The Weinberg Child Development Center and Keshet Center for Autism

Director: Lidia V. Gabis, MD

Edmond and Lilly Safra Children's Hospital
SHEBA MEDICAL CENTER
TEL-HASHOMER, ISRAEL

Vision

The Weinberg Child Development Center

is a tertiary center of excellence

committed to care

for complex disabilities and autism related disorders

by promoting comprehensive diagnosis, treatment, research and education

Mission

Advance children with disability	• to the maximum level of independence and social integration according to their personal potential
Advance standard of care	• Improve treatment • Prevention • Early Diagnosis/ Awareness • Outcome
Research	• Clinical research and collaborations • Prevention, Early Diagnosis, Treatment and Outcome
Support Families	• "Family Centered" for caregivers of children with disabilities • Siblings
Educate	• Students, Residents in Pediatrics, Fellows in Neurodevelopment • Professionals: health and education • Community: Families of normally developing children and families in inclusion and in acceptance

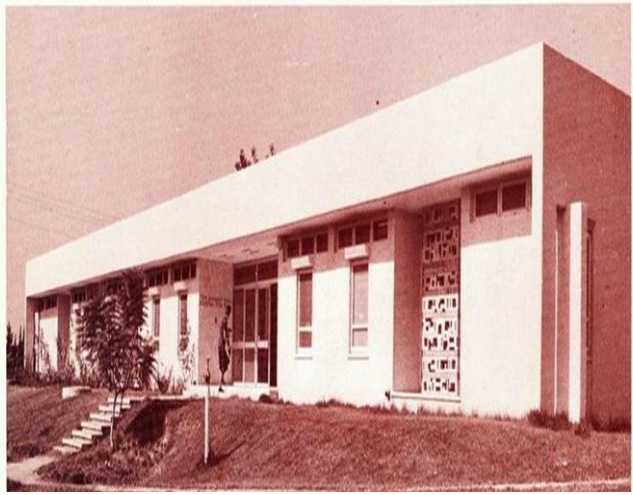
Magnitude and trends

- A marked increase in the incidence of developmental disabilities
  - up to 15-20% of the population
  - 50-70% of premature babies
  - 1:40-59 for Autism spectrum (ASD)
  - 15% for ADHD and learning disabilities
  - 0.2% for cerebral palsy
  - 1% for intellectual disability

- If 170000 births/ year in Israel:
  - 2500-3500 new ASD, 300 new CP, 1500 new ID yearly
  - 25000- 35000 minor LD, ADHD

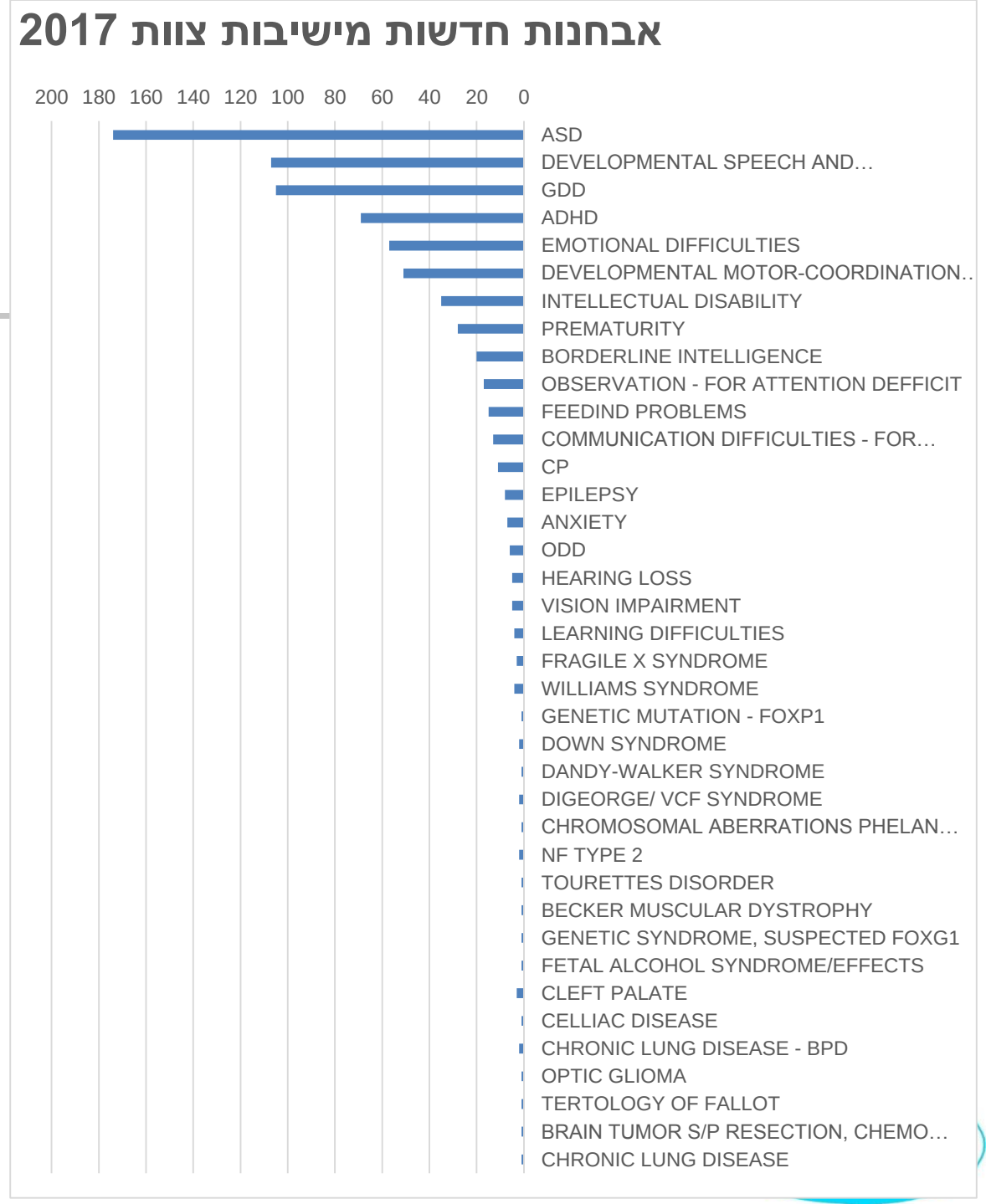
Road map

- 1960 - center for PKU, mental retardation, blind and disabled children
- 1984- Daycare center
- 1990- Prematurity research and F/U
- 2004- Tertiary national referral center for major disabilities
- 2006- Keshet Center for Autism and communication disorders
- 2010- Fragile X Clinic and Resource Center
- 2015- Afternoon programs, "Social Thinking"
- 2016- "Walk-in" clinic for babies at risk



Activities

- **Annual diagnosis/ F-U clinics:**
  - 1600 families
  - 90% of families more than 2 activities
- **”In- House” interventions**
  - 100 children
- **Population:**
  - Fetus, infants, children
  - Up to age 18 years



ASD Diagnoses- per year:

אבחנות asperger	אבחנת pdd	אבחנת asd	אבחנת autism	מספר מטופלים	סה"כ פניות מכון להתפתחות הילד על שם וויינברג	רב שנתי
3	207	383	387	1,405	12,160	2014
2	202	439	433	1,498	14,531	2015
2	186	15	487	1,418	16,137	2016
0	158	20	594	1,673	18,037	2017

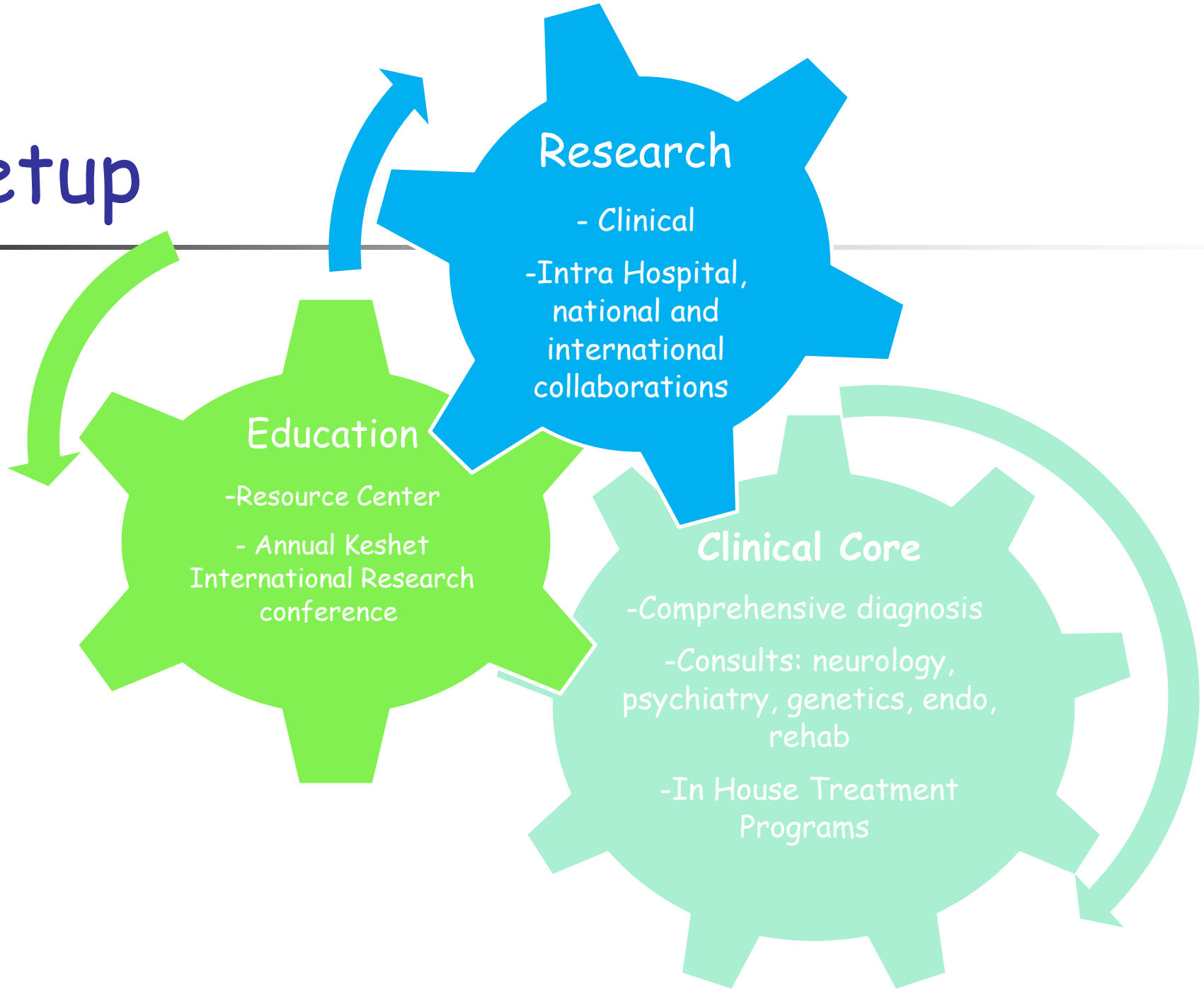
Staff

- 130 professionals

Disciplines

MD board certified in Pediatrics and Neurodevelopmental Disabilities
Administration
Social Workers
Special Education Teachers and aids
Developmental and Neurorehab
Psychologists
Speech and Language Therapists
Occupational therapists
Physical Therapists
Arts, Music, Hydrotherapy therapists
Medical clowns

Setup


Research
- Clinical
-Intra Hospital, national and international collaborations
Education
-Resource Center
- Annual Keshet International Research conference
Clinical Core
-Comprehensive diagnosis
-Consults: neurology, psychiatry, genetics, endo, rehab
-In House Treatment Programs

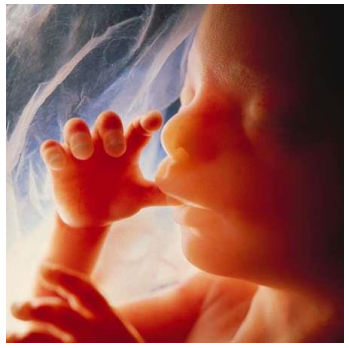
Main Research Topics

Associate: Shahar Shefer, PhD

Coordinator: Yonit Banet, MS

Autism Related Syndromes
Fragile X

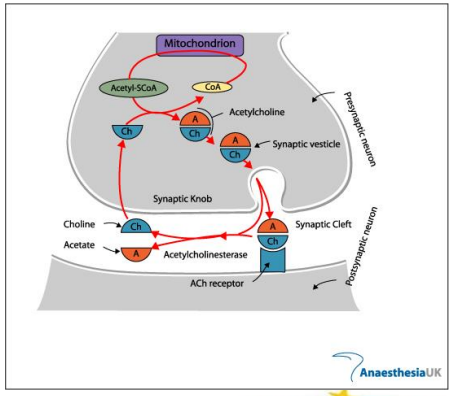
Fetal Studies



International Parents' Advocates

ASD biomarkers

Pharmacological trials



Prematurity

Early signs

Interventions

Keshet Database

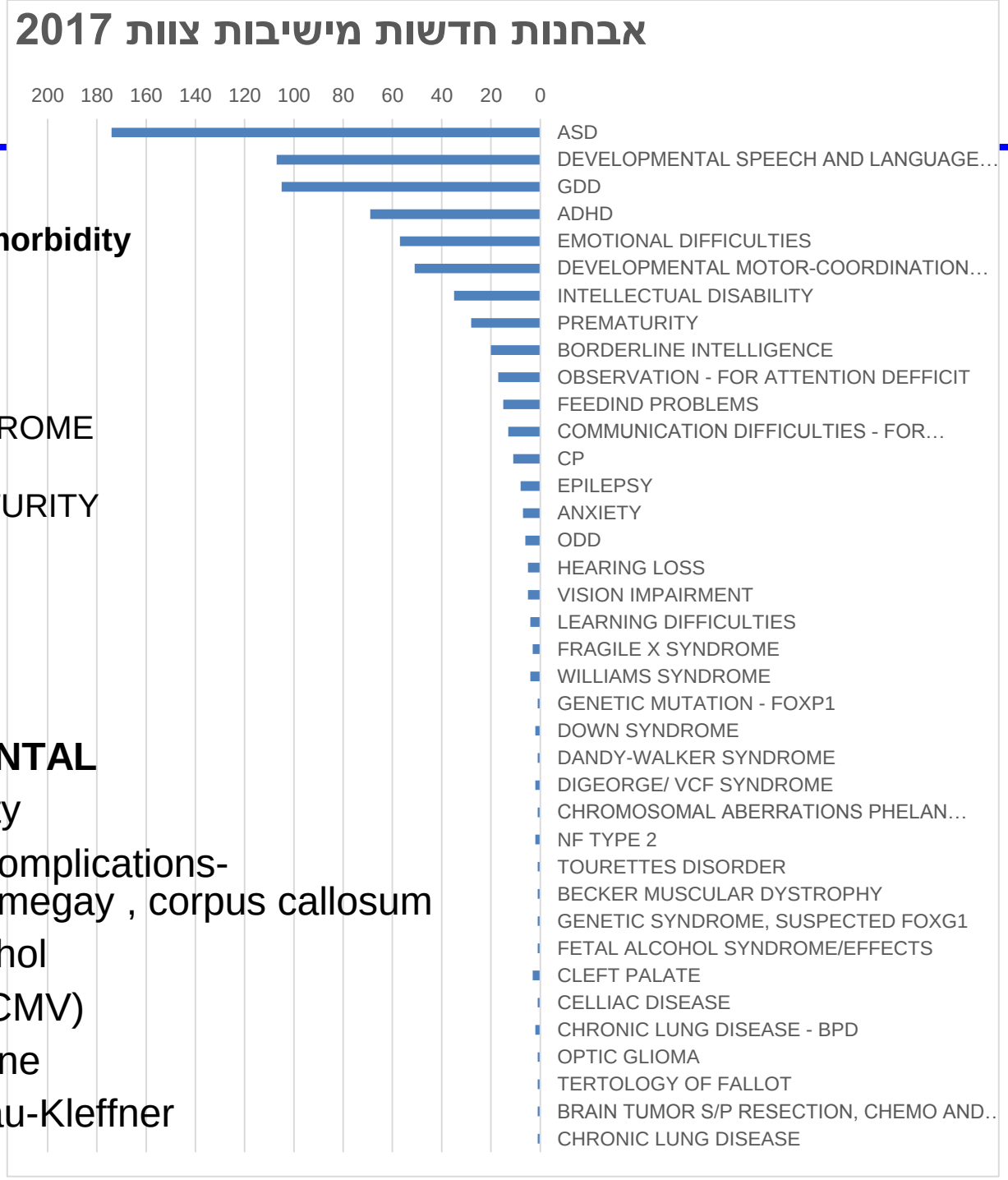
- All children admitted (10 years)
- F/U
  - Electronic charts (more than 10000 entries)
  - Structured- Demographics, Diagnoses
  - Semi structured- measures in each area of disability:
    - MD- perinatal, development, physical,
    - Developmental level/ IQ
      - Other neuropsych as needed
    - PT, OT, Speech measures
- ASD
  - About 2500 families
    - Clinically acquired data
    - ADOS- performed according to clinical indication
  - Layers of data depending on specific study:
    - Interventions- multiple points
    - Complications of Prematurity
    - Adolescents to Adults
    - Drug studies
    - Multipex families
    - Genetics- analysis: National, Sheba, Seaver Center

Autism Related Syndromes at Keshet

- **With ID/ GLOBAL DELAY**
  - **Fragile X*** (national epidem. **)**
  - Tuberous Sclerosis
  - PTEN
  - ANGELMAN SYND
  - Phelan-McDermid (SHANK3)
  - Cofin-Syris (chromatin folding gene)
  - Rett Syndrome*
  - CDKL5 (all Rett-like
  - CREATINE DEFFICIENCY SYNDROMES
- **With Epilepsy**
  - Dravet syn (SCN1A)
  - GRIN3A
  - GRIN1
- **With Psychiatric comorbidity**
  - VCF
  - Williams
  - FOXP1
  - FRAGILE X PREMUTATION
  - NF1

- **With Physical Comorbidity**
  - DD3X*
  - VCF
  - ADNP
  - DOWN SYNDROME (MOSAICISM)
    - PREMATURITY

- **ENIVIRONMENTAL**
  - Prematurity
  - Prenatal complications- ventriclulomegay , corpus callosum
  - Fetal Alcohol
  - TORCH (CMV)
  - Autoimmune
    - Landau-Kleffner



Clinical Heterogeneity of ASD

- Symptoms
- Development and trajectory
- Gender
- Specific Genetics vs. other etiologies

An etiologic classification of ASD

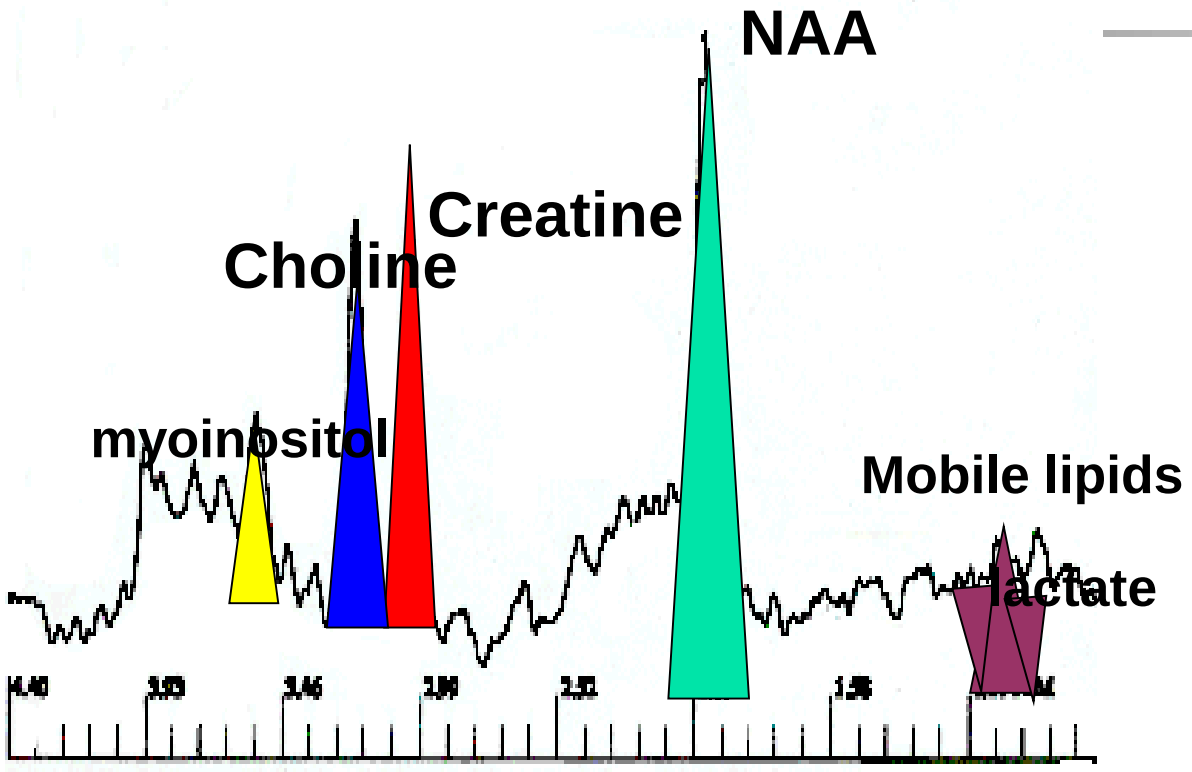
Gabis LV, Pomeroy J. Isr Med Assoc J. 2014 May;16(5):295-8

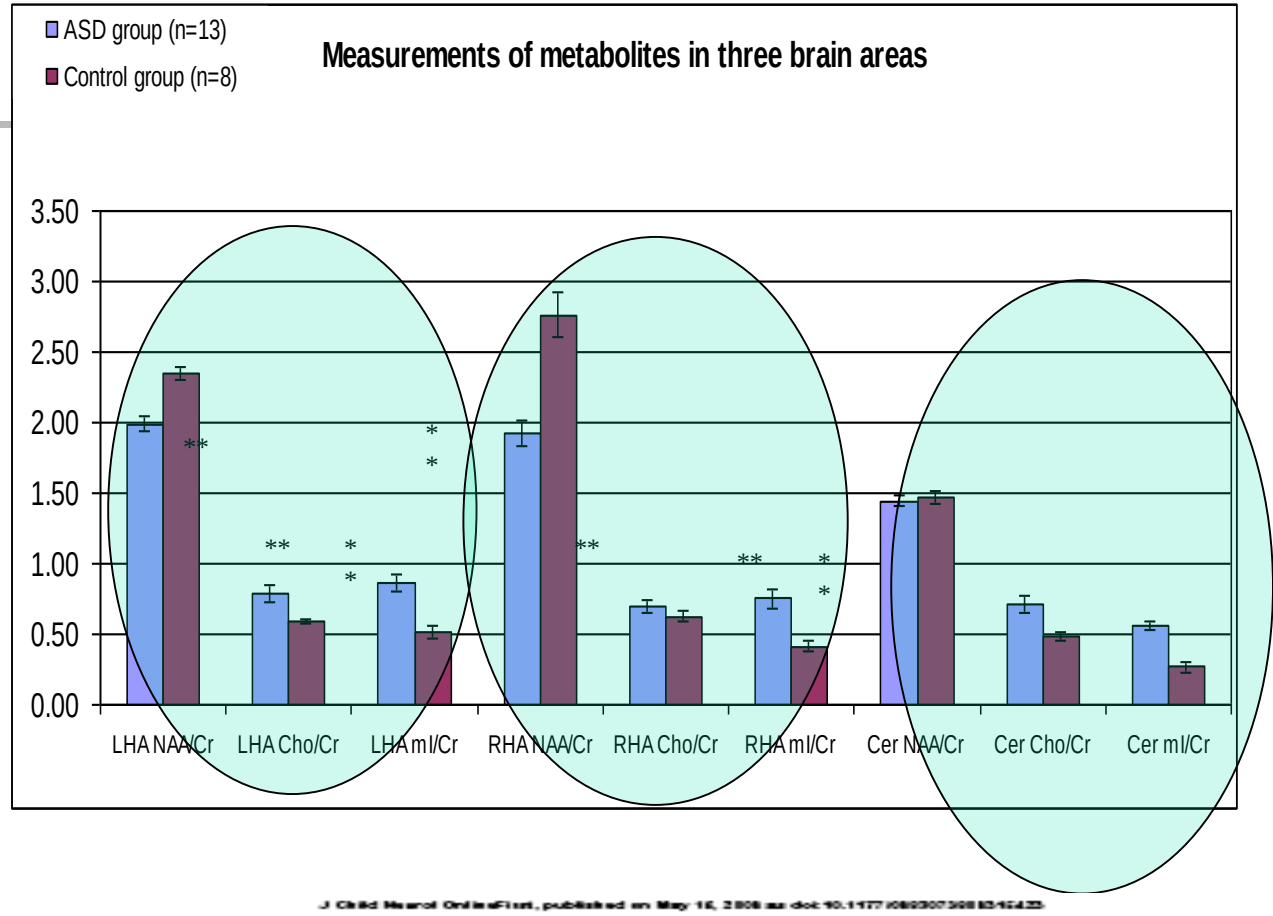
Comparable with epilepsy classification, we separated 436 PDD children to:

- Symptomatic - a diagnosed organic- neurologic disorder was identified
- Cryptogenic - an underlying etiology was suspected (mainly prematurity group)
  - such as abnormal perinatal course, severe infection involving the brain, dysmorphic features, or other severe associated findings
- Idiopathic- without evidence of other neurological disorders
- Groups we compared in terms of diagnosis, developmental and family history and comorbid symptoms

Valid differences between groups in terms of gender and severity
Prematurity more similar to idiopathic

Brain MRI and MR Spectroscopy of ASD children





: Ardon O, Procter M, Mao R, Longo N, Landau YE, Shilon-Hadass A, Gabis LV, Hoffmann C, Tzadok M, Heimer G, Sada S, Ben-Zeev B, Anikster Y. Creatine transporter deficiency: Novel mutations and functional studies. Mol Genet Metab Rep. 2016 Jun 30;8:20-3

Original Article

^{1}H-Magnetic Resonance Spectroscopy Markers of Cognitive and Language Ability in Clinical Subtypes of Autism Spectrum Disorders

Lidia Gabis, MD, Wei Huang, PhD, Allen Adrien, PhD, Carla DeVincent, PhD, Alina Tudorica, PhD, Yael Kemer-Baruch, MSc, Patricia Roche, DO, and John Pomeroy, MBBS, MRCPsych

Specific ASD related etiologies

Genetic

Genetic variations combined with environmental risk factors- ex. Paternal age

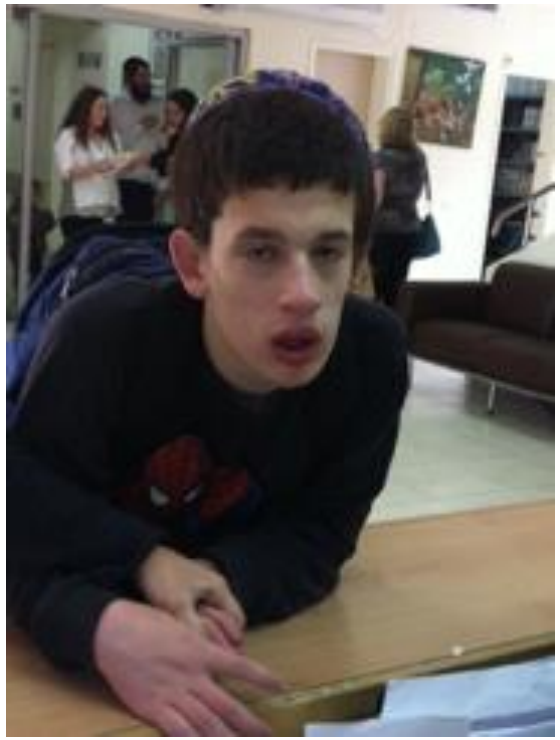
Paternal age in autism spectrum disorders and ADHD.

Gabis L1, Raz R, Kesner-Baruch Y Pediatr Neurol. 2010 Oct;43(4):300-2.

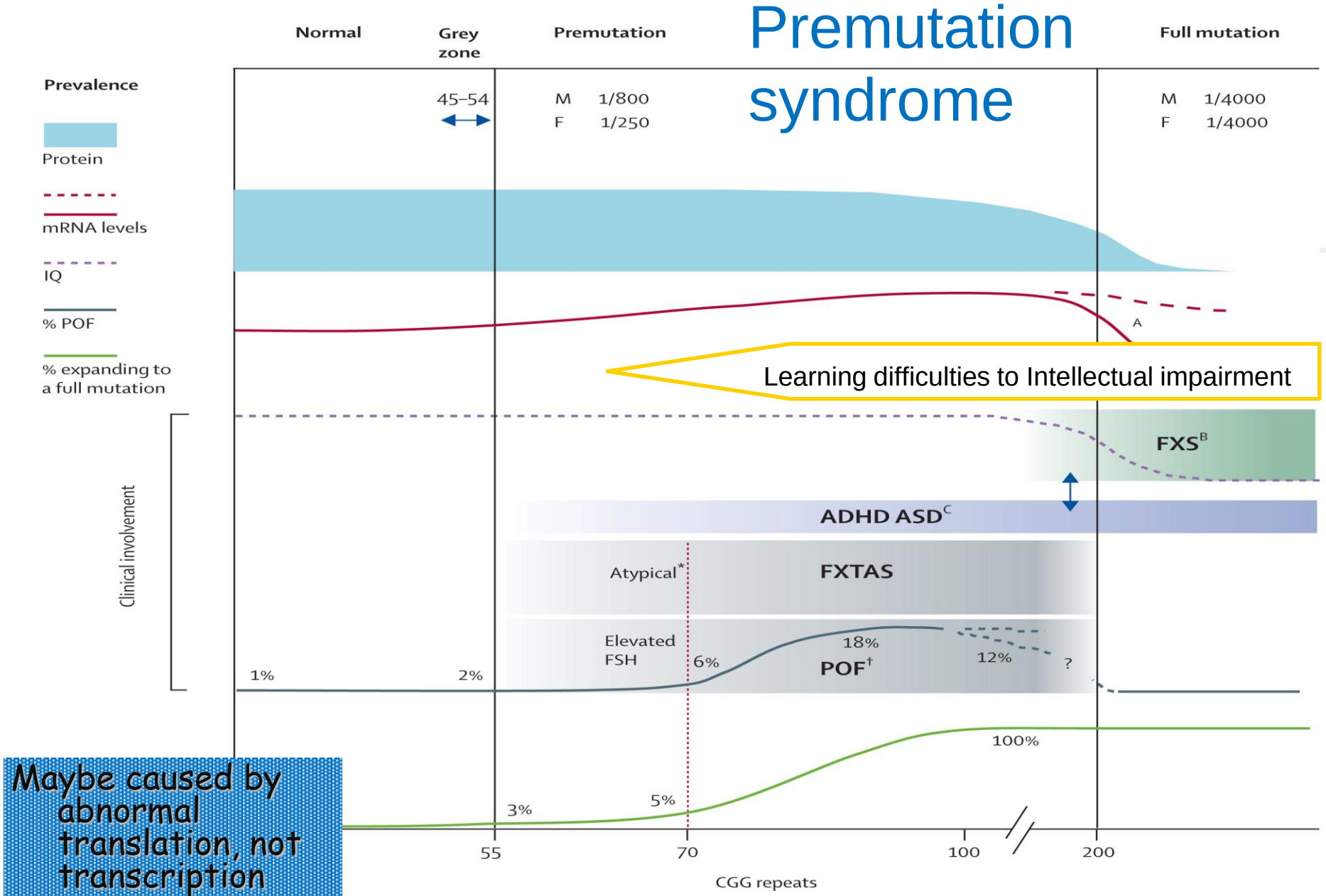
Environmental – ex. Prematurity, brain insult

FRAGILE X

PREMUTATION AND FULL MUTATION
EPIDEMIOLOGY AND TREATMENT



Premutation syndrome



Maybe caused by abnormal translation, not transcription

Too much mRNA can cause apoptosis

1. Gabis LV, Hochberg O, Leon Attia O, Banet-Levi Y, Topf D, Shefer S. Prolonged Time Lag to Final Diagnosis of Fragile X Syndrome. J Pediatr. 2018 Feb;193:217-221.e1. doi: 10.1016/j.jpeds.2017.10.008. Epub 2017 Dec 6.

2. Elizur S, Berkenstadt M, Ries-Levavi L, Gruber N, Pinhas-Hamiel O, Hassin-Baer S, Raas-Rothschild A, Raanani H, Cukierman-Yaffe T, Orvieto R, Cohen Y, Gabis L .]FMR1 PREMUTATION CARRIERS - ARE THEY REALLY ASYMPTOMATIC?]. Harefuah. 2018 Apr;157(4):241-244. Review. Hebrew

34: Gabis LV, Gruber N, Berkenstadt M, Shefer S, Attia OL, Mula D, Cohen Y, Elizur SE. Fragile X Premutation Carrier Epidemiology and Symptomatology in Israel-Results from a Tertiary Child Developmental Center. Cerebellum. 2016 Oct;15(5):595-8.

NON GENETIC ETIOLOGIES

Prematurity
Acquired brain abnormality
(prenatal, perinatal, postnatal)
related ASD

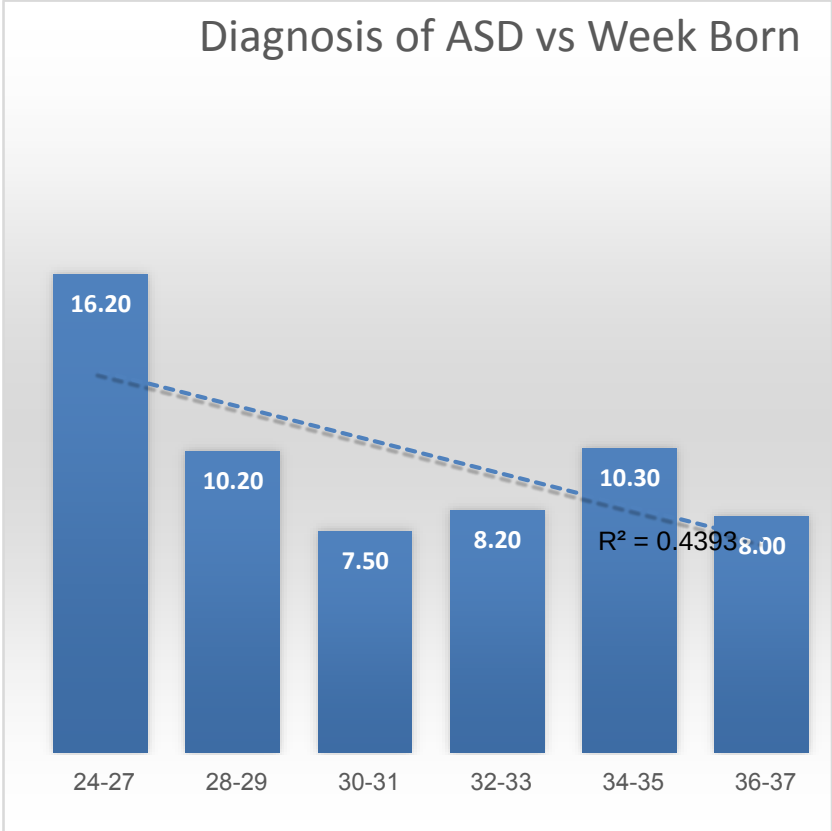
Specific ASD/ etiology
developmental related trajectories ?

Prematurity- initial findings- Keshet study

Leora Allen, MD student- analysis of our database:

- Cohort of 2011-2017 premature babies :
  - 416 children
  - 48.6% twins, 3.6% triplets
  - 30.8 weeks SD 3.3 weeks
  - 1427 gram SD of 557 grams

DIAGNOSIS	N	%
Global Developmental Delay	68	16.8 %
Cerebral Palsy	62	14.9 %
Autism Spectrum Disorder	47	10.3 %



Differences in Trajectory

- Each genetic mutation has a specific and unique trajectory in terms of medical problems, evolution of symptoms and lifelong prognosis
- Prematurity related ASD course is determined significantly by comorbidity and interventions

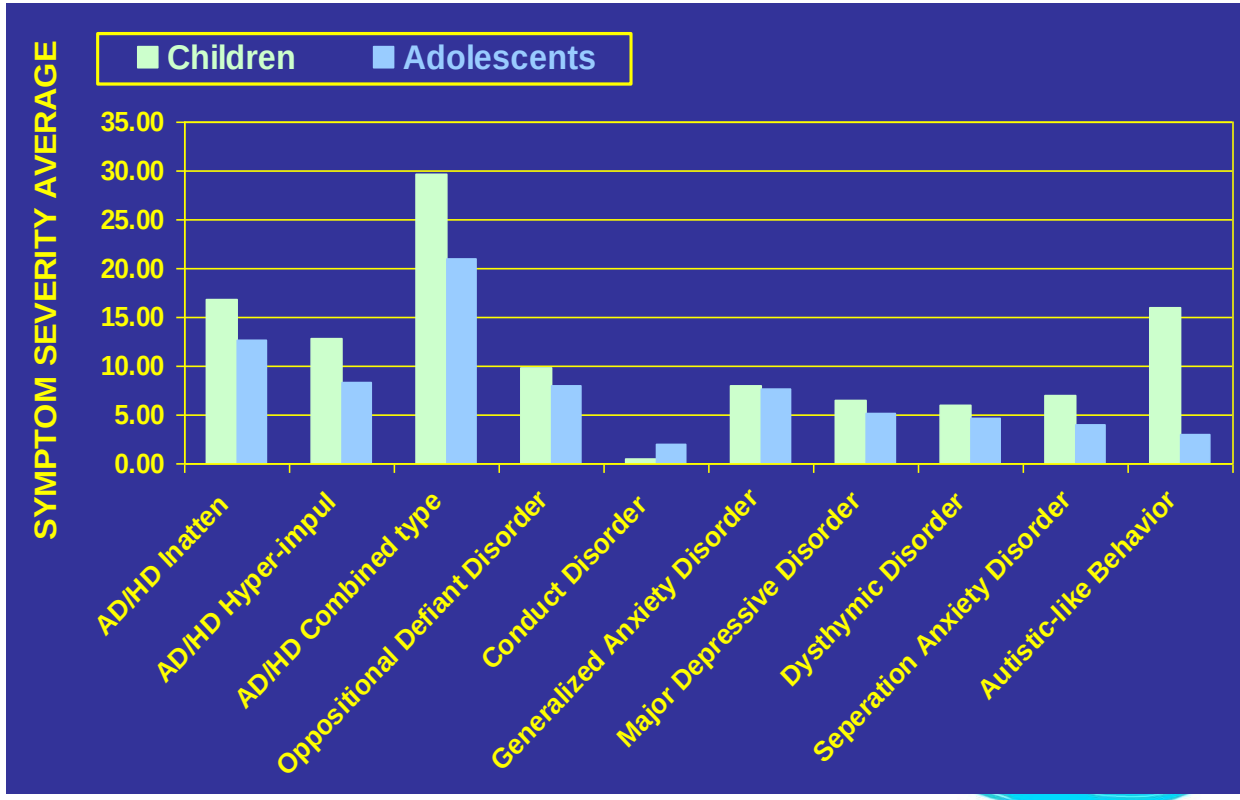
Original Article

Journal of Child Neurology
26(8) 940-948

DOI: 10.1177/0883073810395937
http://jcn.sagepub.com
SAGE

Psychiatric and Autistic Comorbidity in Fragile X Syndrome Across Ages

Lidia V. Gabis, MD[1], Yael Kesner Baruch, MSc[1], Ariela Jokel, PhD[1], and Raanan Raz, PhD



Very early signs / Hints

ABR latencies are significantly prolonged irrespective of their hearing thresholds

Abnormal responses -detected soon after birth

Prenatal sonographic measurements

- Mild Ventriculomegaly
- AGD as a measure of hormonal exposure

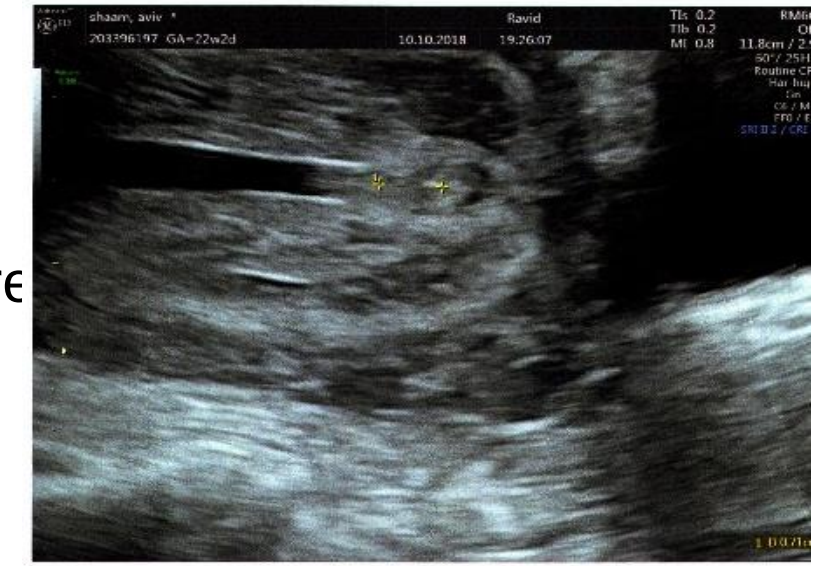
Early (age 6 months) deficits in empathic abilities

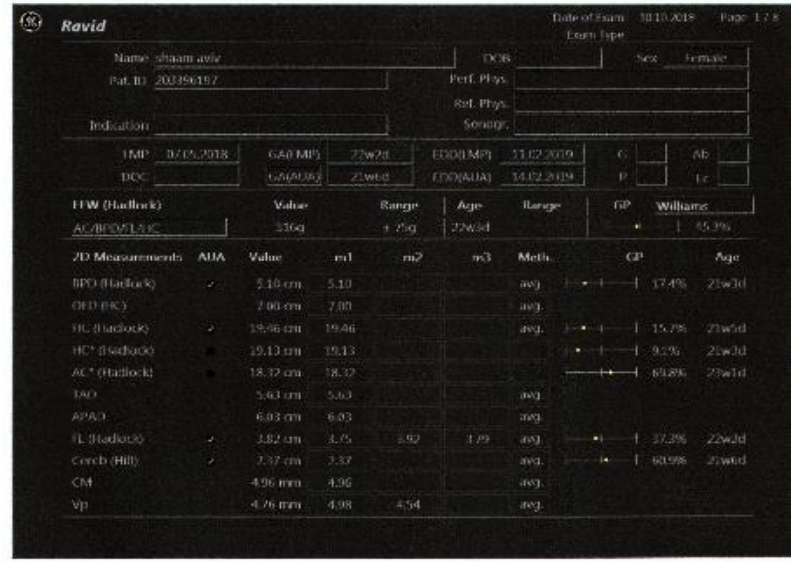
Genetics

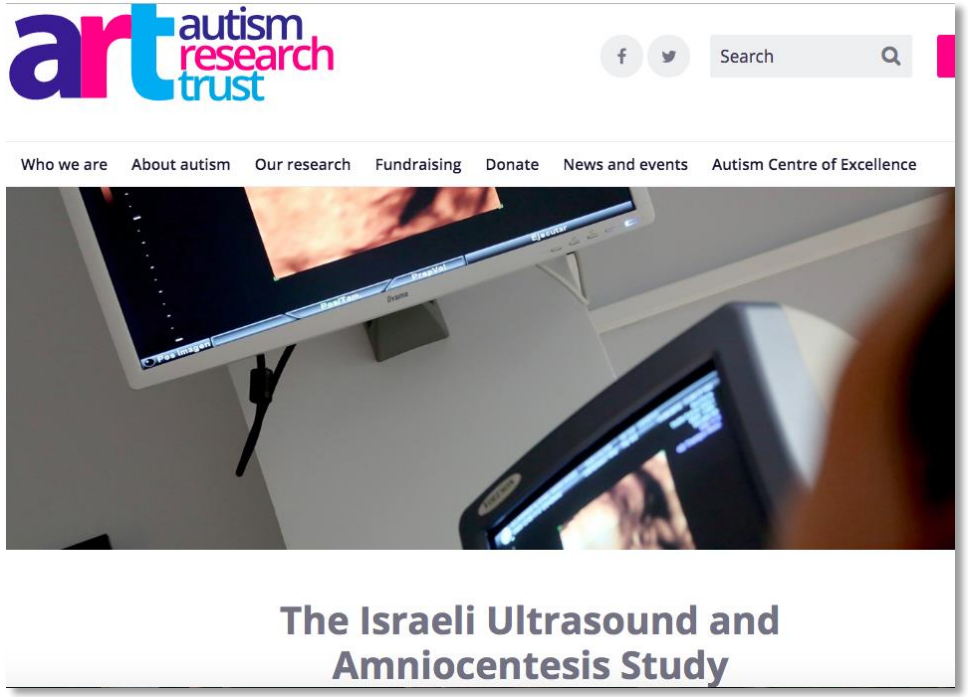
- Fragile X carrier
- WES – 80% of ASD cases have an abnormal finding

Antenatal Risk Indicators for Autism (ARIA)

- Males produce twice as much fetal sex steroids, these masculinize the brain, and exert epigenetic influence
- Ano- Genital Distance (AGD) as a marker of hormonal exposure- non-invasive index of prenatal sex steroid exposure
- Follow-up up to 18-24 months







Specific ASD related treatment response

Related to:

- Age
- Diagnosis/ syndrome
- Gender
- Comorbidity/ dual diagnosis

Combined Donepezil& Choline for ASD

Donepezil (Aricept) – an Acetyl Choline Esterase Inhibitor Drug

Acetyl Choline Esterase Inhibitor Drugs

Acetylcholine Esterase (AChE)

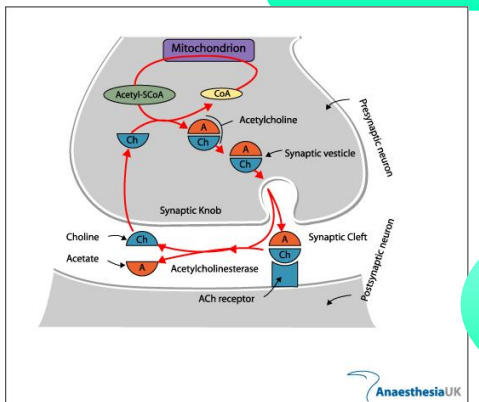
- Enzyme that breaks AcH into acetate and choline

Acetyl Choline

- produced in the presynaptic neuron and released into the neural cleft
- binds to
  - nicotinic receptor
  - muscarinic receptor

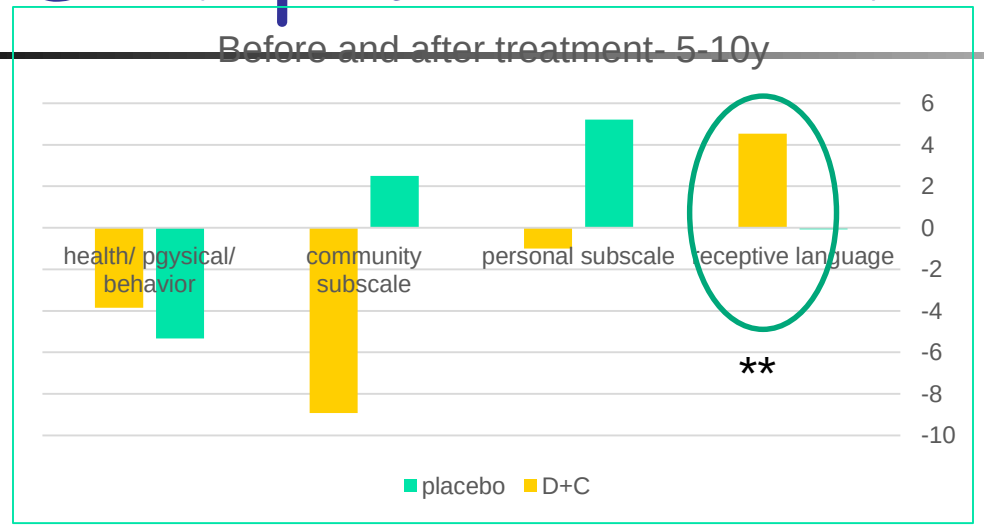
Choline

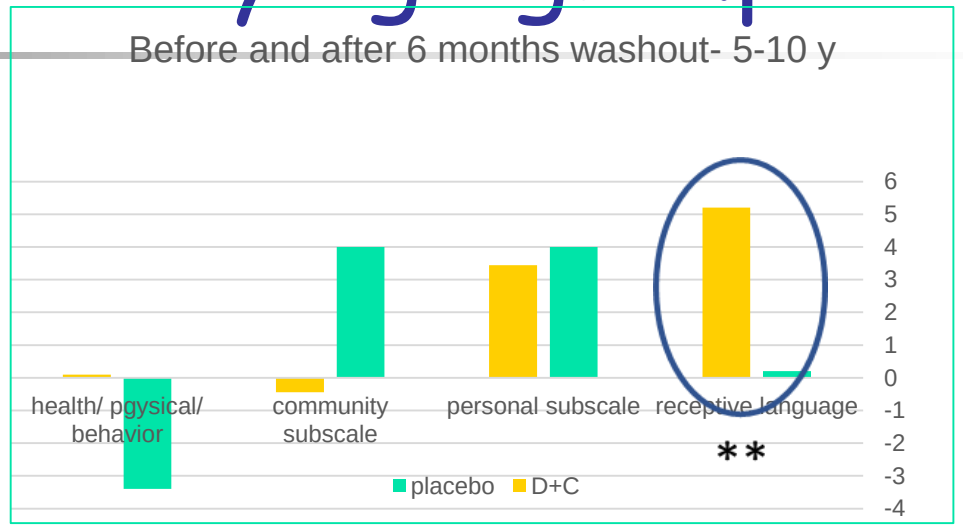
- Choline is reabsorbed into the presynaptic neuron, which recombines it with acetate to form Ach again

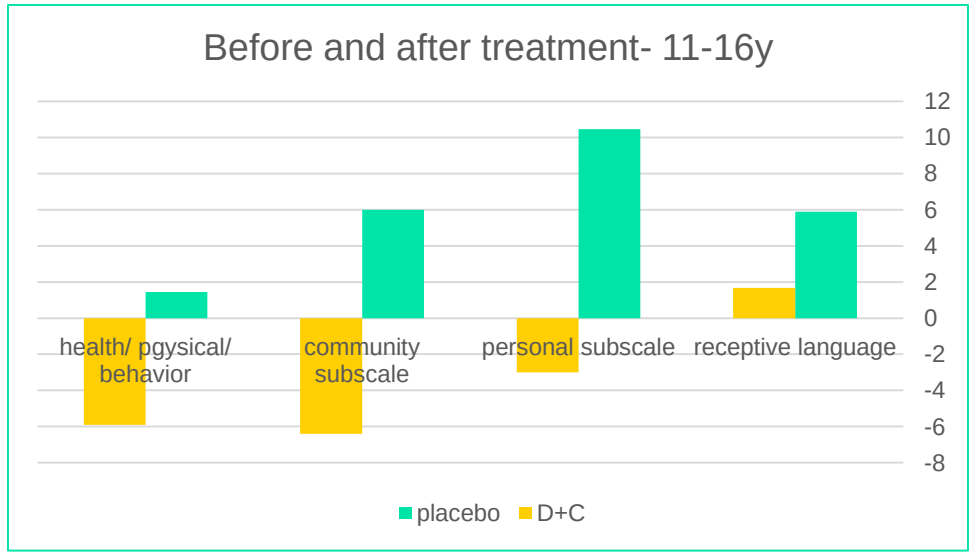


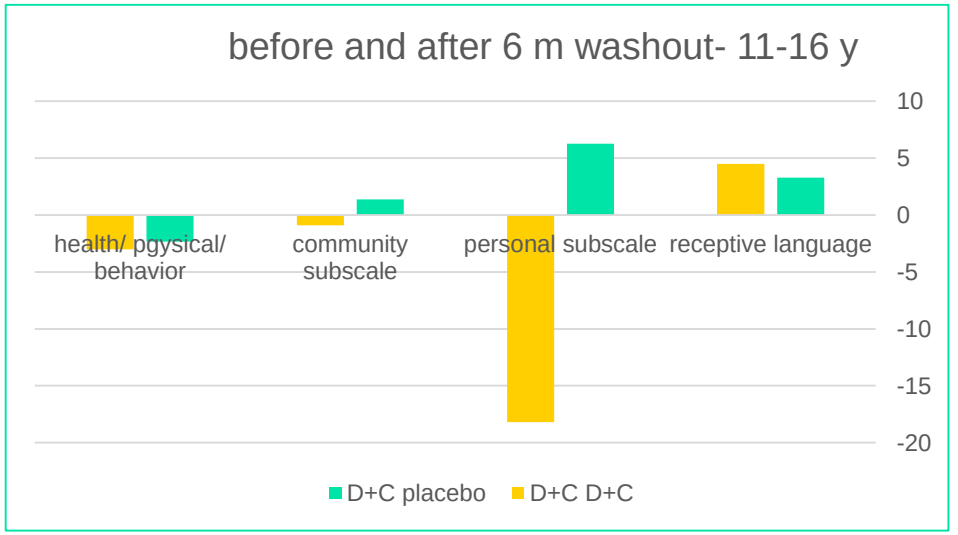
Donepezil + **Choline** = **More Acetyl Choline**

Donepezil+ Choline trial by age groups









Conclusions

"If you've met one person with autism, you've met one person with autism"
(Dr. Stephen Shore)

Shared features along with an individualized approach to the diagnosis and treatment

Thank you!