6q24-related Transient Neonatal Diabetes Mellitus

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6q24-related transient neonatal diabetes mellitus is a type of diabetes that occurs in infants. This form of diabetes is characterized by high blood sugar levels (hyperglycemia) resulting from a shortage of the hormone insulin. Insulin controls how much glucose (a type of sugar) is passed from the blood into cells for conversion to energy.

genetic conditions

1. Introduction

People with 6q24-related transient neonatal diabetes mellitus experience very slow growth before birth (severe intrauterine growth retardation). Affected infants have hyperglycemia and an excessive loss of fluids (dehydration), usually beginning in the first week of life. Signs and symptoms of this form of diabetes are transient, which means that they gradually lessen over time and generally disappear between the ages of 3 months and 18 months. Diabetes may recur, however, especially during childhood illnesses or pregnancy. Up to half of individuals with 6q24-related transient neonatal diabetes mellitus develop permanent diabetes mellitus later in life.

Other features of 6q24-related transient neonatal diabetes mellitus that occur in some affected individuals include an unusually large tongue (macroglossia); a soft out-pouching around the belly-button (an umbilical hernia); malformations of the brain, heart, or kidneys; weak muscle tone (hypotonia); deafness; and developmental delay.

2. Frequency

Between 1 in 215,000 and 1 in 400,000 babies are born with diabetes mellitus. In about half of these babies, the diabetes is transient. Researchers estimate that approximately 70 percent of transient diabetes in newborns is caused by 6q24-related transient neonatal diabetes mellitus.

3. Causes

6q24-related transient neonatal diabetes mellitus is caused by the overactivity (overexpression) of certain genes in a region of the long (q) arm of chromosome 6 called 6q24. People inherit two copies of their genes, one from their mother and one from their father. Usually both copies of each gene are active, or "turned on," in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of

origin: some genes are normally active only when they are inherited from a person's father; others are active only when inherited from a person's mother. This phenomenon is known as genomic imprinting.

The 6q24 region includes paternally expressed imprinted genes, which means that normally only the copy of each gene that comes from the father is active. The copy of each gene that comes from the mother is inactivated (silenced) by a mechanism called methylation.

Overactivity of one of the paternally expressed imprinted genes in this region, *PLAGL1*, is believed to cause 6q24-related transient neonatal diabetes mellitus. Other paternally expressed imprinted genes in the region, some of which have not been identified, may also be involved in this disorder.

There are three ways that overexpression of imprinted genes in the 6q24 region can occur. About 40 percent of cases of 6q24-related transient neonatal diabetes mellitus are caused by a genetic change known as paternal uniparental disomy (UPD) of chromosome 6. In paternal UPD, people inherit both copies of the affected chromosome from their father instead of one copy from each parent. Paternal UPD causes people to have two active copies of paternally expressed imprinted genes, rather than one active copy from the father and one inactive copy from the mother.

Another 40 percent of cases of 6q24-related transient neonatal diabetes mellitus occur when the copy of chromosome 6 that comes from the father has a duplication of genetic material including the paternally expressed imprinted genes in the 6q24 region.

The third mechanism by which overexpression of genes in the 6q24 region can occur is by impaired silencing of the maternal copy of the genes (maternal hypomethylation). Approximately 20 percent of cases of 6q24-related transient neonatal diabetes mellitus are caused by maternal hypomethylation. Some people with this disorder have a genetic change in the maternal copy of the 6q24 region that prevents genes in that region from being silenced. Other affected individuals have a more generalized impairment of gene silencing involving many imprinted regions, called hypomethylation of imprinted loci (HIL).

About half the time, HIL is caused by mutations in the *ZFP57* gene. Studies indicate that the protein produced from this gene is important in establishing and maintaining gene silencing. The other causes of HIL are unknown. Because HIL can cause overexpression of many genes, this mechanism may account for the additional health problems that occur in some people with 6q24-related transient neonatal diabetes mellitus.

It is not well understood how overexpression of *PLAGL1* and other genes in the 6q24 region causes 6q24-related transient neonatal diabetes mellitus and why the condition improves after infancy. The protein produced from the *PLAGL1* gene helps control another protein called the pituitary adenylate cyclase-activating polypeptide receptor (PACAP1), and one of the functions of this protein is to stimulate insulin secretion by beta cells in the pancreas. In addition, overexpression of the PLAGL1 protein has been shown to stop the cycle of cell division and lead to the

self-destruction of cells (apoptosis). Researchers suggest that *PLAGL1* gene overexpression may reduce the number of insulin-secreting beta cells or impair their function in affected individuals.

Lack of sufficient insulin results in the signs and symptoms of diabetes mellitus. In individuals with 6q24-related transient neonatal diabetes mellitus, these signs and symptoms are most likely to occur during times of physiologic stress, including the rapid growth of infancy, childhood illnesses, and pregnancy. Because insulin acts as a growth promoter during early development, a shortage of this hormone may account for the intrauterine growth retardation seen in 6q24-related transient neonatal diabetes mellitus.

3.1. The genes and chromosome associated with 6q24-related transient neonatal diabetes mellitus

- PLAGL1
- ZFP57
- chromosome 6

3.2. Additional Information from NCBI Gene:

- HYMAI

4. Inheritance

Most cases of 6q24-related transient neonatal diabetes mellitus are not inherited, particularly those caused by paternal uniparental disomy. In these cases, genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected people typically have no history of the disorder in their family.

Sometimes, the genetic change responsible for 6q24-related transient neonatal diabetes mellitus is inherited. For example, a duplication of genetic material on the paternal chromosome 6 can be passed from one generation to the next.

When 6q24-related transient neonatal diabetes mellitus is caused by *ZFP57* gene mutations, it is inherited in an autosomal recessive pattern. Autosomal recessive inheritance means both copies of the 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 typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- 6q24-TNDM

- TNDM type 1
- transient neonatal diabetes mellitus 1

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