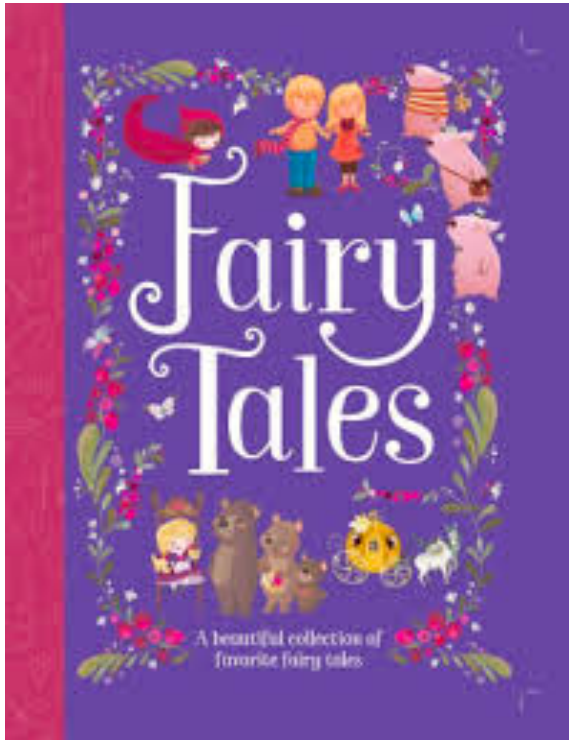
Children's Hospital of Philadelphia

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

> Clin Chim Acta. 1962 Mar;7:206-11. doi: 10.1016/0009-8981(62)90011-6.

REPORTS

Absence of pyruvate decarboxylase activity in man: a cause of

DF Farrell, AF Clark,

+ See all authors and a

Science 21 Mar 1975:
Vol. 187, Issue 4181, p
DOI: 10.1126/science.

Case Reports > Pediatrics. 1976 Nov;58(5):713-21.

Keto deh

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THE JOURNAL OF BIOLOGICAL CHEMISTRY
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Vol. 262, No. 15, Issue of May 25, pp. 7398–7403, 1987
Printed in U.S.A.

The Human Pyruvate Dehydrogenase Complex

ISOLATION OF cDNA CLONES FOR THE E1α SUBUNIT, SEQUENCE ANALYSIS, AND CHARACTERIZATION OF THE mRNA*

(Received for publication, December 12, 1986)

Hans-Henrik M. Dahl, Susan M. Hunt, Wendy M. Hutchison, and Garry K. Brown‡§

From the Murdoch Institute for Research into Birth Defects, Royal Children's Hospital and the ‡Department of Paediatrics, University of Melbourne, Australia

Core point: medicine & science take time

Clinical recognition		Syndrome named	Disease is a spectrum		Multiple genetic diseases		
Diagnostics	Biomarker discovery		Gene discovery	Gene sequencing available		Exome major diagnostic strategy	
Treatment		Diet treatment proposed (1 case)	DCA treatment proposed (1 case)		Animal models for treatment & DCA trial with other diseases		Phase 3 clinical trial

1960's → 1970's → 1980's → 1990's → 2000's → 2010's → 2020's

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

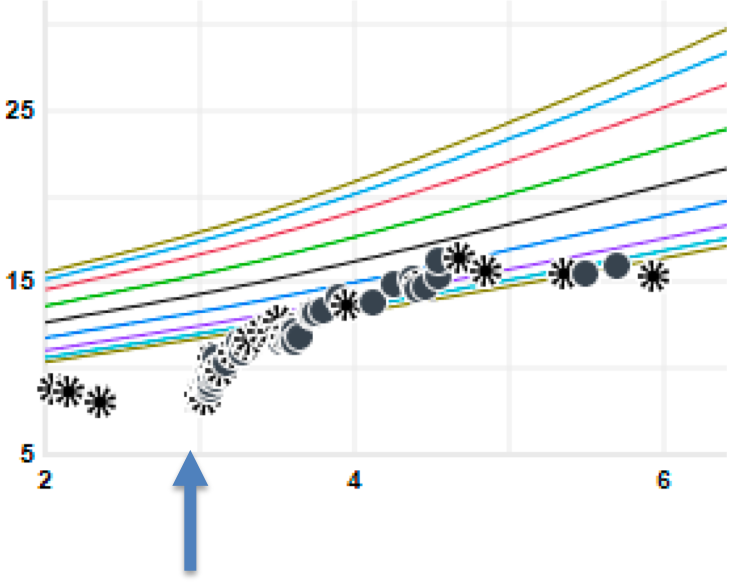
Dear Rebecca,
We are putting together a case series of patients with PDCD deficiency. Can you please contribute some cases?

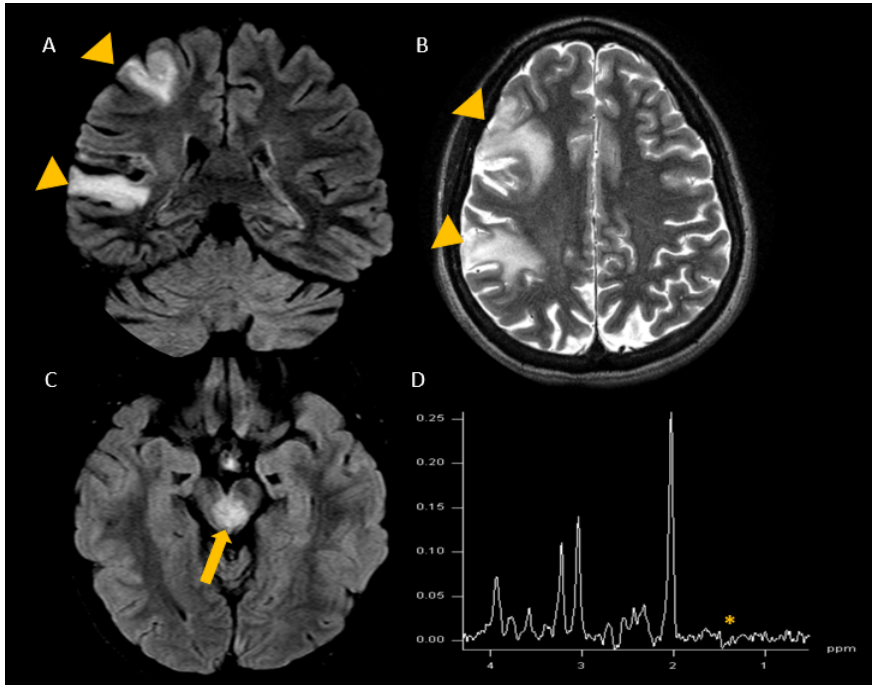
Biomarkers don’t make the diagnosis

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. 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.

X 7

This “can’t” be

Gene	Disease	Mode of Inheritance	Variant	Coding DNA	Zygosity	Inherited From	Classification
PDHA1	PDHA1-Related Disorder	X-Linked	p.N164S	c.491 A>G	Hemizygous	De Novo	Pathogenic Variant

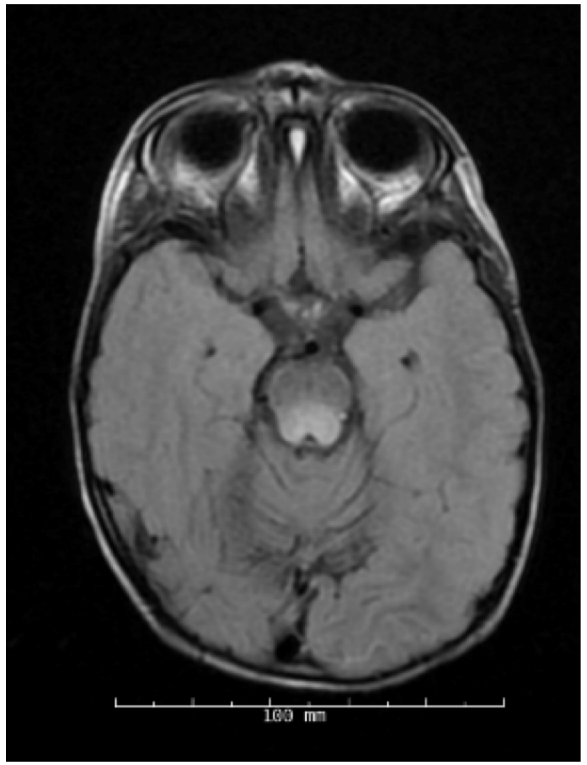
How do we “know” what we know about genetics?

- We have 20,000 genes → 3 **b**illion 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

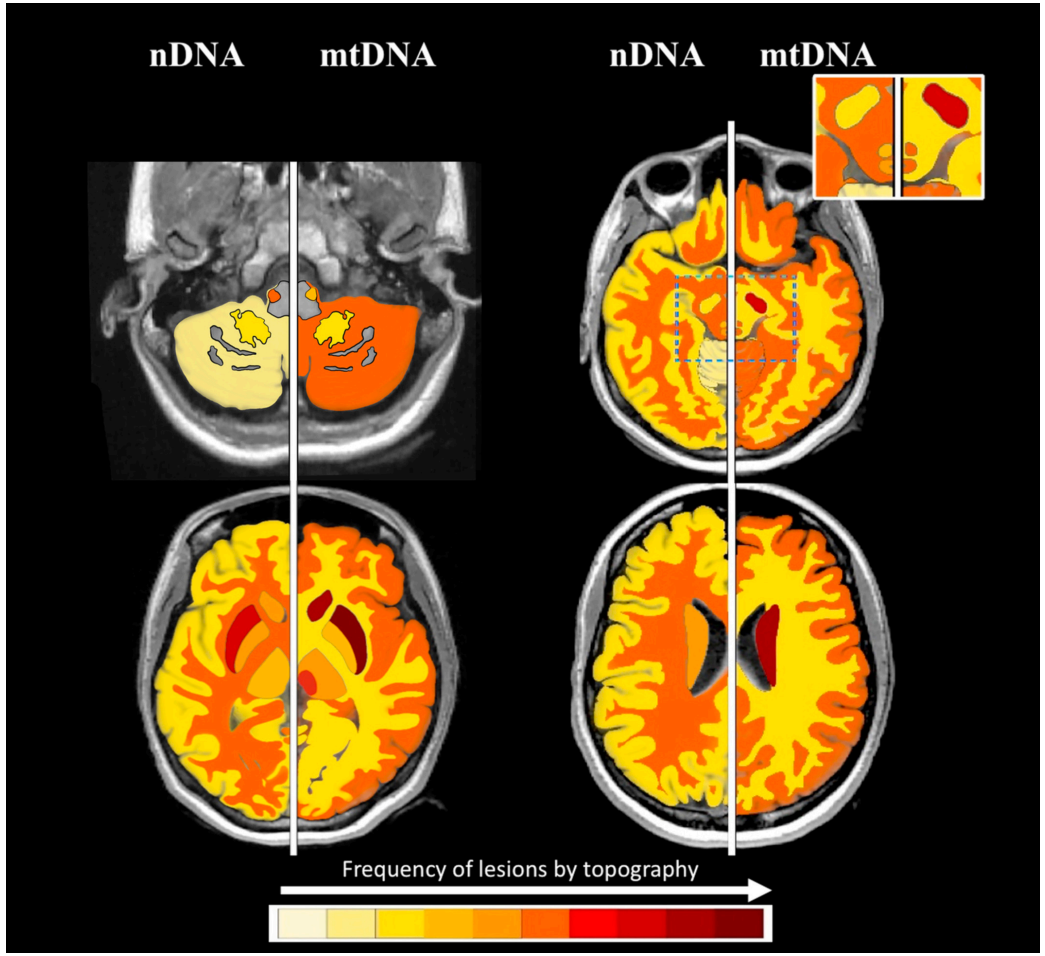
Know when to lump & when to split

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?



Alves, et al. Annals of Neurology, 2020

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

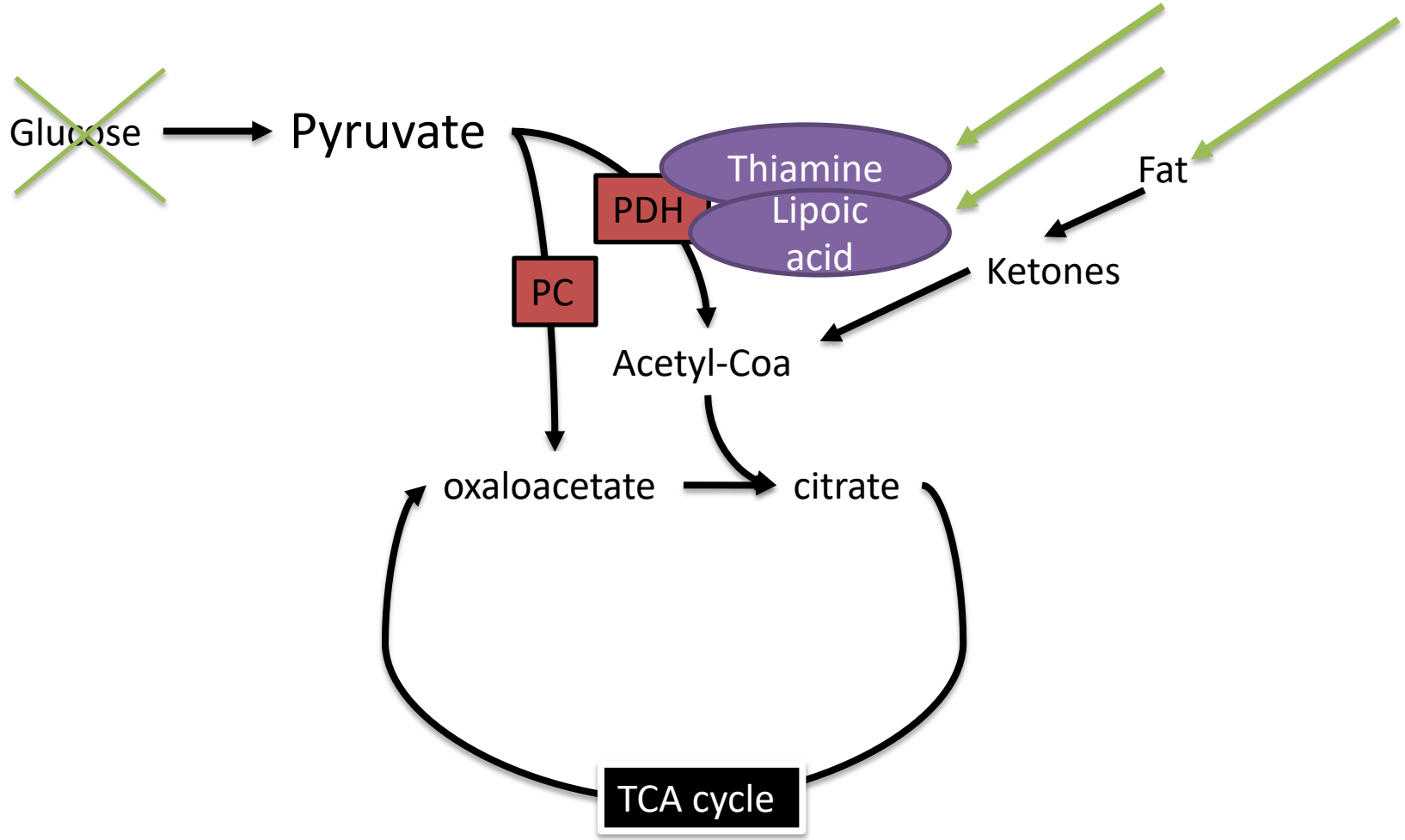
Risks and benefits are individual

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



Risks and benefits are individual

Dr. G,

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

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

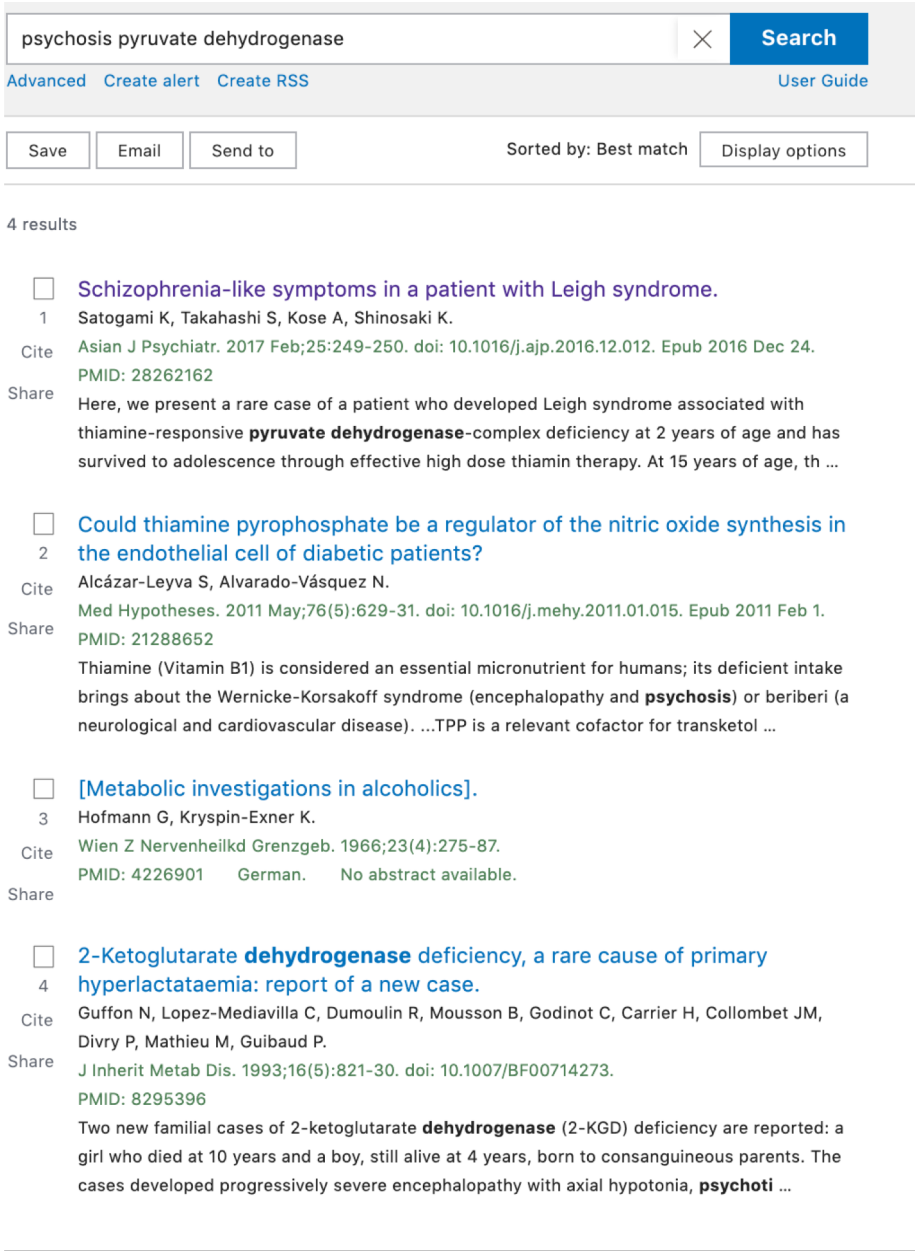
Participated in school, needed some extra help but can read, do math, write

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…

We learn from each other



psychosis pyruvate dehydrogenase

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1 Cite Share

Schizophrenia-like symptoms in a patient with Leigh syndrome.

Satogami K, Takahashi S, Kose A, Shinosaki K.

Asian J Psychiatr. 2017 Feb;25:249-250. doi: 10.1016/j.ajp.2016.12.012. Epub 2016 Dec 24.

PMID: 28262162

Here, we present a rare case of a patient who developed Leigh syndrome associated with thiamine-responsive **pyruvate dehydrogenase**-complex deficiency at 2 years of age and has survived to adolescence through effective high dose thiamin therapy. At 15 years of age, th ...

2 Cite Share

Could thiamine pyrophosphate be a regulator of the nitric oxide synthesis in the endothelial cell of diabetic patients?

Alcázar-Leyva S, Alvarado-Vásquez N.

Med Hypotheses. 2011 May;76(5):629-31. doi: 10.1016/j.mehy.2011.01.015. Epub 2011 Feb 1.

PMID: 21288652

Thiamine (Vitamin B1) is considered an essential micronutrient for humans; its deficient intake brings about the Wernicke-Korsakoff syndrome (encephalopathy and **psychosis**) or beriberi (a neurological and cardiovascular disease). ...TPP is a relevant cofactor for transketol ...

3 Cite Share

[Metabolic investigations in alcoholics].

Hofmann G, Kryspin-Exner K.

Wien Z Nervenheilkd Grenzgeb. 1966;23(4):275-87.

PMID: 4226901 German. No abstract available.

4 Cite Share

2-Ketoglutarate **dehydrogenase** deficiency, a rare cause of primary hyperlactataemia: report of a new case.

Guffon N, Lopez-Mediavilla C, Dumoulin R, Mousson B, Godinot C, Carrier H, Collombet JM, Divry P, Mathieu M, Guibaud P.

J Inherit Metab Dis. 1993;16(5):821-30. doi: 10.1007/BF00714273.

PMID: 8295396

Two new familial cases of 2-ketoglutarate **dehydrogenase** (2-KGD) deficiency are reported: a girl who died at 10 years and a boy, still alive at 4 years, born to consanguineous parents. The cases developed progressively severe encephalopathy with axial hypotonia, **psychoti** ...

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!

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PART 2: CHARTING THE FUTURE

PDCD, clinical trials & you

The history of PDCD

Clinical recognition		**Syndrome named**	**Disease is a spectrum**		**Multiple genetic diseases**		
Diagnostics	**Biomarker discovery**		**Gene discovery**	**Gene sequencing available**		**Exome major diagnostic strategy**	
Treatment		**Diet treatment proposed (1 case)**	**DCA treatment proposed (1 case)**		**Animal models for treatment & DCA trial with other diseases**		**Phase 3 clinical trial**

1960's → 1970's → 1980's → 1990's → 2000's → 2010's → 2020's

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

Component	Rationale	Lesson	Strategy
The disease exists	We only find what we look for!		
A biomarker	Genetics is hard and imperfect	Biomarkers are hard and imperfect	Studies needed to help understand diagnostic use of biomarkers
Gene/s exist	Biomarkers are hard and imperfect	Genetic information requires already having knowledge	Power of large numbers and building experience over time

How do patients do without treatment?

Component	Rationale	Lesson	Strategy
Natural history	How do we know if we're making it better?	We don't understand late symptoms/full spectrum	Longitudinal natural history studies
Quality of life	The patient gets to judge if they're "better"	This is highly individual	Patient-reported outcomes & surveys
Are there markers of response?	Quality of life might take a long time to improve	Biomarkers are hard and imperfect	Quantification of QOL

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

Mitochondrion. Author manuscript; available in PMC 2019 Sep 1.
Published in final edited form as:
Mitochondrion. 2018 Sep; 42: 59–63.
Published online 2017 Nov 10. doi: 10.1016/j.mito.2017.11.003

PMCID: PMC6587967
NIHMSID: NIHMS1530128
PMID: 29129554

Development of a Novel Observer Reported Outcome Tool as the Primary Efficacy Outcome Measure for a Rare Disease Randomized Controlled Trial

Peter W. Stacpoole, PhD, MD, Jonathan Shuster, PhD, Professor Emeritus, and John L. P. (Seamus) Thompson, PhD

- 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

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

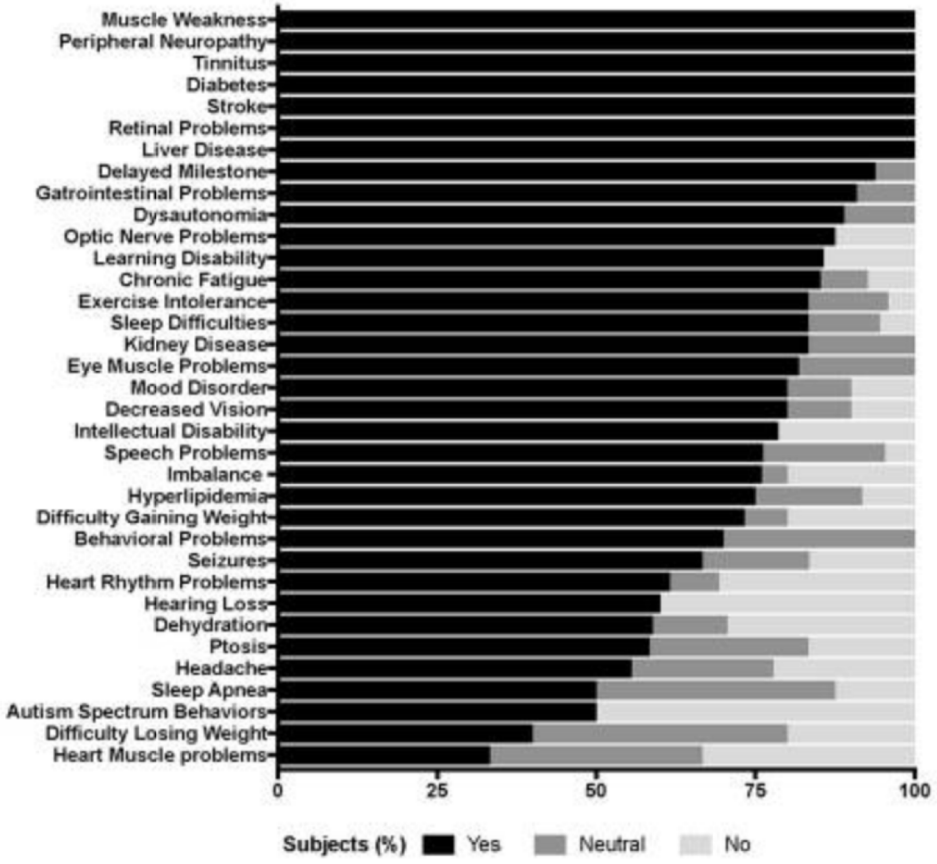
- Validated survey
  - Gave to other patients with PDCD
    - Is it easy to use?
    - Does it capture your child's symptoms?
- In the trial
  - Families get to chose 3-5 scales to be important for them
  - Patients serve as their own control

Treating patients

Component	Rationale	Lesson	Strategy
Identifying a potential treatment		We need to partner to understand risks/benefits	Patient-reported outcomes, surveys on tolerability

Will patients participate in trials?

C. Likely to participate if Experienced Symptom is targeted in a clinical trial (N=30)



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

Zolkipli-Cunningham, et al, 2018, PLoS ONE

Patient advocacy & support

Component	Rationale	Lesson	Strategy
Online advocacy groups	Central voice in patient priorities	Right balance of lump/split groups	Close physician collaboration with advocacy groups

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*

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Katelynn Stanley, BSc

My patients & their families!