Joubert Syndrome

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Joubert syndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals, even among members of the same family.

Keywords: genetic conditions

1. Introduction

The hallmark feature of Joubert syndrome is a combination of brain abnormalities that together are known as the molar tooth sign, which can be seen on brain imaging studies such as magnetic resonance imaging (MRI). This sign results from the abnormal development of structures near the back of the brain, including the cerebellar vermis and the brainstem. The molar tooth sign got its name because the characteristic brain abnormalities resemble the cross-section of a molar tooth when seen on an MRI.

Most infants with Joubert syndrome have low muscle tone (hypotonia) in infancy, which contributes to difficulty coordinating movements (ataxia) in early childhood. Other characteristic features of the condition include episodes of unusually fast (hyperpnea) or slow (apnea) breathing in infancy, and abnormal eye movements (ocular motor apraxia). Most affected individuals have delayed development and intellectual disability, which can range from mild to severe. Distinctive facial features can also occur in Joubert syndrome; these include a broad forehead, arched eyebrows, droopy eyelids (ptosis), widely spaced eyes (hypertelorism), low-set ears, and a triangle-shaped mouth.

Joubert syndrome can include a broad range of additional signs and symptoms. The condition is sometimes associated with other eye abnormalities (such as retinal dystrophy, which can cause vision loss, and coloboma, which is a gap or split in a structure of the eye), kidney disease (including polycystic kidney disease and nephronophthisis), liver disease, skeletal abnormalities (such as the presence of extra fingers and toes), or hormone (endocrine) problems. A combination of the characteristic features of Joubert syndrome and one or more of these additional signs and symptoms once characterized several separate disorders. Together, those disorders were referred to as Joubert syndrome and related disorders (JSRD). Now, however, any instances that involve the molar tooth sign, including those with these additional signs and symptoms, are usually considered Joubert syndrome.

2. Frequency

Joubert syndrome is estimated to affect between 1 in 80,000 and 1 in 100,000 newborns. However, this estimate may be too low because Joubert syndrome has such a large range of possible features and is likely underdiagnosed. Particular genetic mutations that cause this condition are more common in certain ethnic groups, such as Ashkenazi Jewish, French-Canadian, and Hutterite populations.

3. Causes

Joubert syndrome can be caused by mutations in more than 30 genes. The proteins produced from these genes are known or suspected to play roles in cell structures called primary cilia. Primary cilia are microscopic, finger-like projections that stick out from the surface of cells and are involved in sensing the physical environment and in chemical signaling. Primary cilia are important for the structure and function of many types of cells, including brain cells (neurons) and certain cells in the kidneys and liver. Primary cilia are also necessary for the perception of sensory input, which is interpreted by the brain for sight, hearing, and smell.

Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia. Defects in these cell structures can disrupt important chemical signaling pathways during development. Although researchers believe that defective primary cilia are responsible for most of the features of these disorders, it is not

completely understood how they lead to specific developmental abnormalities.

Mutations in the genes known to be associated with Joubert syndrome account for about 60 to 90 percent of all cases of this condition. In the remaining cases, the genetic cause is unknown.

3.1. The genes associated with Joubert syndrome

- CEP290
- KIF7
- NPHP1
- OFD1

4. Inheritance

Joubert syndrome typically has an autosomal recessive pattern of inheritance, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they usually do not show signs and symptoms of the condition.

Rare cases of Joubert syndrome are inherited in an X-linked recessive pattern. In these cases, the causative gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- agenesis of cerebellar vermis
- cerebello-oculo-renal syndrome
- cerebellooculorenal syndrome 1
- CORS
- familial aplasia of the vermis
- JBTS
- Joubert-Bolthauser syndrome

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