SMITH MAGENIS AND DOWN SYNDROMES
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LEARNING OBJECTIVES

The optometrist will be able to:

1. Appreciate the manifestations of common congenital disorders
2. Identify the ocular manifestations of common congenital disorders
3. Understand the basic science aspects of the genomics in congenital disorders
4. Be comfortable with the role of the optometrist in diagnosing and managing common congenital disorders

COURSE DESCRIPTION

The course is introduced with case presentations. Utilizing the cases, a review of basic science aspects of common congenital disorders is reviewed with both Down Syndrome and Smith-Magenis Syndrome being reviewed in detail. Ocular manifestations of these disorders is emphasized along with suggested optometric management.

DOWN SYNDROME CASE REPORT

This is a case of severe acute corneal hydrops in a 10-year-old female patient associated with Down syndrome. The patient was well known to me as I had treated her for refractive error and for multiple episodes of conjunctivitis and chronic marginal blepharitis. Tea tree oil scrubs are the recommended treatment in the case of Demodex blepharitis, as the presumed cause of collarettes is now ocular mites. See Figure 1.

Figure 1: Chronic blepharitis is common in Down syndrome, and may be caused by staph- bacteria or Demodex (mites).

Her mom called me and requested a refill of antibiotics as one of her eyes was red again. Mom was divorced and on a very limited income and had a new job so wished for me to treat her daughter without seeing her in the office this time as she was worried she would lose her job if she took time off work. By telephone I asked a few questions including if she acted differently this time and mom reported that she seemed to be rubbing her eye a lot more and in more discomfort than for other episodes. Therefore I agreed to see her outside routine office hours in order to protect mom’s job.

On examination her visual acuity, which was normally 20/25 was unobtainable but thought to be light perception only. Her eye was bright red and injected and the cornea was observed to be dramatically involved by simple direct observation. By slit lamp examination, the anterior segment of her eye showed an extremely diffuse edematous ectasia of acute corneal hydrops. She continually attempted to rub the eye because of obvious discomfort. See Figure 2.

Figure 2: Corneal hydrops, secondary to eye rubbing, sometimes secondary to keratoconus (not the actual patient)
https://en.wikipedia.org/wiki/Keratoconus

Treatment consisted of topical hypertonic agent (4% NaCl) and patching. Therapy was continued for 6 weeks and at the end of that time, slit lamp evaluation revealed a small central corneal scar with complete resolution of the corneal edema. Her visual acuity improved to 20/40.

It must be kept in mind that in Down syndrome the incidence of an episode of acute corneal hydrops has been reported to occur in approximately 15% of patients sometime during their life.
DOWN SYNDROME CASE DISCUSSION

Acute corneal hydrops, is caused by the rupture of Descemet’s membrane, followed by an influx of aqueous humor into the corneal stroma resulting in a marked edema and the formation of cystic spaces in the cornea.

The frequent occurrence of acute corneal hydrops associated with Down syndrome has been attributed to a high incidence of eye rubbing as a result of increased episodes of blepharitis and conjunctivitis in Down syndrome. Additionally keep in mind that every cell of the body, including corneal cells, have trisomy 21 and cellular dysfunction and corneal cells are no exception.

Occasionally, Down syndrome patients with acute keratoconus will not respond to conservative therapy and may require penetrating keratoplasty for treatment of corneal scars that interfere with vision and rarely even perforation of the cornea. The development of corneal hydrops in association with Down syndrome is well documented, however, fortunately, corneal perforation in association with acute corneal hydrops is quite rare.

CHARACTERISTICS OF DOWN SYNDROME

Down syndrome is named after John Langdon Down, the first physician to identify the syndrome. See Figure 3.

Figure 3: John Langdon Down (1828-1896) who first described the syndrome now named after him. http://en.wikipedia.org/wiki/John_Langdon_Down

Down syndrome is a chromosomal disorder that includes a combination of birth defects. Patients with Down syndrome have diminished intellectual ability, characteristic facial features and commonly also have heart defects and other health problems. The severity of these problems varies greatly among affected individuals.

Down syndrome is the most common easily recognized genetic birth defects. About 1 in 700 babies are born with Down syndrome each year in the United States. According to the National Down Syndrome Society, there are more than 400,000 individuals with Down syndrome in the United States.
Down syndrome is the result of extra genetic material due to the presence of an extra chromosome 21, termed Trisomy 21.

A genetically normal person has 23 pairs of chromosomes. For some reason in Down Syndrome something goes wrong before fertilization in that an egg or sperm cell may divide incorrectly resulting in an egg or sperm cell has an extra chromosome number 21 resulting in an embryo that has 47 chromosomes instead of 46. This problem is associated with approximately 97% of cases in Down Syndrome. See Figure 4.


Occasionally, before fertilization, in a small number of cases a part of chromosome 21 breaks off during cell division and becomes attached to another chromosome in the egg or sperm cell. The resulting embryo may have what is termed Translocation Down syndrome. Affected individuals have two normal copies of chromosome 21, plus extra chromosome 21 material attached to another chromosome. This type of error in cell division causes approximately 3 percent of the cases of Down syndrome.

The outlook for longevity and a healthier, more productive life in individuals with Down syndrome is brighter than it once was in recent past. Most of the health problems associated with Down syndrome can be treated, and life expectancy is now about 60 years on average.
However, individuals with Down syndrome are more likely than unaffected individuals to have one or more of the following health conditions:

- **Heart defects**: Almost half of babies with Down syndrome have heart defects. Some defects are minor and may be treated with medications, while others require surgery. All babies with Down syndrome should have an echocardiogram of the heart during the first 2 months of life so that heart defects can be detected and treated if clinically indicated.

- **Intestinal defects**: About 12 percent of babies with Down syndrome are born with intestinal malformations that require surgery.

- **Vision problems**: Virtually all children with Down syndrome have vision problems including esotropia, hyperopia, myopia and/or cataracts. Glasses, surgery or other treatments usually can improve vision. A child with Down syndrome should have an optometric examination within the first 6 months of life and have regular vision examinations thereafter. See Figure 5.

  **Figure 5**: It is well known that both vision and hearing should be corrected in order to be certain that learning potential is maximized.
  

- **Hearing loss**: About 75 percent of children with Down syndrome have some hearing loss. Hearing loss may be due to fluid in the middle ear and/or defects involving the middle or inner ear. Babies with Down syndrome should be screened for hearing loss at birth and again during the first months of life. They also should have regular hearing exams so any problems can be treated before they hinder development of language and other skills.

- **Infections**: Children with Down syndrome tend to have more frequent colds and ear infections, as well as bronchitis and pneumonia. Children with Down syndrome should receive all the standard childhood immunizations, which help prevent some of these infections.

- **Thyroid problems**: A significant percentage of babies with Down syndrome are born with congenital hypothyroidism, a thyroid hormone deficiency that is devastating on physical growth and brain development. Congenital
hypothyroidism can be detected with routine newborn screening tests and is easily treated with oral doses of thyroid hormone.

• Leukemia: Fewer than 1 in 100 children with Down syndrome develop leukemia. Affected children often can be successfully treated with chemotherapy just as with normal children. During the early years of life, children with Down syndrome are 10-15 times more likely than other children to develop leukemia.

• Memory loss: Individuals with Down syndrome are more likely than unaffected individuals to develop Alzheimer disease, which is characterized by progressive memory loss, personality changes and other problems. Adults with Down syndrome tend to develop Alzheimer disease at an earlier age than unaffected individuals. Studies suggest that about 25 percent of adults with Down syndrome over age 35 have symptoms of Alzheimer's disease.

**Figure 6:** Facial appearance of an infant with Down Syndrome. Note the Brushfield spots and iris heterochromia.

http://en.wikipedia.org/wiki/Brushfield_spots

The physical features of Down syndrome are shown in Figure 6, and include:

- Eyes that slant upward and other visual problems also are commonly present early in life including significant refractive error. Cataracts occur in approximately 3% of children with Down syndrome and can be easily treated by surgical removal. Marginal blepharitis is also more common.

- Small ears that may fold over a little at the top
- A small mouth, making the tongue appear large
- A small nose with a flattened nasal bridge
- A short neck
- Small hands and feet
- Low muscle tone
- Short stature in childhood and adulthood
A newborn baby with Down syndrome often has physical features the attending physician will most likely recognize in the delivery room in the unlikely case that fetal ultrasound did not identify it first. These may include a flat facial profile, an upward slant to the eye, a short neck, abnormally shaped ears, whitish spots of iris atrophy may occur. These are termed Brushfield spots, and can occur in patients without Down syndrome. See Figure 7.

Figure 7: Closeup of Brushfield spots, present in 56% of Caucasian patients with Down syndrome. These are much more likely to occur in Caucasian than Asian children. [Link to Figure 7]

However, a child with Down syndrome may not possess all of these features; some of these features can even be found in the general population. Conformation of the diagnosis is with performance of a chromosomal karyotype by “growing” the cells from the baby’s blood for about two weeks, followed by a microscopic visualization of the chromosomes to determine if extra material from chromosome 21 is present.

Newborn babies with Down syndrome often have hypotonia, or poor muscle tone. Because they have a reduced muscle tone and a protruding tongue, feeding babies with Down syndrome usually takes longer. Mothers breast-feeding infants with Down syndrome should seek advice from an expert on breast feeding to make sure the baby is getting sufficient nutrition. Other signs include a single, deep transverse crease on the palm of the hand. The so-called “simian crease” is shown in Figure 8.
Figure 8: The so-called “simian crease” compared to normal palm creases (left). Muscle hypotonia (right) is also a feature in 80% of patients Down syndrome, among other diseases, among them, cerebral palsy. 

The degree of intellectual disability varies widely. Most affected individuals have intellectual disabilities within the mild to moderate range. There is no way to predict the mental development of a child with Down syndrome based upon physical features.

99% of children with Down syndrome are markedly developmentally delayed. A child with Down syndrome is often slow to turn over, sit, stand, and respond. This may be related to the child’s poor muscle tone. Development of speech and language abilities are typically quite delayed, however, children with Down syndrome very commonly develop meaningful communication skills.

Children with Down syndrome usually can do most things that any young child can do, such as walking, talking, dressing and being toilet-trained. However, due to developmental delays they generally start learning these things at a much later time than unaffected children.

Because Down syndrome is so common, there are special programs beginning in the preschool years to help children with Down syndrome develop skills as fully as possible. Along with benefiting from early intervention and special education, many children are integrated into the regular classroom (called “inclusion”). It is possible in some cases for the affected child to learn to read and write, graduate from high school, go on to post-secondary programs and even to attend college. Many individuals with Down syndrome participate in diverse childhood activities at school and in their neighborhoods.

While there are special work programs designed for adults with Down syndrome, many people with the disorder are able to hold regular jobs. Today, an increasing
number of adults with Down syndrome live semi-independently in community group homes where they take care of themselves, participate in household chores, develop friendships, partake in leisure activities and work in their communities.

There is currently no cure for Down syndrome.

The risk of Down syndrome is definitely related to an increase with the mother’s age as shown in Figure 9, and detailed below:

- At age 25, the risk of having a baby with Down syndrome is 1 in 1,250
- At age 30, the risk is 1 in 1,000
- At age 35, the risk is 1 in 400
- At age 40, the risk is 1 in 100
- At age 45, the risk is 1 in 30

**Figure 9:** The risk of having a Down syndrome pregnancy in relation to a mother’s age. Note that paternal age is likely also a factor.


Even though the risk is greater as the mother’s age increases, about 80% of babies with Down syndrome are born to women under age 35 simply due to the fact that younger women have more babies than older women.

When a patient has a child with Down syndrome, then with each subsequent pregnancy the chance of having another baby with Down syndrome is increased 10 fold up to age 40 and after this age the risk is parallel to others of the mother’s same age.

The diagnosis of Down syndrome can be confirmed with a blood sample taken from the baby for laboratory testing of the chromosomes, as Prenatal DNA testing has a 96-100% detection rate, and only a 0.3% false positive rate. See Figure 10.
During pregnancy pre-delivery screening testing for Down syndrome is readily and safely available. The American College of Obstetricians and Gynecologists recommends that all pregnant women be offered a screening test for Down syndrome, regardless of the woman’s age. Screening may be a maternal blood test done in the first trimester along with a special ultrasound to measure the thickness at the back of the baby’s neck (called nuchal translucency). Or it can be via a maternal blood test done in the second trimester. Screening testing helps identify pregnancies that are at higher-than-average risk of Down syndrome. However, screening tests cannot with absolute certainty diagnose Down syndrome.

Women who have an abnormal screening test result are offered further diagnostic testing which is not as safe as it is an invasive test such as amniocentesis or chorionic villus sampling (CVS).

Most parents-to-be receive reassuring news from a screening or diagnostic test for Down syndrome. However, if a prenatal diagnostic test shows that the baby has Down syndrome, parents have an opportunity to consider the diagnosis and their options. They also can prepare medically, emotionally and financially for the birth of a child with special needs, such as arranging for delivery in a medically appropriate setting.

With rare exceptions, men with Down syndrome cannot father a child. A woman with Down syndrome has a 50-50 chance of conceiving a child with Down syndrome, but many affected fetuses are miscarried.

Families with a child affected by Down syndrome can easily obtain information to help them and there are support groups available and easily found in most communities.

Many organizations provide information and support for families with children affected by Down syndrome, including:

**Figure 10:** Prenatal screening tests for Down syndrome.  
Children with Down syndrome are at a much higher risk for congenital heart
disease. As a comparison: the incidence of congenital heart disease in the general
population is 0.8 percent. The incidence of congenital heart disease in children with
Down syndrome is between 40-60 percent and includes the following:

- **Atrioventricular Septal Defects (AVSDs)** – These are the most common in children with Down syndrome.

- **Ventricular Septal Defects (VSDs)**, including:
  - Atrial Septal Defects
  - Patent Ductus Arteriosus
  - Tetralogy of Fallot

**Figure 11**: Recommended health screenings for patients with Down syndrome.
Note eye exams are recommended at 6 months of age, and annually thereafter.

Because of access to modern medicine and surgery the life expectancy of people
with Down's syndrome has more than doubled over the past decades, from 25 to 50-60 years, and sometimes more.
SMITH-MAGENIS SYNDROME CASE REPORT

A Vision Training Patient with Smith-Magenis Syndrome at the Southern California College of Optometry Clinic

Smith-Magenis Syndrome is a developmental disorder that affects every cell of the body due to a genetic defect and therefore affects many organs/tissues of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features and sleep disturbances. There are associated significant behavioral problems observed due to short attention spans and hyperactivity. Incidence is estimated to be at least 1:25,000, but may be as high as 1:15,000. It is named for NIH geneticist Ann C.M. Smith and the late R. Ellen Magenis, a retired pediatrician and medical geneticist from Oregon Health Sciences University. See Figure 12.

Figure 12: portrait unveiling of R. Ellen Magenis (1925-2014), at Oregon Health Sciences University. Dr. Magenis helped discover the syndrome that now bears her name.

A quick read of the Wikipedia entry will reveal that typical facial characteristics of patients with Smith-Magenis syndrome include a broad, square-shaped face, deep-set eyes with palpebral fissures that up-slant, full cheeks and a prominent lower jaw. The middle of the face and the bridge of the nose often appear flattened, with a down-turning of the mouth and the eyebrows growing across the base of the nose. These facial differences can be subtle in early childhood, but they usually become more distinctive in later childhood and adulthood. However, nothing replaces a case study for the optometric diagnosis and treatment of Smith-Magenis syndrome.
The patient in Figure 13 was referred for vision therapy by a pediatrician for vision therapy for learning disorders and visually-related problems. The patient had been previously diagnosed with ADHD and was receiving medication for it. Despite this, there were reportedly multiple developmental delays. According to her teacher, this patient had trouble focusing, with eye movements for reading, and with visual information processing.

Objectively, the patient was testing for visual-motor and non-motor perceptual delays. Deficits were found in all areas of the Test of Visual Perceptual Skills (TVPS), namely visual discrimination, memory, spatial relations, form constancy, sequential memory, figure-ground and visual closure. See Figure 14.

Figure 14: Test of Visual-Perceptual Skills (TVPS-3) and results

The Beery Visual-Motor Integration (VMI) test showed delays in copy forms accuracy and speed. See Figure 15.
The patient was originally diagnosed as having Down Syndrome (Trisomy 21) but signs and symptoms during routine health care delivery by the pediatrician made for suspicions that there was another diagnosis rather than Down Syndrome. The patient underwent genetic studies at a local laboratory to see if there could be any clarification of the diagnosis. The various genetic studies are performed by a simple cotton-tipped applicator “cheek swab”. In short, a cotton-tipped applicator is twirled between the cheek and upper teeth and gums and sent to the laboratory for analysis...similar to any police detective sending cells from under the fingernails of a victim who has scratched an assailant! These cells are stable without refrigeration or other preservative care for years and years so no special care of the specimen is required. In fact, the swab is simply placed in a standard envelope and mailed to the laboratory. The results are shown in Figure 16.

Genetic testing on the cells derived from the “cheek swab” confirmed that the patient has Smith-Magenis Syndrome. The following is a brief overview of this syndrome:
• Features – Squared face, up-slanting eyes that are deep set, prominent forehead and mid-facial hypoplasia
• Small hands and feet
• Scoliosis of the spine
• Cognitive and adaptive problems
• Motor delay and coordination problems
• Mild to moderate intellectual disability
• Hyperactive, inattention, impulsive, and temper-tantrums
• During infancy, there are feeding problems, sleep problems, hypotonia and often "failure to thrive"
• The disorder is due to a deletion of short arm of chromosome 17, band p11.2

The patient has very dedicated, well-off and loving parents who want only the best for their child and therefore they make certain that she was a faithful VT patient for her optometric care. The patient also enjoys support from her pediatrician and from all her other health care professionals including a child psychologist. All these health care professionals believe that her vision therapy program has helped tremendously as she demonstrated good, steady progress in motor skills and general behavior with the implementation of vision training. The patient was also active in sports, which provided opportunities for tailoring her therapy. See Figure 17.

![Figure 17: Smith-Magenis Syndrome patient demonstrates athletic skill despite mild intellectual disability, which is universal with this genetic disease. (photos used with permission of the family)](image)

The patient continues to do well and has only mild intellectual disability, so she is advancing in her schoolwork, and only a couple years behind what she should be for her age.
CHARACTERISTICS OF SMITH-MAGENIS SYNDROME

The Wikipedia entry will reveal that patients with Smith-Magenis syndrome usually have affectionate, engaging personalities along with behavioral problems. Developmental delays and intelligence are variable but most affected individuals have mild to moderate intellectual disability. Behavioral problems include frequent temper tantrums and outbursts, aggression, anxiety, impulsiveness, and very short attention spans. Self-injury, including biting, hitting, head banging, and skin picking, is very common. Repetitive self-hugging is a behavioral trait that may be unique to Smith-Magenis syndrome. Patients with this condition also compulsively lick their fingers and flip pages of books and magazines (a behavior known as "lick and flip").

Other signs and symptoms of Smith-Magenis syndrome include short stature, abnormal curvature of the spine (scoliosis), reduced sensitivity to pain and temperature, and a hoarse voice. Patients with this disorder commonly have significant hearing loss. Affected individuals may have refractive error requiring correction and strabismus that can be helped with ophthalmic optics, eye muscle surgery, and vision therapy.

Smith-Magenis syndrome affects at least 1 in 25,000 individuals worldwide. It is believed that many people with this condition are not diagnosed, so the true prevalence may be as high as one in 15,000. Subtle changes in appearance over the lifespan of a single patient are shown in Figure 18.

Figure 18: Changes over the lifespan in the appearance of a Smith-Magenis syndrome patient. http://drugline.org/medic/term/smith-magenis-syndrome/

Smith-Magenis syndrome is due to a deletion of genetic material from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, in each cell is responsible for most of the characteristic features of this condition. The loss of other genes in the deleted
region may help explain why the features of Smith-Magenis syndrome vary among affected individuals.

Smith-Magenis syndrome is typically not inherited. This condition usually results from a genetic change that occurs during the formation of reproductive cells (eggs or sperm) or in early fetal development. Therefore, patients with Smith-Magenis syndrome usually have no history of the condition in their family. Pregnancy management is not considered to be an issue because to date there are no published cases of individuals with SMS who have had children. Theoretically, offspring would have a 50/50 chance of having the syndrome.

While no one has studied the life expectancy of individuals with Smith-Magenis Syndrome in detail, they appear to have a fairly normal life expectancy. The oldest known person with Smith-Magenis Syndrome lived into her late eighties.

Knowing the underlying etiology with an accurate diagnosis for developmental delays can facilitate access to critical early childhood intervention services such as speech and language therapy, occupational therapy (OT), vision therapy, and/or physical therapy (PT). Early intervention may help program staff identify areas of specific need or risk. For example, some SMS families have benefited from using sign language with their child before his or her speech developed. Additionally, a diagnosis of SMS opens the doors to a network of information and support from professionals and other families dealing with the syndrome.

Affected individuals may also benefit from use of psychotropic medication to increase attention and/or decrease hyperactivity, and therapeutic management of sleep disorders. Melatonin has been observed to be helpful as a non-addicting sleep aid.

Of special note is the fact that as a part of any therapeutic program, optometric eye care is essential including refractive error correction and vision therapy which has been demonstrated to help with attention span, behavioral problems and to help with reading and other essentials to maximize the patient’s potential for as normal of a life as is possible.

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