Familial Aggregation of Hyperemesis Gravidarum

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Introduction:

Hyperemesis Gravidarum (HG), severe nausea and vomiting of pregnancy, is the most common cause of hospitalization in the first half of pregnancy and the second most common cause of hospitalization during pregnancy overall. HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy, fetal growth restriction, and even maternal and fetal death.

There are several lines of evidence in support of a genetic predisposition to nausea and vomiting in pregnancy including 1) monozygotic twin concordance, 2) higher frequency of severe NVP in patients with conditions that are genetically determined, 3) reports of anorexia of early pregnancy in various animal species, that has been reported (in dogs) to be accompanied by vomiting, and can be severe enough to require termination of pregnancy.

Objective:

Overall, these data suggest that genetics plays a role in the development of nausea and vomiting of pregnancy. To investigate this further, this study was aimed at determining whether there is familial aggregation of the most severe form of nausea and vomiting of pregnancy, Hyperemesis Gravidarum.

Methods:

Family history data were obtained on 1503 cases and 323 controls who completed an online survey administered by the Hyperemesis Education and Research Foundation from 2002-2006. Cases were not actively recruited, but found the survey while browsing the website (www.hyperemesis.org). Controls were mostly members of the Mother's Club of Palo Alto and Menlo Park (www.pampmothersclub.org), a parent support group composed of approximately 1600 families in the Silicon Valley area who, in March 2005, were sent an email inviting their participation in the study as unaffected controls and informing them of the survey location at http://www.HelpHER.org/mothers/current-research/2004-survey/index Using 650 sisters of cases and 151 sisters of controls who had a previous pregnancy, we estimated familial relative risk by fitting Generalized Estimating Equations models.

Results:

Demographic characteristics of cases and controls are shown in Table 1. Controls differed significantly from cases with respect to age at survey ($p<0.01$) and education ($p<0.01$). Although a higher proportion of controls were Asian, the distribution across racial/ethnic categories was not significantly different between cases and controls. The vast majority of both cases and controls were non-Hispanic whites.

Table 1. Demographic characteristics of HG cases and controls

	Controls (N=117)	Cases (N=464)
Race/ethnicity		P=0.13
Non-Hispanic white	96 (82%)	396 (85%)
Hispanic	3 (3%)	11 (2%)
African-American	2 (2%)	15 (3%)
Asian	9 (8%)	9 (2%)
Other	7 (6%)	33 (7%)
Education		P<0.01
High School or less	8 (7%)	37 (8%)
Some college	14 (12%)	162 (35%)
College degree	31 (27%)	128 (28%)
Some grad school	8 (7%)	48 (10%)
Masters	49 (42%)	72 (16%)
Doctorate	7 (6%)	17 (4%)

Results (continued):

A history of HG was more common among sisters of cases (18%) than among sisters of controls (3%). Overall, there was a five-fold estimated familial relative risk after adjustment for age, education, and ethnicity (Table 2). When stratifying cases based on treatment received, estimated familial relative risk was highest for those who were treated with total parenteral nutrition (TPN) or nasogastric feeding (NG) (adjusted OR=6.4).

Substantial genetic relative risks are necessary to produce the familial relative risks observed in this study (Table 3). For example, under the assumption of a single gene contributing to HG risk and no environmental sharing, a genetic relative risk of 19.8 is necessary for an additive gene with MAF (minor allele frequency) of 1% to produce the observed famililal relative risk of 5. Even if the familial relative risk is only 1.9 (the lower 95% confidence bound), a genetic relative risk of 10.6 is required. Larger genetic relative risks would be required under a dominant model as shown in Table 3.

Table 2: Odds ratios for sibling history of HG

	HG prevalence	Unadjusted		Adjusted	
		OR	95% CI	OR	95% CI
Sisters of controls	5 / 151 = 3%				
Sisters of cases	116 / 650 = 18%	5.7	2.2-14.5	5.0	1.9-12.9
No TPN / NG	83 / 482 = 17%	5.4	2.1-14.0	4.5	1.7-11.9
TPN / NG	33 / 168 = 20%	6.7	2.5-18.0	6.4	2.3-18.0

Summary:

- **The familial relative risk for HG is estimated to be 5.0 which translates to a genetic relative risk of 19.8.**
- **The familial relative risk for severe HG defined by TPN/NG is estimated to be 6.4.**

Conclusion:

There is a strong familial component to Hyperemesis Gravidarum, which appears to be stronger for cases that require more aggressive treatment. Thus this study provides evidence for a genetic and/or shared environmental component to extreme nausea and vomiting of pregnancy.

Table 3: Conversion of Familial Relative Risks (FRR) to Genetic Relative Risks

	Additive					Dominant			
	q^a=0.01	q^a =0.05	q^a =0.1	q^a =0.2	q^a =0.3	q^a=0.01	q^a =0.05	q^a =0.1	q^a =0.2
FRR = 1.9	10.6	6.0	5.1	4.9	5.4	12.8	9.9	13.0	na[b]
FRR = 5	19.8	12.3	12.0	19.5	na[b]	35.1	150.0	na[b]	na[b]
FRR=12.9	30.7	22.9	32.5	na[b]	na[b]	116	na[b]	na[b]	na[b]

a: the minor allele frequency
b: the specific genetic model is not possible