Review article

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Modern views on the recurrence of meningiomas

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Meningiomas are common tumors of the central nervous system. Grade I meningiomas are generally considered to be "benign". However, a certain percentage of these tumors have a more aggressive course, similar to malignant tumors. Numerous observations have shown that even in the case of radical removal of the tumor, the latter recur within the next 10 years. Recent molecular studies have shed new light on meningioma subtypes, their behavior, the prospect of new treatment, and prognostic features for patients. The study of V.E. Clark et al. found a number of mutations in NF2 meningiomas, namely TRAF7 (tumor necrosis factor receptor 7 factor), KLF4 (Kruppel-like factor 4c), AKT1 and SMO. The pattern between the type of mutation and the tumor location was established: posterior cranial fossa, parasagittal area, falx, torculae and intraventricular sections - loss of NF2 or chromosome 22, olfactory groove and middle cranial fossa - KLF4 / TRAF7, olfactory groove, - PIK3CA, middle parts of the anterior cranial fossa and middle cranial fossa - AKT1 / POLR2, olfactory groove - SMO. The selection criteria in the study, which analyzed data from 469 meningiomas of a known molecular subgroup, were the degree of resection, postoperative irradiation, postoperative neuroimaging and time to recurrence (if present). Molecular subgroups of meningiomas had different clinical manifestations during the two years of follow-up, with several aggressive subgroups (NF2, PI3K, HH, TRAF7) recurring at an average rate 22 times faster than less aggressive tumors (KLF4, POLR2A, SMARCB1). PI3K-activated meningiomas recurred earlier than tumors in other groups. The potentially more aggressive group of meningiomas with HH, NF2, and TRAF7 mutations demonstrated a high recurrence rate after 60 months of follow-up (35.3, 43.7, and 36.4%, respectively), whereas most tumor recurrences with PI3K mutations were reported within the first 24 months (75,0%).

Classification of meningiomas by genomic mutations is a promising tool. Its introduction into clinical practice will make it possible to predict the aggressiveness of meningiomas and the risk of their recurrence, which will help to give a more accurate prognosis for patients and develop effective therapeutic methods for these tumors.

Key words: *meningioma; skull base; recurrence; NF2; ΦI3K; HH; TRAF7; AKT3; PIK3CA; PI-K3R1; PRKAR1A.*

Introduction

Meningiomas are common tumors of the central nervous system. They account for 36% of all intracranial neoplasms [1]. Historically, the classification of meningiomas according to the degree of malignancy was based on their histological features (WHO grade criteria) - mitotic activity, invasion in brain matter, spontaneous necrosis. Given the prevalence of Grade I tumors [2], meningiomas are often considered to be "benign". However, some Grade I meningiomas have a more aggressive clinical course, similar to that of tumors of high grade (Grade II-III) tumors. Numerous observations have shown that even in case of radical removal (Simpson I-II) 10–32% of Grade I tumors recur within the next 10 years, which requires further explanation in terms of molecular biology [3].

Thus, the WHO classification of meningiomas has limited correlations between the prognosis of tumor recurrence and the degree of removal on the Simpson scale and histological features of removed tumors [4]. Based on recent molecular studies, subtypes of meningiomas, their behavior, the prospect of new treatments and features of prognosis for patients have been identified.

The aim of the review is to systematize the latest literature data on the biological properties of

meningiomas, to determine meningioma subtypes according to molecular studies of tumors, the impact of this distribution on the prognosis of the disease.

Meningioma mutations

The updated 2016 WHO classification of the central nervous system neoplasms emphasizes the importance of identifying mutations in the tumor for different histological subtypes of meningiomas ***(Table 1)*** [5].

Previously, single genetic changes and their impact on tumor aggressiveness have been evaluated in the study of meningiomas [6,7]. Deletion of neurofibromin 2 (NF2, merlin, schwannomine) can be detected in 50-60% of patients with meningiomas, loss of chromosome 22, which contains the gene encoding NF2, in 40-80%. NF2 is a cell membrane-associated protein that regulates other proteins (e.g., paxillin, actin, syntenin) involved in cytoskeletal reconstruction, adhesion and cell migration. Loss of NF2 can trigger oncogenic pathways, in particular Ras/mitogen-activated protein kinase, Notch, phosphoinositide 3-kinase (PI3K) / AKT, Hippo and mTOR [8-13].

Although these studies have helped identify key drivers of mutations in meningioma cells, they have not been able to fully explain tumor aggressiveness and identify potential targets for treatment [14]. However, all authors point to the value of genomic analysis, which allows us to determine the impact of genetic changes on clinical behavior and tumor progression. Thanks to genetic research, a classification of tumors according to the mutations of these genes has been created. Subsequent targeted research will identify possible mechanisms of targeted effect on meningiomas.

Genomic studies and the relationship between mutations and tumor location

A group of key genomic studies has been identified in the current literature that have helped to better understand the relationship between mutations and meningioma location ***(Table).***

The study of V.E. Clark et al. [15] found a number of mutations in NF2-unmutated meningiomas, namely TRAF7 (tumor necrosis factor (TNF) receptor factor 7), KLF4 (Kruppel-like factor 4), AKT1 and SMO. 300 meningiomas were studied using genome-wide genotyping and exome sequencing in 50 grade I and II cases, as well as confirmation in an independent set of 250 cases. Loss of chromosome 22 was found in 79% of tumors, mutations in the NF2 genes were found - in 36% of tumors. Meningiomas with mutations in the TRAF7, KLF4, and AKT1 genes differed from tumors with mutations in the NF2 or SMO genes, justifying the

Table. Correlation of genomic mutations with meningioma location

Gene	Gene function	Meningioma location	Source
NF2	A protein bound to the cell membrane that regulates other cytoskeletal proteins involved in cellular life	PCF (low grade of malignancy); parasagittal region, falx, torcula and intraventricular regions (high grade)	Brastianos et al., 2013; Clark et al., 2013; Clark et al., 2016; Abedalthagafi et al., 2016; Bi et al., 2017
TRAF7	Multidomain protein that regulates tumor necrosis factor, E3 ubiquitin ligase, MEK33	Olfactory groove and MCF	Clark et al., 2013; Clark et al., 2016; Abedalthagafi et al., 2016
KLF4	Involved in induced pluripotent stem cells	Olfactory groove and MCF	Clark et al., 2013; Clark et al., 2016; Abedalthagafi et al., 2016
AKT1	PI3K / AKT activation	Middle parts of the ACF and MCF	Brastianos et al., 2013; Clark et al., 2013; Clark et al., 2016; Abedalthagafi et al., 2016
SMO	Hedgehog activation	Olfactory groove	Brastianos et al., 2013; Clark et al., 2013; Clark et al., 2016; Abedalthagafi et al., 2016
PIK3CA	PI3K/AKT activation	Olfactory groove, the body and lesser wings of the sphenoid bone	Abedalthagafi et al., 2016
POLR2	Regulator of DNA polymerase interaction with transcription factor 2B during complex formation	Middle parts of the ACF and MCF	Clark et al., 2016

Note: PCF - posterior cranial fossa; ACF - anterior cranial fossa; MCF - middle cranial fossa.

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distribution of meningiomas by localization. Mutations in the TRAF7, KLF4, AKT1 and SMO genes were reported in 25.0, 10.3, 12.7 and 3.7% of meningiomas, respectively.

TRAF7 is a multidomain protein that uses coproteins such as MEKK3, which regulate TNF signaling by acting as E3 ubiquitin ligase, selectively designating proteins for degradation.

KLF4 is considered to be one of the key transcription factors involved in the induction of pluripotent stem cells. Mutation of the E17 K peptide in the AKT1 gene leads to PI3K / AKT activation, mutations in the SMO gene lead to Hedgehog (HH) activation.

A certain pattern between the type of mutation and tumors location has been established ***(Fig. 1)***.

This study helped to identify the relationship between mutations in tumor genes and their location.

Another genomic study of 17 tumors confirmed the presence of AKT1 and SMO mutations in meningioma genes [16]. It is important that even a small number of mutations found in meningioma genes significantly affect tumor development. High-grade meningiomas had an average level of SCNA (somatic copy-number alterations) (12.3%) and higher levels of chromotrypsin (large chromosomal rearrangements). Such changes have previously been found in patients with aggressive forms of cancer.

The study of V.E. Clark et al. [17] revealed the significance of POLR2A (RNA polymerase II subunit A) and other mutations in meningioma genes. Meningiomas with POLR2A mutations were more common in the middle part of anterior cranial fossa and middle cranial fossa. The presence of this mutation was detected only in benign tumors. Further research demonstrated that POLR2A alters WNT signaling pathways and transcription factors. Other genes have been identified in meningiomas, in particular SMARCB1 (associated with SWI / SNF matrix-dependent actin-dependent regulator of chromatin B subfamily member 1), AKT3, PIK3CA, PI-K3R1, PRKAR1A (protein kinase CAMP-dependent regulatory subunit of type Iα) and SUFU suppressor of fused homologues). It was found that "super-amplifier regions", i.e. genomic regions with high acetylation of histone 3 lysine 27, support a number of factors involved in the regulation of transcription and malignantly transformed tumor cells in broad segments of meningiomas, such as FOX, HDAC, KLF2, KLF4, WNT and BCL2 proteins. These factors are one of the main regulators of embryonic stem cells signals development and transmission. Consequently, this study proves that meningiomas can originate from embryonic stem cells or their precursors.

Groups of meningioma and their recurrence

Selection criteria in the study of M.W. Youngblood et al. [2], which analyzed data from 469 meningiomas of a known molecular subgroup, were the degree of resection, postoperative irradiation, postoperative neuroimaging and time to recurrence (if present).

Molecular subgroups of meningiomas had different clinical manifestations during the two years of follow-up, with several aggressive subgroups (NF2, PI3K, HH, TRAF7) recurring at an average rate 22 times faster than less aggressive tumors (KLF4, POLR2A, SMARCB1). Meningiomas in which the PI3K signaling pathway is activated, recurred earlier than tumors in other groups. Among low-grade meningiomas (Grade I), tumors with HH and TRAF7 mutations had an increased recurrence rate compared with other subgroups. Recurrence of tumors with NF2 was also found to be associated with male gender and an increase in Ki-67.

The mean duration of follow-up was 54.2 months. The overall two-year recurrence rate was for 12.0%, including 7.4% in low-grade tumors (Grade I) and 33.3% in high-grade meningiomas (Grade II-III).

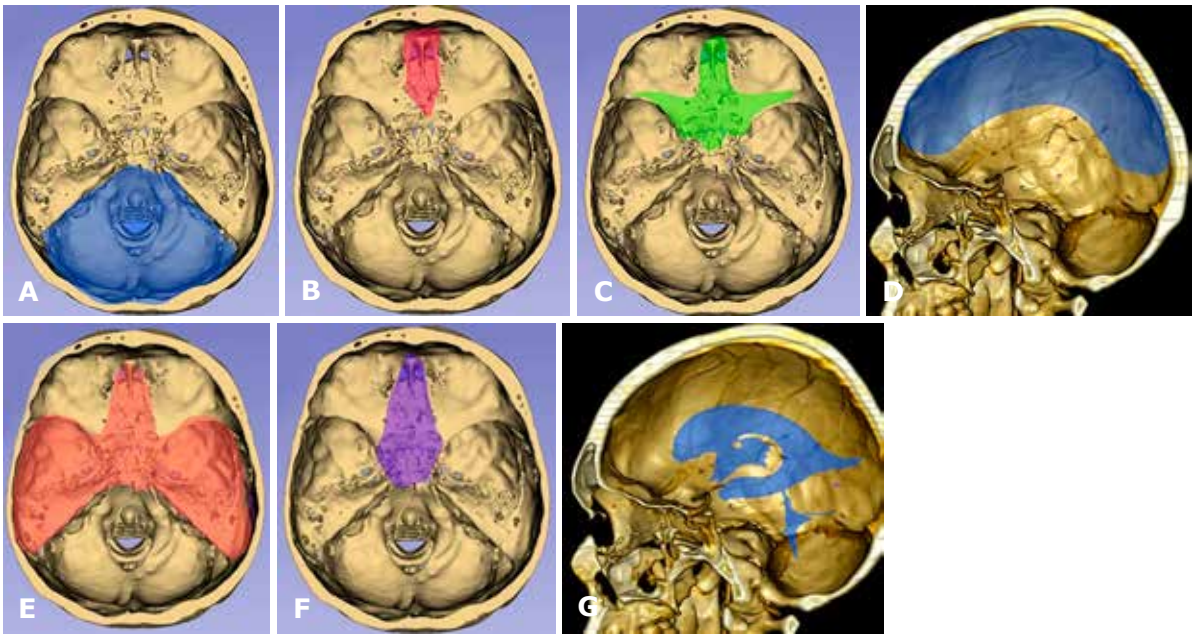

Fig. 1. Tumor location according to the mutation of certain genes: A, D, G - NF2; B - SMO; C - PIK3CA; E - KLF4 and TRAF7; F - AKT1 and POLR2

In four groups of meningioma mutations (Grade I-III) the recurrence rates after two years were as follows: HH (17.4%, 4 of 23), NF2 (16.8%, 26 of 155), PI3K (9.5%, 6 out of 63) and TRAF7 (14.7%, 5 out of 34). Among 75 meningiomas with KLF4, POLR2A and SMARCB1 mutations, only one case of recurrence was registered. Thus, in the first group (HH, NF2, PI3K, TRAF7) recurrence occurred 21.9 times more often than in the second (KLF4, POLR2A, SMARCB1) during the same period.

A potentially more aggressive group of meningiomas with HH, NF2, and TRAF7 mutations demonstrated a high recurrence rate after 60 months of follow-up (35.3 %, 43.7 %, and 36.4%, respectively), while the majority of tumor recurrences with PI3K mutations were reported within the first 24 months (75,0%). The mean time to recurrence of PI3K tumors was 17.4 months, which was significantly different from the mean (40.0 months) for all non-PI3K meningiomas. A strong relationship between mean time to recurrence and PI3K persisted even when only totally removed tumors and Grade I meningiomas were considered. The authors found no correlation between mean time to recurrence and grade, removal volume, Ki-67 index, or tumor location. This proves that activation of PI3K mutations is a predictor of early recurrence, regardless of other prognostic clinical data.

The authors observed recurrence in meningiomas with the POLR2A mutation (n = 3; time range to recurrence from 39 to 91 months), suggesting that these tumors tend to recur later than other groups. The results of the study suggest that meningiomas with mutations in the PI3K gene usually recur earlier, in the POLR2A gene later, and meningiomas with mutations in the HH, NF2 and TRAF7 genes have stable rates of recurrence over time ***(Fig. 2)***.

Conclusions

In routine neurosurgical practice, Grade II and Grade III meningiomas are considered to be more aggressive, although early recurrences of Grade I meningiomas are not considered occasional. Recent molecular studies have identified mutations in Grade I genes of meningiomas with a more aggressive clinical course.

Classification of meningiomas by genomic mutations is a promising tool. Its introduction into clinical practice will make it possible to predict the aggressiveness of meningiomas and the risk of their recurrence, which will help to give a more accurate prognosis for patients and develop effective therapeutic methods of treatment of these tumors.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This article is a literature review, therefore no ethics committee approval was required.

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The study was conducted without sponsorship.

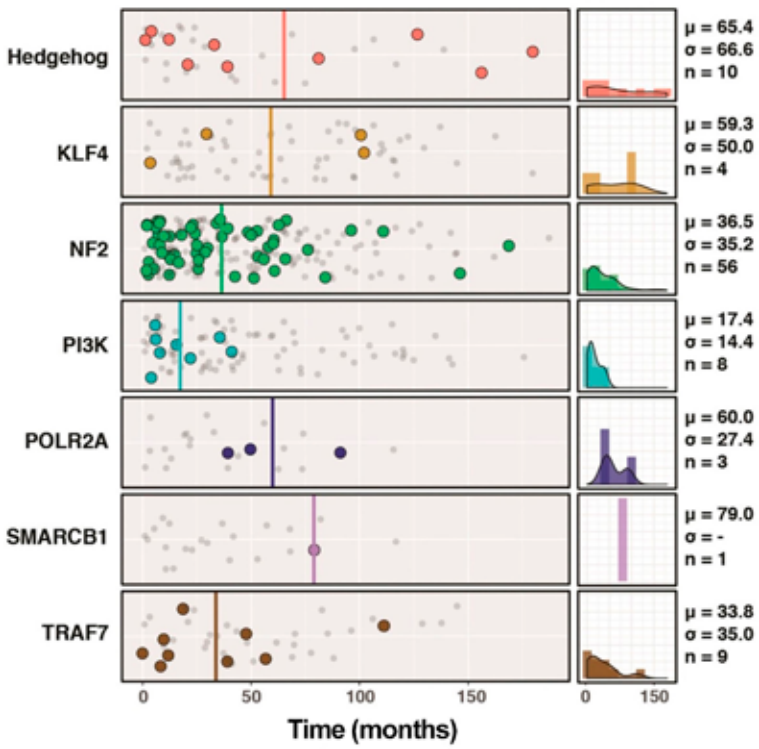

Fig. 2. Time of recurrence of meningioma. Time of recurrence (colored dots) or the last MRI exam without recurrence (gray dots) are given. The mean values for each group are represented by solid lines. Recurrence density plots are shown on the right along with mean (μ), standard deviation (σ) and recurrence rate (n) [2]

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