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Review Article

Spontaneous Pituitary Tumors in Rats: A Review

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Abstract

The purpose of this article is to present the issue of spontaneous pituitary tumors in rats. These are non-metastatic tumors made of pituitary glandular cells and are a common health problem in this species. Depending on age, gender and strain, prevalence may reach 100%. The process of their formation is complex - molecular genetic changes initiate the transformation of cells, and hormones and growth factors play an important role in stimulating their proliferation. A commonly used classification of pituitary tumors is that created by WHO. It is based on the determination of the pituitary glandular cell lines using markers such as hormones and transcription factors. Clinical symptoms can be divided into two groups - neurological and hormonal. Neurological symptoms result from tumor growth and pressure on surrounding structures in the brain. Hormonal symptoms occur as a result of hypothalamic-pituitary axis disorder. Diagnosis in veterinary medicine is usually based on medical history and clinical examination, but additional tests such as CT or MRI can also be used. Bromocriptine and cabergoline are used to treat pituitary tumors in rats. Research on potential markers has been ongoing for years, including p53, Ki-67, MMP-9 or PTTG, however, so far, the results of the research remain ambiguous.

STRESZCZENIE

Celem niniejszego artykułu jest przedstawienie zagadnienia spontanicznych guzów przysadki u szczurów. Są to nieprzerzutujące nowotwory wywodzące się z komórek gruczołowych przysadki. Stanowią one częsty problem zdrowotny u tego gatunku. W zależności od wieku, płci i szczepu prewalencja może dochodzić do 100%. Proces ich powstawania jest złożony - molekularne zmiany genetyczne inicjują przekształcanie komórek, a hormony i czynniki wzrostu grają istotną rolę w pobudzeniu ich proliferacji. Powszechnie stosowaną klasyfikacją guzów przysadki jest ta utworzona przez WHO. Oparta jest ona na oznaczeniach linii komórek części gruczołowej przysadki przy użyciu markerów takich jak hormony czy czynniki transkrypcyjne. Objawy kliniczne podzielić można na dwie grupy - neurologiczne i hormonalne. Objawy neurologiczne wynikają ze wzrostu guza i ucisku na okoliczne struktury w mózgowiu. Objawy hormonalne występują w wyniku zaburzenia osi podwzgórzowo-przysadkowej. Diagnozę w medycynie weterynaryjnej stawia się najczęściej opierając się na wywiadzie i badaniu klinicznym,jednak wykorzystać można do tego też badania dodatkowe takie jak CT bądź MRI. W leczeniu guzów przysadki u szczurów stosuje się bromokryptynę oraz kabergolinę. Od lat trwają badania nad potencjalnymi biomarkerami uwzględniające m.in. p53, Ki-67, MMP-9 czy PTTG, jednak dotychczaswyniki badań pozostają niejednoznaczne.

INTRODUCTION

Pituitary adenomas are non-metastatic tumors composed of pituitary endocrine cells [1]. They are the cause of health problems in many species. In humans, up 20% of population is estimated the have them [1,2]. Very often, these tumors are detected by chance when performing imaging tests - they are then referred to as pituitary incidentaloma. They constitute 15% of intracranial tumors and 25% of tumors operated in the cranial cavity [2] while, the incidence of pituitary adenocarcinomas is estimated at 0.1-0.2% of cases [3]. According to the research, gender does not affect the incidence of pituitary adenomas in humans. An important factor is age - in the age group of 50-60, the frequency of occurrence in the post mortem study was set at 30% [1].

The most common type of pituitary tumor in humans is prolactin-secreting tumors (prolactinoma) - this type constitutes approximately 50% of all pituitary adenomas [3]. About 1/3 of tumors do not show hormonal activity at all.

Due to the high frequency of their occurrence in humans, numerous studies are carried out on an animal model. The laboratory animal commonly used in these studies became a rat. The research conducted over the years in various scientific centers shows that, depending on the age, sex and strain, the prevalence of pituitary adenomas in rats varies from 0 to

100% [4]. The disease mainly affects females over 18 months of age who have not been spayed at an early age. Inbreeds are particularly vulnerable to the occurrence of this neoplasm. Prolactin-secreting tumors (prolactinoma) are the most common ones, in the second place - secreting somatropin. Pituitary tumors secreting other hormones (ACTH, TSH, FSH and LH) are rarely described. Secretory activity can affect several hormones or one of them. Also, hormonally inactive tumors are much less common [5].

PITUITARY ADENOMAS PATHOGENESIS

For many years, the mechanism of pituitary tumor pathogenesis was a controversial issue in the science world. Two theories describing the pathogenesis of these tumors have arisen - one of them is based on the participation of hormones and growth factors, the other on the spontaneous mutation of a single progenitor cell. Currently, it is known that the reason lies on both sides, and the formation of pituitary tumors is a multi-stage process of carcinogenesis, in which the event initiating the transformation of cells is created by molecular genetic changes, while hormones and growth factors play an important role in stimulating cell proliferation.

Genes responsible for the initiation of pituitary adenomas

GNAS1: The GNAS1 gene is responsible for the coding of the stimulatory G alpha subunit that is associated with hormonal receptors. The activating mutation within its alpha subunit causes a decrease in GTPase activity and consequently an increase in the concentration of the cAMP activated transcription factor (CREB). This mutation is the cause of the formation of 40% of somatotropic adenomas, 10% of hormone-deficient tumors and 5% of adrenocorticotropic tumors. It also leads to McCune-Albright syndrome [2] - a genetic disease that manifests itself, among other hormonal disorders, as bone and skin changes.

PRKAR 1: The PRKAR1 gene is responsible for coding of the type 1 regulatory entity (R1) for protein kinase A (PKA). In humans, it is located on the 2p16 chromosome. Mutation within R1 leads to continuous activation of protein kinase A catalase units. In 50% of patients this mutation leads to Carney syndrome, in which one of the co-existing diseases (in about 10% of cases [6]) is pituitary adenomas - mainly somatothroph type. This mutation rarely occurs in spontaneous pituitary adenomas [2].

MEN1: The MEN1 gene encodes a protein - menin. It acts as a repressor of AP-1 mediated transcription by interacting with the factor JunD. Its mutation leads to the occurrence of multiple adenomatous syndrome (MEN 1), which is characterized by the presence of parathyroid hyperactivity, endocrine pancreatic tumors and in 50% of pituitary adenoma human patients, including the majority of lactotropic adenomas (90% of cases). [2,7] This mutation, however, rarely occurs in spontaneous pituitary tumors.

PTTG: The task of PTTG is regulation of the cell cycle and separation of sister chromatids in anaphase of mitosis. As a result of its overexpression, there are disorders of chromatid separation, aneuplody, chromosome instability and, as a consequence - cell cycle disorders [2]. In addition, PTTG acts on pituitary growth and angiogenesis via VEGF and bFGF. Studies in rats have shown that estrogen-induced adenomas increase PTTG expression in the pre-tumor stage [8]. This proves that PTTG is involved in both the initiation and promotion of pituitary tumors [9].

Table 1: Pituitary tumors classification" (WHO, 2017) excerpt

Pituitary adenomas
- Somatotroph adenomas (8272/0)
- Lactotroph adenomas (8271/0)
- Thyrotroph adenomas (8272/0)
- Corticotroph adenomas (8272/0)
- Gonadotroph adenomas (8272/0)
- Null cell adenomas (8272/0)
- Plurihormonal and double adenomas (8272/0)
• Pituitary carcinoma (8272/3)

Table 2: A brief comparison of selected biomarkers.

Biomarker	The most common test method	Advantages	Disadvantages
Ki-67	avidin-biotin immunohistochemistry	easy to calculate, reproducible and reliable	research results are not consistent, associated with many types of cancers
p53	avidin-biotin immunohistochemistry	Easy tests, readily available reagents	associated with many types of cancers, can't be used as an independent factor
PTTG	RT-PCR	sensitive marker in case of pituitary tumors	expensive to test
MMP-9	ELISA (sandwich enzymes immunoassay technique)	reliable marker for predicting the biological behavior of tumors	does not differ between non-invasive adenomas and normal pituitary glands

Figure 1 Patient with typical clinical symptoms.

The role of hormones in the formation of pituitary adenomas

Pituitary adenomas develop in situations where there is overproduction of hypothalamic hormones or in the case of hormone deficits secreted by peripheral endocrine organs that inhibit the production and secretion of the pituitary gland. This is

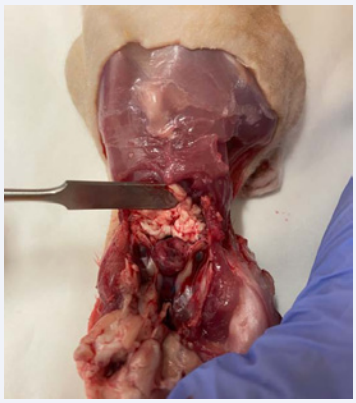

Figure 2 Pituitary tumor in post mortem examination.

one of the arguments confirming the thesis about the participation of hormones in their pathogenesis. Another proof of the validity of this thesis is the paradoxical pituitary hormonal response to exogenous hormone stimulation, which is characteristic of pituitary tumors.

GHRH: In 1985 the generation of transgenic mice for the human fusion gene GRF (hGRF), mouse metallothionein-1 / hGRF (MT-GRF) was described (Hammer, Brinster, Rosenfeld, Evans, Mayo). As a result of strong overexpression of GHRH in these mice, somatotropic cell hyperplasia occurred followed by subsequent development of the pituitary somatotropic adenoma. In the literature there are descriptions of clinical cases of people with hyperplasia of somatotropic cells as a result of chronic stimulation of GHRH secreted by tumors originating from the hypothalamus, bronchus and pancreas [6,1]. This may prove that GHRH plays an important role in the formation of somatotropic cell tumors.

In humans, somatotropic adenoma cells show a response to GHRH stimulation, which means the presence of GHRH-R receptors in them [1]. Studies carried out on these receptors show that their expression is not limited to somatotropic cell adenomas and may suggest that they play another role in the pituitary gland, however, significant forms of active GHRH receptors in pituitary adenomas have not yet been described. [6]

TRH: Prolonged primary hypothyroidism, as a result of excessive TRH secretion, leads to the growth of pituitary thyrotropic cells. It also leads to hyperplasia of lactotropic cells. This condition is most common in young women and is easily reversible by treatment with thyroxine analogues [6].

Studies have shown that in different types of pituitary adenomas, variable expression of TRH receptors occurs, but it is similar to that of healthy pituitary gland [10]. The vast majority of TRH receptors have an unchanged structure, and despite the discovery of truncated forms of these receptors, there has been no evidence of activating mutations within pituitary tumors.

CRH: Studies have confirmed that continuous intravenous infusion of CRH increased the number of corticotropes [11]. However, exposure to continuous infusion of CRH or its continuous production by prostate cancer or gangliocytoma did not contribute to the development of corticotropic cell adenoma. This may mean that internal corticotropic mutation [12] is needed to produce the tumor.

GnRH: There have been reports of gonadotropic cell adenomas as a result of long-term hypogonadism associated with gonadal failure [13]. However, most gonadotropic adenomas arise spontaneously and are not associated with it [1]. Adenomas produce both GnRH and GnRH receptors, as well as truncated forms of these receptors, however, no pituitary mutation activating GnRH receptors has been described so far [6].

Estrogens: Studies have shown that in rodents high doses of estrogen induce lacto tropic cell hyperplasia and the formation of prolactin adenomas. This happens as a result of increased expression of PTTG, bFGF, TGF, VEGF and galanin. A similar effect in humans was observed only in transsexual persons who were found to have receptors for estrogen alpha, beta and estrogen receptor isoforms that are activated regardless of the presence of the ligand [2].

The role of growth and angiogenic factors in the formation of pituitary adenomas

Pituitary gland cells are a source of many growth factors. These are polypeptides that regulate pituitary cell proliferation and migration by controlling the expression of specific genes. Their action is based on autocrine and paracrine. Among the growth factors, bFGF, FGF4, TGFa and B, and NGF are seen as playing an important role in the formation of pituitary tumors. Numerous oncogen products are homologues of growth factors, their receptors or enzymes involved in the process of mitogenesis [1].

TGF-a: TGF-a is a protein anchored in the cell membrane of both normal pituitary and tumor cells. It is a strong mitogen for lactotropes. It can interfere with GH, PRL and TSH production and cell proliferation. It was found that TGF-α mediates the action of estrogens, whose over expression causes an increase in TGF-α mRNA and causes hyperplasia of lactotropes. According to studies performed in mice overexpressing TGF-α, lactotropic hyperplasia and development of lactotropic adenomas occurs in animals aged 12 months [14]. Bromocriptine treatment causes a decrease in RGF-a mRNA levels [15].

TGF-B: The transforming growth factor beta superfamily includes inhibin, activin, anti-Mullerian hormone (AMH), and Bone Morphogenetic Proteins (BMP). They control the proliferation and differentiation in most cell types. Inhibin subunits are expressed in pituitary gonadotropic adenomas, and activin is known to stimulate hormone secretion by these tumors [1].

bFGF and FGF-4: Like TGF-a, bFGF occurs in both normal pituitary and tumor cells. In rodents, it regulates pituitary secretion of GH, PRL and TSH [16]. FGF-2 is a mitogen for lactotropes - when inducing their hyperplasia using estrogens, rodents have an increase in bFGF expression and adenoma formation [6]. FGF-4 is also a mitogen for lactotropes, both in vivo and in vitro. Its expression is not observed in the normal pituitary gland, only in cancerous and embryonic tissue [17].

NGF: Nerve growth factor is also present in the normal pituitary gland. It participates in differentiating lactotropes and maintaining their phenotype [2]. Its overexpression affects intense hyperplasia of lactotropic cells. However, this does not cause tumor formation [1]. Together with bFGF and EGF, it stimulates prolactin synthesis and expression of D2 dopaminergic receptors [2]. According to studies conducted, exposure of human pituitary tumor cells to NGF in vitro resulted in a reduction in their proliferation. In mice, a reduction in tumorigenesis was also observed [18].

CLASSIFICATION OF PITUITARY ADENOMAS

There are various classifications of pituitary tumors in the literature, but the most widely used is the one created by the World Health Organization. Currently, the 4th edition of the classification is available, last updated by WHO in 2017. The classification created by WHO is based on the determination of pituitary glandular cell lines using markers such as hormones and transcription factors. In this division, tumors are assigned numerical codes (ICD 0 codes) - the first 4 digits indicate the histological term, and the fifth digit, after the / sign, indicates tumor behaviour (0 - benign tumors, 1 - indefinite, borderline or uncertain behaviour, 2 - cancer in situ and endothelial neoplasia grade III, 3 - malignant neoplasms).

Somatotroph adenomas

These are tumors originating from the Pit-1 glandular cell line of the anterior pituitary gland, secreting mainly somatotropin. The cell composition of this type of tumor is most often densely granulated somatotropic cells (DGSA). Less common are pure tumors composed from sparsely granulated somatotropic cells (SGSA). There are also mixed somatotropic and lactotropic adenomas, mammosomatotropic adenomas and multi-normal adenomas. In most cases, they are macroadenomas [19].

Lactotroph adenomas

Prolactinomas are also tumors originating from the pituitary glandular cells of the pituitary line Pit-1. The main hormone they release is prolactin. Due to the cellular composition, Acidophilic Stem Cell Adenomas (ASCA), Densely Granulated Lactotropic Cell Adenomas (DGSA) and sparsely granulated lactotropic cell adenomas (SGSA) can be distinguished.

Corticotroph adenomas

These are tumors that originate from the anterior pituitary lobe T-pit cell line. They secrete ACTH and other Proopiomelanocortin-Derived Peptides (POMC). Due to the histological structure, they are divided into: Crooke cell adenomas, the most common densely Granulated Corticotropic Adenomas (DGCA) and sparsely granulated corticotropic adenomas (SGCA). Most often these are microadenomas [19].

Gonadotroph adenomas

These are adenomas secreting gonadotropins, luteinizing hormone (β-LH) and follicle-stimulating hormone (β-FSH). This is the most common subtype of hormonally inactive adenomas. The differences between the hormonally inactive gonadotroph adenoma and zero cell adenoma require clarification and are still being analyzed.

Null cell adenomas

According to the previous classification (from 2004), these adenomas were treated as hormonal negative. According to the latest classification, this subtype is defined as adenomas composed of pituitary glandular cells that cannot be differentiated by cell type specificity using pituitary hormones, transcription factors and ultrasound features [20]. This is a very rare type of pituitary adenoma - it accounts for only 5% of all hormonally immuno-negative tumors [21].

Plurihormonal adenomas

These are adenomas secreting more than one pituitary hormone, with the exception of somatotropin and prolactin secreted together with luteinizing and follicle stimulating hormone. Some of them are from different cell lines, others are from the same (monomorphic) line. They should not be confused with two or more tumors co-existing with and originating from other cells.

Pituitary adenocarcinomas

These are pituitary tumors that metastasize within the cranial cavity or metastasize within the rest of the body. Apart from metastases, there are no differences between adenocarcinomas and adenomas, and therefore histological features do not affect their definition.

CLINICAL SYMPTOMS

The development of clinical signs of pituitary tumors in rats is closely correlated with the rate of tumor growth. In most individuals, this development is gradual, but there are cases in which symptoms appear suddenly [22]. Symptoms can be divided into two groups - neurological and hormonal symptoms.

Neurological symptoms

Neurological symptoms caused by pituitary tumors result from the presence of an abnormal mass in the skull cavity that presses on the surrounding structures - this is called mass effect. In human medicine, the neurological symptoms of all brain tumors are divided into general and focal [23]. General symptoms result from an increase in intracranial pressure caused by tumor growth. In turn, focal symptoms arise by pressing the tumor mass on specific parts of the brain and damaging them.

General symptoms: As mentioned earlier, they are caused by intracranial hypertension caused by the growth of cancerous tissue. The most frequently reported symptom of brain tumors among human patients are headaches - they are found in 50% of patients in the initial stage of the disease and in 90% in the advanced stage [23]. They occur due to stretching of the dura mater or have a vascular background [5]. Also, common symptoms are disturbance of consciousness and drowsiness. Visual disturbances appear due to the presence of congestive disc - swelling of the optic disc as a result of increased intracranial pressure. The neurological symptoms of general brain tumors also include dizziness, balance disorders, neck stiffness and so-called Cushing's symptom expressed in bradycardia and an increase in blood pressure [23].

Focal symptoms: They are associated with damage to specific

structures in the brain as a result of tumor growth. In human medicine, they are divided into defective - occurring in the form of paresis and sensory disorders, and irritation - mainly in the form of focal epileptic symptoms [23].

As a result of tumor compression on the frontal lobe of the brain, behavioral disorders and mental state occur. These disorders are widely described in human patients. However, for obvious reasons, only some of them can be found in animals. This includes apathy, dementia, reduced propulsion, aggression, pressure on the obstacles, and olfactory disorders (resulting from damage to the olfactory nerve) [5,22,23].

When a tumor causes damage to the temporal lobe, a broad spectrum of speech disorders occur in humans [23]. In rats, this type of disorder cannot be diagnosed. However, epileptic seizures can be diagnosed due to temporal lobe displacement and tumor compression on the hippocampus bend [5].

As a result of compression on the parietal lobe, various types of sensory disturbances occur on the opposite side to the damage. Occipital lobe tumors result in visual impairment ranging from half-sightedness to complete blindness [23].

It is unfavorable for the tumor to grow into the posterior cranial pit. This causes a spectrum of symptoms associated with damage to the pyramidal pathways, testicles, and cranial nerves that originate in the brainstem. Stem disorders include disorders such as dysphagia, respiratory distress [22,23]. As a result of damage to the upper motor neuron, so-called pyramidal syndrome manifested itself by sensory disturbances and paresis of the thoracic and pelvic limbs [5,23].

Pressure on midbrain structures results in disturbed consciousness, pupil inequality, drooping eyelids, tremors and muscle stiffness [23].

The occurrence of cerebellar syndrome occurs as a result of compression of the tumor mass on the cerebellum or by damage to the spinal-cerebellar pathways. There is uncertain gait, dysmetry, muscle weakness, ataxia, intentional tremor and nystagmus [5,22,23].

Due to the location of the pituitary gland, pressure on structures located in its close vicinity is very common - the optic nerve crossing, the so-called oculomotor nerves (oculomotor, block, abdomen). This causes visual disturbances, blindness, widening of the eyeballs (usually one-sided) and impaired mobility of the eyeballs [5, 24].

Due to the compression of the tumor mass on the hypothalamus, thermoregulation disorders, disorders of food intake and disorders of consciousness occur [25]. Sleep disorders are alsodescribed.

Hormonal symptoms

As a result of dysfunction of the hypothalamic-pituitary axis, hormonal symptoms occur. Compression of tumor mass on the hypothalamus leads to impaired transfer of hypothalamic hormones to the pituitary gland and can lead to hyperthyroidism or hypothyroidism. Hormonal symptoms also result from excessive activity of the adenoma and therefore depend on its type - patients show hormonal symptoms associated with an imbalance of specific hormones [26]. The most common type of adenoma in rats is prolactinoma. As a result of hyperprolactinemia, galactorrhoea occurs in older, non-pregnant females. Pituitary adenoma may lead to Cushing's syndrome. In rats hyperadrenocorticism causes fertility disorders, muscle weakness, dermatological disorders, liver enlargement, polyuria and polydipsia [27]. As a result of a decrease in the level of vasopressin in the blood, diabetes insipidus occurs. Hypothyroidism or acromegaly can be found much less frequently [5].

RECOGNITION

Most often, the diagnosis in veterinary medicine is made based on the interview with the animal's owner and the co-occurring symptoms observed in the general and neurological clinical examination. However, it is important to remember about differential diagnosis with other diseases that may affect the functions of the nervous system, such as e.g. otitis externa, encephalitis, senile spinal cord degeneration or metabolic diseases [28]. To this end, all necessary tests should be performed, such as skull and spine x-ray, morphological and biochemical blood tests. The final confirmation of the diagnosis is post-mortem histopathological examination.

Diagnosis of pituitary adenomas should be supplemented with imaging tests such as CT or MRI. At present, in human medicine, MRI using contrast media is the most preferred method of imaging pituitary tumors [29]. If microadenomy is suspected, the imaging protocol should contain a sequence with dynamic contrast administration (intravenous gadolinium is used for this). However, due to the availability of equipment, the cost of the examination and the need for proper patient preparation, these examinations in veterinary medicine are rarely performed and only in large scientific or therapeutic centers.

TREATMENT

In human medicine until the 1970s, radiotherapy and surgery were the methods of choice used to treat pituitary tumors. The situation changed due to discoveries made in Sandoz laboratories. In 1967, Edward Fluckinger synthesized the first selective D2 dopamine agonist, 2-bromo-alpha-ergocriptine (bromocriptine). Then in 1982 Bauer and partners obtained the first long-acting somatostatin analogue - ocreotide. These findings created the prospect of pharmacological treatment of pituitary tumors [30].

Currently, in the treatment of prolactinoma tumors in both human and veterinary medicine, the most frequently chosen method is pharmacotherapy using D2 dopamine agonists - bromocriptine and cabergoline. Both substances are very well absorbed after administration per os, reach dopamine receptors located in lactophores and cause dopamine secretion. As a result of their action, inhibition of prolactin secretion, contraction of lactotrophs and their apoptosis occur, which leads to a decrease in tumor mass [5,22]. Both substances can also, although with less success, be used to treat gonadotropic tumors. According to available publications, cabergoline is more effective in treating pituitary adenomas than bromocriptine. It is influenced by its almost twice higher affinity for dopamine receptors, longer half-life and slower elimination from the pituitary gland. It is successfully used in patients who have the phenomenon of bromocriptine resistance. In addition, cabergoline causes fewer

side effects than bromocriptine, which makes it a safer drug [31,32,3]. In the therapy of somatotropic adenomas, somatostatin analogues, such as periodotide, lanreotide and SOM230, are effective, especially those assisted by cabergoline [3].

Surgical removal of the tumor from the transsphenoidal approach is recommended in patients with enlarged hormone inactive tumors who do not respond to pharmacotherapy and are at risk of having a stroke. In prolactinoma, surgical removal of the tumor normalizes prolactin concentration in 65-85% of patients with microadenomas and in 30-40% of patients with macroadenomas. The recurrence rate is 20% over the next 10 years. With somatotropic cell adenomas, the therapeutic efficacy of surgical resection is up to 90% for microadenomas and up to 60% for macroadenomas [3].

Radiation therapy is rarely performed as the therapy of choice. It is used in atypical patients who do not respond to pharmacological and surgical treatment, do not tolerate medication given to them, cannot tolerate surgery, and in people who do not agree to long-term pharmacological therapy. Most often, radiation therapy is used after surgery and according to reports reduces the risk of tumor recurrence [3].

POTENTIAL MARKERS

Researchers have been researching potential markers for years, which can predict human and animal pituitary tumors and, most importantly, help predict the invasion and malignancy of an existing tumor. Despite many studies carried out in this field, the results are ambiguous and so far, no marker has been chosen that meets the requirements set by the world of science in 100%.

Ki-67

Ki-67 is a cell cycle-related protein. It is present in the cell during the G1, S and G2 phases, but it cannot be detected in the G0 phase. Ki-67 accumulates on the surface of chromosomes - one of its ends is attracted to chromatin, the other is repelled from it (with affinity to the cytoplasm), this mechanism helps maintain the distance between chromosomes [33]. Of all proteins associated with cell proliferation, Ki-67 is the most widely studied. The MIB-1 antibody is used to detect Ki-67 antigen, and the most commonly used technique is immunohistochemistry using the avidin-biotin method. After performing the immunohistochemical test, the so-called Ki-67 labeling index is being calculated, which is the percentage of cells stained positively. It is an easy to calculate, reproducible and reliable indicator [34]. For this reason, it was used in the classification prepared by the World Health Organization [34-36]. Despite this, the results of many scientific studies conducted so far are not consistent with each other. In the article from 2016. Zheng et al. presents the results of 28 studies conducted with the participation of the Ki-67 protein - in 18 of them a relationship was found between the increase in Ki-67 expression and the invasion of the pituitary adenoma, in the remaining 10 no such correlation was found [35].

p53

The p53 protein was first discovered in 1979. by Arnold. J. Levine. It is a product of the TP53 gene, which in rats is located on chromosome 10 (in humans at 17p31 [2]. In a normal cell that has not been subjected to any stress, it appears in an inactive form and is kept low. In its active form it is a tetramer composed of four identical subunits and consists of 7 domains with different functions [37]. Its main function in the body is to maintain the genetic stability of cells, thanks to which it exhibits anti-tumor activity. It performs its function based on various mechanisms. It conditions cell apoptosis in the case of irreversible DNA damage, induces inhibition of cell proliferation, takes part in the so-called cell cycle arrest consisting in stopping the cycle in G1 / S and G2 / M phase (at that time DNA damage repair can take place and the cell cycle can be restored) and in DNA repair. Causing null mutation of the TP53 gene in mice led to to the formation of various cancers in 75% of individuals before 6 months of age [38]. In turn, other studies in the mouse model have shown that when the production of endogenous p53 is restored, tumor regression occurs [39]. The immunohistochemical method (avidin-biotin) using anti-p53 antibody is used to study the presence of p53 protein in cells [40].

PTTG

PTTG (Pituitary tumor transforming gene) is an oncogen specific for pituitary tumors. It was first isolated and described in 1977 in rat pituitary GH4 cells [41]. The task of PTTG is to regulate the separation of sister chromatids during the anaphase of the mitosis process and the induction of apoptosis through mechanisms dependent and independent of the p53 protein. The cloning of the PTTG gene was important for research on pituitary tumors - it has been shown that about 90% of adenomas have an increase in PTTG expression relative to normal pituitary cells. PTTG plays an important role in tumorogenesis - its overexpression leads to genetic instability. In addition, it is involved in the activation of growth factors (e.g. VEGF, FGF-2). This means that PTTG is involved in both the initiation and promotion of pituitary carcinoma [9].

Studies have shown that PTTG and Ki67 score> 2.9 predict adenoma behaviour as aggressive [42]. However, PTTG is considered a more sensitive marker in the case of pituitary tumors due to their association with them rather than with all cancers in general, such as Ki67.

MMP-9

MMP-9 belongs to the group of extracellular matrix metalloproteinases. These are zinc-dependent proteolytic enzymes whose primary function is to participate in the processes of remodeling and degradation of extracellular matrix components, both in physiological and pathological conditions. In addition, they have a significant role in the progression of all types of cancer by stimulating: the growth of cancer cells, their migration, metastasis and angiogenesis. Invasive tumor cells, especially fibroblasts, secrete MMPs and are an important source of these enzymes in the tumor environment [35]. Of all MMPs, MMP-9 is the most studied in the context of pituitary tumors. According to most studies, MMP-9 activity is significantly increased in invasive pituitary adenomas but does not differ between non-invasive adenomas and normal pituitary glands [43-47]. These results suggest that MMP-9 may be regarded as a potential biomarker for predicting the biological behaviour of pituitary tumors.

SUMMARY

Statistical data on the occurrence of pituitary tumors in humans certainly make this issue relevant. Pituitary adenomas are also becoming more and more important in the field of veterinary medicine. The growing popularity of rodents as companion animals and the change in the owners' approach to their treatment opens the way for veterinarians to explore the subject, develop new detection methods and treat this disease.

The vast majority, if not all, studies are carried out on animals with laboratory-induced tumors. The authors believe that it is important to do research on spontaneous tumors, as this is a significant problem in the medicine of small companion mammals especially rats. It is important to check whether the behavior of such tumors is different from those caused farmacologically and to study which markers will be most appropriate in their case.

In medicine, there are still many unknowns, both in the subject of pathogenesis, detection and prediction of the behaviour of these cancers. In many research centers, intensive research is being conducted on the biomarkers of pituitary tumors, but their results remain inconclusive. Undoubtedly, this is a matter that requires refinement and harmonization.

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