MALAN SYNDROME

Malan Syndrome

Malan Syndrome, also known as Sotos-like Syndrome or Sotos Syndrome 2, is described as a result of deletion of the short arm of chromosome 19 – 19p13.2. Later it was shown that the main acting factor in this condition is the NFIX gene located at this segment. Currently the term Malan Syndrome is used both for the patients having deletions of this area and for the patients with point mutations of the NFIX gene. NFIX is a part of the nuclear factor I family of transcription factors[1]. Its expression is vital for normal skeletal and brain development. In most patients, these mutations or deletions occur de novo and are not inherited from a parent.

Malan Syndrome is a rare disorder. Approximately 100 patients with this condition have been reported so far. The ratio between patients caused by mutations and patients with deletions is not known. Some recent publications allow thinking that patients with deletions are less common than patients with mutations of the NFIX gene.

Malan Syndrome is characterized by postnatal overgrowth and macrocephaly, intellectual and developmental delays, distinctive facial features, and various behavioral abnormalities. Individuals with deletions of NFIX instead of other mutations are more likely to have seizures along with the other main manifestations.

Postnatal overgrowth and macrocephaly are the main features that define Malan Syndrome. Individuals often have a height or weight greater than two standard deviations of the average for other individuals their age[1]. Either separately or in combination with overgrowth in height and weight, individuals with Malan Syndrome may also have macrocephaly. Their head sizes tend to, again, be greater than two standard deviations of the mean in size. It is suggested that macrocephaly is a more accurate clinical marker for the syndrome than overgrowth in height and weight[2].

All individuals with the disorder have some degree of intellectual and developmental delays. About 5% of individuals have mild delays, 75% moderate delays, and 20% have severe delays[3]. Patients typically have low performance levels in terms of their communication, daily life skills, socialization, and motor skills. They also tend to struggle understanding verbal instructions and may only communicate through meaningful gestures or vocalizations[2]. Included in developmental delays, motor delays are frequent. Individuals frequently have delayed control of the head, rolling over, crawling, sitting on their own, and walking[4].

There are several distinctive facial features seen in those with Malan Syndrome. This includes a long or triangular face, deep-set eyes, long philtrum, small mouth, thin upper vermillion, everted lower lip, prominent chin, prominent forehead, depressed nasal bridge, and palpebral fissures[2].

Some individuals with Malan Syndrome also present with various behavioral abnormalities. This can include anxiety, tantrums, and self-aggression. However, individuals normally have a cheerful demeanor[5]. Many individuals will show characteristics of autism spectrum disorder[2].

For patients who have deletions of NFIX, seizures are frequent and observed in 56% of patients[4]. This can include febrile and epileptic seizures[6]. Onset can vary among individuals but can start as early as infancy. However, these seizures do have the potential to be controlled by medication[2].

REFERENCES

[1]Malan V., Rajan D., Thomas S., et al. Distinct effects of allelic NFIX mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. Amer J Hum Genet 2010, v. 87, 189-198.

[2]Bellucco F.T., de Mello C.B., Meloni V.A., et al. Malan syndrome in a patient with 19p13.2p13.12 deletion encompassing NFIX and CACNA1A genes: Case report and review of the literature. Molec Genet Genomic Med. 2019, v. 7:e997.

[3]Klaassens M., Morrogh D., Rosser E.M., et al. Malan syndrome: Sotos-like overgrowth with de novo NFIX sequence variants and deletions in six new patients and a review of the literature. Eur J Hum Genet. 2015, v. 23, 610-615.

[4]Kuroda Y., Mizuno Y., Mimaki M., et al. Two patients with 19p13.2 deletion (Malan syndrome) involving NFIX and CACNA1A with overgrowth, developmental delay, and epilepsy. Clin Dysmorphology 2017, v. 26, 224-227.

[5]Jezela-Stanek A., Kucharczyk M., Falana K., et al. Malan syndrome (Sotos syndrome 2) in two patients with 19p13.2 deletion encompassing NFIX gene and novel NFIX sequence variant. Biomed Papers Med Fac Univ Palacky, Olomouc, 2016, v. 160, 161-167.

[6]Shimojima K., Okamoto N., Tamasaki A., et al. An association of 19p13.2 microdeletions with Malan syndrome and Chiari malformation. Amer J Med Genet. 2015, v. 167, 724-730.