LONG TERM FOLLOW-UP IN DOWN SYNDROME

PROF. GÜLEN EDA UTİNE
HACETTEPE UNIVERSITY  FACULTY OF MEDICINE
DEPARTMENT OF PEDIATRICS
DEPARTMENT OF PEDIATRIC GENETICS

5. IRAN - TURKISH PEDIATRIC MEETING
16TH NOVEMBER 2018
LONG TERM FOLLOW-UP IN DOWN SYNDROME

- Down syndrome is the most common chromosomal disorder in population (1/800)
- Patients with Down syndrome are seen by physicians from many disciplines, owing to its…
  - High prevalence
  - Improved survival today
  - Many causes of morbidity involving various organ systems
  - Developmental delay and intellectual disability
Major Morbidity

- Growth retardation with prenatal onset, developmental delay and intellectual disability, various malformations and dysmorphic features.

- Major causes of morbidity are
  - Hearing loss (75%)
  - Obstructive sleep apnea (50-79%)
  - Otitis media (50-70%)
  - Ophthalmologic problems (60%)
  - Thyroid disease (4-18%)
  - Gastrointestinal atresia (12%)
  - Transient myeloproliferative disease (4-10%)
  - Hip dislocation (%6)
  - Neurologic dysfunction (1-13%)
  - Seizures (1-13%)
  - Celiac disease (5%)
  - Atlantoaxial instability (1-2%)
  - Leukemia (1%)
  - Autism (1%)
  - Hirschsprung disease (<1%)
All patients with Down syndrome are affected. Average IQ is 50 (range 30-70).

Hypotonia is evident in early postnatal period and it leads to delay in motor skills.

Cognitive disabilities are encountered later, may not be evident in all areas of development. Particularly social development may be relatively spared.

Education must be personalized considering the strong and weak aspects of individual patients in all developmental ages.
Nonverbal learning and memory are more preserved than verbal skills.

Receptive language is better preserved than expressive language.

Language skills gradually increase in childhood until when they get weaker in adolescence and there is obvious loss during adulthood.

On the contrary, nonverbal learning abilities progressively improve.

Attention, reaction time, and executive functions are affected during childhood and progressively deteriorate.

Children with Down syndrome are characteristically cheerful, positive and social. Psychopathology risk is lower than other patients with similar levels of intellectual disability (18-38%).

Adults may have emotional and behavioral problems as a result of neurodegeneration.
CARDIAC DISEASE

- Congenital heart disease (50%)
- Atrioventricular septal defect (AVSD) (x2000)
- Ventricular septal defect, atrial septal defect ve patent ductus arteriosus
- Valvular disease and endocarditis

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac malformations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular disease or endocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Check and evaluate for the following conditions at the specified time intervals.
ENDOCRINOLOGIC DYSFUNCTION

- Hypothyroidism
- Decreased bone mineral density
- Short stature
- Obesity
- Infertility
Lifelong prevalence of thyroid disease is 13-63%

- Transient hyperthyrotropinemia *
- Congenital hypothyroidism 1.5-6.1% (x28)
- Subclinical hypothyroidism 25.3-60%
  - It is usually recommended to start treatment when TSH >10 mU/L
- Autoimmune thyroid disease

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
Osteoporosis is:

- Increased bone resorption
- Decreased bone formation
- Increased parathyroid hormone levels
- Vitamin D deficiency is more frequent
  
  - Daily vitamin D supplementation may be recommended in doses higher than the routine dose of 400 IU.
**Puberty and Fertility.**

- Hypergonadotropic hypogonadism with increased FSH and LH
- Sertoli and Leydig cell dysfunction
- Timing of puberty is similar to normal controls

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puberty and reproductive issues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Short stature and obesity.

- Average height is shorter (1988)
- Average body weight is higher than normal peers (1988)
- Improvement in body weight in patients younger than 36 months and in height in patients 2-20 years-old (2015)
- Prevalence of obesity remained as high as before.

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puberty and reproductive issues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HEMATOLOGIC DISEASE

- Neutrophilia (80%) and thrombocytopenia (66%), polycythemia (34%) in neonates.
  - Usually improves in 1-3 weeks followed by macrocytosis and thrombocytosis.
- Transient myeloproliferative disease in 3-10%
- Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)
- Low counts of T and B lymphocytes (60-80%)

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>/ 2 mns</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
HEMATOLOGIC DISEASE

Transient myeloproliferative disease

- Characterised by myeloid blasts in peripheral blood.
- Usually appear around postnatal 7th day (1-65 days) and complete remission is achieved in 3 months in 60% → Acute leukemia in 10-30%
- Most common findings are hepatosplenomegaly, bleeding diathesis and effusions.
- Numerous megakaryoblasts in peripheral blood with variable severity of leukocytosis, thrombocytopenia or thrombocytosis.
- Hydrops fetalis and progressive hepatic fibrosis → mortality in 15-20%.

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. myeloproliferative disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Leukemia. x10-20

- Acute megakaryoblastic leukemia in 10-30% of patients, mostly after recovery of TMD.
- ALL is seen at around 4 years of age and AML at around 2 years.
- ALL = 1.7 x AML
- > 90% of ALL in Down syndrome is precursor B cell ALL.
- Except retinoblastoma and germ cell tumors, risks for developing solid tumors are low.
Recurrent Pulmonary Infections.
- Due to hypotonia, feeding problems, gastroesophageal reflux, chronic pulmonary disease, congenital cardiac malformations, rarely airway anomalies and IgG subclass or IgA deficiencies.

Obstructive Sleep Apnea. 31-79%
- It causes abnormalities in blood gases, disordered sleep, snoring and daytime sleepiness.
- Polysomnography is diagnostic.
- Midface hypoplasia, narrow nasopharyngeal passage, macroglossia, obesity, hypotonia, immaturity of central nervous system increase the risk.

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GASTROINTESTINAL DISEASE

- Gastrointestinal problems (75% of neonates); mostly due to feeding difficulties or developmental anomalies.
- Esophageal, duodenal, intestinal atresias and stenoses, imperforated anus and Hirschsprung disease are relatively common.
- Most common structural gastrointestinal defect is duodenal atresia.
- Adults may be prone to reflux, constipation, diarrhea and *Helicobacter pylori* infections.

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal or anal atresias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding problems and GE reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Celiac disease (gluten enteropathy) (0-18.6%)
- First line screening with tissue transglutaminase IgA (tTG IgA)
- Test for anti endomisium IgA (EMA IgA) levels, if only tTG IgA is weak positive.

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal or anal atresias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding problems and GE reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### EAR, NOSE AND THROAT

- Increased frequency of chronic ear infections and hearing loss.
- Hearing loss 38-78%
- Sensorineural type rare.
- Bilateral mild conduction type hearing loss *

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle ear problems</td>
<td></td>
<td>6 &amp;12 mns</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td></td>
<td>6 &amp;12 mns</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>
OPHTHALMOLOGIC PROBLEMS

Increased frequency of

- Refractive errors
- Strabismus and ambliopia
- Cataracts
- Lid anomalies, nasolacrimal canal obstructions
- Nystagmus, keratoconus, glaucoma,
- Iris hypoplasia, abnormalities of optic disk and retina

<table>
<thead>
<tr>
<th>Check and evaluate for...</th>
<th>First month</th>
<th>2-12 months</th>
<th>2-5 years</th>
<th>6-12 years</th>
<th>13-21 years</th>
<th>&gt;21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologic problems</td>
<td>6 &amp;12 mns</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
NEUROLOGIC DISEASE

Increased risk for

- Cervical spinal instability
- Seizures
- Moyamoya disease
- Strokes
Cervical instability 10-30%

Atlantoaxial instability: Hypermobility of the joint between atlas and axis.

Increased anterior atlanto-odontoid space detected in direct radiographs.

Upper limit of normal by AAP 4.5 mm (1980)

< 15 years 4 mm and > 15 years 3 mm
- Epilepsy 0-13% (mean 5.5%)
- In infancy in 40%: infantile spasm and tonic-clonic seizures
- In the 3rd decade in another 40%: partial epilepsy and tonic-clonic seizures
Moyamoya disease and cerebrovascular events (x26)

Alzheimer disease and dementia (x2-3) after 4th decade

Early period findings: Short term memory, learning abilities and fluency in speech are affected.

Middle period findings: Long-term memory and behaviour are affected.

Late period findings: Complete dependency and loss of basic functions like movement and feeding, severe psychiatric problems
LONG-TERM FOLLOW-UP IN DOWN SYNDROME
NEONATAL PERIOD

- Prenatal and antenatal history taking and pedigree drawing
- Medical history should include feeding issues and activity
- Physical examination; Down syndrome stigmata, anthropometric measurements, congenital anomalies, muscular tonus.
- Parental karyotyping if recurrence of the condition or previous history of recurrent abortions
- Karyotyping; even if there was prenatal diagnosis from fetal samples
- Cardiac evaluation and echocardiography
- Screening for hearing and for presence of red reflex
NEONATAL PERIOD

- History taking and physical examination for gastrointestinal atresias, airway anomalies, sleep problems.
- Complete blood count for leukomoid reaction and transient myeloproliferative disease.
- TSH and free T4 testing for congenital hypothyroidism.

Inform parents on
- Feeding problems
- Respiratory infections
- Cervical instability – posture, positioning, head movements and car seats
- Developmental weaknesses and strengths of children with Down syndrome
INFANCY

- Antropometric measurements and determining growth rate comparing to Down syndrome-specific growth curves in every visit.
- Hearing test at 6 months of age.
- History taking for obstructive sleep apnea and sleep studies on suspicion.
- Inform parents on neutral positioning of cervical vertebrae and on myelopathy signs.
- Test thyroid functions at 6 and 12 months and then at yearly intervals.
- Complete blood count at 1st birthday and then yearly.
- Vaccination according to national immunization program unless there are any contrindications.
EARLY CHILDHOOD

- Evaluation of growth and development
- Test for hearing loss yearly
- Yearly ophthalmologic examination for ambliopia and refractive errors.
- Test thyroid functions and complete blood count yearly
- Test for Celiac disease if there are consistent signs and symptoms.
- Inform parents on neutral positioning of cervical vertebrae and on myelopathy signs
- Adequate evaluation of cervical vertebrae is possible after 3 years of age when vertebral myelinization and epiphyseal development are achieved.
EARLY CHILDHOOD

- Question on symptoms of obstructive sleep apnea
- Echocardiography to follow pulmonary hypertension in patients with congenital cardiac anomalies.
- Consider presence of any behavioural problems like autism or ADHD.
- Yearly vaccination for influenza
- 23-valent pneumococcus vaccine for those > 2 years with chronic cardiac and pulmonary disease.
- Inform families on delayed tooth eruption or missing teeth.
LATE CHILDHOOD

- In every visit, evaluate growth and development.
- Dietary recommendations to prevent obesity.
- Control hearing yearly and vision every two years.
- Yearly control of thyroid functions and blood count.
- Question presence of Celiac disease symptoms in every visit.
- Inform parents and the adolescent on myelopathy symptoms, as well as obstructive sleep apnea and pubertal issues.
ADOLESCENCE

- In every visit, evaluate growth and development.
- Dietary recommendations to prevent obesity.
- Yearly control of hearing and valvular cardiac disease.
- Yearly control of thyroid functions and blood count.
- Control vision every three years.
- Question presence of Celiac disease symptoms in every visit.
- Inform parents and the adolescent on myelopathy symptoms, as well as obstructive sleep apnea and dementia.
Besides all medical issues, **psychological needs** of the patients and families should be monitored.

- **Social support groups** should be introduced to the family.
- **Genetic counseling and education** should be provided to the family as frequently as needed.
THANK YOU FOR YOUR ATTENTION…