RECURRENT MICROLISSENCEPHALY: A CASE REPORT

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INTRODUCTION

Microcephaly with simplified gyral pattern (MSGP) is a type of congenital microcephaly with no extra-neurologic anomalies. This condition derives from a defective neuronal migration and causes a lack of development of brain folds and grooves. These findings are usually common in a wide range of pathologies such as lissencephaly. Usually, children with lissencephaly, have important developmental delays although there is a great variability.

The MSGP has an autosomal recessive inheritance, and it is commonly caused by mutations of the ASPM gene.

CLINICAL CASE

We present the case of a 29-year old woman, with a previous termination of pregnancy due to a lissencephaly diagnosed by ultrasound examination. The genetic study was negative for the LIS1 gene, the most frequent mutation in female fetuses.

In her second gestation, ultrasound examination at 19 weeks revealed a normal fetal head and an isolated interventricular communication of the heart. Two weeks after (21+5w) a decreased cephalic circumference <p3, grade 1 Sylvian fissure, and absence of parieto-occipital sulcus was observed. An amniocentesis was performed with normal array-CGH and karyotype results. TORCH and Zika serologies were also normal. A lissencephaly panel including 24 causing genes showed no pathogenic mutations.

Follow-up scans demonstrated a persistent microcephaly and a severe lack of the brain sulcation, subsequently confirmed by neurosonography and Magnetic Resonance Imaging (MRI). Because of the bad prognosis of this condition, the couple decided to terminate gestation and post-mortem studies confirmed the prenatal findings. Due to a recurrence of microlissencephaly and the negativity of the previous genetic tests, whole exome sequencing (WES) was performed.

RESULTS

At WES, mutations c.7551T>G (p.Tyr2517Ter) and c.9279G>A (p.Trp421Ter) in heterozygosis in the ASPM gene were observed. Both mutations cause a changed protein of 2517 and 3093 aminoacids instead of the normal protein which has 3477 aminoacids.

Both mutations of this gene were found to cause MSGP and they can usually be seen, as in our case, in heterozygosis. Subsequently, parents were shown to be healthy carriers of both mutations, c.7551T>G was of paternal and c.9279G>A of maternal origin.

CONCLUSIONS

This case highlights the importance of an accurate knowledge of the genetic basis of diseases and the proper application of a genetic testing algorithm.

Alterations in chromosome number and structure can be detected by the karyotype. When a genetic disorder is caused by microdeletions and microduplications, array-CGH should be used. However, when we are searching for single mutations in a particular gene we may need to sequence gene panel. Finally if all these techniques fail to find a genetic alteration, whole exome sequencing (WES) is the best choice.

In our case, it was not until WES was used that we could find two mutations of the ASPM gene which were the cause of recurrent lissencephaly.

Image A: grade 1 Sylvian fissure (21+5w)

Image B: decreased cephalic circumference <p3 (21+5w)

Image C: MRI 27+4w, lack of the brain sulcation (above), compared with a normal examination (below), 1- interhemispheric fissure, 2- Sylvian fissure, 3- parieto-occipital fissure, 4- calcarine fissure, 5- hippocampal fissure.

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