Charting the Future: What PDCD Teaches Us About Mitochondrial Disease

Rebecca Ganetzky, MD
Why talk about pyruvate dehydrogenase (PDCD) deficiency?

• People learn from stories

• PDCD has one of the largest, longest mito stories

• What can we learn from this for
  – How we diagnose & treat mitochondrial disease
  – How we expand our knowledge of existing syndromes
  – How we design new trials?
The history of PDCD
# Core point: medicine & science take time

<table>
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<tr>
<th>Clinical recognition</th>
<th>Syndrome named</th>
<th>Disease is a spectrum</th>
<th>Multiple genetic diseases</th>
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Core point: we learn from patients

Things I thought I knew about PDCD in 2010

• Pyruvate/lactate is high. This is a good biomarker
• PDCD causes Leigh syndrome and that’s the same as other Leigh syndromes
• We should always treat them with diet.
• Everyone has intellectual disability
• Everyone dies in childhood
• Symptoms are

2010
Dear Rebecca,
We are putting together a case series of patients with PDCD deficiency. Can you please contribute some cases?
Biomarkers don’t make the diagnosis

Case 1: 3 yo boy with failure to thrive
Leigh syndrome
Now not breathing well

The levels of pyruvate and lactate and the ratio of lactate to pyruvate are essentially normal. This test was developed and its performance characteristics determined by the Palmieri Metabolic Lab at the Children’s Hospital of Philadelphia. It has not been cleared nor approved by the FDA. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.
This “can’t” be

How do we “know” what we know about genetics?

• We have 20,000 genes → 3 billion base pairs

• Each of us has 4-6 serious genetic variants (in a gene, changes the meaning)

• We know what’s real when
  • We’ve studied it in the lab and prove it causes disease
  • We’ve seen it before
Learning from patients #1

• Very few tests are 100% sensitive and specific

• Biomarkers can be very helpful in increasing our index of suspicion

• Genetic testing is very helpful, but requires building experience over time
But do I have Leigh Syndrome or PDH?

Dr. G,

You said exome showed X has PDCD. The other geneticist said she has Leigh Syndrome. Are they wrong?

Leigh syndrome

- Objective brain MRI findings that suggest mitochondrial disease
  - Bilateral signal abnormality
  - Basal ganglia or brainstem
- ~90 genes
- ~10% PDCD
Know when to lump & when to split

**Advantages of lumping**
- Power of clinical trial
- Grouping patients to learn natural history (LS natural history study)
- Coming together for advocacy (PALS)

**Disadvantages of lumping**
- Are we looking at the same outcomes?
- Is the prognosis the same?
- Does it prevent a “real” diagnosis?

Learning from patients #2

• There are advantages and disadvantages of an umbrella label, like “mitochondrial disease”

• Not every clinical trial is right for every patient – are they looking at an outcome that matters to you?

• Different aspects for each person involved in a person’s care
Risks and benefits are individual

Case 2:
~20 yo woman, diagnosed with mito in infancy
New diagnosis of PDHA1 mutation

Treatment philosophy of metabolic disease:
• Give cofactors to optimize energy production
• Avoid types of food that can’t be used
• Encourage intake of foods that can
Dr. G,

We’ve been doing this for twenty years. Her favorite food is PB&J

Risks and benefits are individual

Deciding when to treat

What will we get out of it?
Lower lactate...but hers is fine
Less seizures...but hers are under control

Will it help the things that bother the family?
It’s getting hard to carry her around...but this is unlikely to help

What are the downsides?
No more favorite food
Learning from patients #3

• Treatments need to be individualized

• Patient-centered outcomes: what matters to the patient and their family & will it help?

• Risks and benefits may be perceived uniquely by each patient & family
“Childhood” diseases have unpredictable adult courses

Case 3:
~15 yo man longstanding diagnosis of PDHA1 mutation

Participated in school, needed some extra help but can read, do math, write

Now having audio & visual hallucinations

Parents feel like he is disengaged

• He seems mild overall

• Are hallucinations related to his disease? To his meds? Seizures?

• Schizophrenia isn’t rare...
Dear Mito listserv,

Is this an association?

Hi Rebecca,

We had an engineer with PDCD in his middle age. He was doing great, had an advanced degree and then developed schizophrenia symptoms.
Learning from patients #4

• Doctors need to share stories with each other to help us understand what outcomes can be
  – Please say “yes” to publication!

• Diseases change over time
  – It is new that people with pediatric-onset disease are surviving to adulthood
  – Mild-Severe is just a snapshot

• Rare manifestations of rare disease are important
Part 1 Summary

• **Diagnosis is hard**
  – This is baked in to complex texts that are never perfect
  – Genetic testing is only as helpful as the information we already know about the gene

• **Lumping & Splitting each have advantages**

• **Treatment is imperfect**
  – Needs to be personalized in terms of both
    • is it worth it? and
    • What are we treating?

• **Natural history is hard**
  – Influence of age
  – Mild v. severe cases
How can you be a good patient advocate

• Physicians need to see “a lot” of patients with the same rare disease
  – Form groups of patients
  – Don’t feel bad about a second opinion

• Find umbrella groups for advocacy & trials.
• But make sure to remind people that you’re an individual

• Be honest about your values & how you’re actually feeling

• Understand we’re on a journey with you & it takes time!
PART 2: CHARTING THE FUTURE

PDCD, clinical trials & you
# The history of PDCD

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1. What are the necessary components to learning how to diagnose and treat a disease?
2. How can we do it in under 60 years?
We need to be able to identify rare disease

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<th>Rationale</th>
<th>Lesson</th>
<th>Strategy</th>
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<td>The disease exists</td>
<td>We only find what we look for!</td>
<td></td>
<td>Studies needed to help understand diagnostic use of biomarkers</td>
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<tr>
<td>A biomarker</td>
<td>Genetics is hard and imperfect</td>
<td>Biomarkers are hard and imperfect</td>
<td>Power of large numbers and building experience over time</td>
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<tr>
<td>Gene/s exist</td>
<td>Biomarkers are hard and imperfect</td>
<td>Genetic information requires already having knowledge</td>
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<td>Natural history</td>
<td>How do we know if we’re making it better?</td>
<td>We don’t understand late symptoms/full spectrum</td>
<td>Longitudinal natural history studies</td>
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<tr>
<td>Quality of life</td>
<td>The patient gets to judge if they’re “better”</td>
<td>This is highly individual</td>
<td>Patient-reported outcomes &amp; surveys</td>
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<tr>
<td>Are there markers of response?</td>
<td>Quality of life might take a long time to improve</td>
<td>Biomarkers are hard and imperfect</td>
<td>Quantification of QOL</td>
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Patient-reported outcomes

• **The problem:** drug trials look at short-term outcomes, e.g.
  – 6 minute walk test
  – Brain MRI
  – Lactate

• These don’t necessarily correlate with what patients want

• **FDA** has now asked drug trials to focus on patient-centered outcomes

• How will doctors know what patients want?
PDCD: addressing patient-reported outcomes

- Sent survey to 25 families with a child with PDCD
  - “What do you notice when your child is ill?”
    - How often does that happen?
    - How much does it worry you when it does?
- Found via online support group
ObsRO as a clinical trial outcome

- Validated survey
  - Gave to other patients with PDCD
    - Is it easy to use?
    - Does it capture your child’s symptoms?
- In the trial
  - Families get to chose 3-5 scales to be important for them
  - Patients serve as their own control

| Motor          | • Weakness                  
|                | • Incoordination            
|                | • Hypotonia/low muscle tone 
|                | • Rigidity/hypertonia       
|                | • Involuntary movements     
| Breathing      | • Breathing difficulty      
| Seizures       | • # seizures in the last 24 hours 
| Eating         | • # vomiting or retching episodes in the last 24 hours 
|                | • Feeding tube present      
|                |   - If Yes, proportion of tube feedings 
|                | • Refusal to eat by mouth   
| Fatigue        | • Tires more easily         
| Sleep          | • Sleep disturbance         
| General health | • Irritability (emotional)  
|                | • Irritability (interactive) 
| Other health issues | • Emergency room visit in the last 24 hours 
|                | • Hospitalized in the last 24 hours |
Treating patients

Identifying a potential treatment

We need to partner to understand risks/benefits

Patient-reported outcomes, surveys on tolerability
Will patients participate in trials?

iii. How likely would you/your child be to participate if the clinical trial is:

<table>
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<tr>
<th>Condition</th>
<th>All N=30</th>
<th>Adults N=15</th>
<th>Children N=15</th>
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</thead>
<tbody>
<tr>
<td>Conducted by your local doctor</td>
<td>85.2 (23/27)</td>
<td>92.3 (12/13)</td>
<td>78.6 (11/14)</td>
</tr>
<tr>
<td>Conducted by an academic hospital</td>
<td>88.9 (24/27)</td>
<td>84.6 (11/13)</td>
<td>92.9 (13/14)</td>
</tr>
<tr>
<td>Conducted by a pharmaceutical company</td>
<td>40.7 (11/27)</td>
<td>30.8 (4/13)</td>
<td>50.0 (7/14)</td>
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<tr>
<td>Conducted by a patient advocacy group or support group</td>
<td>69.2 (18/26)</td>
<td>53.8 (7/13)</td>
<td>84.6 (11/13)</td>
</tr>
<tr>
<td>A single-site trial</td>
<td>66.7 (18/27)</td>
<td>61.5 (8/13)</td>
<td>71.4 (10/14)</td>
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<tr>
<td>A multi-site trial (different locations are working together on the same trial)</td>
<td>66.7 (18/27)</td>
<td>53.8 (7/13)</td>
<td>78.6 (11/14)</td>
</tr>
<tr>
<td>In phase 1 (screening for safety)</td>
<td>51.9 (14/27)</td>
<td>53.8 (7/13)</td>
<td>50.0 (7/14)</td>
</tr>
<tr>
<td>In phase 2 (establishing the efficacy of the drug, usually against a placebo)</td>
<td>59.3 (16/27)</td>
<td>53.8 (7/13)</td>
<td>64.3 (9/14)</td>
</tr>
<tr>
<td>In phase 3 (final confirmation of safety and efficacy)</td>
<td>70.4 (19/27)</td>
<td>61.5 (8/13)</td>
<td>78.6 (11/14)</td>
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*Nonrespondents on individual questions (maximum 4 [13.3%] for all, 2 [13.3%] for Adults and 2 [13.3%] for Children) are excluded.*
Patient advocacy & support

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<td>Online advocacy groups</td>
<td>Central voice in patient priorities</td>
<td>Right balance of lump/split groups</td>
<td>Close physician collaboration with advocacy groups</td>
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Conclusions

• We only learn by seeing patients

• How to best diagnose disease

• How to balance the risks/benefits of treatment

• How to predict the natural history of disease

• All of these steps are ultimately essential for clinical trials
Acknowledgements

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My patients & their families!