



Today's Webinar:

Rare Epilepsies

Presented by:

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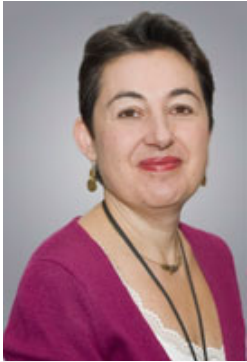
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Today's Speakers



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What are the Rare epilepsies?

Orphan diseases

- Diseases or disorders that affect $< 200,000$ people in the US (based on the orphan disease act of 2002), or 1/1,500 people
- These diseases have been highlighted in legislature because of the concern that treatments will not be developed for them
- Rare epilepsies are the “Orphan Diseases” of epilepsy

Incidence of Epilepsy Overall

- By a conservative estimate, 50 million people worldwide have epilepsy¹
- The annual incidence ranges from 20-70 cases per 100,000
- Overall, 5% of persons report a seizure at some time in their lives (excluding febrile seizures)
- Incidence rates are highest in childhood, plateau from 15-65 years of age, and rise again among the elderly
- About 30% of patients with seizures have an identifiable neurologic or systemic disorder, and the remainder have either a genetic cause or an unknown cause

1. Brodie MJ and Dichter MA. *N Engl J Med.* 1996;334(3):168-175.

Epilepsy classification

- Epilepsy can be classified in a number of ways-Some of these include:
 - What caused the epilepsy
 - For example, stroke, genetic defect, **hypothalamic hamartoma**
 - What kind of seizures happen
 - For example simple focal seizures, **infantile spasms**
 - What are the characteristics of the epilepsy
 - Age of onset, likelihood of remission, EEG pattern-
These add up to an epilepsy “syndrome”
 - For example **Dravet syndrome, Lennox-Gastaut syndrome, photosensitive epilepsy**

Epilepsy Classification

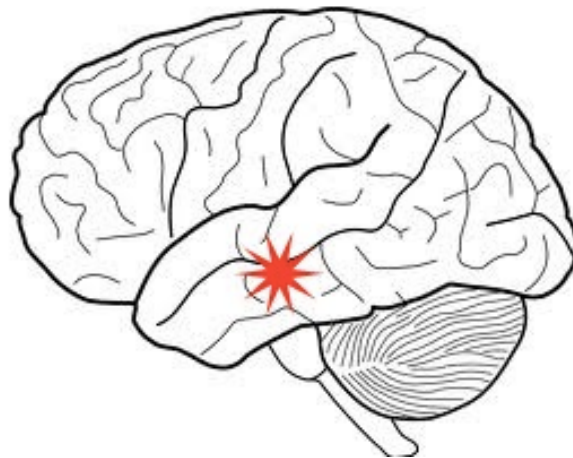
- Any of the ways we classify (cause, seizure type, seizure syndrome) can be the basis of a rare (orphan) epilepsy
- These characteristics are not mutually exclusive
- For example, a child may have a *genetic disorder such as Tuberous sclerosis (Cause)* that leads to *Lennox-Gastaut (syndrome)*
- Since both of these are rare, such a person would have 2 orphan epilepsies

Why do we classify Epilepsy?

- Sometimes if types of epilepsy can be characterized into clusters, groups or syndromes, it may inform us about:
 - What the long-term outcome (prognosis) might be?
 - Including whether the epilepsy is likely to respond to drugs
 - What the cause is (for example a genetic mutation)
 - What is the best treatment
 - Drugs? Specific drugs? Surgery?
 - What treatments should be avoided

Common vs rare epilepsies

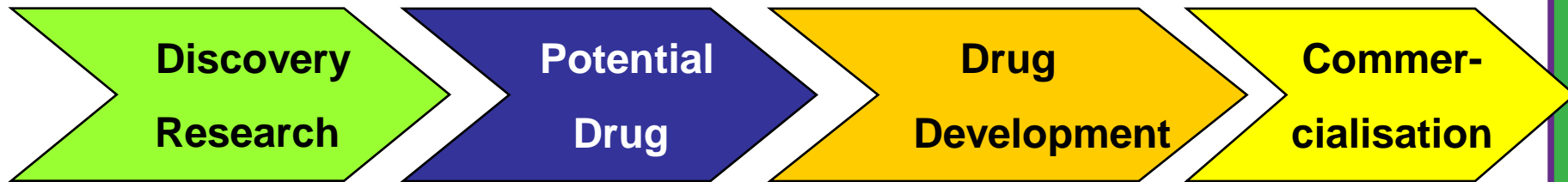
- 70% of epilepsy is “focal” (used to be called partial) which means that epilepsy begins in one or two spots. This is the epilepsy type that is the target of most new drugs and treatments



Common Epilepsy Syndromes With >1M Patients Worldwide:

- Febrile Seizures in Children
- Focal Epilepsy in Adults and Children
- Idiopathic (Genetic) Generalized Epilepsy with Tonic-Clonic Seizures in Adults in Children
- Juvenile Myoclonic Epilepsy

The discovery and development of a new medicine



Investment to bring 1 new drug to the market: \$4-11Billion
Industry with highest project attrition and longest development cycles

Regulatory Issues: Orphan Drug

- If companies develop drugs for orphan diseases they get special FDA benefits intended to motivate them to develop treatments
- Small population may make return on investment difficult, even with these benefits
- Drugs, once approved, may be priced very high
 - Acthar Gel(ACTH) went from **\$1,650 to \$23,000 Per Vial**

Examples: Very Rare Epilepsy Syndromes With <100K Patients Worldwide:

- Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome) 1:40,000 births)
- Landau-Kleffner Syndrome
- Rasmussen's Syndrome-1:40,000
- Lafora body myoclonic epilepsy -1:1,000,000
- Myoclonic Astatic Epilepsy (Doose) 1:10,000

Rare Epilepsy Network

- 10 orphan diseases that have collaborated through a grant from the Patient Centered Outcomes Research Institute (PCORI)
- An attempt to find out more information to help us diagnose, classify and treat the rare Orphan) epilepsies.

What are the Risks?

Dale C Hesdorffer, PhD
GH Sergievsky Center
Columbia University

Outcomes of the rare epilepsies

- Cognitive
- Behavioral
- Seizure persistence
- Mortality

Cognitive outcomes

Intellectual disability in Lennox-Gastaut Syndrome

Study	Kurokaw a	Ohtsuk a	Yagi	Ogun i	Goldsmi h
Number	123	89	102	72	74
Follow-up in years	>5	>5	>10	>1	>3
% Intellectual disability	93%	91%	~75 %	99%	92%

Change in intellectual disability from onset to the final visit more than 10 years later:
Onset: 69% Final visit: 99%

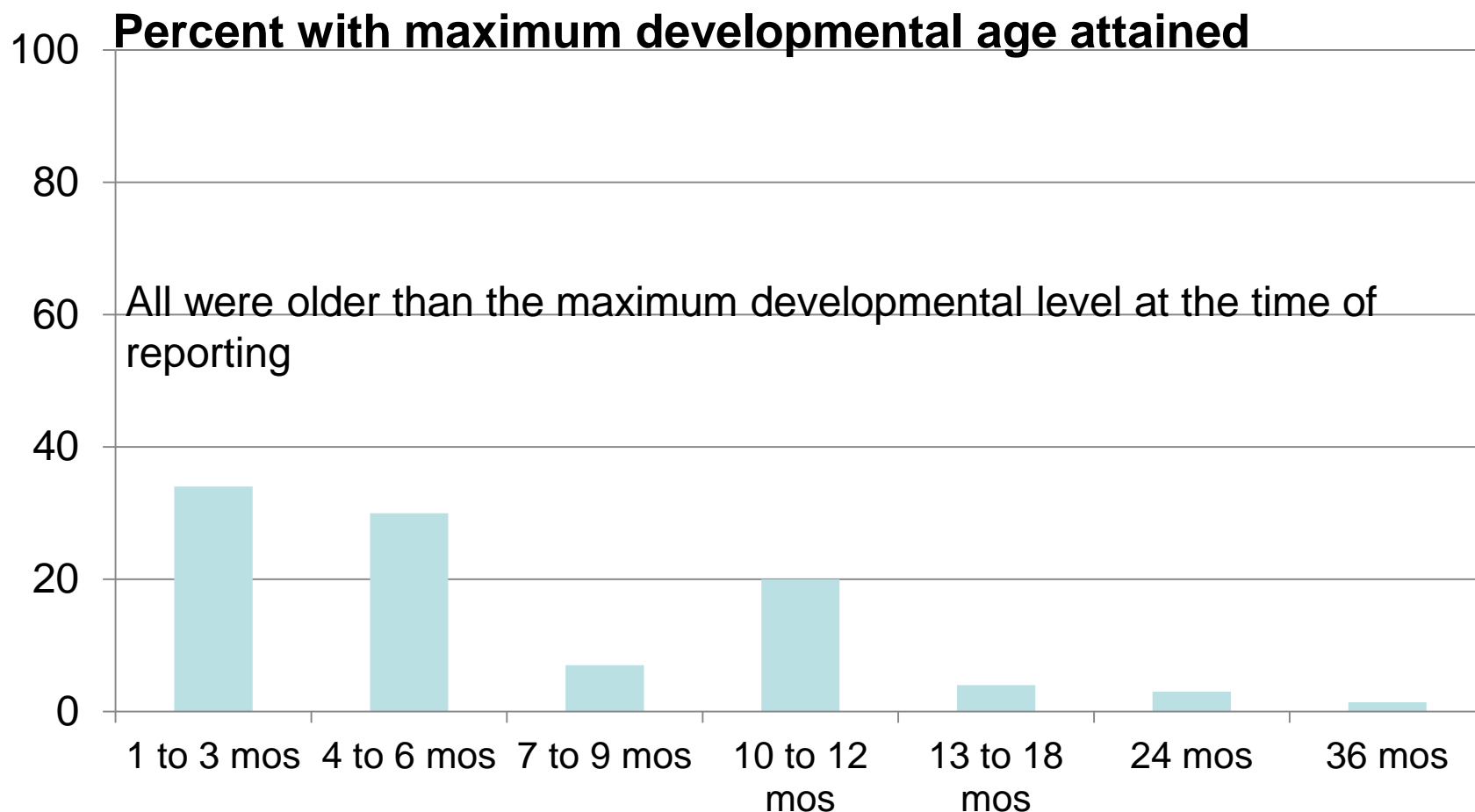
Kurokawa et al. Pediatrics 1980;65:81-8; Ohtsuka et al Japan J Psychiatry Neurol 1990;44:257-64; Yagi. Epilepsia 1996;37 (suppl 3):48-51; Oguni et al. Epilepsia 1996;37(suppl 3):44-47; Goldsmith et al. Epilepsia 2000;41:395-9

Development and developmental quotient in Aicardi syndrome

Study	N patients	Walk	Talk	DQ>12 mos
Chevrie & Aicardi, 1986	184	Some unable	none	--
Donnenfeld, 1989	18	11%	One used words	17%
Neidich, 1990	7	14%	One used words	14%
Menezes, 1996	14	14%	2 spoke in sentences 2 used words	21%
Rosser, 2002	77	21%	3 spoke in sentences	9%

From: Rosser et al. Pediatr Neurol 2002;27:343-346.

Severe intellectual disability in girls with CDKL5



Rosser et al. Pediatr Neurol 2002;27:343-346.

Severe intellectual disability in presurgical patients with Hypothalamic Hamartoma and refractory epilepsy

Number of patients	49
Age range	5-55 years
Precocious puberty	26.5%
Severe intellectual disability (untestable)	14.3%

No difference in IQ by age for all IQ components in testable patients

IQ was correlated with number of AEDs at evaluation

IQ was not associated with:

- Age at seizure onset

- Epilepsy duration

- Size of Hypothalamic Hamartoma

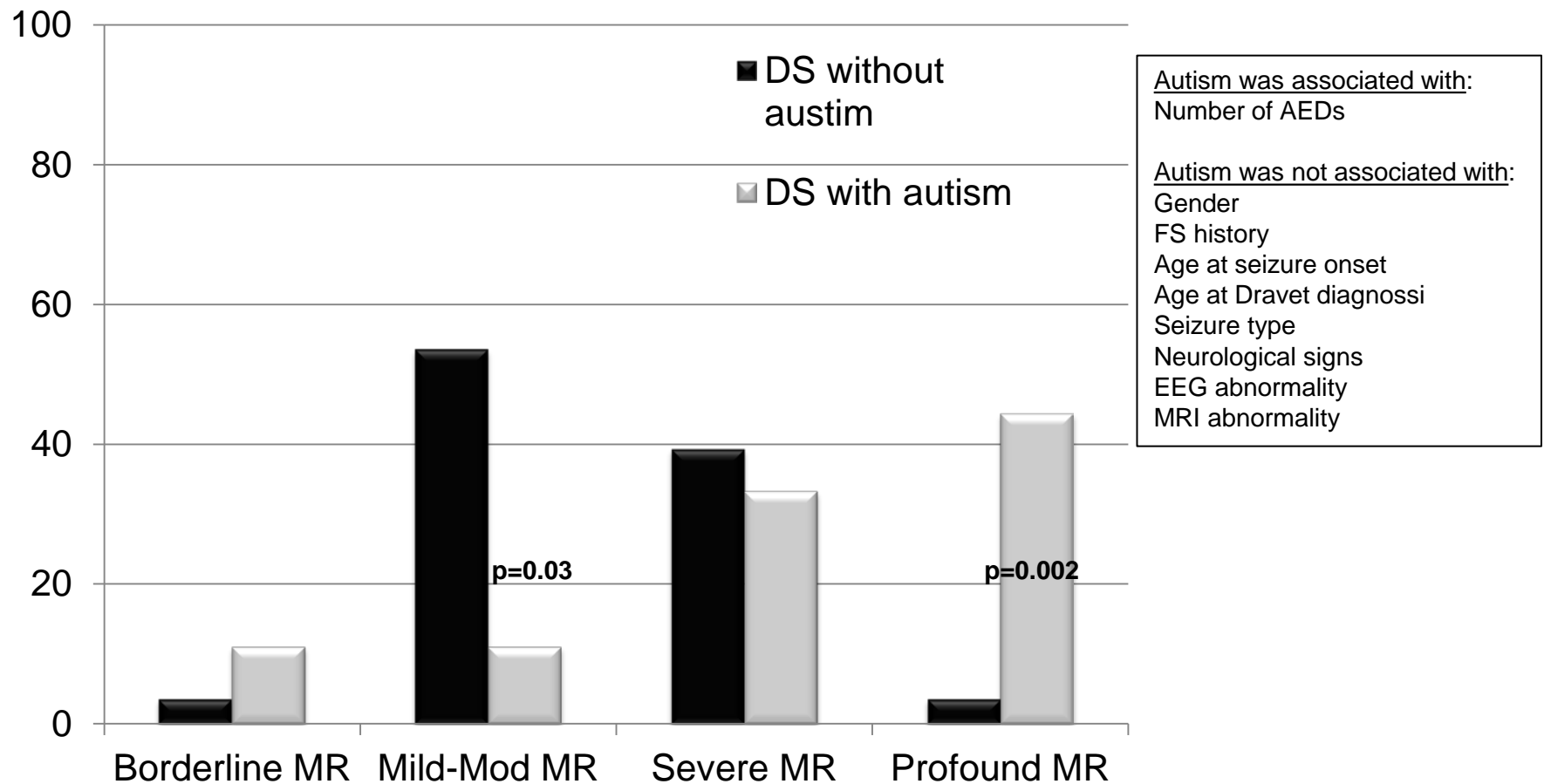
- Side of attachment of Hypothalamic Hamartoma

- Anatomical classification of Hypothalamic Hamartoma

- based on MRI

Behavioral disorders

Autism spectrum disorder in Dravet syndrome

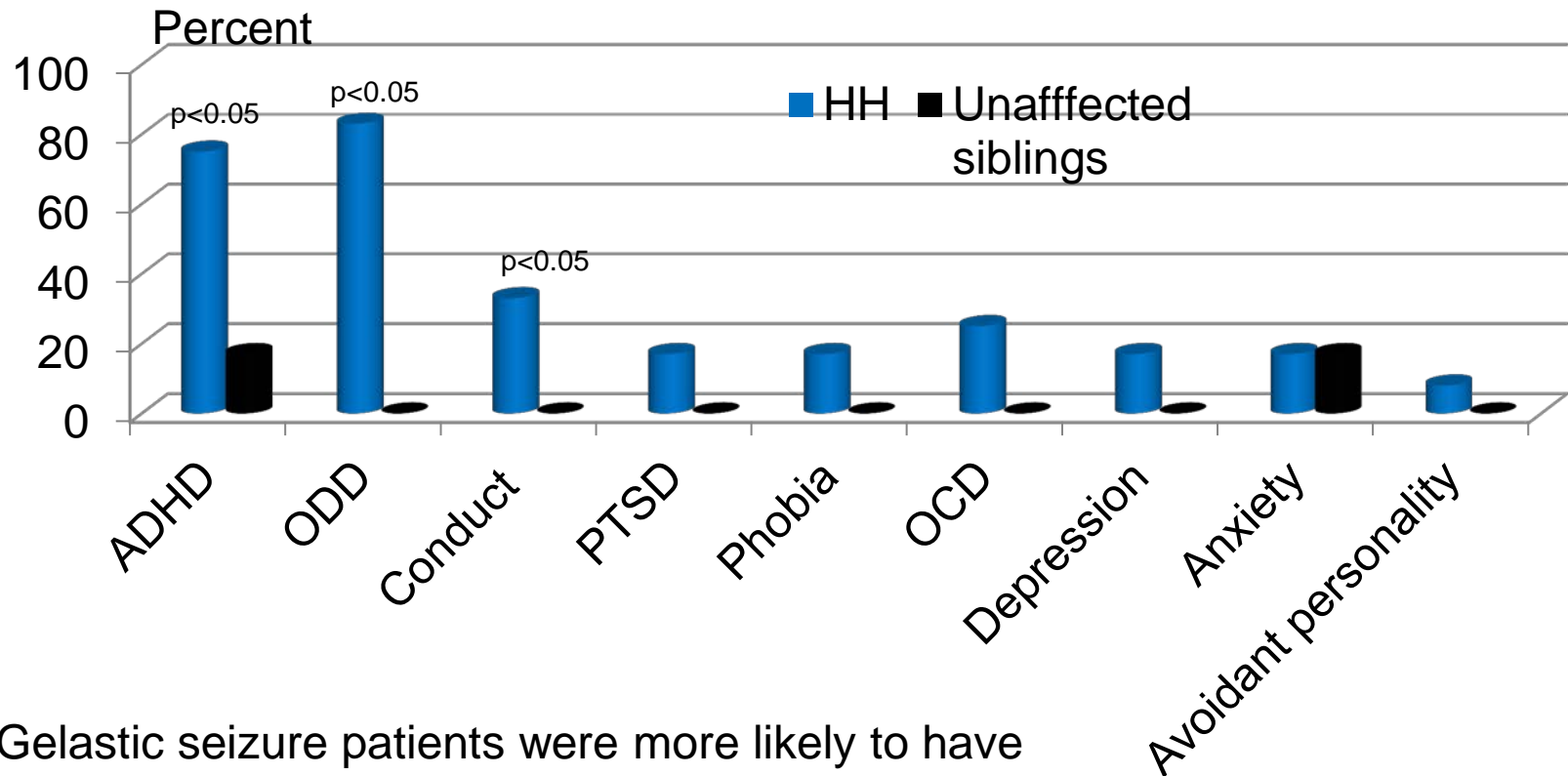


Behavior in Lennox-Gastaut syndrome

- Among 83 patients
 - ~50% had behavior problems that required mention in the medical record.
 - These included:
 - Hyperactivity
 - Aggression
 - Autism
 - Destructive behaviors
 - Antisocial behaviors
 - Hypersexual behaviors

Behavior in 12 children with hypothalamic hamartoma

Compared to unaffected siblings



Gelastic seizure patients were more likely to have affective aggression, $p=0.028$

Behavioral findings in 98 unrelated patients with Tuberous Sclerosis

- Compared to a TSC1 mutation, a TSC2 mutation was associated with a higher risk for:
 - IQ less than 70 ($p=0.0004$)
 - Adjustment for infantile spasms did not change this relationship
 - Autism ($p=0.03$)
- 36 adults were able to complete depression and anxiety scales
 - 56% screened positive for anxiety
 - 19% screened positive for depression
- There was no association between positive screens for anxiety or depression and TSC1 or TSC2 mutations

Seizure persistence

Seizure persistence in Lennox-Gastaut Syndrome

Study	Kurokawa	Ohtsuka	Yagi	Oguni	Goldsmith
Number	123	89	102	72	74
Follow-up in years	>5	>5	>10	>1	>3
% Seizure persistence	66%	76%	92%	92%	95%

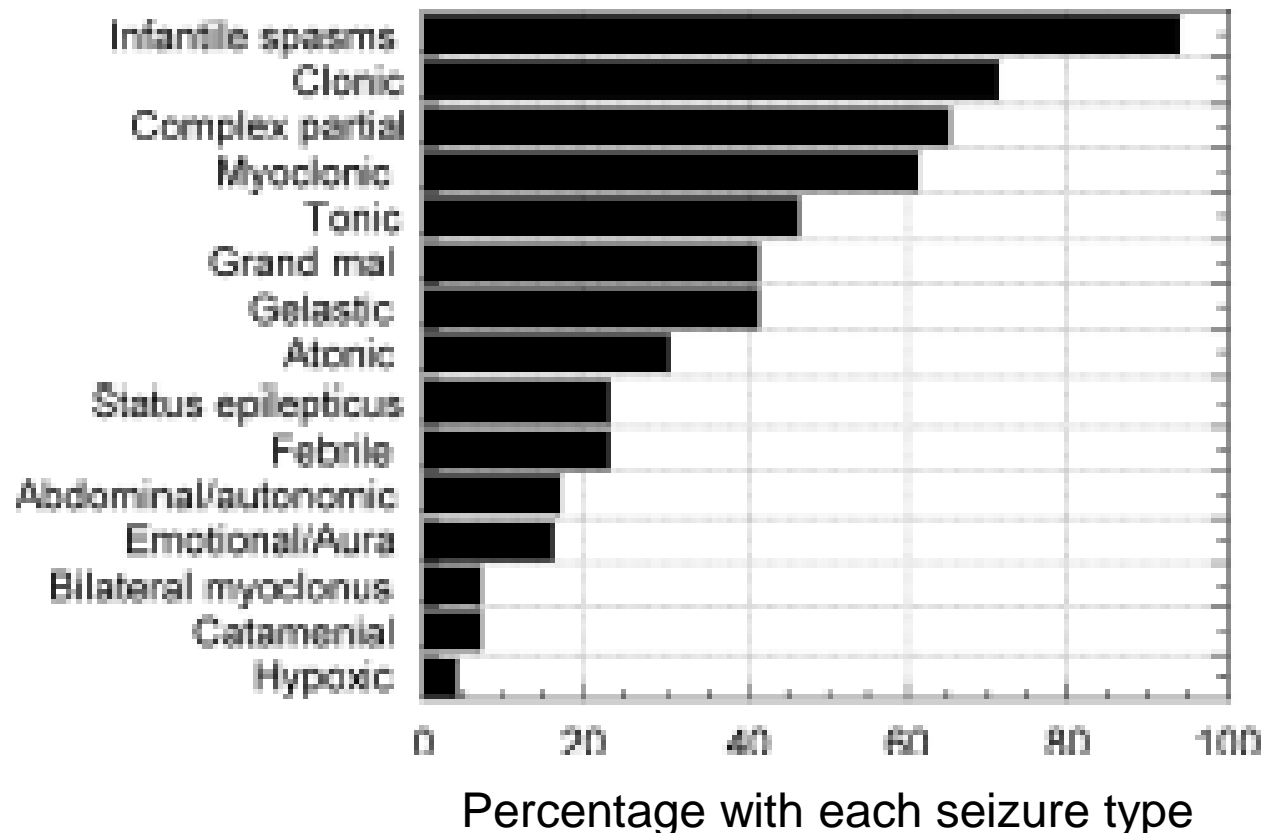
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Seizure frequency in Aicardi syndrome

Study	N patients	Seizure frequency
Chevrie & Aicardi	184	--
Donnenfeld	18	67% daily seizures
Neidich	7	57% 'intractable' seizures
Menezes	14	78% daily seizures
Rosser	77	67% daily seizures

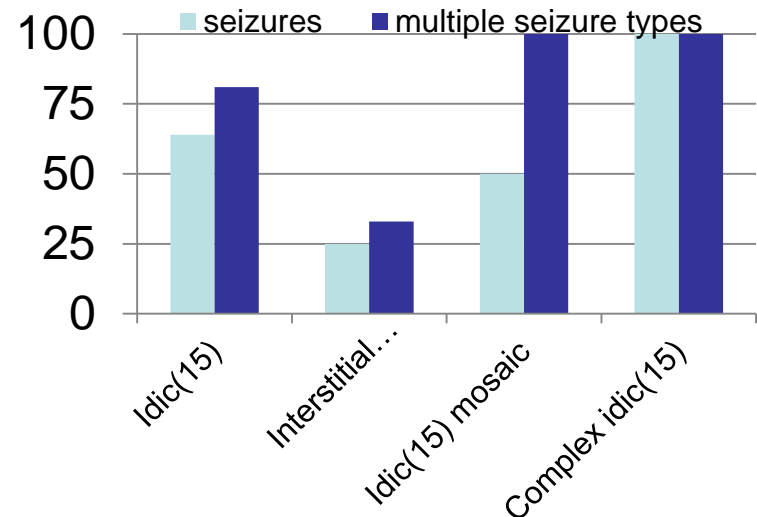
From: Rosser et al. Pediatr Neurol 2002;27:343-46.

Seizure types and frequency in Aicardi syndrome



Seizures in patients with Dup15q syndrome

- 95 responded
 - 83 had variation in a marker idic(15) chromosome
 - Seizures in 52 (63%)
 - 42% had a history of infantile spasms
 - 33% had SE of which 80% had >10 SE episodes
 - 12 had int dup(15)
 - Seizures in 3 (25%)



Patient characteristics and surgical outcome in Hypothalamic Hamartoma

- Complete resection of HH in patients with:
 - Moderate to severe delay
 - Progressive cognitive decline
 - Behavioral abnormalities (e.g., autism, tantrums)
- Outcome:
 - 2/13 seizure free after 2.5 and 4.5 years
 - 6/13 no major seizures or >90% reduction in seizures
 - 5/13 less than 50% reduction in major and minor seizures

Gamma knife surgery for epilepsy in Hypothalamic Hamartoma

- 10 patients were treated
- All exhibited improvement after surgery
 - 4/10 seizure free
 - 1/10 rare nocturnal seizures
 - 1/10 rare focal seizures and no GTCS
 - 2/10 reduced seizure frequency and rare GTCS
 - 2/10 now seizure free after a repeat procedure

AED treatment to reduce the onset of epilepsy and cognitive problems in Tuberous Sclerosis

Standard: Vigabatrin treatment within a week of the first seizure (N=31)

Preventive: Vigabatrin treatment after epileptiform discharges only (N=14)

	Standard	Preventive	p-value
Normal EEG at 24 months	35.5%	85.7%	0.005
EEG normalized			
Whole group	6.5%	57.1%	0.0007
Patients on AEDs	9.1%	80%	0.0001
Seizure free at age 2 years	35.5%	92.9%	0.004
Mean IQ at 2 years	68.7	92.3	<0.05
Moderate, severe or profound intellectual disability at 2 years	32.3%	0%	0.036

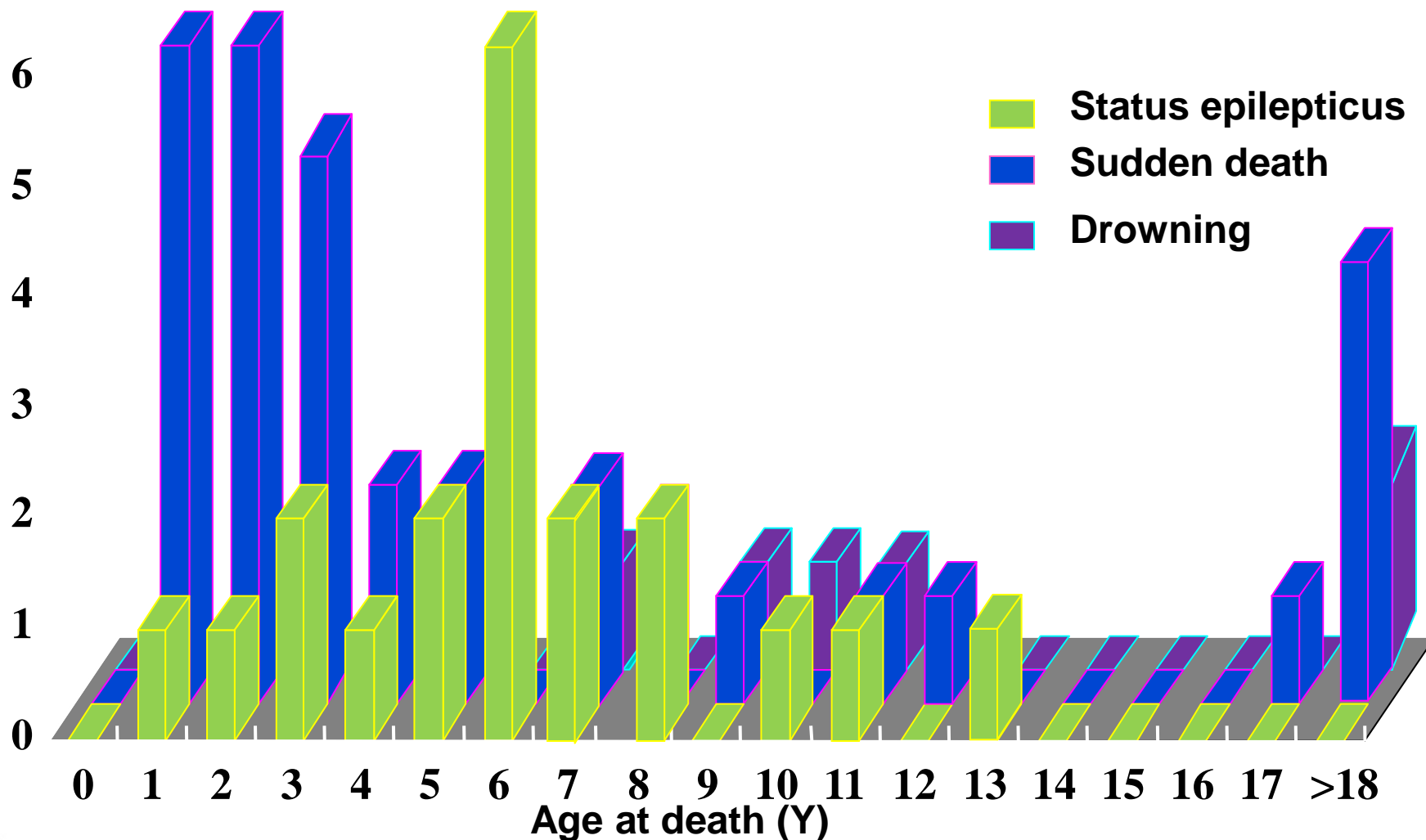
Mortality

Causes of death in Dravet syndrome

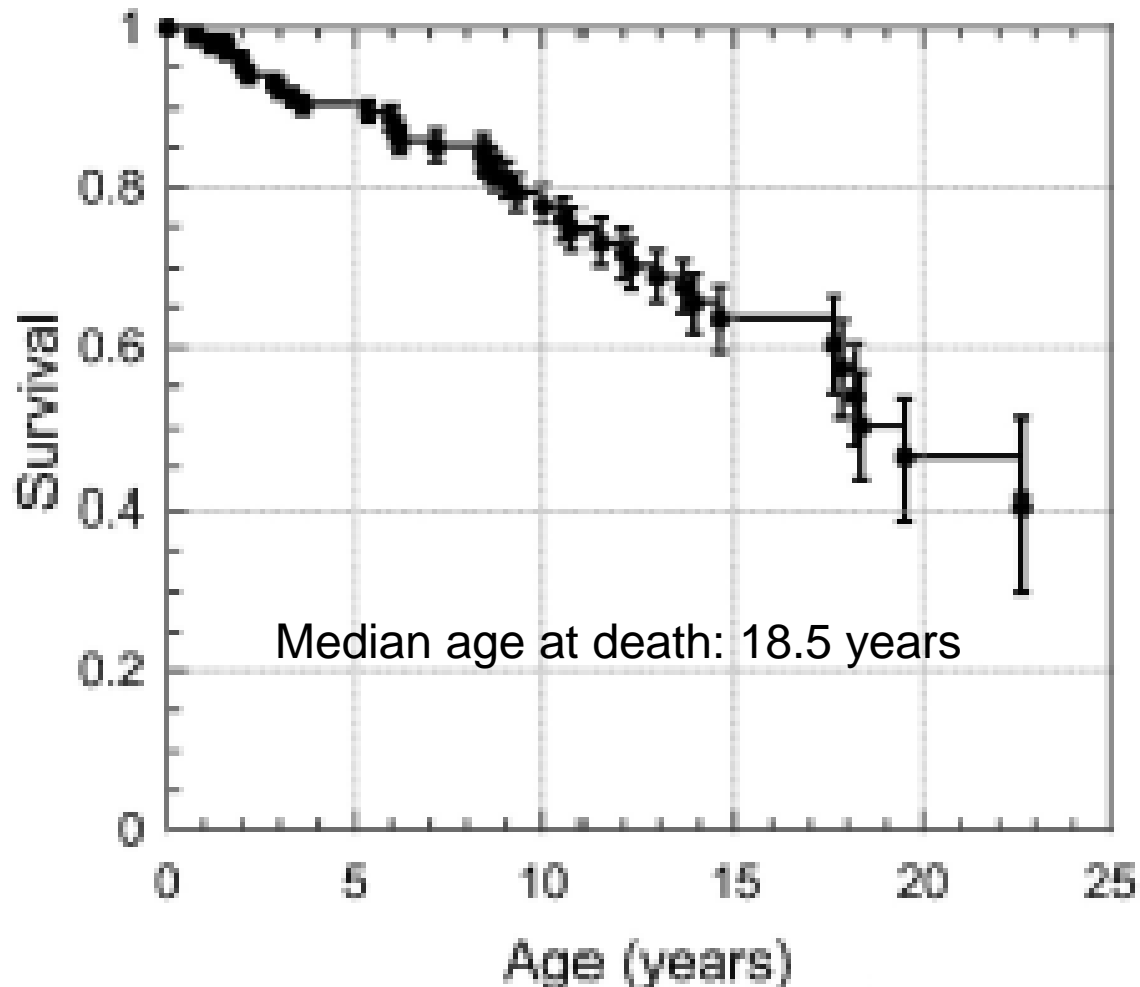
	Genton et al, 2011	Dravet et al, 1992	Akiyama et al, 2010	Oguni et al, 2001	Sajauchi et al 2011
Population (N, range)	24 Adults	63, 3-27 yrs	37, <43 yrs	84 Pediatric	438, <24 yrs
Deceased N (%)	5 (20.8%)	11 (16%)	7 (16.2%)	12 (14.3%)	59 (10.1%)
Age at death	24.8 yrs	11 yrs	5-12 yrs	6 yrs	NA
Percent of deaths by cause					
SE	1 (4.2%)	3 (4.8%)	4 (10.8%)	6 (7.1%)	21 (4.8%)
SUDEP	3 (12.5%)	2 (3.2%)	1 (2.7%)	0	31 (7.1%)
Pneumonia	0	1 (1.6%)	2 (5.4%)	1 (1.2%)	0
Drowning	0	3 (4.8%)	0	1 (1.2)	6 (1.4%)
Other	0	1 (1.6%)	0	0	1 (0.2%)
Unknown	1 (4.2%)	1 (1.6%)	0	4 (4.8%)	0

Distribution of causes of death by age in 59 Dravet syndrome deaths

Number of Patients



Mortality in 182 children with Aicardi syndrome



Conclusion -1

- Many of the rare epilepsies are associated with intellectual disability
- Behavioral problems are common in Dravet, hypothalamic hamartoma, LGS, and TS
- Seizure remission is very rare and some syndromes have many different co-occurring seizure types
- Mortality is high for Dravet syndrome and Aicardi syndrome

Conclusion-2

- Seizure frequency is reduced by:
 - Epilepsy surgery in hypothalamic hamartoma
 - Vigabatrin in Tuberous Sclerosis with epileptiform discharges only

Conclusion-3

- There is a paucity of research in many of the rare epilepsies
- The Rare Epilepsy Network hopes to change this with your help

- REN link

<https://ren.rti.org/>





Rare Epilepsy Network

Janice M. Buelow RN, PhD, FAAN



The REN is a collaboration between the Epilepsy Foundation, Columbia University, New York University, Research Triangle Institute and 10 rare epilepsy organizations:

Aaron's Ohtahara

Aicardi Syndrome Foundation

Dravet Syndrome Foundation

Dup15q Alliance

Hope for Hypothalamic Hamartomas

International Foundation for CDKL5 Research

Lennox-Gastaut Syndrome Foundation

PCDH19 Alliance

Phelan-McDermid Syndrome Foundation

Tuberous Sclerosis Alliance

- The Rare Epilepsy Network (REN) PPRN is an initiative created by and for patients with catastrophic rare epilepsies.

-

- Goal -- build a patient-centered and driven data base

- Designed to provide the patients and their families an opportunity to participate in research

- Improve lives and quality of care for people with rare epilepsies.

Sustainability

- Further funding by PCORI
- We are building a sustainability plan
 - At the EF – Rare Epilepsy Institute that includes
 - Education
 - Social networking
 - Research
 - Partnerships with all organizations

- The PCORnet award has allowed 10 rare epilepsy organizations to collaborate with the Epilepsy Foundation, Columbia University and The Research Triangle
- Institute to build a common network for the conduct of research and for participation in non-REN initiated research
- The whole is greater than the sum of its parts – this is an incredible opportunity for all involved.

- How does this project impact patient outcomes.
 - The rare epilepsy diagnosis is often not studied
 - Difficult to find a sample
 - Not enough people to make an impact through research
 - Fewer people with a problem often are not able to generate interest.

REN can help

- We will have a registry of patients in one place allowing researchers easier access to patients for studies
- Because we are generating a data base there will be more accessible patients thus generating more research interest
- A larger sample creates a bigger research impact

REN can also

- Answer certain question that we have not been able to answer in the past.
- What are differences and similarities between rare epilepsies.
- What are specific computable phenotypes of each rare epilepsy
- What research questions can we ask that can study across rare epilepsies and also can we ask that study within each rare epilepsy

REN can also

- Create a data base and registry for clinical trials
- Create a data base for researchers to ask new questions

REN is part of a much bigger project

-We will not only be able to answer specific questions about rare epilepsies but also:

- Be a part of studies that query other rare conditions such as Duchene's Muscular Dystrophy
- Partner with Clinical data research networks to answer large cohort question that can have an impact on the rare epilepsies. For example, if someone is doing an intervention for care givers – the utility of that interventions could also be tested in our group

The award enabled all participants in PCORnet to discuss a larger world of collaborative research. We are part of those discussions and are still considering how our rare epilepsy network will interact with the larger community of both common disease and CDRNs with huge populations.

Because of the PCORnet award, we think differently about how research may be conducted in the future. The PCORnet plans have implications for the REN but also for the entire epilepsy community.

- Importantly for the REN, we can participate with larger groups to answer questions that may affect some of our participants. All is not about epilepsy in the REN as studies that focus on the systemic comorbidities may also offer our network important opportunities for research in areas that impact the quality of life for people with devastating epilepsy.

•Conclusion

- This is a critically important project that will provide data to do research in a timeframe that matters to patients and families
- The PCORnet is visionary in that it begins to build a framework to let systems talk to one another
- Improves the potential for greater research opportunities.
- Learning more about these disorders will help to better understand the role they play in SUDEP.

Q&A