HEREDITARY DIFFUSE GASTRIC CANCER: A REVIEW

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Abstract

Hereditary diffuse gastric cancer is caused by a germline mutation in the CDH1 gene. Individuals found to carry a CDH1 mutation are at a significantly increased risk of diffuse type gastric cancer, as well as an increased risk of lobular type breast cancer for females. This review outlines the criteria for a clinic diagnosis of hereditary diffuse gastric cancer and indications for genetic testing. The management options for CDH1 mutation carriers include surveillance by chromo-endoscopy, or prophylactic gastrectomy. These management options will be addressed including a discussion on their efficacy and potential to impact on carriers' quality of life.

Case history

A germline CDH1 mutation was identified in a 39 year old woman diagnosed with signet ring cell gastric cancer. The only significant family history was that her sister was diagnosed with gastric cancer at the age of 20. Both women are now deceased. The identification of this mutation confirmed the diagnosis of hereditary diffuse gastric cancer in the family.

This finding raises significant issues for at-risk family members, including whether or not to take up predictive testing, the age at which predictive testing should be offered to children and then the management options for those found to carry the mutation, such as endoscopic screening or preventative gastrectomy. Hereditary Diffuse Gastric Cancer (HDGC) is a rare condition. Genetic testing can be helpful in clarifying risks and management for other family members.

Genetic susceptibility to gastric cancer

The incidence of gastric cancer in Australia per 100,000 people was 14.3 and 5.5 among males and females respectively in 2004.[1] This accounts for approximately 2000 people being diagnosed with gastric cancer per year within Australia.[2] Of all gastric cancers, approximately 5-10% show familial clustering, with two or more cases in the same family.[3] However, only 1-3% of all gastric cancers occur in families with autosomal dominant gastric cancer susceptibility.[4,5]

A single gene has been identified with a causative role in HDGC, the CDH1 gene, encoding the protein E-Cadherin. Germline mutations in the E-cadherin gene cause an increased risk of diffuse type gastric cancer and lobular breast cancer.[6] In a recent population based study of 81 patients with gastric cancer (diagnosed under the age of 50) and unselected for family history, the frequency of CDH1 mutations was 1.2% (1/81).[7] Germline mutations in the mismatch repair genes, causing hereditary non-polyposis colorectal cancer (HNPCC), lead to an increased risk of intestinal type gastric cancer.[8] There is also an increased risk of gastric cancer associated with other inherited cancer predisposition syndromes, including Peutz Jeghers syndrome,[9] familial adenomatous polyposis[10] and Li-Fraumeni syndrome.[11]

In 1998, the CDH1 gene was identified by genetic linkage analysis as a candidate gene within several large Maori families with early onset autosomal dominant diffuse gastric cancer.[12] Sequencing revealed germline CDH1 mutations in the three families. A study of 18 gastric cancer families of European descent (England, Italy, Portugal) also found CDH1 mutations in three families with diffuse type gastric cancer.[13] In 1999, a further six CDH1 mutations were identified in families of mixed ancestry with diffuse type gastric cancer,[14] confirming that a germline mutation in CDH1 is a common determinant of a dominantly inherited susceptibility to diffuse gastric cancer.

In 1999, the International Gastric Cancer Linkage Consortium (IGCLC) was established with the aims of developing common terminology for the disease and to produce evidence-based management guidelines.[15] In formulating a definition of familial gastric cancer syndromes, a distinction was made between the different histopathological sub-types of gastric cancer (intestinal, diffuse or mixed/diffuse with glandular component) that segregate within families. The IGCLC initially defined the criteria for a clinic diagnosis of HDGC as any family fulfilling one or more of the following:

1. Two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosed under the age of 50.
2. Three or more cases of documented diffuse gastric cancer in first or second-degree relatives, independent of age.

Based on the limited data available at that time, the IGCLC predicted up to 25% of families that met the criteria for HDGC would have a CDH1 mutation.[15] Since then, CDH1 mutations have been identified in approximately 30-40% of HDGC families, fulfilling the IGCLC criteria.[16] In response to concerns that the criteria may be too stringent, revised criteria were established and assessed in a second study of 42 HDGC families.[17]

The six revised criteria were any family fulfilling one or more of the following:

1. Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years.

2. Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer.
3. An individual diagnosed with diffuse gastric cancer before 45 years of age.
4. An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met).
5. One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met).
6. One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met).

The second study found CDH1 mutations in 48% (12/25) of families meeting Criteria 1, but only 5.5% (1/18) of those meeting the less stringent criteria. The conclusion was that families with a CDH1 mutation are those with a strong family history of early onset diffuse gastric cancer, and therefore Criteria 1 provides the best guide for CDH1 mutation screening.[17] This study also indicated that a single individual with early onset diffuse gastric cancer, without a family history, is unlikely to carry a CDH1 mutation.

Several other studies have examined the frequency of E-cadherin germline mutations in patients with early onset gastric cancer (diagnosed before the age of 45 years) without a family history, in populations with a low incidence of gastric cancer. The overall reported frequency of cases diagnosed under 50 years that are attributable to E-cadherin mutations is about 1%.[7] Screening for CDH1 germline mutations in individuals without a family history should therefore be limited to those early onset cases diagnosed before the age of 35.[7]

The CDH1 gene is located at 16q22.1 and consists of 16 exons covering approximately 100kb of genomic DNA encoding the E-cadherin protein.[18] CDH1 mutations are dominantly inherited. So far 439 families with aggregation of gastric cancer have been analysed for CDH1 mutations, with 56 (12.8%) families having been found to carry a CDH1 germline mutation (50 distinct mutations).[19] The majority are truncating mutations (80.4%), with pathogenicity caused by down-regulation or inactivation of protein expression. Missense mutations have also been identified (19.6%), however functional impact of missense mutations is difficult to predict.[19] One hundred and eighteen families fit the IGCLC criteria for HDGC (26.9%); of these, 43 have had mutations identified (36.4%).[19] There have been no 'hot spots' identified, with mutations dispersed along the full sequence of the gene. There have been at least 18 sequence variants identified.

The E-cadherin protein is a member of the cadherin family of adhesion molecules, which are transmembrane glycoproteins mediating calcium dependent cell-cell adhesion.[20] E-cadherin is a tumour suppressor gene, therefore inactivation of CDH1 in hereditary diffuse gastric cancer requires the somatic inactivation of the wild type allele, as predicted by the Knudson two-hit hypothesis. The first hit in HDGC is the germline mutation. In sporadic diffuse gastric cancer there is an initial somatic mutation. The second hit is then usually due to one of the following mechanisms: silencing of the gene by promoter hypermethylation, somatic mutations or loss of heterozygosity affecting wild type copy.[21] Abolishment of the E-cadherin function induces loss of adherens junctions and impairment of the cell adhesiveness and cell proliferation signalling pathways.[22] Tumour cells with abolished E-cadherin expression demonstrate abnormal morphogenesis and architecture of epithelial tissue, loss of cellular polarity and contact inhibition, unregulated growth and invasion of adjacent tissues.[22]

Cancer (and other risks) in carriers of a CDH1 mutation

Germline mutations in the CDH1 gene cause a greatly increased risk of diffuse gastric cancer and an increased risk of breast cancer (of the lobular subtype).

Lifetime penetrance of gastric cancer, based on the original three Maori families, was estimated at 70%.[12] A penetrance analysis of E-cadherin mutations in 11 families was used to estimate the cumulative risk of both gastric and lobular breast cancer.[6] The cumulative risk of gastric cancer by age 80 was estimated at 67% for men (95% CI, 39-99) and 83% for women (95% CI, 58-99). Ascertainment bias may have resulted in higher penetrance estimates than those obtained from population-based studies. The age of onset is variable, ranging from 14 to 69 years, with the mean age at diagnosis between 31-51 years.[13]

The cumulative risk of lobular breast cancer by age 80 for women with a germline CDH1 mutation has been estimated at 39% (95% CI, 12-84), with the combined risk of gastric and breast cancer in women by age 80 around 90%.[6] Signet ring cell carcinomas of the colon, prostate and ovarian cancers have been observed in HDGC families.[17, 19, 23] However, there is no evidence of a significantly increased risk of these cancers, beyond the population risk. Cleft lip, with or without cleft palate, has been described in two HDGC families.[24] As cell adhesion molecules are considered to play a major role in craniofacial morphogenesis, germline CDH1 mutations may contribute to clefting.

There are some general risk factors associated with in an increased risk of gastric cancer which include gastritis and *Helicobacter pylori* infection. It is possible *H. pylori* as well as dietary and environmental factors may modify the disease risk in HDCG patients. *H. pylori* is associated with an increased risk for both intestinal and diffuse GC, however *H. pylori*-associated pre-neoplastic lesions are usually a feature of intestinal gastric cancer, not diffuse gastric cancer.[8] Intestinal type cancer is more often related to environmental exposures, including diet (particularly salted fish/meat and smoked foods), cigarette smoking and alcohol.

Management of carriers of CDH1 gene mutation

The five-year survival rates for all gastric cancer remains low in Western countries, ranging from 20-45%.[25] The

poor prognosis is mostly attributable to the late stage at presentation and diagnosis. Once a diffuse gastric cancer is symptomatic, it is lethal in 80% of cases.[8] However, if detected early and resected before invasion through the gastric wall, there is a 90% five-year survival rate (regardless of histological type).[26] Effective management of HDGC, requires intensive clinical surveillance with the aim of identifying early gastric cancers or consideration of risk reducing strategies. For individuals with a germline CDH1 mutation, the therapeutic options currently available are either endoscopic surveillance or prophylactic gastrectomy.

The recommendations for surveillance from the IGCLC is an endoscopy every six months, performed by a team experienced at diagnosing early gastric cancer, including multiple biopsies of gastric mucosa.[23] Chromo-endoscopy with congo red-methyl blue may provide improved surveillance. In a recent study of 33 CDH1 mutation carriers, chromo-endoscopy detected 23 early signet ring cell carcinoma foci in 10 patients, which were not visible with standard white light endoscopy.[27] The efficacy of endoscopic surveillance is unproven. The difficulties in detecting diffuse gastric cancer are due to the lesions tending to spread in the submucosa (beneath morphologically normal mucosa), rather than as exophytic masses, which makes them difficult to identify. Finally, it would appear reasonable to recommend H.pylori eradication treatment, in an effort to minimise exposure to other gastric carcinogens.[23]

In two studies examining prophylactic gastrectomy specimens from CDH1 mutation carriers, all patients were found to have multi-focal signet ring cell (SRC) carcinoma, with the number of distinct foci as high as 161.[28,29] This finding has been supported with the histopathological mapping of an additional 20 gastrectomy specimens from 4 HDGC kindred, where all stomachs had multiple foci of SRC carcinoma, with the mean number of foci approximately 100/stomach (range 4-487).[30] In the earlier two studies, standard white light endoscopy and multiple biopsies had failed to detect the cancers in all cases. The early invasive cancers were spread throughout the entire stomach, not isolated to a particular region.

These studies suggest there may be a significant risk reduction for CDH1 mutation carriers by undergoing a prophylactic gastrectomy. It is suggested this surgery should be performed by centres performing at least 25 gastrectomies per year, resulting in a surgical mortality of less than 5%.[15]

Prophylactic gastrectomy must be considered in the context of the morbidity, mortality and long-term consequences. Total gastrectomy is associated with a 2-4% risk of mortality, 10-20% risk of post-operative complications and 100% risk of long-term consequences.[22,27] The long-term implications affect nutritional status, with possible side-effects including weight loss, lactose intolerance, fat mal-absorption and steatorrhoea, dumping syndrome, bacterial overgrowth, postprandial fullness and vitamin deficiencies.[31] Although the severity and degree of complications are well described in older gastric cancer patients (60-70 years), this has not been evaluated in young individuals (without coexisting morbidity). However, almost all the reported patients who have undergone gastrectomy have experienced one or more of the above symptoms.[22] Prophylactic gastrectomy may lead to a significant decrease in quality of life.

Finally, women with a CDH1 mutation are recommended to commence annual mammography from the age of 35, or five years younger than the age at which the youngest person in the family was diagnosed with breast cancer.[32]

Conclusion

Germline mutations in the CDH1 gene are present in almost 50% of families with multiple cases of gastric cancer, including at least one documented case of diffuse type gastric cancer diagnosed under the age of 50. Individuals found to carry a germline CDH1 mutation have a significantly increased risk of gastric cancer and data is supportive of an increased risk of lobular breast cancer for women carriers. Overall, current data suggests that standard endoscopic screening is insufficient to detect gastric cancers, therefore prophylactic gastrectomy may be recommended. For those CDH1 mutation carriers who choose not to proceed with prophylactic gastrectomy, chromo-endoscopy provides improved surveillance.[27]

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