LONG TERM FOLLOW-UP IN DOWN SYNDROME

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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%)

DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

- All patients with Down sydrome 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.

DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

- 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

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Cardiac malformations						
Congestive heart failure						
Valvular disease or endocarditis						

ENDOCRINOLOGIC DYSFUNCTION

- Hypothyroidism
- Decreased bone mineral density
- Short stature
- Obesity
- Infertility

ENDOCRINOLOGIC DYSFUNCTION

- Lifelong prevalence of thyroid disease is 13-63%
  - Transient hyperthyrotropinemia *
  - Congenital hypothyroidism 1.5-6.1% (x28)
  - Subclinic hypothyroidism 25.3-60%
    - It is usually recommended to start treatment when TSH >10 mU/L
  - Autoimmune thyroid disease

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Hypothyroidism		6 &12 mns	Y	Y	Y	Y

ENDOCRINOLOGIC DYSFUNCTION

Osteoporosis.

- 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.

ENDOCRINOLOGIC DYSFUNCTION

Puberty and Fertility.

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

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Puberty and reproductive issues						

ENDOCRINOLOGIC DYSFUNCTION

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.

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Puberty and reproductive issues						

HEMATOLOGIC DISEASE

- Neutrophilia (80%) and thrombocytopenia (66%), polycytemia (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%)

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Complete blood count		/ 2 mns	Y	Y	Y	Y

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%.

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
T. myeloproliferative disease						

HEMATOLOGIC DISEASE

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.

RESPIRATORY DISEASE

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.

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Respiratory infections						
Obstructive sleep apnea						

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.

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Duodenal or anal atresias						
Feeding problems and GE reflux						
Constipation						

GASTROINTESTINAL DISEASE

- 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.

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Duodenal or anal atresias						
Feeding problems and GE reflux						
Constipation						
Celiac disease						

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 *

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Middle ear problems		6 &12 mns	Y	Y	Y	
Hearing loss		6 &12 mns	Y	Y	Y	

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

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Ophthalmologic problems		6 &12 mns	Y	Y	Y	

NEUROLOGIC DISEASE

Increased risk for

- Cervical spinal instability
- Seizures
- Moyamoya disease
- Strokes

NEUROLOGIC DISEASE

- 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

Check and evaluate for…	First month	2-12 months	2-5 years	6-12 years	13-21 years	>21 years
Cervical vertebral position						
Myelopathy signs and symptoms						

NEUROLOGIC DISEASE

- 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

NEUROLOGIC DISEASE

- 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 adolecent 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 adolecent 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…