>
<td>Neck only</td>
</tr>
<tr>
<td></td>
<td>Neck plus shoulder</td>
</tr>
<tr>
<td></td>
<td>Neck plus platysma</td>
</tr>
<tr>
<td>Segmental dystonia</td>
<td></td>
</tr>
<tr>
<td>with neck involvement</td>
<td>Neck plus shoulder and upper arm</td>
</tr>
<tr>
<td></td>
<td>Neck plus shoulder and whole arm/hand</td>
</tr>
<tr>
<td></td>
<td>Neck plus jaw/tongue</td>
</tr>
<tr>
<td></td>
<td>Neck plus lower face</td>
</tr>
<tr>
<td></td>
<td>Neck plus larynx</td>
</tr>
<tr>
<td></td>
<td>Neck plus trunk</td>
</tr>
</tbody>
</table>

Kilic-Berkmen et al, Mov Clin Pract 2022

N = 1258
Cervical Dystonia: Objective Video quantification (CMOR): n=185

Zhang Z et al,
Ann Clin Transl Neurol, 2022
Bleph subtypes (motor/psych): cluster analysis (n=188)

- 3 subtypes: mild, moderate & severe motor
depression/anxiety: bleph > controls

severity of depression/anxiety:
moderate > severe > mild

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Defazio G et al, Parkin Relat Disord, 2022
Q & A

Natural History (NH) Project
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Data Manager: Jo Wright (laurajwright@wustl.edu)