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ORPHANETICS OF AGGRESSIVE PITUITARY ADENOMAS: CHALLENGES AND PROSPECTS IN DIAGNOSIS

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XULOSA

Orfanetika tibbiyot fanining sohasi sifatida kam uchraydigan kasalliklarni, shu jumladan agressiv gipofiz adenomalarini o'rganishga bag'ishlangan. Ushbu sohadagi tadqiqotlar ushbu o'smalarni tashhislash, davolash va prognozini yaxshilash uchun juda muhimdir. So'nggi yillarda aggressive gipofiz adenomalari asosidagi genetic va molekulyar mexanizmlarni tushunishda muhim qadamlar qo'yildi. Bu aniqroq diagnostika usullari va individual davolashni ishlab chiqish uchun yangi istiqbollarni ochadi. Biroq, bu yutuqlarga qaramay, tajovuzkor gipofiz adenomalarini tashhislashda muammolar saqlanib qolmoqda, masalan, klinik simptomlarning noaniqligi, ta'lim ma'lumotlarini sharhlashda qiyinchiliklar va yanada samarali biomarkerlarni ishlab chiqish zarurati. VEGFA, HIF-1A, p53, IL-17, gipofiz adenomalari ifodasini tartibga soluvchi genetik nuqsonlar agressivlikni targ`ib qilishi tekshirildi. Barcha bemorlar klinik tekshiruvdan o'tkazildi va Knops tasnifi bo'yicha adenoma invaziya darajasini aniqlash uchun magnit-rezonans tomografiya (MRT) qo'llanildi. VEGFA, HIF-1A, Tp53 va IL-17A genlarining polimorfizmlari chastotasini aniqlash uchun real vaqtda PCR ishlatilgan. Taqdim etilgan natijalar VEGFA, HIF-1A, TP53 va IL-17A ning geterozigot mutatsiyasining agressiv gipofiz adenomalarining invazivlik modeli bilan bog'liqligi haqidagi argumentni aniq qo'llab-quvvatlashni ko'rsatdi. Bundan tashqari, VEGFA va HIF-1A mutatsiyalari ko'proq 3 va 4 darajali birlamchi invaziyasi bo'lgan bemorlarda va operatsiyadan keyin takroriy o'sadigan adenomalarda, TP53 va IL-17A ning geterozigotli mutatsiyalari ko'proq aniqlanganligi topildi, an'anaviy terapiyaga qarshilik ko'rsatadigan gipofiz bezining agressiv adenomalari. Shunday qilib, o'rganilgan har bir molekulyar genetik mutatsiya tajovuzkorlikning turli mezonlariga javob beradi va agressivlikning o'ziga xos diagnostik belgisi sifatida ishlatilishi mumkin deb taxmin qilish kerak. Biroq, olingan natijalarni tasdiqlash uchun qo'shimcha tadqiqotlar talab qilinadi.

Kalit so'zlar: *agressiv gipofiz adenomalari, molekulyar genetika.*

РЕЗЮМЕ

Орфанетика, как область медицинской науки, посвящена изучению редких заболеваний, в том числе агрессивных аденом гипофиза. Исследования в этой области имеют важное значение для улучшения диагностики, лечения и прогноза этих опухолей. В последние годы были сделаны значительные шаги в понимании генетических и молекулярных механизмов, лежащих в основе агрессивных аденом гипофиза. Это открывает новые перспективы для разработки более точных методов диагностики и индивидуального лечения. Однако, несмотря на эти достижения, сохраняются проблемы с диагностикой агрессивных аденом гипофиза, такие как двусмысленность клинических симптомов, трудности с интерпретацией образовательных данных и необходимость разработки более эффективных биомаркеров. Было исследовано, способствуют ли генетические дефекты, регулирующие экспрессию VEGFA, HIF-1A, p53, IL-17, аденомы гипофиза агрессивному поведению. Все пациенты прошли клиническое обследование и для определения степени инвазии аденом по классификации Knops, а также для всех пациентов была применена магнитно-резонансная томография (МРТ). ПЦР в реальном времени использовали для идентификации частоты полиморфизма генов VEGFA, HIF-1A, Tp53, IL-17A. Статистический анализ был проведен с помощью программного обеспечения R. Приведенные результаты показали четкую поддержку аргумента о корреляции гетерозиготной мутации VEGFA, HIF-1A, TP53 и IL-17A с моделью инвазивности агрессивных аденом гипофиза. Кроме того, было выявлено, что мутации VEGFA и HIF-1A чаще обнаруживались у пациентов с первичной инвазией 3 и 4 степени и у аденом с рецидивирующим ростом после операции, в то время как гетерозиготные мутации TP53 и IL-17A были более идентифицированы в агрессивных аденомах гипофиза с устойчивостью к традиционной терапии. Таким образом, следует предположить, что каждая исследованная молекулярно-генетическая мутация отвечает различным критериям агрессивности и может использоваться в качестве специфического диагностического маркера агрес-

сивности. Однако для подтверждения полученных результатов требуются дальнейшие исследования.

Ключевые слова: *агрессивные аденомы гипофиза, молекулярная генетика.*

One of the essential features of aggressive pituitary adenomas is invasion, although the overwhelming majority of pituitary adenomas are regarded as benign tumors (Picó et al, 2020). Numerous biological and clinical studies have been carried out to distinguish aggressive pituitary tumors from tumors with less aggressive behavior (Mastronardi et al, 20017). However, there is no specific differentiated lineage between invasive and non-invasive types of aggressive pituitary adenomas (Kovacs et al., 1996;) Generally, pituitary adenomas maintain a cleavage plane with respect to surrounding tissues, although some of them may attain the impressive size and show a variety of extension patterns (Di Ieva et al 2014). A group of adenomas as aggressive pituitary adenomas demonstrate a propensity for infiltrative and destructive growth (Dai et al, 2021). Termed “invasive adenomas,” they demonstrate the biochemical means of infiltrating blood vessels, dura, bone, adventitia, and nerve sheath (Sav et al, 2014). Brain invasion is unusual for aggressive pituitary adenomas and is generally considered a manifestation of “pituitary carcinoma”. This is the main differential feature between aggressive pituitary adenomas and carcinoma that only carcinomas have prone to metastasis (Heaney et al, 2014). Invasive adenomas may be difficult, if not impossible, to eradicate by surgical means alone. Thus, invasive adenomas are usually evaluated equivalently as aggressive adenomas. Although the majority are macroadenomas, small intrasellar adenomas may also demonstrate radiographically or grossly apparent invasion (Dai et al, 2021). For the purpose of our discussion, the definition of invasion will be that of radiographically or operatively apparent invasion of dura, cavernous sinus, bone, and so forth. It is this subset of tumors, as opposed to that showing microscopic dural invasion alone, which is thought to be clinically and prognostically relevant (Dhandapani et al, 2016). Indeed, simple microscopic dural involvement alone is not considered significant in that it is an all too common finding, one directly related to tumor size (Ceccato et al, 2017).

According to recent investigations, the most important aspects of the pathogenesis of invasion and uncontrolled growth of adenomas are neo-vascularization induced by the hypoxia (Ilie et al 20220), which results from the unregulated onco-suppressor activation of p53 (Levy et al 1994).

In addition, the chronic inflammation promoting by interleukin signaling promotes tumor growth by changing the cell microenvironment (Qiu et al, 2014). Hence, we have investigated whether genetic defects regulating the expression of the VEGFA, HIF-1A, P-53, IL-17 promote pituitary adenomas’ aggressive behavior.

THE AIM OF THIS STUDY was to identify the frequency of polymorphism G634C of the VEGFA gene, G-197A in gene IL17A, C/T of the TP53 gene, and the HIF1A genes in invasive and non-invasive pituitary adenomas. These results will add prognostic significance to the clinical diagnosis of invasive pituitary adenomas.

MATERIALS AND METHODS

The study included 100 patients with a clinically proven diagnosis of pituitary adenoma (main group) and 83 practically healthy people (control group).

The inclusion criteria were hormonally active and hormonally inactive adenomas with endo, para, infra, and suprasellar growth, microadenomas (smaller than 1cm) and macroadenomas (larger than 1cm).

Exclusion criteria were: age up to 10 years, oncology history, genetic diseases.

According to the primary history and laboratory instrumental data, all patients were divided into 2 main groups: non-invasive pituitary adenomas (n = 35) and invasive pituitary adenomas (n = 65), the last one was divided into 2 subgroups: 2A - 26 patients with invasive adenomas 1-2 grades and 2B- 39 patients 3-4 invasion grade. The control group was 83 practically healthy people. Depending on hormonal activity, patients were divided into 4 groups: prolactin-secreting adenomas, patients with ACTH dependent Cushing syndrome (ACTH. CS), patients with acromegaly, with hormonal inactive pituitary adenomas (HIA) and a comparison group incidentalomas.

To diagnosis of pituitary adenoma, all examined were performed an MRI study using an MRI scanner (Philips 1.5T, India) on indications with or without administration of contrast agents. Scanning technique: T2-TSE transversal projection, T2-TSE sagittal projection, T1-TSE, coronary projection, T1-TSE sagittal projection.

To evaluate the invasion, we used the Knops classification, according to which the following imaging features were evaluated:

1. The size of the adenoma was estimated in three projections: anterior size × height × width [5]. The volume of the adenoma was calculated using the formula of the ellipsoid Di-Chiro-Nelson according to the parameters of three mutually perpendicular sections with measurement of pituitary dimensions

2. Tumor intersection with inter-carotid lines (Knops classification (Vieira et al, 2004) was assessed.

- 0 degree - adenoma does not affect cavernous sine (intact cavernous sine)
- 1st degree - tumor does not cross the middle intra-carotid line;
- 2nd degree - tumor spread to the lateral line;
- 3rd degree - tumor spread beyond the lateral line;
- 4th degree – a cavernous segment of the internal carotid artery is occupied by tumor.

Molecular genetic analysis.

Molecular genetic studies were carried out in the laboratory of the molecular genetics department of the Specialized Scientific Practical Medical Center for Hematology, Uzbekistan. Venous blood was used as biological sample. Sampling was done in special ETDA anticoagulant tubes. DNA isolation was performed by a standard phenol-chloroform extraction method. DNA was isolated from peripheral blood leukocytes of patients of the main group and the control group (healthy) using the standard phenol-chloroform extraction method using the DNA-express blood reagent (Synthol, Russia). The polymorphism of the studied genes was investigated by the method of Polymorphism of regions of the studied genes in VEGFA gene G634C positions (rs2010963 locus), TP53_2 gene C/T (rs17884159 locus), HIF1A gene C/T (rs11549465 locus) and G-197A in a gene of IL-17A carried out by method an allele - specific polymerase chain reaction with the use of sets of reagents of SNP-express (Sintol, Russia) (RT-PCR).

Statistical analysis.

In both groups, the distribution of allele frequencies and genotypes across all the polymorphisms studied was applied to the x^2 criterion.

The degree of allele and genotype associations of the study groups was evaluated in odds ratio odds ratio, OR values, by the formula: OR = (a x d)/(b x c), where a is the frequency of the allele (genotype) in the patient sample, b is the frequency of the allele (genotype) in the control sample, c is the sum of the frequencies of the remaining alleles (genotypes) in the patient sample, d is the sum of the frequencies of the remaining alleles (genotypes) in the control sample.

Table 1

Frequency of the polymorphism of genotypes VEGFA, HIF-1A,TP53_2 and IL-17A

Polymorphism G634C of VEGFA gene								
Polymorphism	Control	Non-invasive	OR	p	Control	Invasive	OR	p
	n=83 (%)	n=29 (%)	(95%CI)		n=83 (%)	n=52 (%)	(95%CI)	
G/G	68 (81.9)	25 (86.2)	1.37	0.59	68 (81.9)	31 (59.6)	0.32	0.005
			(0.4-4.5)				(0.14-0.71)	
G/C	13 (15,7)	4 (13.8)	0.86	0.8	13 (15,7)	17 (32.7)	02.6	0.02
			(0.25-2.8)				(1.14-5.98)	
C/C	2 (2,4)	0 (0)	-	-	2 (2,4)	4 (7.7)	03.3	0.17
							(0.6-19.1)	
Polymorphism C/T of HIF1A gene								
C/C	74 (89.2)	25 (86.2)	0.76	0.67	74 (89.2)	36 (69.2)	0.27	0.005
			(0.21-2.68)				(0.11-0.67)	
C/T	8 (9.6)	4 (13.8)	1.5	0.53	8 (9.6)	13 (25.0)	3.1	0.02
			(0.4-5.4)				(1.2-8.1)	
T/T	1 (1.2)	0 (0.0)	-	-	1 (1.2)	3 (5.8)	5.0	0.16
							(0.5-49.6)	
Polymorphism C/T of TP53_2 gene								
C/C	79 (95.2)	26 (89.6)	2.3	0.30	79 (95.2)	43 (82.7)	0.24	0.02
			(0.47-10.8)				(0.07-0.83)	
C/T	4 (4.8)	3 (10.3)	2.3	0.30	4 (4.8)	8 (15.4)	3.6	0.04
			(0.47-10.8)				(1.02-12.6)	
T/T	0 (0.0)	0 (0.0)	-	-	0 (0.0)	1 (1.9)	-	-
Polymorphism G-197A of IL17A gene								
G/G	53 (63.9)	20 (69.0)	1.25	0.61	53 (63.9)	29 (55.8)	0.71	0.34
			(0.5-3.1)				(0.35-1.44)	
G/A	26 (31.3)	8 (27.6)	0.83	0.70	26 (31.3)	19 (36.5)	1.26	0.53
			(0.32-2.1)				(0.60-2.6)	
A/A	4 (4.8)	1 (3.4)	0.70	0.75	4 (4.8)	4 (7.7)	1.64	0.49
			(0.07-6.6)				(0.39-6.8)	

RESULTS

According to the given results the invasion grade 3 and 4 mostly were identified in the patients with non-functioning pituitary adenomas (NFPA) 45.5% (n=10), acromegaly 41.2%(n=7) and with the lower percentage in the patients with prolactinomas 25.0% (n=6). Thus, patients with NFPA should be taken into consideration as a prospective types of adenomas with aggressive behavior.

Genetic analysis.

Our findings of genetic analysis of VEGFA polymorphism at least hint that heterozygote mutation (G/C) in patients with invasive adenomas was detected twofold higher 32.7% (n=17.2) compared to the control group 15.7% (n=13). Moreover, homozygote mutation C/C is also observed more in the group of patients with invasive adenomas 7.7% (n=4), which supports the fact that mechanistic progression of invasive adenomas are con-

tributed by mutation of angiogenesis via VEGFA.

As reported earlier the main regulator of the VEGFA is HIF1A. We have conducted the next experiment to detect, whether VEGFA mutation is correlated simultaneously with HIF-A mutation in patients with invasive adenomas compared to the control group. The results of the experiment found that heterozygote mutation C/T of HIF-1A gene detected significantly higher (p=0.02) in patients with invasive adenomas compared to the control group, with 25% (n=13) and 9.8% (n=8) respectively. While in non-invasive adenomas this mutation observed approximately three times lower. Our results clearly support the argument of correlation of the VEGFA and HIF-1A with invasiveness pattern of aggressive pituitary adenomas.

To identify tumorigenic mechanism and proliferative prototype of aggressiveness, we have investigated the role of the most well-known onco-suppressor P-53 and whether genetic mutation of TP-53_2 may contribute to the tumor invasive growth. It was observed that in patients with invasive adenomas the frequency of heterozygote mutation (C/T) of the TP-53_2 gene was found significantly higher 15.4% (n=8) compared to the control group 4.8% (n=4). It was observed that the frequency of heterozygote mutation in non-invasive adenomas is constitute 10.3% (n=3) and no homozygote mutations have been detected in both control and non-invasive adenomas.

Another hypothesis of our study was to identify the role of the IL-17 in adenomas invasion. It was found that heterozygote G\A mutation of IL-17A has been found in 36.5% (n=19) of invasive adenomas and 27.6% (n=8) in non-invasive one. The frequency of the homozygote mutation observed in 7.7% (n=4) in invasive adenomas and 3.4% (n=1) in non-invasive adenomas, which can support the inflammatory role of IL-17 in tumorigenesis of APA.

To see, whether genetic findings have correlated with tumor aggressive behavior, we grouped all patients in the four different behavioral category:

- adenomas with progressive growth after transsphenoidal surgery (TSS) (n=35),
- resistant adenomas to the traditional medications (n=12),
- primary invasive adenomas grade 3-4 by Knops classification (n=21) and
- incidentalomas or silent microadenomas (n=13).

Given all together, it was found that the frequency of the heterozygote mutation of the VEGFA 33.3% (n=7) and HIF-1A 57.1% (n=12) were highly detected in adenomas with primary invasive adenomas with invasion grade 3 and 4. While TP53 and IL-17A heterozygote mutations were more frequently found in resistant tumors with 41.6% (n=5) and 58.3% (n=7) respectively (Table 2).

Table 2

Difference of polymorphism and the APA behavior

	TSS (progressive growth) (n=35)	Resistant APA (n=12)	Invasion grade 3-4 (n=21)	Incidentalomas (n=13)	p-value
VEGFA					
G\C	11(31%)	2(16,6%)	7(33,3%)	1(7,6%)	0.27
C\C	1(2%)	0	3(14,2%)	0	-
Tp53					
C\T	3(8,5%)	5(41,6)	3(14,2%)	0	0.013
T\T	1(2%)	0	0	0	-
HIF-1A					
C\T	3(8,5%)	2(16,6%)	12(57,1%)	0	<0.001
T\T	2(5,7%)	1(8,3%)	1(4,7%)	0	0.798
IL-17A					
G\A	12(34,5%)	7(58,3%)	6(28,5%)	0	0.017
A\A	3(8,5%)	0	2(9,5%)	0	-

DISCUSSION

The mechanistic link of pituitary adenomas' development with genetic mutations is still a questionable topic of researchers. We have investigated whether genetic defects regulating the expression of the VEGFA, HIF-1A, P-53, IL-17 promote pituitary adenomas aggressive behavior and whether these markers can add prognostic significance to the clinical diagnosis of invasive pituitary adenomas.

Our results approved that the most pivotal mechanism of aggression is hidden in the angiogenesis processes. VEGF is a key molecule of angiogenesis observed by many studies including pituitary adenomas and this molecule can be an equivalently predictable marker of aggressiveness together with Ki-67 and P53 (Yarman et al, 2010). VEGF induces neovascularization through the PI3\AKT, MAPK pathways stimulating tumor proliferation (Onofri et al, 2006). Moreover, recent studies demonstrated that VEGF initiates immune escape of the cells, which distracts normal cell microenvironment and induces tumor growth (Voron et al, 2015). According to Turner et al, (2000), excess vascularization is not spread in all types of adenomas, however invasive prolactinomas and non-functional adenomas were found to be more vascular compared to non-invasive adenomas, which were found in surgical samples. Current results support

the literature findings that the vascularization process is a dynamic and complex process including proliferation, matrix degeneration, migration, and remodeling consequently this mechanism promotes tumor growth and invasion (Turner et al, 2000).

Earlier researchers demonstrated overexpression of VEGFA and HIF-1A, which correlated with tumor invasion. However, the investigation has been observed immunohistochemically in the samples obtained after surgery. However, this method is inconvenient as a prognostic method of diagnosis, while genetic analysis is easy to manage without surgical intervention.

It has been revealed that there is statistically significant associations between VEGFA, HIF-A, TP-53, IL-17 genetic mutations, and pituitary adenomas invasion risk. It was found that heterozygous VEGFA G634C G\C genotype and HIF-1A C\T genotype detected higher in invasive pituitary adenomas compared to the control and non-invasive pituitary adenomas. In addition, these mutations were found to be associated with tumor invasion grades 3 and 4 by Knops classification. This result supports the fact that neoangiogenesis induced via hypoxia is the pivotal mechanism of tumor invasion and aggressive behavior.

In addition, it was found that VEGFA and HIF-1A is strongly correlated with aggressive pituitary adenomas behavior and detected more in primary invasive adenomas grade 3 and 4 which are equivalent of the aggressiveness. Thus, both VEGF and HIF-1A can be prospectively used as predictive markers of aggressiveness in the molecular-genetic level of APA development.

According to Qiu et al (2011), a high expression MMP-9, IL-17and IL-17R is linked to the invasive pattern of pituitary adenomas. It was noted that by tumor growth and extension of the volume, there is also more damage in pituitary adenomas as necrosis, cystic degeneration, bleeding especially in invasive adenomas, suggesting that invasive behavior may be accompanied by a chronic inflammatory response induced via IL-17. Moreover, it was observed that after surgical adenoma ectomy the level of the IL-17 decreased over time (Numasaki et al, 2004). Thus, increasing the level of the IL-17 can be a prediction of the recurrence. It has been investigated that IL-17 mutation may be prognostic in resistant pituitary adenomas and in patients with recurrence after surgery, which strongly supports literature findings as well.

CONCLUSION

1. It was found that non-functioning adenomas and GH producing adenomas are the most frequent types of aggressive adenomas with invasive growth patterns up to 4th grade.

2. Polymorphism of the genes of VEGFA, HIF-1A, Tp-53, and IL-17A detected significantly higher in invasive pituitary adenomas. Thus, genetic analysis can predict tumor growth before the surgical intervention.

3. VEGFA and HIF-1A polymorphism were detected significantly higher in adenomas with primary massive invasion grades 3 and 4 compare to the other genetic polymorphisms. While T-p53 and IL-17A mutation were found higher in resistant adenomas to traditional medical therapy. Thus, it should be hypothesized, that each investigated molecular-genetic mutation is responsible for the different criteria of aggressiveness and can be used as a specific diagnostic marker of aggressiveness. However, further researches are required to support obtained results.

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