The Weinberg Child Development Center
and Keshet Center for Autism

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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:

<table>
<thead>
<tr>
<th>Year</th>
<th>Asperger</th>
<th>PDD</th>
<th>ASD</th>
<th>Autism</th>
<th>Total Referrals</th>
<th>Total Visits</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>207</td>
<td>383</td>
<td>387</td>
<td></td>
<td>1,405</td>
<td>12,160</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>202</td>
<td>439</td>
<td>433</td>
<td></td>
<td>1,498</td>
<td>14,531</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>186</td>
<td>15</td>
<td>487</td>
<td></td>
<td>1,418</td>
<td>16,137</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>158</td>
<td>20</td>
<td>594</td>
<td></td>
<td>1,673</td>
<td>18,037</td>
<td></td>
</tr>
</tbody>
</table>
Staff

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

• 130 professionals
Setup

Clinical Core
- Comprehensive diagnosis
- Consults: neurology, psychiatry, genetics, endo, rehab
- In House Treatment Programs

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

ASD biomarkers

Prematurity

International Parents’ Advocates

Pharmacological trials

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
    - Multiplex 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 DEFICIENCY 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 (MOASICISM)
  - PREMATURETY

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

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![Graph showing various conditions and their prevalence](image-url)
Clinical Heterogeneity of ASD

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

Measurements of metabolites in three brain areas

NAA
Creatine
Choline
myo-inositol
Mobile lipids
Lactate

LHA NAA/Cr
LHA Cho/Cr
LHA mI/Cr
RHA NAA/Cr
RHA Cho/Cr
RHA mI/Cr
Cer NAA/Cr
Cer Cho/Cr
Cer mI/Cr

ASD group (n=13)
Control group (n=8)

*: p<0.05
**: p<0.01

Specific ASD related etiologies

Genetic

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

Paternal age in autism spectrum disorders and ADHD.

Environmental - ex. Prematurity, brain insult
FRAGILE X

PREMUTATION AND FULL MUTATION
EPIDEMIOLOGY AND TREATMENT
Learning difficulties to Intellectual impairment

Maybe caused by abnormal translation, not transcription
Too much mRNA can cause apoptosis


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

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Developmental Delay</td>
<td>68</td>
<td>16.8%</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>62</td>
<td>14.9%</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>47</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Diagnosis of ASD vs Week Born

\[ R^2 = 0.43938.00 \]
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.
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
Donepezil (Aricept) – an Acetyl Choline Esterase Inhibitor Drug

**Acetyl Choline Esterase Inhibitor Drugs**

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

**Choline**
- Enzyme that breaks AcH into acetate and choline
- Choline is reabsorbed into the presynaptic neuron, which recombines it with acetate to form Ach again

**Combined Donepezil & Choline for ASD**

Donepezil + Choline = More Acetyl Choline
Donepezil+ Choline trial by age groups

Before and after treatment- 5-10y

Before and after 6 months washout- 5-10 y

Before and after treatment- 11-16y

Before and after 6 m washout- 11-16 y
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!