Genetics in Special Education Series

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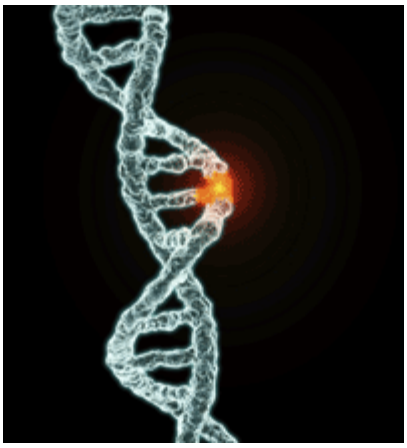

Genetic disorders presented in this issue:

Duane Syndrome

What is Duane syndrome?

Duane syndrome (DS) is a rare, congenital (present from birth) eye movement disorder. Most patients are diagnosed by the age of 10 years and DS is more common in girls (60 percent of the cases) than boys (40 percent of the cases).
DS is a miswiring of the eye muscles, causing some eye muscles to contract when they shouldn't and other eye muscles not to contract when they should. People with DS have a limited (and sometimes absent) ability to move the eye outward toward the ear (abduction) and, in most cases, a limited ability to move the eye inward toward the nose (adduction).

Often, when the eye moves toward the nose, the eyeball also pulls into the socket (retraction), the eye opening narrows and, in some cases, the eye will move upward or downward. Many patients with DS develop a face turn to maintain binocular vision and compensate for improper turning of the eyes.

In about 80 percent of cases of DS, only one eye is affected, most often the left. However, in some cases, both eyes are affected, with one eye usually more affected than the other.

Other names for this condition include: Duane's Retraction Syndrome (or DR syndrome), Eye Retraction Syndrome, Retraction Syndrome, Congenital retraction syndrome and Stilling-Turk-Duane Syndrome.

In 70 percent of DS cases, this is the only disorder the individual has. However, other conditions and syndromes have been found in association with DS. These include malformation of the skeleton, ears, eyes, kidneys and nervous system, as well as:

- Okihiro's syndrome, an association of DS with forearm malformation and hearing loss
- Wildervanck syndrome, fusion of neck vertebrae and hearing loss
- Holt-Oram syndrome, abnormalities of the upper limbs and heart
- Morning Glory syndrome, abnormalities of the optic disc or "blind spot"
- Goldenhar syndrome, malformation of the jaw, cheek and ear, usually on one side of the face.

What are the symptoms of Duane syndrome?

Clinically, Duane syndrome is often subdivided into three types, each with associated symptoms.

• **Type 1:** The affected eye, or eyes, has limited ability to move outward toward the ear, but the ability to move inward toward the nose is normal or nearly so. The eye opening narrows and the eyeball pulls in when looking inward toward the nose, however the reverse occurs when looking outward toward the ear. About 78 percent of all DS cases are Type 1.

• **Type 2:** The affected eye, or eyes, has limited ability to move inward toward the nose, but the ability to move outward toward the ear is normal or nearly so. The eye opening narrows and the eyeball pulls in when looking inward toward the nose. About 7 percent of all DS cases are Type 2.

• **Type 3:** The affected eye, or eyes, has limited ability to move both inward toward the nose and outward toward the ears. The eye opening narrows and the eyeball pulls in when looking inward toward the nose. About 15 percent of all DS cases are Type 3.

Each of these three types can be further classified into three subgroups, depending on where the eyes are when the individual looks straight (the primary gaze):

- **Subgroup A:** The affected eye is turned inward toward the nose (*esotropia*).
- **Subgroup B:** The affected eye is turned outward toward the ear (*exotropia*).
- **Subgroup C:** The eyes are in a straight, primary position.

What causes Duane syndrome?

Common thought is that Duane syndrome (DS) is a miswiring of the medial and the lateral rectus muscles, the muscles that move the eyes. Also, patients with DS lack the abducens nerve, the sixth cranial nerve, which is involved in eye movement. However, the etiology or origin of these malfunctions is, at present, a mystery.

Many researchers believe that DS results from a disturbance - either by genetic or environmental factors - during embryonic development. Since the cranial nerves and ocular muscles are

developing between the third and eighth week of pregnancy, this is most likely when the disturbance happens.

Presently, it appears that several factors may be involved in causing DS. Therefore it is doubtful that a single mechanism is responsible for this condition.

How is Duane syndrome diagnosed?

The diagnosis of Duane syndrome is based on clinical findings. Mutations in the CHN1 gene are associated with familial isolated Duane syndrome. Direct sequencing of the CHN1 gene is available as a clinical test, and has to date detected missense mutations in seven patients and affected family members. The CHN1 mutations have not been found to be a common cause of simplex Duane retraction syndrome.

What do we know about heredity and Duane syndrome?

Most likely, both genetic and environmental factors play a role in the development of Duane syndrome (DS). For those cases that show evidence of having a genetic cause, both dominant and recessive forms of DS have been found. (When a gene is dominant, only one gene from one parent is needed for the individual to express it physically. However, when a gene is recessive, a copy of the gene from both parents is needed for expression.)

The chromosomal location of the proposed gene for this syndrome is currently unknown. Some research shows that more than one gene may be involved. There is evidence that a gene involved in the development of DS is located on chromosome 2. Also, deletions of chromosomal material from chromosomes 4 and 8, as well as the presence of an extra marker chromosome thought to be derived from chromosome 22, have been linked to DS.

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Phenylketonuria (PKU)

What is Phenylketonuria (PKU)?

Phenylketonuria (PKU) is an inherited disorder of metabolism that causes an increase in the blood of a chemical known as phenylalanine. Phenylalanine comes from a person's diet and is used by the body to make proteins. Phenylalanine is found in all food proteins and in some artificial sweeteners. Without dietary treatment, phenylalanine can build up to harmful levels in the body, causing mental retardation and other serious problems.

Women who have high levels of phenylalanine during pregnancy are at high risk for having babies born with mental retardation, heart problems, small head size (microcephaly) and developmental delay. This is because the babies are exposed to their mother's very high levels of phenylalanine before they are born.

In the United States, PKU occurs in 1 in 10,000 to 1 in 15,000 newborn babies. Newborn screening has been used to detect PKU since the 1960's. As a result, the severe signs and symptoms of PKU are rarely seen.

What are the symptoms of PKU?

Symptoms of PKU range from mild to severe. Severe PKU is called classic PKU. Infants born with classic PKU appear normal for the first few months after birth. However, without treatment with a low-phenylalanine diet, these infants will develop mental retardation and behavioral problems. Other common symptoms of untreated classic PKU include seizures, developmental delay, and autism. Boys and girls who have classic PKU may also have eczema of the skin and lighter skin and hair than their family members who do not have PKU.

Babies born with less severe forms of PKU (moderate or mild PKU) may have a milder degree of mental retardation unless treated with the special diet. If the baby has only a very slight degree of PKU, often called mild hyperphenylalaninemia, there may be no problems and the special dietary treatment may not be needed.

How is PKU diagnosed?

PKU is usually diagnosed through newborn screening testing that is done shortly after birth on a blood sample (heel stick). However, PKU should be considered at any age in a person who has developmental delays or mental retardation. This is because, rarely, infants are missed by newborn screening programs.

What is the treatment for PKU?

PKU is treated by limiting the amount of protein (that contains phenylalanine) in the diet. Treatment also includes using special medical foods as well as special low-protein foods and taking vitamins and minerals. People who have PKU need to follow this diet for their lifetime. It is especially important for women who have PKU to follow the diet throughout their childbearing years.

Is PKU inherited?

PKU is inherited in families in an autosomal recessive pattern. Autosomal recessive inheritance means that a person has two copies of the gene that is altered. Usually, each parent of an individual who has PKU carries one copy of the altered gene. Since each parent also has a normal gene, they do not show signs or symptoms of PKU.

Gene alterations (mutations) in the PAH gene cause PKU. Mutations in the PAH gene cause low levels of an enzyme called phenylalanine hydroxylase. These low levels mean that phenylalanine from a person's diet cannot be metabolized (changed), so it builds up to toxic levels in the bloodstream and body. Having too much phenylalanine can cause brain damage unless diet treatment is started.

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