PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "Down Syndrome." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Down Syndrome

Developed Grayson Beecher and Dr. Melanie Lewis for PedsCases.com.
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Hi, I'm Grayson Beecher, a medical student from the University of Alberta. Today we will be discussing Down syndrome. This podcast is designed to provide students with an overview of Down syndrome, its types, diagnosis, features, and management.

Down syndrome is very common, but just how prevalent is it, and why should students know about it?

Well, Down syndrome is the most common chromosomal syndrome, affecting approximately 1 in 800 births, and is the #1 genetic cause of intellectual disability worldwide. The incidence of Down syndrome rises dramatically with increasing maternal age, from 1 in 1500 births at age 20, to approximately 1 in 35 births by age 45. The diagnosis of Down syndrome carries with it a wide array of potential complications and associated conditions that will require adequate follow-up throughout a patient's life. While this diagnosis is a difficult one for a patient's family members to cope with initially, it is important to stress that it is very difficult to predict the impact that the syndrome will have on any one child's future, or their capacity for development.

So, what exactly is Down syndrome?

As mentioned previously, Down syndrome is a chromosomal syndrome, caused by the presence of a third copy of chromosome 21. Down syndrome is recognized for causing varying degrees of intellectual disability, which potentially co-exists with characteristic dysmorphic features, cardiac malformations, gastrointestinal abnormalities, auditory and visual problems, autism, and other medical conditions. These will be discussed later in the podcast.

So, how exactly does someone end up with an extra copy of chromosome 21?

Well, it is important to understand that there are three different types of Down syndrome, each characterized by a different method of inheritance of a third copy of chromosome 21. The first possibility, called Trisomy 21, is responsible for nearly all cases of Down syndrome. In Trisomy 21, nondisjunction occurs during meiosis in one of

the parents, leading to the production of a gamete with an extra, full copy of chromosome 21. When this gamete combines with a regular gamete produced by the other parent, the resultant embryo will carry 47 chromosomes, the extra one being chromosome 21. Overexpression of genes on chromosome 21 will then lead to the syndrome we know. Robertsonian Translocation may also produce a child with Down syndrome. In this scenario, in one of the parents, an extra piece of chromosome 21 attaches, or "translocates" itself onto another chromosome (usually 14). While the parent is unaffected, it is possible for them to produce gametes with extra material from chromosome 21 that then combines with a regular gamete from the other parent, giving an embryo with three copies of chromosome 21. The final route through which a child can inherit three copies of chromosome 21 is known as mosaicism, where an error of cell division after fertilization leads to generation of some cells with 47 chromosomes, while others have the normal 46.

Ok, so now we know how someone can inherit a third copy of chromosome 21. But what puts someone at greater risk for giving birth to a child with Down syndrome?

Well, the single-most identifiable risk factor for having a child with Down syndrome is advancing maternal age. Advanced paternal age may play a role, however, it is widely believed that advanced maternal age contributes to a far greater extent. The risk of Down syndrome is mainly constant from maternal ages 15-25 years, with a slight, steady rise in prevalence in ages 25-35 years. From age 35-40 years however, the risk of having a child with Down syndrome almost quadruples, and from age 40-45, the risk increases by nearly 10 times.

Alright, so how do we diagnose Down syndrome?

When suspected postnatally, usually because of the presence of dysmorphic features typical of Down syndrome, a karyotype can be performed for diagnosis. It is important to note that there are screening and diagnostic tests that can be performed during pregnancy that can suggest the presence of, or diagnose Down syndrome, respectively.

Ok, so what screening tests are available during pregnancy?

Normally, a first trimester combined test can be performed from 9-13 weeks gestation, with assessment of nuchal translucency, gestational age, and the serum markers beta-human chorionic gonadotropin (beta-hCG), and pregnancy-associated-plasma protein A (PAPP-A). Should first trimester screening not be performed, a maternal serum screen (quadruple screen) can be performed in the second trimester from 15-18 weeks, with assessment of alpha fetoprotein (AFP), unconjugated estriol (uE3), hCG, and inhibin A. Both screening tests have similar sensitivity for Down syndrome at 85%, but the first trimester combined test has a slightly lower false positive rate at 4.8% compared to 7.2% for the maternal serum screen. It is important to note, that should a woman have a "negative" screen, this only implies that the risk of having a child with Down syndrome is below a certain cut-off score (say, for example < 1/250) at which no further screening

should be recommended. Thus it is unlikely, although not impossible, to have a child with Down syndrome if your estimated risk is below the pre-determined cut off score.

So, what should be done if someone has a positive screening test?

Well, a positive screen suggests that an individual's risk of having a child with Down syndrome is above a given cut-off score, and further testing should be offered. A fetal karyotype can be obtained by chorionic villus sampling (CVS) in the first trimester, or through amniocentesis in the second trimester. Both procedures carry with them certain complications, including a slight risk of pregnancy loss, with a 1% risk in CVS and a 0.5% risk in amniocentesis. It should be noted that even in the presence of a positive screening test, diagnostic testing does not need to be performed if the mother does not wish for it. It is important to connect parents with a genetic counselor to discuss the options they have regarding further testing, as well as the potential risks that testing brings.

Ok, so now that you have had a good overview about how Down syndrome can be diagnosed, lets talk about the many features that are common to the syndrome.

Perhaps the most salient aspect of Down syndrome is the presence of classic dysmorphic features. Head and neck dysmorphisms include: brachycephaly (a short, broad head), epicanthal folds, Brushfield spots (white specks on the iris), up-slanting palpebral fissures, flattened nasal bridge, small ears set lower on the head, overfolded ear helix, excessive skin at nape of neck, open mouth with tendency towards tongue protrusion, a fissured and furrowed tongue, macroglossia, and various teeth deformities (including tooth agenesis, delayed tooth eruption, microdontia in both primary and secondary teeth, partial anodontia, hypocalcified teeth, malocclusion, increased periodontal destruction and taurodontism). While this is an exhaustive list, there are additional dysmorphisms of the extremities that are also common to Down syndrome, including: a single palmar crease, brachydactyly (slightly shortened fingers), clinodactyly (inward curving of the fifth finger), a large gap between the first two toes (sandal toe deformity), joint hyperflexibility, and hypotonia.

Now, while these dysmorphic features are the most readily apparent aspect of Down syndrome, there are a multitude of other medical conditions that may be present with the syndrome.

As mentioned previously, intellectual disability is common to nearly all individuals with Down syndrome, however, the severity of disability varies with the individual. Some individuals may have severe impairment with IQ scores in the 20-34 range, however, most individuals exhibit mild to moderate impairment, with IQ scores in the ranges of 50-70 and 35-49, respectively. Cognitive impairment in children with Down syndrome largely presents with impairments in speech and language, with the majority of children displaying expressive language delay. Given that communication is so important to daily living and functioning, difficulty with expressive language is a large barrier to

development in these areas. Furthermore, these children may also present with delayed attainment of developmental milestones, particularly gross and fine motor development, to which both intellectual disability and the aforementioned hypotonia contribute. Autism is also present in up to 7% of children with Down syndrome, which can further compound developmental delay and poor communication skills, while also leading to self-injurious and disruptive behavior, repetitive motor behaviours, unusual sensory responsiveness (such as spinning, staring at lights, or sensitivity to certain sounds), feeding problems, and increased anxiety and irritability common in autism spectrum disorder.

Up to half of children with Down syndrome have comorbid cardiac defects. The most common include atrioventricular septal defects, ventricular septal defects, and atrial septal defects, with patent ductus arteriosus, Tetralogy of Fallot, and other miscellaneous defects also occurring to a lesser extent.

Approximately 5% of patients exhibit gastrointestinal abnormalities, with duodenal atresia being the most prevalent at 5%. About another 2% have poor colonic and rectal motility due to the absence of autonomic ganglia that normally innervate these areas; this is called Hirschsprung disease. Constipation is also quite common in this population.

Hearing loss is extremely common in Down syndrome, with 60-80% of individuals being affected. The hearing loss can be conductive, sensorineural, or mixed, with many cases of conductive hearing loss being due to otitis media, which affects up to 70% of patients.

Visual problems are also very common and increase in frequency with age, with nearly half of patients affected by refractive errors, strabismus, or nystagmus. Cataracts may also be present, affecting about 3% of individuals.

Obstructive sleep apnea is present in almost half of patients with Down syndrome, and can lead to excess daytime fatigue and mental impairment.

Children and adults with Down syndrome are at higher risk for autoimmune diseases in general, with Hashimoto's thyroiditis or hypothyroidism being the most common, followed by celiac disease, and then numerous others, including: alopecia areata, type 1 diabetes mellitus, juvenile idiopathic arthritis, and Crohn's disease.

Children with Down syndrome also have a relative immune deficiency, compared to the general population, and as such, are more prone to upper respiratory tract infections, sinus infections, pneumonias, and other various infectious processes.

Ok, so everything that we've just talked about is relatively common in Down syndrome, but there are a few other conditions that may be found with the syndrome that you should be aware of.

While approximately 13% of individuals with Down syndrome have asymptomatic atlantoaxial instability, there is a 2% risk of major neurological damage as a result of spinal cord compression from cervical spine subluxation. It is also important to note that patients are at higher risk for developing leukemia, with a prevalence of 1-2%. In contrast to the rest of the pediatric population however, acute myeloid leukemia (AML) is more common in the Down syndrome population than is acute lymphoblastic leukemia (ALL). In addition, patients tend to have a higher rate of recovery with treatment than would a typical child.

Ok, so given the wide variety of medical conditions that may be present in a child with Down syndrome, it is extremely important to have a comprehensive management plan in place to help monitor for, and treat these conditions as they arise. Let's now talk about some general management guidelines that should be followed in a patient with Down syndrome.

All newborns with Down syndrome should be evaluated for cardiac defects with an echocardiogram and a consult with a pediatric cardiologist at birth. Tests for hearing loss, including auditory brainstem response (ABR) or oto-acoustic emission (OAE) testing should be performed at birth and then again at 6 months. Regular audiology assessment is then done yearly, with any failed test being grounds for referral to otolaryngology. It is also important to assess for otitis media at each visit. All children with Down syndrome should receive routine immunization, and are also eligible for RSV prophylaxis in the first year of life. Assessment for cataracts, strabismus, and nystagmus should be done at birth or by 6 months at the latest, and if positive, referral to ophthalmology is indicated. Annual visual assessment with either an optometrist or ophthalmologist (determined on a case-by-case basis) is then recommended. Thyroid function testing should be done at birth, again at 6 and 12 months, and then annually thereafter, to assess for hypothyroidism. Should a newborn have recurrent feeding difficulties, choking, pneumonia, failure to thrive, or marked hypotonia, consultation with a feeding specialist is recommended, and a radiographic swallowing assessment may be warranted. Constipation in the first year of life can generally be managed with dietary control and stool softeners, however, any constipation that is refractory to stool softener use should raise suspicion for Hirschsprung disease. A complete blood count should be done at birth to assess for transient myeloproliferative disorders and polycythemia, with an annual hemoglobin test being done until age 13 to monitor for anemia. Anemia in the Down syndrome patient could be due to poor oral intake or may indicate leukemia.

Given the wide array of periodontal disease present in Down syndrome, dental visits every 6 months starting at 2 years of age are recommended. In the childhood period, it is also important to monitor for symptoms of celiac disease, and further investigation may be required if symptoms are present. An annual clinical neurologic exam is needed to assess for any signs or symptoms of spinal cord compression secondary to atlantoaxial instability. Cervical spine X-rays have no predictive validity for subsequent acute dislocation/subluxation at the atlantoaxial joint and thus, should not be performed. It is also important to stress that children with Down syndrome should not be prevented from taking part in sporting activities because of the potential for atlantoaxial instability.

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Annual assessment for symptoms indicative of sleep apnea is also needed, with polysomnography recommended prior to 4 years of age. Growth should also be plotted annually on appropriate World Health Organization growth charts.

It is important to note that early developmental intervention with a speech and language pathologist (SLP), occupational therapist (OT), and physiotherapist (PT) is crucial to overcome the speech delay that is prevalent in this population. Such intervention can aid a child in reaching their full potential while also helping to establish skills that promote meaningful interactions and relationships throughout their life.
Last but not least, it is important to ensure that parents have adequate social supports, whether that be through direction to local Down syndrome support groups, early intervention programs, homecare, disability tax forms, or the Family Support for Children with Disabilities (FSCD) plan.

Ok, so we've talked a lot about Down syndrome over the last little while, but what in particular should you take away from this podcast?

Well, it is important to remember that Down syndrome is a chromosomal syndrome that is characterized by intellectual disability that may co-exist with many other medical conditions, including cardiac, gastrointestinal, thyroid, and auditory-visual disease, to name a few. Appropriate screening and management is essential to maximize the health and neurodevelopmental potential of all children with Down syndrome.

References

References available upon request.