REVIEW ARTICLE

The Role of Mutations on Genes NSD1 and NFIX, In Sotos Syndrome

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ABSTRACT

Sotos syndrome (cerebral gigantism) is a rare genetic disorder caused by mutation in the NSD1 gene on chromosome 5. It is characterized by excessive physical growth during the first few years of life. Children with Sotos syndrome tend to be large at birth and are often taller, heavier, and have larger heads (macrocrania) than is normal for their age. Symptoms of the disorder, which vary among individuals, include a disproportionately large and long head with a slightly protrusive forehead and pointed chin, large hands and feet, hypertelorism (an abnormally increased distance between the eyes), and down-slanting eyes. The disorder is often accompanied by mild cognitive impairment; delayed motor, cognitive, and social development; hypotonia (low muscle tone), and speech impairments. Clumsiness, an awkward gait, and unusual aggressiveness or irritability may also occur.

Key words: Genetic disorder, NFIX genes, NSD1, Sotos syndrome

OVERVIEW OF SOTOS SYNDROME

Sotos syndrome, also known as giant brain disorder or Sotos Dodge syndrome, is a rare genetic disorder that occurs with over physical growth during the early years of human life. Excessive physical development in these patients often begins in the early stages of life (birth) and continues until early adolescence. Children with Sotos syndrome at birth are larger in size, taller, and heavier, and the skull is relatively larger than their age. Bone physiological age in patients with Sotos syndrome is 75–85% more advanced than others.[1]

SIGNS AND SYMPTOMS OF SOTOS SYNDROME

Growth rates in children with Sotos syndrome, especially in the first 3–4 years of life, are extremely normal and return to normal after this age. The average height of childhood Sotos syndrome sufferers is usually 2–3 years ahead of their peers. However, weight is usually appropriate for these children's height and bone age develops from childhood to over 2–4 years of chronological age. Adult stature with Sotos syndrome is usually higher than the average stature of normal men and women. Some adults with Sotos syndrome may be overweight, so men with Sotos syndrome can be up to 193 cm tall and women with Sotos syndrome up to 188 cm tall. Sotos syndrome may also be associated with autistic neurological disorder.[1]

Head and face configuration is the most characteristic symptom of Sotos syndrome. About 96% of people with Sotos syndrome have prominent forehead and retractable forehead hairline. Large or long head (double encephalus), extended eyes (hypertelorism), diagonal eyelid, slender coma in the mouth, prominent chin, long slender face and pear-shaped head upside down, and symptoms of syndrome it is Sotos. Head-to-face features are typically evident in childhood as a result of Sotos syndrome.[1,2]

In adults with Sotos syndrome, the features of the head and face are less pronounced, but their chin is prominent and the head is large and long (dulcephalic) and the frontal hairline remains permanently in Sotos syndrome sufferers. In

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addition to the large head size, the hands, feet, and mandibles of Sotos syndrome patients will be larger than their peers. Infants and children with Sotos syndrome may be delayed in learning development, for example, crawling on the ground or walking. These children may also start developing gait learning from the ages of 15–17 months.[1,3]

The central nervous system manifestations in Sotos syndrome are frequent. Delay in reaching developmental milestones such as: Walking, talking, and improperly performing these cognitive movements occurs in 60–80% of Sotos patients. There is also a decrease in muscle tone (hypotonia) and joints in Sotos syndrome. Mild to moderate intellectual disability occurs in 80–85% of patients with Sotos syndrome with an average IQ of 72, and about 15–20% of Sotos syndrome patients may have normal intelligence. In addition, seizures can also occur in up to 30% of patients with Sotos syndrome, and some brain disorders (large cerebral ventricles) may also occur. People with Sotos syndrome experience behavioral problems at all ages, making it difficult for them to communicate with others.[1,4]

Infants with Sotos syndrome often have jaundice, nutritional problems, and hypotonia. Heart failure also occurs in about 8% to 35% of children with Sotos syndrome, but is not usually severe. Genital or urinary tract disorders also occur in about 20% of Sotos patients. Other findings related to Sotos syndrome include: Conductive hearing loss that may be associated with an increased frequency of respiratory infections, upper eyelid disorders such as strabismus, and skeletal problems. About 40% of those affected by Sotos syndrome have a curved spine (scoliosis) but are usually not severe enough to require surgery to correct the curvature of the spine. Early eruption of teeth occurs in 60–80% of Sotos patients.[1,5]

Approximately 2.2–3.9% of patients with Sotos syndrome develop tumors including bone marrow teratoma,

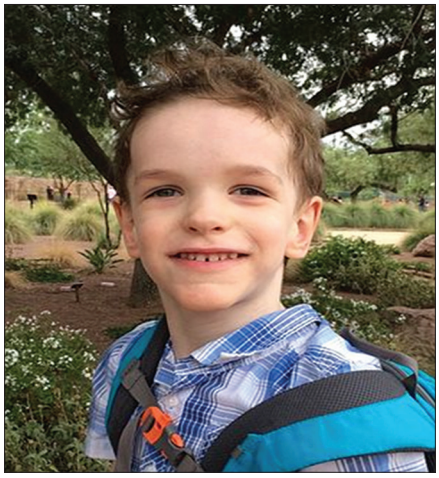

Figure 1: Image of a child with Sotos syndrome, be careful with giant ears

Figure 2: Image of a person with giant bodybuilding syndrome

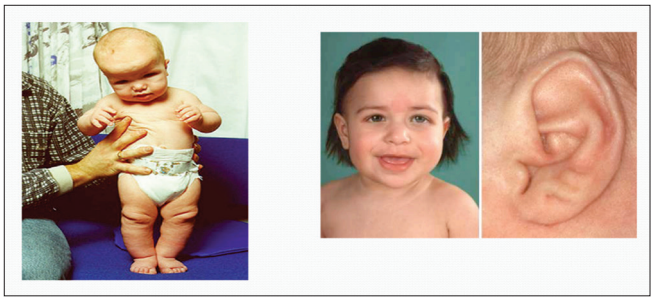

Figure 3: Image of a child with large body and large ears of Sotos syndrome

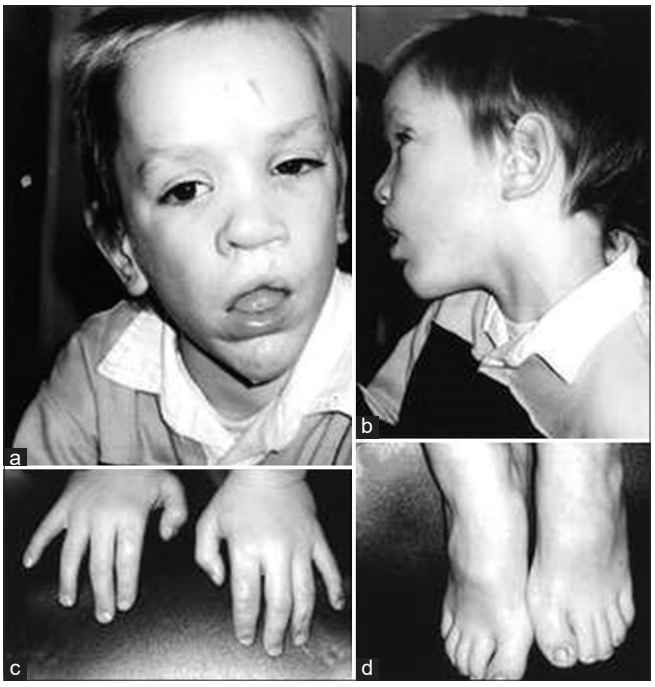

Figure 4: (a-d) Other images of Sotos syndrome sufferers

neuroblastoma, pre-sacral ganglia, and acute lymphoblastic leukemia[1,5]

ETIOLOGY OF SOTOS SYNDROME

Researchers have divided Sotos syndrome into two types: Sotos type 1 and Sotos type 2. Sotos type 1 syndrome (SOTOS1) is caused by a mutation in the NSD1 gene that is located on the long arm of chromosome 5 as 5q35.3.1,6.

Sotos type 2 syndrome (SOTOS2) is also caused by a mutation in the NFIX gene located on the short arm of chromosome 19 at 19p13.13.1,6.

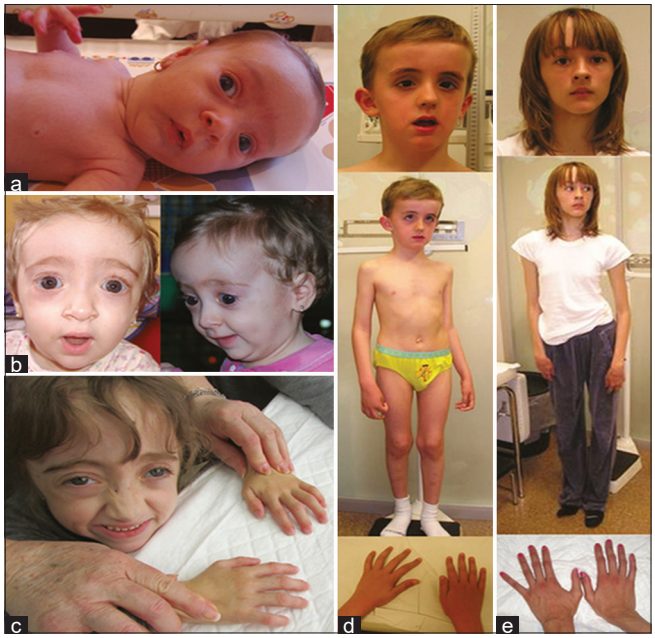

Figure 5: (a-e) Images of Sotos syndrome patients In both sexes, be aware of the status of the affected boy and girl with overweight

About 80–90% of SOTS cases are caused by mutations in the NSD1 gene, so at least 80% and up to 90% of Sotos patients are type 1. Both cases follow the dominant autosomal inherited pattern. Therefore, only one copy of the NSD1 or NFIX mutant gene, whether carrying the parent or carrier, is required for the syndrome, and the chance of having a child with Sotos syndrome from the parent carrying the corresponding mutant genes is 50% for each possible pregnancy is. It is worth noting that most people with Sotos syndrome are due to a new mutation in the NSD1 gene that has not been transmitted from parents. Symptoms of Sotos syndrome also vary from person to person, even when they have the same mutation in the NSD1 gene.[1,6]

FREQUENCY OF SOTOS SYNDROME

Sotos syndrome affects men and women in equal numbers across all races and ethnicities. The frequency of this syndrome worldwide is about 1 in 14,000 live births.[1,7]

DIAGNOSIS OF SOTOS SYNDROME

There are no biochemical markers for Sotos syndrome. It is possible to diagnose this syndrome based on clinical findings of head and face configuration and growth retardation. Head and face configuration, the most prominent symptom of Sotos syndrome, is absent in only <1% of cases. Furthermore, about 10–15% of patients with Sotos syndrome may not experience growth retardation. The diagnosis of Sotos syndrome can be made by DNA studies using fluorescence *in situ* hybridization (FISH) technique to evaluate the deletion mutation in chromosome 5 arm 5q35.3, which results in deletion of the NSD1 gene in about 10–15% of Western populations can be done.

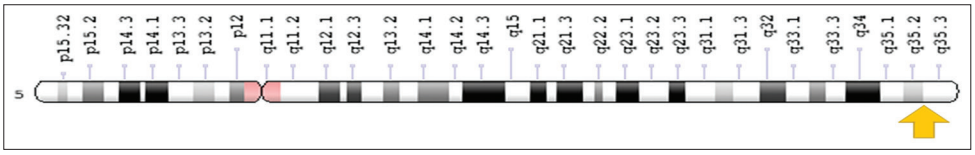

Figure 6: Schematic overview of chromosome 5, where the NSD1 gene is located on the long arm of chromosome 5q35.3 and its mutation is the cause of the type 1 syndrome

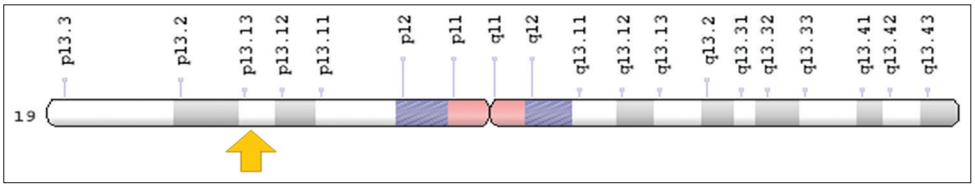

Figure 7: Schematic overview of chromosome 19 in which the NFIX gene is located in the short arm of chromosome 19p13.13 and its mutation is the cause of type 2 syndrome

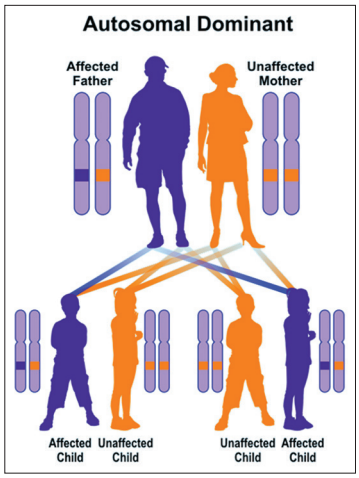

Figure 8: Schematic overview of the dominant autosomal inherited pattern that follows the pattern of Sotos syndrome in both type 1 and type 2 cases

However, more than 85% of patients with sotos syndrome result from a mutation in the NSD1 gene nucleotide sequence that is detectable by the nucleotide sequence or sequencing of this gene. In addition to the NSD1 gene, the NFIX gene should also be analyzed and analyzed for type 2 syndrome. Prenatal diagnosis of sotos syndrome is also possible by sampling fetal amniocentesis fluid and placental chorionic villus sampling. Sotos syndrome is clinically similar to weaver's syndrome but should not be mistaken for weaver's syndrome.[1,7]

THE THERAPEUTIC PATHWAYS OF SOTOS SYNDROME

The treatment of sotos syndrome is based on the symptoms that each person has. The treatment of this syndrome may be coordinated by a team of specialists such as: Pediatrician, pediatrician, molecular genetic and medical specialist, neurologist, surgeon, speech pathologist, orthopedist, ophthalmologist, physical therapist, or other care professional healthy. When a child is diagnosed with Sotos syndrome, a cardiac examination and ultrasound of the kidney should be performed. Children with Sotos syndrome should have a full examination every year or every 2 years, including: A screening for spinal scoliosis, an eye examination, blood pressure measurement, and speech and speech assessment. Genetic counseling is especially important for parents who have a family history of Sotos syndrome or any type of genetic damage and for parents who want a healthy, natural child.[1,8]

DISCUSSION AND CONCLUSION

Sotos syndrome, also known as giant brain disorder or Sotos Dodge syndrome, is a rare genetic disorder that occurs with over physical growth during the early years of human life. Excessive physical development in these patients often begins in the early stages of life (birth) and continues until early adolescence. The diagnosis of Sotos syndrome can be made by DNA studies using FISH technique to evaluate the deletion mutation in chromosome 5 arm 5q35.3, which results in deletion of the NSD1 gene in about 10–15% of Western populations. Children with Sotos syndrome should have a full examination every year or every 2 years, including: A screening for spinal scoliosis, an eye examination, blood pressure measurement, and speech and speech assessment.[1,9]

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