IN BRIEF

Trisomy 21

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Trisomy 21 (T21), or Down syndrome, is the most common aneuploidy, with an incidence of 1 in 700 live births in the United States. T21 can be suspected prenatally with an abnormal quad screen (α-fetoprotein, human chorionic gonadotropin, estriol, inhibin A) with an 80% to 95% detection rate, or by noninvasive prenatal screening of cell-free placental DNA in the mother's blood with a positive predictive value closer to 91%. If invasive genetic testing is not performed, the likelihood of having a child with T21 increases when ultrasonography shows increased nuchal translucency, congenital heart defects, ventriculomegaly, signs associated with gastrointestinal obstruction, or shortened long bones.

The gold standard test to confirm T21 is a chromosome analysis, which can be performed prenatally or postnatally. Fluorescent in situ hybridization can identify 3 copies of chromosome 21 within 1 to 2 days, while the full karyotype, which takes approximately 2 weeks, is pending. The karyotype helps distinguish among T21 caused by maternal nondisjunction leading to 3 full copies of chromosome 21 (96% of cases), Robertsonian translocations (2%–4% of cases), or mosaicism, where only a portion of the cells have 3 copies of chromosome 21 (1%–2%). Regardless of the mechanism, there are health supervision guidelines that pediatricians can follow to ensure that the affected child is as healthy as possible.

Many children with T21 are identified clinically at birth due to facial features that include brachycephaly (shortened head length compared with width), epicanthal folds (skin folds that start at the upper eyelid and cover the medial canthus), upward slanting palpebral fissures, and midface retrusion from a hypoplastic maxilla. The ears and mouth can be subjectively small. If increased nuchal translucency was noted prenatally, increased skin can be found at the nape of the neck. For the extremities, a single palmar crease and a widened gap between the first and second toe are commonly seen. Although each of these features can be a normal variant, in combination with hypotonia they are concerning for T21.

If the diagnosis is expected at birth, a cardiology evaluation including an echocardiogram can identify 1 of the structural changes seen in 50% of children with T21, most commonly an endocardial cushion defect. A complete blood cell count should be performed within the first 3 days to evaluate for different hematologic problems, including polycythemia. Although most abnormalities resolve within 1 week, the 9% of infants who have transient abnormal myelopoiesis should be referred to a hematologist: transient abnormal myelopoiesis that persists beyond 3 months of age may require chemotherapy. Given that 2% to 7% of infants with T21 have congenital hypothyroidism, thyrotropin and free

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thyroxine levels should be checked at birth if they have not been reported from the routine state newborn screen: any abnormality should prompt an endocrinology evaluation. Issues with feeding may arise during the newborn period because of structural changes (gastrointestinal atresia affects 12% of infants with T21), dysphagia from hypotonia, and/or reflux.

General pediatricians can certainly provide primary care for children with T21, following established guidelines for their special needs, including growth charts specific to them, and evaluations not indicated for other children. By the 6-month visit, a child with T21 should have another thyrotropin level to assess for hypothyroidism and another hearing screen to address the 50% to 75% risk of otitis media with effusion. Once normal hearing has been verified, hearing can be evaluated annually. Because 60% to 80% of children with T21 have vision issues, including refractive errors, strabismus, nystagmus, and nasolacrimal duct occlusion, by 6 months of age they should be evaluated by an ophthalmologist. Starting at 1 year old, annual blood work can be done to evaluate for iron deficiency (complete blood cell count with either ferritin and C-reactive protein levels or serum iron with total iron binding capacity) and for hypothyroidism (thyrotropin level). At 3 or 4 years old, a child with T21 should be referred for a sleep study; both obstructive sleep apnea and behavioral sleep disturbances are common. Any new neurologic symptom or sign (neck pain, abnormal gait, change in urinary/bowel function, spasticity), should prompt an evaluation for atlantoaxial instability, which occurs in 1% to 2% of patients with T21. If neutral cervical radiographs are normal, flexion/extension films should be performed, with prompt referral to a neurosurgeon if an abnormality is found.

All children with T21 have some degree of intellectual disability. Although most children fall into the moderate category with an IQ of 35 to 50, some are more severely affected, and others function closer to the normal range. This, along with the hypotonia seen in many infants with T21, qualifies them for early intervention and/or school therapies to help them reach their fullest potential.

As children with T21 get older, differences in cognitive abilities may become more noticeable. Some teenagers experience regression, which can involve repetitive thoughts, mood changes, and loss of skills. Families are often tempted by complementary/alternative treatments that might be promoted as effective in improving the function of patients with T21. One example is epigallocatechin gallate, a component in green tea that has been touted as an antioxidant that can enhance cognitive performance. Not only has a randomized clinical trial in Europe found no such benefit in children with T21, but when used as a supplement, epigallocatechin gallate can have significant adverse effects, including liver and kidney damage. Unless they ask about such use with families, pediatricians cannot offer appropriate advice.

Ultimately, as children with T21 transition to adulthood, their individual capabilities should be kept in mind as the primary care provider helps families navigate issues of guardianship, day programs, vocational programs, or long-term facilities that may be needed. Multiple support groups are available to patients of all ages and their families to help navigate the medical and social aspects of T21.

Comments: There was a time, actually within the memory of some of us, when trisomy 21, as well as other trisomies, was considered a diagnosis of doom. Often, families were urged to save themselves the heartache of raising a "mongoloid" child with no hope for a meaningful future by sending "it" off to an institution for the "feeble-minded." Thankfully we've moved forward with a more enlightened view.

And, interestingly, an irony here is that back in the mid-19th century, Dr John Down, who first described the syndrome and for whom it was named, was an advocate for the humane care of children with intellectual disabilities, establishing a home for such children with the aim of nurturing them with kindness and providing them with stimulating educational opportunities.

After a step backward, we have happily made a leap ahead.

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