195- Is there an increased risk of brain tumors during Sotos syndrome?

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INTRODUCTION

Sotos syndrome or cerebral gigantism is a rare genetic disorder that is often misidentified.

It was first described in 1964 by Juan SOTOS (1). After the discovery in 2002 of the NSD1 gene encoding a histone methyltransferase responsible for catalyzing the transfer of methyl groups to lysine residues of histone tails (2), which is crucial for various aspects of normal embryonic development, molecular diagnosis became available as more than 75% of cases of Sotos syndrome harbored NSD1 mutations (3).

Clinical suspicion of Sotos syndrome is based on the typical facial dysmorphia, excessive growth associated with macrocephaly and intellectual disability of varying degrees from mild to moderate (4).

The characteristic facial morphology (Fig 1) includes:

- A long face
- A broad forehead with high hairline
- Lower and lateral palpebral slits
- A pointed chin

There is also a broad spectrum of behavioural disorders, a delayed acquisition of developmental milestones and other signs including neonatal hypotonia and feeding difficulties (5).

Sotos syndrome is suggested to be with an increased risk of tumorigenesis (6).

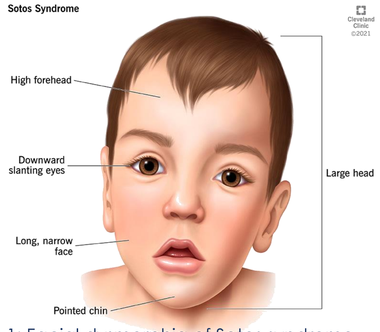

Fig 1: Facial dysmorphia of Sotos syndrome

OBJECTIVES

Here, we report medical and genetic assessment of a Tunisian child from Sfax town, who harbor a suspected Sotos syndrome.

Assessment of the neurologic cancer risk was conducted to provide enlightening genetic counseling for appropriate clinical follow-up of the patient and his family.

METHODS

A 12-year-old male child was seen at our genetic counselling for genetic management of intellectual disability.

Physical and dysmorphological examinations were conducted.

Cytogenetic exploration of the child and his parents was carried out using RHG banding.

RESULTS

The index case was diagnosed with Sotos syndrome based on the three major clinical manifestations that are:

- Facial dysmorphism
- Learning difficulties
- Excessive growth

The characteristic facial features included a long, narrow face, a high forehead, flushed cheeks, a small, pointed chin, down-slanting palpebral fissures and an unusually large head or a macrocephaly. There was a macrosomia, tall stature, and an advanced bone age.

Mental retardation was severe with an autistic behavior.

Cytogenetic analysis revealed normal karyotypes.

Genetic counselling offered to the boy's parents consisted in informing them of the 50% risk of transmitting the syndrome with each pregnancy, the availability and the importance of a genetic testing and the gains of a multidisciplinary management in particular regarding intellectual disability and the increased risk of developing cancer, particularly in childhood.

CONCLUSION

Approximately 3% of individuals with Sotos syndrome develop tumors (7).

Neurological cancers are rarely described in patients with Sotos syndrome and the genotype-phenotype correlation is unclear (8).

Very few Sotos cases with NSD1 anomalies have been reported with ganglioglioma, neuroblastoma and astrocytoma (9).

While, the risk of tumors in childhood appears low and the absolute risk of sacrococcygeal teratoma and neuroblastoma is low (~1%), the relative risk of sacrocoggygeal teratomas and neuroblastoma may be increased (7, 8).

Recently, a heterozygous germline NM_022455.4 (NSD1): c.5510-1G > A mutation was detected in a child harboring Sotos syndrome and a pineoblastoma (Fig 2) (11).

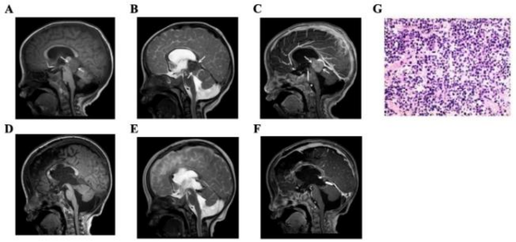

Fig 2: MRI revealed a space-occupying lesion in the preoperative (A-C) and postoperative (D-F) pineal region. HE staining from pineal regions suggested pineoblastoma (G) (11).

Molecular studies are needed in Sotos patients in order to improve the management of brain cancer predisposition and to improve molecularly targeted therapies.

REFERENCES

1. Sotos JF. Sotos syndrome 1 and 2. Pediatr Endocrinol Rev. 2014;12(1):2-16.
2. Ha K, Anand P, Lee JA, et al. Steric Clash in the SET Domain of Histone Methyltransferase NSD1 as a Cause of Sotos Syndrome and Its Genetic Heterogeneity in a Brazilian Cohort. *Genes (Basel)*. 2016;7(11):96.
3. Visser R, Matsumoto N. Genetics of Sotos syndrome. *Curr Opin Pediatr*. 2003;15(6):598-606.
4. Fagali C, Kok F, Nicola P, et al. MLPA analysis in 30 Sotos syndrome patients revealed one total NSD1 deletion and two partial deletions not previously reported. *Eur J Med Genet*. 2009;52(5):333-336.
5. Riccioni A, Siracusano M, Arturi L, et al. Short report: Autistic symptoms in Sotos syndrome, preliminary results from a case-control study. *Res Dev Disabil*. 2024;145:104655.
6. Berdasco M, Ropero S, Setien F, et al. Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma. *Proc Natl Acad Sci U S A*. 2009;106(51):21830-21835.
7. Tatton-Brown K, Cole TRP, Rahman N. Sotos Syndrome. 2004 Dec 17 [Updated 2022 Dec 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
8. Marini TJ, Mistry D, Jetty S, Chaturvedi A, Lin E, Ellika S. The Big Brain Theory: A Review of Overgrowth Syndromes for the Neuroradiologist. Neurographics. 2023 Oct 1;13(4):257-71.
9. Deardorff MA, Maisenbacher M, Zackai EH. Ganglioglioma in a Sotos syndrome patient with an NSD1 deletion. *Am J Med Genet A*. 2004;130A(4):393-394.
10. Theodoulou E, Baborie A, Jenkinson MD. Low grade glioma in an adult patient with Sotos syndrome. *J Clin Neurosci*. 2015;22(2):413-415.
11. Yue X, Liu B, Han T, Guo D, Ding R, Wang G. The first pineoblastoma case report of a patient with Sotos syndrome harboring NSD1 germline mutation. BMC Pediatr. 2024;24(1):166.