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Low-Grade Gliomas Genetics In The Pediatric Patients Group, A Review On Some Important Notes

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Abstract

Low-grade gliomas are among the most common CNS tumors in the pediatric patients group. From the genetics, histopathology, treatment strategies, distribution and molecular points of view, these tumors are different from ones which can be seen in the adult patients group. From the histological point of view, low-grade gliomas in the pediatric patients group encompass tumors of oligodendroglial, astrocytic and mixed glial-neuronal histology. Transforming into malignancy would usually not occur in most of these tumors. Understanding the genetics of these tumors is of importance in learning their behaviors. This brief review tries to point to some important notes about the genetics of the low-grade gliomas in the pediatric patients group.

Keywords: Tumors; Central Nervous System; Gliomas; Low-grade; Genetics; Pediatrics

Introduction and Explanation of Some Specific Terms

Tumors of the central nervous system include both malignant and nonmalignant brain and spinal cord tumors. In the pediatric patients group, astrocytomas are the most common brain tumors. The general brain tumors classification is related to their original cell. Based on the origin, brain tumors can be classified into various groups including neuroepithelial, nerve sheath, germ cell, pituitary and metastatic tumors. Also tumor-like malformations and lymphomas are among this classification. Gliomas which are among the neuroepithelial brain tumors include astrocytomas, ependymomas, oligodendrocytomas and choroid plexus tumors. Intracranial tumors are the most common type of solid tumors in children. Low-grade gliomas which based on the classification of the world health organization are among the grade one and two tumors, are usually nonvascular lesions with a consistency which is typically firmly fibrotic or rubbery in their nature. Based on some histological characteristics, low-grade gliomas can be differentiated from high-grade ones including anaplasia, necrosis, atypia and microscopic proliferation. In low grade gliomas, the glia which is hypercellular in its nature and also is well-differentiated with atypia in the nucleus and scarce mitotic activity can be seen.

Studying the cellular appearances can be used to differentiate tumors from each other. For instance cells with extremely large sizes with pleomorphism can be seen in astrocytomas. Also oligodendrogliomas show themselves as some round cells which are moderately large in their sizes and are infiltrating the parenchyma of the normal brain tissue and forming some unclear nodules which make an image like fried egg. Overall, low-grade gliomas classification based on molecular pathology can be done into three groups with regard to 1p/19q co-deletion and mutation in the IDH. These two factors are of importance in the molecular classification of low-grade gliomas. As a marker for astrocytomas, glial fibrillary acidic protein or GFAP which is a type three

intermediate filament protein and encoded by GFAP gene in humans, plays an important role both in basic and clinical settings. Differentiating in the glia can be determined by glial fibrillary acidic protein. It is of importance in the study of the tumors since such differentiating in the glia has relations with lower tendency for malignancy in tumors. So tumors with lower tendency for malignancy may have such glial fibrillary acidic protein marker.

Mitogen activated protein kinase signaling would be done while the BRAF kinase has a significant role in this signaling process. Such signaling process has an important role in mutations activity in various cancers. BRAF as a human gene encodes a protein called B-Raf which is involved in the process of sending signals in the cells and cell growth direction. Communication in and between the cells would be done in a way which the RAS/RAF/MEK/ERK signaling pathway plays an important role in that by regulating the essential functions of the cells including differentiation, survival and growth and also signals integration between the cells. Any alteration in the activity of the RAS/RAF/MEK/ERK signaling pathway would result in the formation of tumors.

Genetic alterations in the pediatric low-grade gliomas include NF1 protein loss, tyrosine kinases receptor activated mutations and BRAF kinase gene alterations. These alterations result in the activation of the MEK and accelerated progression in the cell cycle which is mediated by the ERK. These changes would finally result in increasing in the amount of cell growth. Tumors growth can be affected by targeting this signaling pathway.

Treatment strategies for low-grade gliomas depend on various factors including the tumor size and its location in the brain, patients age and general condition, the presence of neurological deficits and the effects of the tumor on surrounding structures etc. Various management and treatment strategies include observation, performing surgery, chemotherapy and radiotherapy. The condition of the patient and the tumor should be considered first to make appropriate decision for management and treatment.

Body

Low-grade glioma tumors in the pediatric patients group are among the most common pediatric central nervous system tumors. Their tendency to transform into the malignant tumors is low unlike their adult counterparts. These tumors usually show an indolent behavior. Their proliferative indices are low and they express proteins like glial fibrillary acidic protein which can be found in the population of the glial cells [1,2]. Genetic mutation rates are low in pediatric low-grade gliomas in comparison with the tumors in the adult groups. Most of the mutations in the pediatric low-grade gliomas result in growth factor signaling elevated rates and all of these would come together on the mitogenic pathway of the RAS [3,4].

In these regards, some mutations will happen. Causative mutations spectrum include biallelic loss of suppressor gene in type one of the neurofibromatosis tumor which result in more activity of the RAS, Receptor kinase mutations activation including FGFR1 and NTRK2 genes which result in the increased activation of the RAS and rearrangements of the chromosomes including BRAF gene like BRAF-KIAA1549 (B-K) fusion which result in BRAF kinase increased activation [5,6]. All of these changes in the genes will result in increasing in the amount of growing rates of the cells and activation of the RAS/MEK/ERK signaling pathway. These changes are normally not cause any transforming into the malignancy since these are not alterations which known as malignant mutations in their nature in most of the cases. Eventually these changes would result in increased amount of growing in the precursor cells and formation of the low-grade glioma tumors [2,3,7].

Conclusion

It is important for the researchers who are working on the brain tumor cases to have knowledge about the genetics of the low-grade glioma tumors in the pediatric patients group. This knowledge can be of help to better understand the nature and behavior of such tumors and may lead to find more detail about the pathogenesis of such tumors which hopefully can result in finding novel treatment options for such tumors.

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