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Genetic factors in uterine fibromatosis

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ABSTRACT

Uterine fibroids represent the most commonly encountered benign tumors among women at childbearing age which might significantly influence their capacity of carring a normal pregnancy. Therefore, due to the significant impact which might be encountered, attention was focused on determining which are the most important risk factors for developing such lesions. In this respect, nowadays particular attention was given to genetic factors. In this article we discuss the implications of genetic chromosomal abnormalities aswell as chromosomal rearrangements in the formation of fibroids. We also report diseases that should not be overlooked when differentially diagnosing leiomyomatosis (MCUL1 and HLRCC).

Keywords: genetics in uterine fibromatosis, MCUL1, HLRCC, leiomyomas

INTRODUCTION

Uterine fibroids are noncancerous growths of the uterus that often appear during childbearing years affecting almost 25% of women worldwide [1]. Also called leiomyomas they are the most common benign tumors of the uterus among women of fertile age [1,2]. The exact causes and risk factors that lead to fibroids has not yet been fully elucidated. Howeevr, it is considered that uterine leiomyomas occur due to the presence of a mutation at the level of a single smooth muscle cell which will further exhibit exponential multiplication. Meanwhile, higher levels of estradiol have been reported at the level of the cells in fibroids when compared to those reported at the level of the normal, myometrial cells [3]. Another incriminated factor is represented by the presence of higher levels of growth factors in fibroids when compared to normal miometrial cells. However, recently it has been demonstrated that genetic factors also play a crucial role [3,4].

ASSESSMENT

Uterine fibromatosis is the most common pelvic tumor in women of childbearing potential. From the point of view of the formation of uterine fibroids, the promoters of their formation are estrogen and progesterone. Cytogenetically, chromosomal abnormalities were observed in chromosomes 6,7,12,14 in patients with leiomyomatosis [3].

The formation of uterine fibroids in association with mutations in the FH gene (fumarate hydratase) has recently been observed. Germline mutations in this gene produce autosomal dominantly transmitted syndromes:

1) MCUL1 (multiple cutaneous and uterine leiomyomata)/Reed's Syndrome
2) HLRCC (hereditary leiomyomatosis and renal cell cancer) [1,11].

Multiple cutaneous and uterine leiomyomatosis, also known as Reed's syndrome, is an autosomal dominant genetic condition. Affected individuals have an increased predisposition to develop benign smooth muscle tumors (leiomyomas) in the skin and uterus. Affected females frequently develop uterine leiomyomas (fibroids) that are larger and more numerous and emerge earlier than those in the general population [14].

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a rare autosomal dominant disorder that

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results from a germline mutation in the fumarate hydratase gene (FH). Individuals with FH mutations are also at risk of developing renal cell carcinoma. Patients with HLRCC and associated renal cell carcinoma have aggressive clinical courses [13,15].

The physiopathology of the disease is based on a mutation in the gene that encodes the activity of the essential enzyme of the Krebs cycle, fumarate hydratase. As a result of this mutation, the activity of the enzyme is reduced, which leads to the above-mentioned pathologies [2].

Uterine leiomyomatosis involves benign tumors that develop from the myometrium (smooth muscle layer). In addition to the smooth muscle, leiomyomas are also composed of an extracellular matrix (collagen, fibronectin, proteoglycans etc.). Leiomyomas are present in about 25% of women of childbearing potential. Although on closer inspection, the prevalence of leiomyomas increases from 25% to 70%, due to the fact that many leiomyomas are asymptomatic. Leiomyomas are usually detected in women between the ages of 30 and 50. After menopause in the absence of estrogen hormone treatments, leiomyomas decrease in volume.

There are 2 important components in the formation of fibroids:

1) Transformation of normal myocytes into abnormal myocytes
2) Growth of abnormal cells in seemingly tumor formations

Apart from their tumorigenic potential, these abnormal cells are morphologically similar at the cellular level to the smooth muscle tissue cells in the myometrium.

Leiomyomas have both mutated smooth muscle tissue cells in the form of tumor nodules and normal smooth muscle tissue cells. The mutated cells can be of various sizes and can be in the myometrium as well as adherent to it. Tumors are generally surrounded by fibrous extracellular connective tissue. The pathophysiological way that determines the formation of leiomyomas is still incompletely elucidated, speculatively it is assumed that there are also genetic changes that affect the genes that influence estrogen or progesterone receptors.

Genomic and proteomic studies have provided new evidence for changes in the molecular environment of the myometrium in the presence of leiomyomas compared to the environment in a healthy myometrium [4,12].

By profiling the gene expression of uterine leiomyomas, the irregularity of those with a functional role, a role in cell proliferation and the production of extracellular matrix was observed. To date, only a few genes have been identified as specific in association with the formation of uterine leiomyomas. However, the identified genes most likely have a promoting or effector role in the growth of leiomyomas, but the tumorigenic mechanism that leads to symptomatic leiomyomas is undiscovered [5].

Classification of leiomyomas is according to their location as it can be seen in Table 1:

TABLE 1. Uterine leiomyomas classification

Type of fibroid	Location of the uterine fibroid:
Subserous	- Immediately below the uterine serosa - Can be further classified as pedunculated or sesil
Intramural	- In the thickness of the myometrium
Submucosal	- Under the endometrial lining - Can be further classified as pedunculated or sesil

Subserous and intramural leiomyomas account for approximately 95% of tumors found in medical practice, and submucosal tumors 5% [6].

Changes from benign to malignant in leiomyomas are very rare [7].

Another classification is the genetic one of leiomyomas, which includes the partial deletion of 7q, trisomy 12, rearrangements in the cytogenetic areas 12q15, 6p21, 10q22. Other uncommon abnormalities include rearrangements in the X, 1, 13 chromosomes. One of these changes was observed in 40% of leiomyomas tested in a selective and tumor-specific manner [8].

Another observation in some studies was the relationship between tumor size and genetic changes:

1) The largest tumors with t (12,14)
2) Mosaic tumors of medium size
3) The smallest tumors with del (7) [9].

The most common abnormality is t (12, 14) (q15; q24) observed in 20% of karyotyped leiomyomas. Rearrangements in the 12q region have also been observed in other solid tumors, which may refer to 12q14-12q15 as a region with genes essential for tumor formation.

Several studies have identified karyotyping region 7q22-q32, being approximately 30 megabases, to be deleted. Deletions in this region were observed in 17% of the cases tested.

Rearrangements in the 6p21 region have been observed in other types of tumors. In leiomyomas they were observed in 5% of the tested cases and include t (1.6) (q23p21), t (6.14) (p21q24) and t (6.10) (p21q22).

CONCLUSION

These findings paved the way for the realization of the importance of HMGIC and HMGIY gene irregularities. Another gene, RAD51L1, functions as a translocation partner for the HMGIC gene, resulting in the formation of uterine fibroids.

The appearance of PCOLCE (Procollagen C-Endopeptidase Enhancer) in a sequence of at least 8 Alu is relevant in the involvement of 7q22 rearrangements that are encountered in leiomyomatosis. The activity of Alu sequences causes damage to this gene, leading to loss of gene expression, resulting in uncontrolled cell proliferation. This also results in the production of fibroids [10].

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