THE CHROMOSOME 18 REGISTRY & RESEARCH SOCIETY

SCHOOL OF MEDICINE UT HEALTH SCIENCE CENTER THE CHROMOSOME 18 CLINICAL RESEARCH CENTER

Distal 18q-
Treatment and Surveillance

ICD-10 = Q99.9 or Q93.89

These recommendations are inclusive of the entire population of people with Distal 18q deletions even though each person has a unique deletion. Therefore each person's deletion could have different genes that are hemizygous. The specific hemizygous genes for an individual patient will dictate the probability of particular phenotypes. Guidance for creating an individualized plan for evaluation and management based on the person's specific deletion can be found in the next section. However, the information in this document encompasses the global distal 18q- evaluation and management plan.

Distal 18q- (18q21.1–q23)
An interstitial or terminal deletion between 46.7 Mb and the end of the chromosome at 78,077,248 bp*; a region that includes 103 genes.

*hg 19 nucleotide scale

Potential conditions in a neonate

- Structural
  - Hernias (inguinal, umbilical)
  - Cryptorchidism, chordee, and hypospadias in >50% of males
  - Palate abnormality
- Functional
  - Respiratory and feeding difficulties
  - Hypotonia
- Biochemical
  - Jaundice

Initial evaluations after diagnosis

- Cardiology evaluation -29% have cardiac defects
- Orthopedic exam -74% with foot defects
- Otolaryngology including audiology evaluation - >50% with hearing loss
- Thyroid levels - 15% with hypothyroidism
- Renal ultrasound -18% with reflux or malformations
- Ophthalmology exam- 72% with optic problems
- Genitourinary
- Neurology / cerebral MRI evaluation
- Pediatric anesthesiology if surgery is indicated

Referrals to

- Appropriate subspecialist as indicated by initial evaluations
- Genetics Follow-up
  - Parents genotyped for balanced rearrangements
- Early intervention/developmental services
- The Chromosome 18 Registry & Research Society
- The Chromosome 18 Clinical Research Center

Closely monitor and manage

- Failure to thrive/ growth failure
  - Weight gain
  - Linear growth
- Sinus/ ear infections
- Genitourinary
  - Reflux
- Immunology/Rheumatology
  - IgA deficiency
  - Atopic disorders
  - Arthritis
  - Other autoimmune conditions
- Neurology
  - Seizure disorder
  - Intention tremors
  - Hypononia
- Orthopedics
  - Scoliosis or kyphosis
- Development
  - Milestones
  - School performance
- Behavioral/ mood changes

Annual Screenings

- Thyroid
- Vision
- Hearing

Updated 2016

Potential conditions in a neonate:

- Structural
  - Hernias (inguinal, umbilical)
  - Cryptorchidism, chordee, and hypospadias in >50% of males
  - Palate abnormality
    - >40% with abnormalities, including: high, narrow, wide, bifid uvula, submucus cleft, cleft palate alone or cleft lip and palate.
- Functional
  - Respiratory and feeding difficulties
  - Hypotonia
- Biochemical
  - Jaundice

Initial Evaluations:

- **Cardiology**
  - 29% had a cardiac abnormality and of those
    - 43% has an ASD or VSD
    - 38% had pulmonic stenosis.
    - No definitive region of the chromosome is associated with CHD implying there is more than one gene on 18q impacting the development of the heart.
  - The actual incidence of heart defects may be higher as ultrasound and ECG evaluations have not been consistently been performed on all affected individuals.
- **Orthopedics**
  - 74% have a foot deformation:
    - Clubfoot, vertical talus, metatarsus adductus, pes planus or pes cavus.
  - The critical region for vertical talus is between 73 and 75.5 Mb
  - Scoliosis or kyphosis –possibly related to hypotonia
- **Audiology**
  - Within the total population of people with 18q deletions:
    - 49.5% had conductive hearing loss
    - 28% had sensorineural hearing loss
  - 78% of individuals whose deletion includes the TSHZ1 gene at 73 Mb have ear canal stenosis/atresia often leading to conductive hearing loss.
- **Otolaryngology**
  - Aural atresia/stenosis common
  - Middle ear effusion common
  - Normal pinnae
- **Thyroid levels**
  - 15% have developed thyroid dysfunction, often at <10 years of age
    - Antibody positive hypothyroidism is the most common, by far
    - Hyperthyroidism has been reported

- **Renal ultrasound**
  - 25% with a deletion including the region from 73.1 – 75.1 Mb have a renal malformation
- **Ophthalmology**
  - Strabismus 40%, nystagmus 29 % , myopia 35%
  - Nystagmus critical region is from 72.6-75.1 Mb
- **Genitourinary**
  - Infants with genital abnormalities should be evaluated by a pediatric urologist in the first month of life. Treatment should be initiated on the same timetable as would be used for typical infants
- **Neurology**
  - MRI findings:
    - 97% have CNS dysmyelination (i.e. delayed myelination), although 100 % of those individuals missing a region between 74.3 and 73.5 Mb have dysmyelination, it is not a progressive degenerative condition.
    - 47% Paranasal Sinus Disease (Maxillary or Ethmoid sinusitis)
    - 26% Mastoiditis
    - 34% Enlargement of Ventricular System (possibly related to brain hypoplasia; corpus callosum hypoplasia or white matter loss)
    - 32% Delayed maturation of Occipital lobes
    - 14% Brain abnormal signals
    - 14% Corpus Callosum abnormalities (thinner, smaller, partial or total agenesis)
    - 14% Iron deposition
    - 6% Pituitary gland abnormalities
    - 3%Virchow-Robin Perivascular spaces
    - 2.5% Deep white matter ischemia
    - 1.7% Periventricular Leukomalacia
    - 1.7% Dandy-Walker variant
    - 1.7% Chiari I malformation

Referrals to:

- **Genetics Follow-up**
  - Genetics follow-up may be necessary if parental chromosomes have not been evaluated to rule out inherited rearrangement. 3% of the participants in our study have a parent with a balanced rearrangement. Even if no other children are planned, if one parent has a balanced rearrangement then their other children or the siblings of that parent are a risk for having the same rearrangement and consequently have a very high risk of passing on an unbalanced chromosome compliment.

  - A genetics follow-up may also be indicated if the original diagnosis was performed using cytogenetic techniques or low resolution microarray technology. A high resolution SNP or CGH microarray can determine exactly which genes are involved in the deletion. This information will become increasingly important over time as gene-specific interventions are developed.

- **Early intervention/developmental services**
  - All children with chromosome 18 abnormalities are at significant risk for developmental delay. Prompt referral to a program the includes physical, occupational and speech therapy is important in order maximize their development.
  - 100% have developmental delay
    - 91% have speech problems
    - 32% articulation
    - 17% non-verbal
    - 18% delayed speech development
    - 7% apraxia
    - 26% not-specified
  - 79% have hypotonia
  - 68% have an intellectual disability

- **Referral to Chromosome 18 Registry & Research Society**
  - The Chromosome 18 Registry is a parent support organization that provides family members with the opportunity to meet and learn from those who have gone before them. These are complex conditions to manage even in the least affected children making the establishment of a network of support a crucial component for maximizing the affected child's potential. The Registry has annual national and international conferences, regional get-togethers and social media outlets, all with programs for parents, siblings and affected adults. The Registry works closely with and financially supports the Chromosome 18 Clinical Research Center. (www.chromosome18.org)

- **Referral to the Chromosome 18 Clinical Research Center**
  - The goal of the Chromosome 18 Clinical Research Center is to make the chromosome 18 abnormalities the first treatable chromosome abnormalities. Anyone with any chromosome 18 abnormality is eligible to enroll and encouraged to enroll. Once enrolled, participants have the opportunity to be involved in longitudinal studies of developmental progress, and when available, other studies that could include surveys or treatment trials. Families enrolled in the Research Center will also be the first to know new information about the conditions when it becomes available. Enrollment is a key part of proactive clinical management (www.pediatrics.uthscsa.edu/centers/chromosome18)

Closely monitor and manage:

- **Failure to thrive/ growth failure**
  - Weight gain

    Due to their hypotonia, suckling or feeding may be more difficult for the child. In addition, many affected children have gastroesophogeal reflux, which increases not only their risk for aspiration, but also for pain, discomfort or emesis after feeding. Children <3 years who are failing to meet expected rates of weight gain, they should be evaluated for reflux and potentially for placement of a feeding tube
  - Linear growth
    - 64% are short (<2SD) and the majority are growth hormone deficient
    - IGF1 and IGFBP3 are not definitive tests for GH deficiency in these children
    - Children that are failing to grow linearly (length or height) at expected rates for age and sex should be tested using growth hormone stimulation (provocative) testing. This testing is typical done by a pediatric endocrinologist.
    - All treated individuals responded to GH replacement therapy (0.3 mg/kg/week) with rates of growth comparable to children with classical isolated GH deficiency

- **Sinus/ ear infections**
  - Due to abnormal midface architecture, affected children are at increased risk of otitis media and sinusitis. Many have atretic or stenotic ear canals, making visual inspection difficult. In addition, they often do not present with the typical signs of a sinus or ear infection. Therefore there should be a high index of suspicion of sinus infections when there are behavioral changes which then dictate a longer duration of antibiotic treatment; recommendations are 10 days for otitis media, and 14 days for sinusitis.

- **Genitourinary:**
  - Renal anomalies and ureteral reflux are more frequent in children with distal 18q. Affected children should have a renal ultrasound at the time of initial evaluation and referral to an pediatric nephrologist or urologist if abnormalities are noted. Affected children who have recurrent urinary track or kidney infections should have urodynamic studies

- **Immunology/Rheumatology:**
  - Immunodeficiency – 18%
    - IgA deficiency – most common
      - The exact gene responsible has not been identified but it is known to be within a region between 62.5 and 76.9 Mb (Linnankivi et al., 2006). Only persons with a deletion including this region have this risk for this condition.
  - Hypersensitivity
    - Asthma, Allergic rhinitis, Food Allergy, Atopic Dermatitis (Eczema) – 41%
  - Autoimmune conditions – 41%
    - Tyroid disease -16%
    - Skin /hair condiotns -12%
    - Arthritis – 4%
    - Other conditions – Lupus, Sjogren's, Diabetes

Closely monitor and manage

- **Neurology**
  - 96% have decreased reflexes
  - 79% have hypotonia
  - 68% have gait abnormalities
  - 62% have tremors
  - 38% have a seizure disorder. Average age at onset = 5 yrs., range = neonate to 27 yrs.
    - The seizures are treated with anticonvulsants medications. Sometimes more than one medication is needed to control seizures. Usually , but not always, the seizures are under control while on medications. 34 (67%) out of 51 diagnosed with seizures had no seizure relapse for >12 month. The most common medication used was Valproic acid (Depakene or Depakote) followed by Carbamazepine (Tegretol); Levatiracetam (Keppra); Oxcarbazepine (Trileptal).

- **Orthopedics**
  - 7% develop Scoliosis or kyphosis

- **Development**
  - There are two broad groups of people with distal 18q deletions; those with deletions that include the *TCF4* gene and those whose deletion does not include *TCF4*. People whose distal 18q deletion does not include *TCF4* have IQ scores from above normal to mild intellectual disability. Those whose deletion includes *TCF4* generally do not develop skills beyond that of a typical 18 month old.
  - Milestones
    - For those children whose deletion does not include the *TCF4* gene, milestones are delayed but they are achieved. (Cody et al., 2013).
  - School performance

- **Behavioral/ mood changes**
  - 73% have a lifetime risk of a mood disorder
  - 64% have an anxiety disorder
  - 63% have at least some autistic features
  - 37% with an ADHD diagnosis
  - 36% with other externalizing disorders

- **Annual Screenings**
  - Thyroid hormone and TSH
  - Vision
  - Hearing
    - 70% have hearing loss – Conductive, sensorineural or mixed

- **Early Death**
  - In the group with deletions that include the *TCF4* gene, 25% died. The ages at death were between 22 months and 32 years, primarily due to complications from aspiration.
  - In the group whose deletion did not include the *TCF4* gene, only 1.7% have died. The age at death was between 12 and 32 years and was sudden and unexpected in all cases.

- There is no reason to think that they are at increased risk for surgical or anesthesia complications although they may need increased monitoring due to hypotonia.

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