FAMILY GASTRIC CANCER SYNDROMES

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Abstract: *The syndromes of familial gastric cancer were recently described. Ten years ago, Guilford was the first scientist who identified a germline mutation of CDH1 (E-cadherine) gene in a Maori family from New Zeeland. Other similar discoveries in families with agregability of gastric cancer led to an international symposium in Vancouver were the syndromes of familial gastric cancer were defined.*

Cuvinte cheie: *cancer gastric, sindroame familiale*

Rezumat: *Sindroamele de cancer gastric familial reprezintă o patologie documentată recent în literatura medicală. Guilford a fost primul cercetător care, în urmă cu 10 ani, a identificat o mutaţie germinală a genei CDH-1 (E-cadherina) la o familie Maori din Noua Zeelandă. Această descoperire a fost urmată de semnalări similare în cadrul familiilor cu agregabilitate de cancer gastric, ceea ce a determinat organizarea unui simpozion la Vancouver în care s-au definit sindroamele de cancer gastric familial.*

SCIENTIFICAL ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

Until recently, evidence supporting the existence of a distinct syndrome of hereditary gastric cancer have been indirectly based on clinical evidence. Bonaparte family is one of the most famous in the world, primarily on historical considerations, but also from a health perspective, given the high incidence of gastric cancer reported: Napoleon's father and grandfather, a brother and three sisters, all have died of gastric cancer, some of them at a young age (2). More recently, it was reported in the literature of New Zealand Maori family (originally described by Jones in 1964), the period of 30 years died 25 members due to gastric cancer with no evidence of associated malignancies. Guilford was the first scientist who in 1998 documented the existence of germinal mutations in the gene CDH1 (E-cadherin) from a study of this family (12). A number of other researchers recently reported gene mutations in CDH1 germ (Richards et al. In 1999, Dussaulx-Garin et al. In 2001, Humar et al. In 2002, Oliveira et al. In 2002), which is associated with literature known as hereditary diffuse gastric cancer (25).

Emergence of new hereditary cancer syndrome caused organizing a symposium in Vancouver (International Gastric Cancer Linkage Consortium) in 1999 in which a group of geneticists, gastroenterology, surgeons, oncologists and molecular biologists have issued consensus statements and guidelines for familial gastric cancer.
According IGCCL gastric cancer there are four categories of family:

- Hereditary diffuse gastric cancer (HDGC)
- Familial diffuse gastric cancer (FDGC)
- Familial intestinal gastric cancer (FIGC)
- Gastric cancer in other familial cancer syndromes.

That gastric cancer syndromes can be characterized morphologically or entities not covered in the above are called familial gastric cancer syndromes (FGC) (21).

5.1. Hereditary diffuse gastric cancer (HDGC) defined (5) family as cancer, germinal Mutation substrate that meets the following criteria:

1. two or more documented cases of diffuse gastric cancer relatives Grade 1 or 2, with at least one diagnosis made before 50 years
2. three or more cases of documented diffuse gastric cancer in relatives of grade 1 or 2, regardless of age onset.

These criteria were based on a recently completed study by Brooks-Wilson et al., Which proposed that the diagnosis of hereditary diffuse gastric cancer should be suspected if a person or family meets one of the following circumstances (4, 15)

1. two or more cases of diffuse gastric cancer family, with at least one diagnosis made before 50 years;
2. three or more cases of gastric cancer in the family, regardless of age, with at least one documented case of diffuse gastric cancer;
3. an individual diagnosed with diffuse gastric cancer before 45 years;
4. an individual diagnosed with diffuse gastric cancer and lobular breast cancer (no other inclusion criteria);
5. a family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other inclusion criteria);
6. a family member diagnosed with diffuse gastric cancer and another with colon cancer with signet ring cells (no other inclusion criteria).

Hereditary diffuse gastric cancer is between 1-3% of all gastric cancers (9). It is a poorly differentiated adenocarcinoma that infiltrates the stomach wall causing thickening it (linita plastic) without forming a distinct tumor mass. The average age of onset is 38 years, as far described cases with onset between 14 and 69 years. Cumulative risk of gastric cancer by the age of 50 years is estimated at 21% to 49% for males and females (11), increasing to 80 years from 67% to 83% for males and females (10) . Women behave and a 39% risk for breast cancer (27).

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HDGC is transmitted by autosomal dominant pattern, altered gene is passed from one parent. So far, only discovered gene whose mutations are associated with HDGC is E-cadherina (CDH1). Risk of transmission of the mutation of the sample to each descendant is 50%. Once inherited this mutation, it is considered that the risk of developing gastric cancer is 2,000 times higher than the control population (31). It was considered and the possibility of a de novo mutation in the E-cadherinei, but the situation has not hitherto been documented. Thus, if none of the parents of a sample with an apparent autosomal dominant mutation is not affected by possible non-medical explanations as alternative paternity or adoption Unravelled (10).

To date 56 have been documented germ of CDH1 mutations, 43 were found in HDGC group and 13 in families with FDGC (21). In contrast to somatic mutations in sporadic diffuse gastric cancer, which are concentrated in the exons 7-9, where HDGC lesions were documented throughout the CDH1 gene, not reported any "hot spot" to represent a fragile locus high, exposed to mutations (3, 8, 11). These mutations have been described in families from different geographical areas and different ethnicities. Guilford et al. (12) were first identified germinal mutations of CDH1 gene in three families of Maori ethnicity in New Zealand in 1998 cecetători other families showed similar abnormalities in Europe, Africa and America (16, 22, 33).

As with other genes that predispose to hereditary cancer syndromes, one allele undergoes mutation germ, most of which are deletions (83%) resulting in the emergence of active protein, a rate of 17% is represented by nonsense mutations unknown functional significance (23). Frequently encountered and somatic mutations of the other allele (loss heterozigozității) bialelică inactivation leading to reduction or absence imunoreactivității E-cadherinei in gastric cancer cells. Similar cases of sporadic gastric cancer, the main mechanism of inactivation of wild allele is hipermetilarea CDH1 gene promoter. (9).

Other candidate genes are the suppressor genes HDGC FEZ1/LZTS1 and SMAD (13, 14.30), RUNX3 (19) or caspase (26).

5.2. Diffuse gastric cancer families (FDGC) is cancer that has agregabilitate family to meet all criteria HDGC. These cases have been identified so far 13 germ of CDH1 mutations. Among patients with diffuse gastric cancer and family agregabilitate, 70-80% fall in group FDGC. A study in the western region of Poland in 2001 aimed at determining the prevalence of families with genetic cancer syndromes revealed 113 families with FDGC. As a feature, it appears that both hereditary diffuse gastric cancer, and especially the diffuse family tends to locate in the region cardiei, showing a more aggressive than sporadic gastric cancer (20).

5.3. Familial intestinal gastric cancer (FIGC) was defined according to gastric cancer incidence in the population. Thus, in countries with high incidence (Japan, Portugal) have used similar diagnostic criteria for HNPCC Amsterdam criteria: (a) at least three relatives with intestinal gastric cancer and one of them is relative degree one with the other two; (2) at least two successive generations affected; (3) to one of the relatives, the diagnosis is made before 50 years. In countries with low incidence (USA, England), FIGC was defined as: (a) at least two grade 1 or 2 relatives affected by intestinal gastric cancer, one diagnosed before 50 years (2) three or more relatives with intestinal gastric cancer, regardless of age of onset. At present there is no mutation was identified in families with germ FIGC (23).

5.4. Gastric cancer in other familial cancer syndromes is reported that a significant proportion: nonpolipos hereditary colon cancer, familial adenomatous polyposis, SDR. Peutz-Jeghers, SDR. Cowden and SDR. Li-Fraumeni (5).

5.4.1. Nonpolipos hereditary colon cancer (HNPCC) is a well characterized familial cancer syndrome that comprises about 5-10% of all cancers rectocolonice (CRC). In this entity describes two distinct syndromes: SDR. Lynch I, which includes patients with increased risk of developing CRC and SDR. Lynch II, which covers those who associate an increased risk of extracolonice cancers (stomach, ovary, endometrium) (24). Gastric cancer is the most common malignancies associated with HNPCC, as seen in 13-20% of these patients (6,7), intestinal type is more common (9). Occurs due to defects in mating system errors repair genes, hMLH1 and hMSH2 gene mutations are seen in more than half of cases. Abnormalities of these two genes are associated with complete inactivation of the MMR system (missmatch repair), while other mutations, such as those present in the hPMS1 and PMS2 genes are associated with incomplete inactivation (1). A study (26) conducted in Korea showed a risk of 2.1 for gastric cancer patients with HNPCC and their first degree relatives, the relative risk was 11.3 times higher at young age.

5.4.2. Familial adenomatous polyposis (PAF) is an autosomal dominant disease that occurs through mutation of APC gene and colorectal cancer typically presents with early onset secondary malignizării multiples present in the colon polyps. They are also developing in the upper gastrointestinal tract. Ribbons gland polyps are the most common gastric polyps in the PAF, some of whom may develop into malignant (9, 32).

5.4.3. Peutz-Jeghers Syndrome (PJS) associated with the presence of multiple polyps that can interest any segment of the gastrointestinal tract, especially jejunum. Malignant degeneration of these polyps is rare. Several cases of gastric cancer associated with PJS have been described in the literature associated with gene inactivation STK11/LKB1 germ, which normally acts as a suppressor gene (23).

5.4.4. Cowden syndrome is an autosomal dominant abnormality transmitted with high punch, also known as multiple hamartoamelor syndrome (gastrointestinal, skin, mucous membranes). Associated with various neoplasms (stomach, breast, thyroid, mucosal). (17) This syndrome occurs in succession a PTEN gene mutations located at 10q23, but has been shown (23) that has lost all gastrointestinal hamartoamele heterozigotivității in this locus.

5.4.5. Li-Fraumeni syndrome is a familial cancer syndrome that include various sarcomas, neoplasms of breast and other carcinomas, including gastric cancer, characterized by onset in childhood and frequent occurrence metacronă (29). It was first mentioned in literature in 1969 when revăzând medical records and death certificates of 648 patients with childhood onset rabdomiosarcoame, Li and Fraumeni have noticed the presence of various types of cancer in siblings and cousins of four patients. Over 70% of families with this syndrome have mutations in p53 gene. Another germinal heterozygous mutation identified by Bell et al. the CHK2 gene is also associated with Li-Fraumeni syndrome (23), but there seems to be responsible for the occurrence of gastric cancer in these families (18).

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