Familial aggregation of hyperemesis gravidarum

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OBJECTIVE: This study was undertaken to determine whether there is familial aggregation of hyperemesis gravidarum (HG), making it a disease amenable to genetic study.

STUDY DESIGN: Cases with severe nausea and vomiting in a singleton pregnancy treated with intravenous hydration and unaffected friends controls completed a survey regarding family history.

RESULTS: Sisters of women with HG have a significantly increased risk of having HG themselves (odds ratio, 17.3; \( P = .005 \)). Cases have a significantly increased risk of having a mother with severe nausea and vomiting; 33% of cases reported an affected mother compared to 7.7% of controls (\( P < .0001 \)). Cases reported a similar frequency of affected second-degree maternal and paternal relatives (18% maternal lineage, 23% paternal lineage).

CONCLUSION: There is familial aggregation of HG. This study provides strong evidence for a genetic component to HG. Identification of the predisposing gene(s) may determine the cause of this poorly understood disease of pregnancy.

Key words: familial aggregation, genetic, hyperemesis gravidarum, nausea, pregnancy

TABLE 1
Distribution of number of pregnant sisters (n = 317)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 110)</th>
<th>Cases (n = 207)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pregnant sisters, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74 (67.27)</td>
<td>146 (70.53)</td>
<td>.4854</td>
</tr>
<tr>
<td>2</td>
<td>23 (20.91)</td>
<td>45 (21.74)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>13 (11.82)</td>
<td>16 (7.73)</td>
<td></td>
</tr>
</tbody>
</table>


TABLE 2
Summaries for several characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37.92 (5.65)</td>
<td>35.77 (6.13)</td>
<td>.0016</td>
</tr>
<tr>
<td>Pregnancy losses</td>
<td>0.55 (0.88)</td>
<td>0.62 (1.43)</td>
<td>.7597</td>
</tr>
<tr>
<td>No. of living children</td>
<td>2.48 (1.00)</td>
<td>1.89 (1.07)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Pregnancy termination</td>
<td>0.16 (0.44)</td>
<td>0.24 (0.74)</td>
<td>.0664</td>
</tr>
<tr>
<td>Currently pregnant, n (%)</td>
<td>9 (8.65)</td>
<td>36 (19.25)</td>
<td>.0166</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>.0346</td>
</tr>
<tr>
<td>White</td>
<td>107 (97.27)</td>
<td>181 (87.44)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0 (0.00)</td>
<td>10 (4.83)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.00)</td>
<td>3 (1.45)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (1.82)</td>
<td>4 (1.93)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.91)</td>
<td>9 (4.35)</td>
<td></td>
</tr>
</tbody>
</table>


Including monkeys. In dogs, anorexia can be accompanied by vomiting and can be severe enough to require pregnancy termination.

Several lines of evidence suggest a genetic predisposition to NVP. Firstly, in the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins. Secondly, several investigators have noted that siblings and mothers of patients affected with NVP and HG are more likely to be affected than siblings and mothers of unaffected individuals. Thirdly, the higher frequency of severe NVP in patients with certain genetically determined conditions such as defects in taste sensation, or latent disorders in fatty acid transport or mitochondrial oxidation, suggests that some portion of HG cases may be related to discrete, genetically transmitted disease states that are unmasked or exacerbated in pregnancy. Finally, in a previous survey administered by the Hyperemesis Education and Research Foundation, approximately 28% of cases reported their mother had severe NVP or HG while pregnant with them. Of the 721 sisters with a pregnancy history, 137 (19%) had HG. Among the most severe cases, those requiring total parenteral nutrition (TPN) or nasogastric (NG) feeding tube, the proportion of affected sisters was even higher, 49 of 198 (25%). Nine percent of cases reported having at least one affected relatives including sister(s), mother, grandmother(s), daughter(s), aunt(s), and cousin(s). There is a high prevalence of severe NVP/HG among relatives of HG cases in this study population. Overall, these data suggest that genetic predisposition may play a role in the development of NVP. However, to our knowledge, a case-control study of familial aggregation of severe NVP and HG has never been done. The goal herein is to determine whether there is familial aggregation of severe NVP and HG in a case-control setting.

MATERIALS AND METHODS

Recruitment

The University of Southern California–Los Angeles and the University of California–Los Angeles are currently conducting a study of the genetics and epidemiology of HG, and >650 participants have been recruited, primarily through advertising on the Hyperemesis Education and Research Foundation World Wide Web site at www.HelpHer.org. The inclusion criteria for cases are a diagnosis of HG and treatment with intravenous (IV) fluids and/or TPN/NG feeding tube. Participants are asked to: (1) submit their medical records; (2) provide a saliva sample; and (3) complete an online survey regarding family history, treatment, and outcomes. Each case is asked to recruit a friend with at least 2 pregnancies that went >27 weeks to participate as a control. Controls are eligible if they experience normal (did not interfere with their daily routine) or no nausea, no weight loss due to NVP, and no medical attention in their pregnancy due to nausea. Eligibility questions for cases and controls are attached in the Appendix.

Survey

Participants were asked to report on the severity of NVP of their family members according to the following definitions:

1. **No nausea and vomiting:** never felt nauseated and never vomited in this pregnancy.
2. **Very little nausea and vomiting:** felt nauseated and/or vomited for a total of 1–7 days during this pregnancy.
3. **Typical nausea and vomiting:** may have nausea and/or vomiting in this pregnancy but (all of the following must be true): (1) did not lose weight from nausea/vomiting; and (2) was able to sustain normal daily routine most days with little change in productivity due to nausea/vomiting.
most of the time; and (3) no need to consult health professional for medical treatment due to nausea and vomiting.

4. **More severe morning sickness**: (1) persistent nausea and vomiting that interfered with normal daily routine in this pregnancy but did not require IV hydration or TPN due to persistent nausea/vomiting; (2) may have consulted a medical professional to treat nausea and vomiting; and (3) may have lost a few pounds or 1 kg.

5. **HG**: persistent nausea and vomiting with weight loss that interfered significantly with daily routine, and led to need for: (1) IV hydration or nutritional therapy (feeding IV [TPN] or by tube [NG] through the nose); and/or (2) prescription medications to prevent weight loss and/or nausea/vomiting.

6. **Other or unsure**: please describe in text box at end of section.

The survey used for this study can be found at: http://www.helpher.org/HER-Research/2007-Genetics/.

### Statistical methods

Characteristics were summarized for both the case group and the control group, and compared between the 2 groups. For the characteristics race and current pregnancy, the χ² test was used to compare the difference between the 2 groups. For the characteristics age, pregnancy losses, number of living children, and voluntary termination, Wilcoxon rank sum test was used to compare the 2 groups.

The familial aggregation of HG was examined by modeling the probability of having ≥1 sister with HG using the logistic regression method. The status whether a participant was a case or a control was assumed to affect the probability of having ≥1 affected sister through a logistic fashion, in this way the effect of being a case on having at least 1 affected sister can be expressed in odds ratio (OR). If we use Y to denote the status whether a participant had ≥1 sister with HG, ie, Y = 1 if a participant has ≥1 affected sister, and Y = 0 otherwise, then the probability that a participant had ≥1 affected sister Pr(Y = 1) was modeled as follows:

\[ Pr(Y = 1) = \frac{\exp(\beta_0 + \beta_1 X)}{\exp(\beta_0 + \beta_1 X) + 1} \tag{1} \]

Where, X denotes the status of whether a participant was a case or a control, ie, X = 1 if a participant was a case, and X = 0 if a participant was a control; \( \beta_0 \) is the regression intercept that was estimated OR of being a case on having at least 1 affected sister, ie, the odds of having ≥1 affected sister for a case over the odds of having ≥1 affected sister for a control. In this analysis, 2 definitions were used to define that a sister had HG. In the first definition, a sister was said to have HG if she had severity 4, more severe morning sickness and severity 5, HG. In the second definition, a sister was said to have HG only if she had HG severity 5. Since the cases and controls were not perfectly matched in terms of race and white was the dominating race for distribution of the number of pregnancy history and were included in the study of affected sisters. Age, race, and pregnancy characteristics of cases and controls with informative sisters are shown in Table 2. Cases were significantly more likely to report having a sister with more severe morning sickness or HG than controls (odds ratio [OR], 5.6; P < .001) (Table 3).

Because the cases and controls were not perfectly matched with respect to race, and the majority of participants were white, the analysis was repeated with whites only and the ORs were very similar (OR, 5.2; P < .001).

When excluding the less severe definition (more severe morning sickness) and looking at reports of sisters with HG only, cases were even more likely to report having a sister with HG than controls (OR, 17.3; P = .005) (Table 4). Again, the analysis was repeated with whites only and the ORs were very similar (OR, 17.9; P = .005). Very few cases and controls were missing data on the nausea and vomiting in pregnant sisters and the distribution of missingness was

### RESULTS

#### Sisters

Cases and controls were well matched for distribution of the number of pregnant, and therefore informative, sisters, as shown in Table 1. In all, 207 cases and 110 controls had at least 1 sister with a pregnancy history and were included in the study of affected sisters. Age, race, and pregnancy characteristics of cases and controls with informative sisters are shown in Table 2. Cases were significantly more likely to report having a sister with more severe morning sickness or HG than controls (odds ratio [OR], 5.6; P < .001) (Table 3).

Because the cases and controls were not perfectly matched with respect to race, and the majority of participants were white, the analysis was repeated with whites only and the ORs were very similar (OR, 5.2; P < .001).

#### Conclusions

This study was approved by institutional review boards at University of Southern California (HS-06-00056) and University of California–Los Angeles (09-08-122-01A).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected sisters</td>
<td>68 (33.83%)</td>
<td>9 (8.33%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Unaffected sisters</td>
<td>133 (66.17%)</td>
<td>99 (91.67%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Distribution of affected sisters (all races, more severe nausea and vomiting of pregnancy and hyperemesis gravidarum)


<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected sisters</td>
<td>28 (13.93%)</td>
<td>1 (0.93%)</td>
<td></td>
</tr>
<tr>
<td>Unaffected sisters</td>
<td>173 (86.07%)</td>
<td>107 (99.07%)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Table 4. Distribution of affected sisters (all races, hyperemesis gravidarum)

Cases and controls were not well matched for distribution of missing data on affected and unaffected mothers (Table 8). This study demonstrates a remarkably high risk of more severe morning sickness and HG among relatives of HG cases as approximately one third of cases reported an affected mother and/or sister.

**Comparison between cases and controls**

The OR is highest (OR, 17) when comparing the proportion of affected sisters of cases to the proportion of affected sisters of controls using the most stringent definition of HG, rather than grouping HG with severe morning sickness.

Although we realize that shared environmental risk factors can also contribute to the observed high prevalence of affected family members, to our knowledge no such factors have been identified. In addition, although sisters commonly have a similar in utero and childhood environment, it is unlikely that they share the same environment during their own pregnancy, when HG occurs. This study also suggests grandmothers, mothers, and daughters commonly share severe nausea of pregnancy and it is unlikely that this can be entirely explained by shared cross-generational environmental factors. Other reports of half-siblings reared in separate states and identical twins pregnant and diagnosed with HG while residing in different countries, although anecdotal, lend further support to a role for genetics.  

The pedigree presented in this study, the fact that mothers and sisters are commonly affected, and the similar frequency of maternal and paternal grandmothers affected suggest that HG may be

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**TABLE 5**

**Distribution of missingness of affected sisters (all races)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>2 (1.82%)</td>
<td>6 (2.90%)</td>
<td>.7186</td>
</tr>
<tr>
<td>Not missing</td>
<td>108 (98.18%)</td>
<td>201 (97.10%)</td>
<td></td>
</tr>
</tbody>
</table>


**TABLE 6**

**Distribution of missingness of affected sisters (white only)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>2 (1.87%)</td>
<td>4 (2.21%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Not missing</td>
<td>105 (98.13%)</td>
<td>177 (97.79%)</td>
<td></td>
</tr>
</tbody>
</table>


**TABLE 7**

**Distribution of affected mothers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected mothers</td>
<td>15 (7.73%)</td>
<td>143 (32.65%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Unaffected mothers</td>
<td>179 (92.27%)</td>
<td>295 (67.35%)</td>
<td></td>
</tr>
</tbody>
</table>


**TABLE 8**

**Distribution of missingness of affected mothers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>22 (10.19%)</td>
<td>31 (6.61%)</td>
<td>.1233</td>
</tr>
<tr>
<td>Not missing</td>
<td>194 (89.81%)</td>
<td>438 (93.39%)</td>
<td></td>
</tr>
</tbody>
</table>


**COMMENT**

This study demonstrates a remarkably high risk of more severe morning sickness and HG among relatives of HG cases as approximately one third of cases reported an affected mother and/or sister.
inherited in an autosomal dominant manner with incomplete penetrance, although other modes of inheritance in some families cannot be ruled out. Regardless of the mode of inheritance, this is the first case-control study of familial aggregation for HG and, in addition to previous studies showing higher concordance for NVP in monozygotic vs dizygotic twins and a high prevalence of HG among family members of affected individuals, provides strong support for a genetic contribution to severe NVP.

HG often leads to extreme weight loss and may result in a state of nutrient deprivation, malnutrition, and starvation for both the mother and the developing fetus. Fetal outcome remains controversial. Some studies suggest infants exposed to HG in utero are significantly more likely to be born earlier, weigh less, be small for gestational age, and die be-some to HG in utero are significantly
sial. Some studies suggest infants ex-
fetus. Fetal outcome remains controver-
sis and low-pregnancy weight gain,7 and that, if treated early, severe nausea may be associated with a protective effect against major malformations.27 While few long-term studies of HG offspring have been conducted, there is a body of literature on starvation in pregnancy in human beings and animals, providing convincing evidence that nutritional de-
privation in utero can have lasting or lifelong significance.28 These data, along with the evidence of a familial compo-
net on family history. Thus this study is
s the first case-control report of its kind.

Admittedly, this study has some method-
ological concerns. One potential limita-
tion arises from the use of an Internet-
based survey. While Internet-based research is quickly becoming scientifically recognized as a reliable recruiting tool, the study population consists only of cases with Internet access, and thus may represent women of higher educa-
tion and income. We believe, however, that the generalizability of our study re-
sults should be reasonably good since we have no reason to suspect that education level and income would affect the likelihood of having a family history of HG.

Further work should focus on repro-
ducing these results in other populations and on the identification of genetic vari-
ants that may contribute to HG suscept-
tibility. Identification of genetic factors will elucidate the biology of NVP and al-

REFERENCES

1. Jiang HG, Elikhauser A, Nicholas J, Steiner C, Reyes C, Brierman AS. Care of women in US...
controls eligibility questions

Thank you for your interest in serving as a control in this study. For my records, please answer each of the following questions in all capital letters next to each question to determine your eligibility to serve as a control. Are you living in the US?
How did you hear about this study?
Are you currently living in the US?

Did you have severe nausea and vomiting in a singleton (not twins or multiples) pregnancy?
Were you treated with IV and/or TPN (total parenteral nutrition) or other form of feeding tube (ie nasogastric feeding tube) in this pregnancy due to nausea and vomiting?

Did your HG pregnancy have an abnormal outcome such as molar pregnancy, Down Syndrome, or any other chromosomal abnormalities or malformations?
If yes, please explain.

Do you think you will be able to identify an unaffected family member of the same race/ethnicity (not a family member) with at least 2 pregnancies that went beyond 27 weeks to participate in the study as a control?
Do you have any of your relatives enrolled in this study as a control?

To the best of your knowledge, are you willing to identify a relative/friend with at least 2 pregnancies that went beyond 27 weeks to participate in the study as a control?

5. To the best of your knowledge, are any of your relatives enrolled in this study as a control?

6. Are you between the age of 18-50?

7. Did your HG pregnancy have an abnormal pregnancy outcome such as molar pregnancy, Down Syndrome, or any other abnormal outcome such as molar pregnancy?

8. Were you treated with IV and/or TPN (total parenteral nutrition) or other form of feeding tube (ie nasogastric feeding tube) in this pregnancy due to nausea and vomiting?

9. Are you currently living in the US?

10. How did you hear about the study?

11. Thank you for your time!
comes survey, and 2) submit a saliva
sample for DNA analysis. If you are still
interested in participating, please answer
the following questions for my records to
determine eligibility:
1) Have you had at least 2 pregnancies
that went beyond 27 weeks?
2) Did you have a) no nausea and vom-
itting or b) mild (meaning that it did
not interfere with your daily routine)
in all of your pregnancies?
3) Did you have any weight loss due to
nausea and vomiting in any preg-
nancy?
4) Did you seek medical attention to
treat symptoms of nausea and/or
vomiting in any pregnancy?
5) Are you between the age of 18-50?
Thank you for your time!
Marlena