Brain MRI, Neurologic and Psychiatric Findings in the NCI DC Cohort

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A few definitions

- **Neurology** – medical specialty dealing with the structure, function and disorders of the nervous system

- **Psychiatry** – the practice or science of diagnosing and treating mental disorders
A few definitions

- **Developmental delay** – when a child does not reach their developmental milestones at the expected time

- **Intellectual and Developmental Disabilities** – present at birth and negatively affect the trajectory of the individual’s physical, intellectual, and/or emotional development. These conditions may affect multiple body parts or systems
Medical problems may develop at different ages, with different severity, or not at all

- Nail dystrophy
- Oral leukoplakia
- Skin Pigmentation
- Bone Marrow Failure
- Pulmonary Fibrosis
- Cancer
  - Head & Neck
  - Leukemia
  - Anogenital
- Liver Fibrosis
- Gastrointestinal
  - Non-specific enteropathy
  - Esophageal stenosis & webs
- Urogenital
  - Urethral stenosis
- Neurologic
  - Microcephaly
  - Cerebellar hypoplasia
  - Development delay
  - Psychiatric
- Orthopedic
  - Osteoporosis
  - Avascular necrosis
- Ophthalmologic
  - Lacrimal duct stenosis
  - Exudative retinopathy
- Hair
  - Early graying
  - Early alopecia

Traditional diagnosis:
Diagnostic Triad or 1 of the triad, + BMF + 2 other findings, Vulliamy et al, Blood, 2006, 107(7):2680-5
Brain Areas Affected by DC
Grey vs. white matter

- **Grey matter:** consists mainly of neuronal cell bodies, from which nerve impulses originate
- **White matter:** consists largely of nerve fibers; its main role is to transmit nerve impulses
Clinical Variants of DC

• Hoyeraal Hreidarsson (HH) Syndrome
  • Cerebellar hypoplasia (small cerebellum) may result in lack of coordinated muscle movement (ataxia)
    o Uncoordinated/unstable walking, uncoordinated movements, trouble speaking
  • Small head (microcephaly)
  • Developmental Delay

• Revesz Syndrome
  • Intracranial calcifications
    o Need to rule out other causes such as infection or history of bleeding
  • Small head (microcephaly)
  • Developmental Delay

• Coats Plus/CRMCC
  • Intracranial calcifications and/or cysts
  • Leukodystrophy (white matter abnormality)
Research Question

What brain MRI, neurologic, and psychiatric findings do we see in the National Cancer Institute DC Patients?
### NCI DC Patients with Brain MRIs, 2001-2015

<table>
<thead>
<tr>
<th>Characteristics (n=44)</th>
<th>Total (n=44)</th>
<th>XLR/AR (n=18)</th>
<th>AD (n=11)</th>
<th>TINF2 (n=9)</th>
<th>Unknown (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs) at MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15</td>
<td>14</td>
<td>18</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Range</td>
<td>1-60</td>
<td>2-46</td>
<td>1-60</td>
<td>1-24</td>
<td>6-31</td>
</tr>
<tr>
<td><strong>Age group (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>16</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>10-17</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18-29</td>
<td>11</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>30+</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>17</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

XLR: X-linked recessive inheritance, pathogenic variants in *DKC1*. AR: autosomal recessive, pathogenic variants in *RTEL1, PARN, ACD, TERT*, and *WRAP53*. AD: autosomal dominant, pathogenic variants in *TERT, TERC*, and *RTEL1*.
Cerebellar hypoplasia exists in DC at varying levels of severity
Example of abnormal cysts and a white matter abnormality in the brain MRI of a patient with DC
# Summary of Brain MRI Findings

- 25 of 44 (57%) patients had a brain MRI finding

<table>
<thead>
<tr>
<th>Brain MRI Finding</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar Hypoplasia/Atrophy</td>
<td>25/44 (32%)</td>
</tr>
<tr>
<td>Cerebral Atrophy/Delayed Myelination (White Matter Abnormality)</td>
<td>10/44 (23%)</td>
</tr>
<tr>
<td>Abnormal Cysts</td>
<td>12/44 (27%)</td>
</tr>
<tr>
<td>Corpus Callosum/Colpocephaly</td>
<td>8/44 (18%)</td>
</tr>
</tbody>
</table>
Incidental Brain MRI Findings
Unaffected People vs. Patients with DC

<table>
<thead>
<tr>
<th>Finding</th>
<th>Unaffected People (n=3966)*</th>
<th>NCI Patients (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mega Cistern Magna</td>
<td>104 (2.6%)</td>
<td>11 (25.0%)***</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>86 (2.2%)</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Pineal gland cyst</td>
<td>665 (16.8%)</td>
<td>3 (6.8%)</td>
</tr>
<tr>
<td>White matter abnormalities</td>
<td>8 (0.2%)</td>
<td>7 (15.9%)***</td>
</tr>
<tr>
<td>Cavum septum pellucidum abnormalities</td>
<td>79 (2.0%)</td>
<td>20 (45.5%)***</td>
</tr>
</tbody>
</table>

***p<0.001
Head Size

Males

Females

ACD
RTEL1
TERC
TINF2
DKC1
WRAP 53
TERT
PARN
PAR
Unknown
## Neurologic or Psychiatric Findings

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pediatric (n=26)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>17 (65%)</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>15 (57%)</td>
</tr>
<tr>
<td>Neuro-motor</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>4 (15%)</td>
</tr>
</tbody>
</table>

We collaborated with a neurologist and psychiatrist in these assessments.
Summary

- 77% (34 out of 44) had a brain MRI, neurologic, or psychiatric finding
- Younger patients had more neurologic findings
  - More likely to have AR/XLR as genetic cause
  - Neuro-motor findings and cerebellar hypoplasia
  - Microcephaly
- Older patients had more psychiatric findings, primarily mood disorders
- Shorter telomeres were associated with more neurologic findings
Recommendations for People with DC (a.k.a. How can this help you?)

- Routine screening for neurologic and psychiatric conditions
- Referral to specialty mental health services
- Early neuropsychological assessment for intellectual disability, pervasive developmental disorders, and learning disorders

- *This study highlights the need for thorough evaluations*
Management of Neurologic Complications

• Early intervention is key
• Evaluation by a neurologist and a brain MRI are recommended at diagnosis of DC, HH, RS, or related telomere biology disorder
• Work closely with pediatrician
• Evaluation by a developmental and behavioral pediatrician
Management of Neurologic Complications

• Ask your school system, in writing, for an evaluation of your child, even if a baby, toddler, or preschooler

• Work with your school to develop an Individual Education Plan (IEP) or a 504 plan, as needed

Self-Advocacy: Know Yourself, Know What You Need, Know How to Get It
Management of Neurologic Complications

https://www.ninds.nih.gov/Disorders/All-Disorders/Learning-Disabilities-Information-Page
Mental Health Information

Mental Health Information

NIMH, a part of the National Institutes of Health (NIH), funds and conducts research to help answer important scientific questions about mental illnesses. Though research, NIMH works to determine what is promising, what helps and why, what doesn’t work, and what is safe. NIMH also communicates with scientists, patients, providers, and the general public about the science of mental illnesses based on the latest research.

Mental Disorders and Mental Health Topics

NIMH offers expert-reviewed information on mental disorders, a range of related topics, and the latest mental health research. Use our A to Z list to find basic information on signs and symptoms, risk factors, treatment, and current clinical trials. This information should not be used as a guide for making medication decisions or for the diagnosis or treatment of any medication condition. A health professional should be consulted. Call 911 for medical emergencies.
Caregivers need support too

- Parents of children with neurodevelopmental abnormalities often experience more stress, depression, and poorer health.


- Peer mentors can help

- Seek out the support of your community!