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ORIGINAL PAPER

Perinatal complications in unaffected sisters of anorexia nervosa patients: testing a covariation model between genetic and environmental factors

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Abstract Although perinatal complications are hypothesized to be risk factors for the development of anorexia nervosa (AN), no study to date explored this issue using a discordant sibling design. This type of design allows to explore whether the risk for obstetric complications is itself a consequence of the genetic vulnerability for AN (covariation model) or whether obstetric complications increase the risk of AN independently of (additive model), or in interaction with (interaction model), the disorder's genetic liability. The presence of perinatal complications was assessed through review of the obstetric records of 60 AN subjects, 60 unaffected sisters, and 70 healthy subjects. Unaffected sisters and healthy controls were compared in relation to perinatal characteristics and complications. There was no evidence for an elevated rate of complications in unaffected siblings of AN patients. Mothers with a positive psychiatric history tended to have more perinatal complications. Perinatal complications seem to be independent risk factors that may interact with, but are not caused by, familial risk factors for AN. In terms of prevention, a particular attention should be paid to mothers with a lifetime history of psychiatric disorders.

Keywords Anorexia nervosa · Obstetric complications · Genetic factors

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Introduction

Although genetic factors account for a significant proportion of liability to anorexia nervosa (AN), there are evidences that attest a significant environmental contribution [1–3]. Perinatal complications are among the putative environmental risk factors for this illness, because recent studies have found higher rates of perinatal complications in AN patients in comparison with asymptomatic subjects [4–7]. However, to elucidate the pathways underlying the development of this illness is critical to understand the relationship between genetic and environmental factors. As only a small proportion of subjects exposed to perinatal complications will develop a psychiatric disorder, it is generally believed that an interaction between perinatal complications and a genetic vulnerability is probably necessary to explain the development of the illness. However, other models are possible and should be explored [8]. For example, it is possible that obstetric complications are, completely or in part, a consequence of the genetic liability to AN (covariation model). To test a covariation model, it is necessary to evaluate whether the exposure to perinatal complications occurs more frequently in groups at elevated genetic risk for the illness than in groups without a known genetic risk [8]. The most used design to test this model is a comparison between unaffected first-degree relatives of ill subjects and a control group without family morbidity [8–12]. In the hypothesis of a covariation, we would expect to find higher rates of obstetric complications in unaffected relatives of AN patients in comparison with those found in control subjects [8]. On the contrary, in the hypothesis of an interaction between genetic factors and perinatal complications, unaffected relatives would be expected to report a rate of obstetric complications similar to that of unrelated control subjects. In schizophrenia, an

illness for which perinatal complications are a proven risk factor, discordant twins and siblings seem to have a rate of potentially hypoxic obstetric complications lower than that of patients and similar to that of the general population [9–11]. This means that for schizophrenia the prevailing evidence does not support the covariation model [8].

The causes of perinatal complications are largely unknown, although both genetic and environmental factors are probably implicated. Viral infections, exposure to toxic agents, and nutritional factors are considered among the possible environmental causes of several types of perinatal complications [13, 14]. In addition, both maternal and child genetic factors might have a role. Maternal genetic factors are more likely to be implicated in the pathogenesis of pregnancy and delivery complications, such as anemia, pre-eclampsia, or inertia uteri [11, 13]. On the contrary, child genetic characteristics may be more relevant for increasing the risk of neonatal complications and dysmaturity and for successful recovery after exposure to hypoxia.

The present study aims at assessing the rate of different types of perinatal complications in a sample of unaffected sisters of AN patients in comparison with controls. As a secondary aim, we will explore the effects of maternal psychiatric history in increasing the risk of perinatal complications in AN patients and their sisters.

Materials and methods

Subjects

The sample consisted of 60 unaffected female siblings of 60 AN women and 70 female controls. AN patients, their healthy sisters, and controls belonged to similar birth cohorts: AN patients were born between 1969 and 1993, healthy sisters between 1965 and 1991, and controls between 1969 and 1991.

The recruitment of the sample of AN and female controls started with our previous study [7] whose aim was to investigate the rates of perinatal complications in AN and healthy subjects born in Padua Hospital between 1971 and 1979. After the conclusion of the previous study, we continued to recruit both AN and healthy subjects using the same criteria and methods. For the purposes of the present study, we considered as eligible for the present study all the AN subjects with perinatal data available and with at least one healthy sister ($n = 72$). The final sample of AN patients consisted in those 60 cases (41 participants to the previous study and 19 new cases) for which we were able to retrieve the perinatal data of the unaffected sister. AN patients had an average age of onset of 17.1 years (SD = 2.8) and a lifetime lowest body mass index of 15.6 kg/m^2 (SD = 1.7). For the control sample, a subsample of those subjects who participated in our previous study was selected by randomization ($n = 48$). Other 22 healthy volunteer subjects born before 1971 or after 1979 were recruited. Criteria of exclusion for the control sample were as follows: having an eating disorder and having a sister, or any other first-degree relative, with an eating disorder. In addition, we excluded all subjects who suffered from a psychiatric disorder such as schizophrenia, bipolar disorder, major depression, alcohol/substance dependence. The average number of perinatal complications in the final control sample ($n = 70$) did not differ from those reported by the population control sample of our previous cohort study [7]. For the sister sample, we used the same criteria of exclusion of control subjects. In addition, sisters whose age was below the average age of onset for AN at the time of assessment were not included [15].

All subjects and their relatives gave their written informed consent to participate in the study. The study obtained Institutional Review Board approval.

Assessment

Lifetime anorexia nervosa was defined according to the fourth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria. All interviewed subjects (all AN subjects, all healthy controls and 15 sisters) underwent the ED section of the Structured Clinical Interview for DSM-IV. The diagnostic status of sisters was assessed by direct interview ($n = 15$) or using the family history method [16], that is by interviewing both the AN patients and their parents ($n = 45$). In these cases, a modified version of the ED section of the Structured Clinical Interview for DSM-IV was administered to the AN patients and their parents to investigate the presence of an eating disorder in the sisters. The agreement between the diagnostic status of sisters reported by two family members (the AN patient and at least one of the parents) as informants and the diagnostic status of directly interviewed sisters was evaluated in 15 healthy sisters (included in the study) and 16 eating disordered sisters (not included in the study). The agreement was 100%.

Maternal psychiatric morbidity was investigated using the family history method [16]. Information was collected about all first-degree relatives by interviewing the patients and at least one of the parents (usually the mother). We found 16 cases of positive maternal psychiatric history among AN patients. Diagnoses were carried out for the mood disorders ($n = 8$), mood disorder and alcoholism ($n = 2$), panic or obsessive compulsive disorders ($n = 4$), eating disorders ($n = 2$). We did not assess maternal psychiatric history (except for eating disorders) in control subjects.

Obstetric complications

Most study subjects were born in the Padua Hospital (52 AN subjects, 54 healthy sisters, and 68 controls), and data about obstetric complications were available from hospital archives. As in our previous studies [7], we reviewed the obstetric records to collect any relevant information. In all the other cases, we interviewed the parents using an adapted version of the Pregnancy History Instrument [17], an interview that covers a wide range of pregnancy, delivery, and neonatal complications. In addition, in all cases, we were able to obtain a copy of the birth certificate with a detail of major complications, gestational age, birth weight/length, head circumference, and Apgar scores. All interviews were performed in a face-to-face fashion to the mother ($n = 9$) or to both the parents ($n = 7$). The mean age of interviewed parents was 50.9 (DS = 6.7), and none of the interviewed parents reported a positive family psychiatric history.

Recorded information about the mothers included age at birth (age in completed years at the infant's birth), marital status at birth, parity (number of births, including the present birth), and weight gain during pregnancy. According to indications in the previous literature [10, 18–22], we divided the main obstetric complications into four groups: a) pregnancy complications (anemia, urinary infections, diabetes, pre-eclampsia, placental infarctions, bleeding); b) delivery complications (inertia uteri, premature rupture of the membranes, breech delivery, Cesarean section due to acute fetal distress, forceps or vacuum extraction, cephalopelvic disproportion); c) hypoxia-related neonatal complications (cyanosis, respiratory or cardiac problems, cephalhematoma, meconium staining of the amniotic fluid, umbilical cord knotted or wrapped tightly around the neck, need for resuscitation, need for oxygen, need for intubation); d) signs of dysmaturity and/or retarded fetal growth (being small or short for gestational age, early feeding difficulties, gestational age shorter than 37 weeks, tremors, hypotonia, hyporeactivity, hypothermia). Weight and length were considered low when they were below the 10th percentile for sex and gestational week. The McNeil-Sjöström Scale [23] was used for the definition of obstetric complications. Only those complications scored at level 3 (potentially harmful) or more (clearly harmful) by the McNeil-Sjöström Scale were considered in the present study.

Statistical analyses

The analyses were carried out using the SPSS software. Crude odds ratio (OR) with 95% confidence intervals was used to compare groups on categorical variables. Most variables had a skewed distribution (for example, number of complications). For this reason, we used nonparametrical statistical tests for comparison of raw data: Wilcoxon test for dependent groups (AN patients vs. their healthy sisters) and Mann–Whitney U test for independent groups (healthy sisters or AN patients vs. controls). Generalized linear model has been used to test differences between groups adjusting for potential confounding factors, such as maternal age, parity, and socio-economic status.

Results

Comparison between unaffected sisters and healthy controls

Table 1 reports the number of obstetric complications and the main perinatal characteristics of AN patients, their unaffected sisters, and controls. We found no significant differences between unaffected sisters and controls as regards the number of perinatal complications and any perinatal characteristics, including parity and birth measures. No difference emerged even adjusting the analyses for possible confounders, such as parity, maternal age, and socio-economic status.

Comparisons between AN patients and controls, and between AN patients and their unaffected sisters

AN patients differed from controls as regards the presence of any one complication (OR, 3.9, 95% C.I. 1.4–10.3; $P = 0.007$), the total number of complications ($z = 3.37$; $P = 0.001$), the presence (OR, 2.0, 95% C.I. 1.0–4.2; $P = 0.049$) and number of neonatal hypoxic complications ($z = 2.48$; $P = 0.013$), and presence (OR, 2.5, C.I. 1.2–5.1; $P = 0.012$) and number of dysmaturity signs ($z = 2.68$; $P = 0.007$). We did not observe any change in the findings after adjusting the analyses for possible confounders, such as parity, maternal age, and socio-economic status.

The comparison between AN patients and their unaffected sisters (60 pairs) revealed a significant difference in relation to the total number of perinatal complications ($z = 2.29$; $P = 0.022$) and the number of dysmaturity signs ($z = 3.35$; $P = 0.001$). Excluding the subjects who were not born in Padua Hospital did not change any of the findings.

Maternal psychiatric morbidity and perinatal complications

AN patients whose mothers had a lifetime psychiatric disorder tended to have a greater number of total perinatal complications (4.6 ± 3.8 vs. 2.8 ± 2.6; $z = 1.93$; $P = 0.053$) and a significantly greater number of delivery complications (0.9 ± 1.0 vs. 0.3 ± 0.5; $z = 2.60$; $P = 0.009$).

Table 1 Perinatal characteristics and complications in AN subjects, their healthy sisters, and controls

	AN subjects ($n = 60$)	Healthy sisters ($n = 60$)	Controls ($n = 70$)	Sisters vs controls	
*Perinatal characteristics**					
Parity				$\chi^2 = 0.62$	n.s.
1	20 (33%)	29 (48%)	29 (41%)		
2–3	32 (53%)	28 (47%)	37 (53%)		
4 or more	8 (13%)	3 (5%)	4 (6%)		
Low or medium–low socio-economic status	27 (45%)	27 (45%)	35 (50%)	$\chi^2 = 0.42$	n.s.
Maternal age at birth (years)	29.3 (4.4)	28.4 (5.5)	28.6 (5.2)	$z = 0.44$	n.s.
Gestational age (weeks)	39.4 (1.8)	39.5 (1.7)	39.6 (1.5)	$z = 0.35$	n.s.
Maternal weight gain (kg)	11.5 (2.6)	11.7 (3.6)	11.5 (4.0)	$z = 0.39$	n.s.
Birth weight (grams)	3,198 (493)	3,178 (478)	3,247 (477)	$z = 1.14$	n.s.
Birth length (cm)	49.0 (2.2)	49.1 (1.8)	49.4 (1.8)	$z = 1.29$	n.s.
Head circumference (cm)	33.8 (1.4)	34.0 (1.2)	34.3 (1.2)	$z = 0.46$	n.s.
Ponderal index	27.0 (2.2)	26.7 (2.5)	27.0 (2.2)	$z = 0.63$	n.s.
Placental weight (grams)	582 (100)	576 (143)	601 (126)	$z = 1.18$	n.s.
*Perinatal complications**					
Total number of complications	3.3 (3.0)	2.0 (2.1)	1.8 (1.9)	$z = 0.60$	n.s.
Number of pregnancy complications.	0.7 (1.0)	0.6 (0.8)	0.4 (0.8)	$z = 0.96$	n.s.
Number of delivery complications.	0.4 (0.7)	0.5 (0.8)	0.3 (0.5)	$z = 0.52$	n.s.
Number of hypoxic complications.	1.0 (1.3)	0.6 (1.0)	0.4 (0.7)	$z = 0.77$	n.s.
Number of dysmaturity signs	1.0 (1.2)	0.4 (0.8)	0.5 (0.7)	$z = 0.76$	n.s.

NS not significant

* Incomplete data were available for maternal weight gain during pregnancy (available for 56 AN patients, 32 sisters, 60 controls), birth length and ponderal index (available for 58 AN patients, 60 sisters, 64 controls), placental weight (available for 48 AN patients, 52 sisters, 62 controls), and head circumference (available for 34 AN, 28 sisters, 31 controls)

Among the unaffected sisters, the number of perinatal complications tended to be higher in subjects with a positive maternal psychiatric history in comparison with those without (3.2 ± 2.9 vs. 1.6 ± 1.6; $z = 1.89$; $P = 0.059$). Figure 1 represents the number of perinatal complications according to case ness and maternal psychiatric history.

Discussion

The present study explored for the first time whether the exposure to perinatal complications occurs more frequently in a sample of women at elevated genetic risk for AN than in women without a known genetic risk. Our findings indicated that unaffected sisters of AN patients, although sharing on average 50% of their genes with their affected sisters, did not show an increased rate of perinatal complications in comparison with subjects without affected first-degree relatives. Our study does not support a covariation model and seems to indicate that an additive or an interaction model is more suitable to explain the role of perinatal factors in increasing the risk for AN. These findings are in line with previous studies carried out on schizophrenia [8–11] that found a similar rate of hypoxic

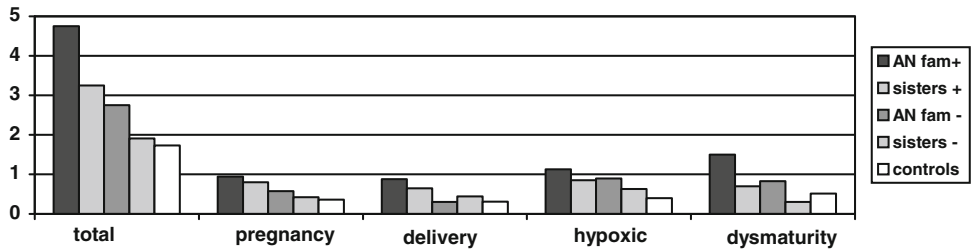

Fig. 1 Number of perinatal complications according to caseness and maternal psychiatric disorder. AN fam+: AN patients with a positive maternal psychiatric history sisters+: sisters with a positive maternal psychiatric history AN fam−: AN patients without a positive maternal psychiatric history sisters+: sisters without a positive maternal psychiatric history

complications in healthy siblings of schizophrenic patients and controls.

In this study, we considered a large range of perinatal complications and we subdivided them according to timing and type (pregnancy, delivery, neonatal, dysmaturity) of complications. As expected, pregnancy and delivery complications did not differ between AN patients and their unaffected sisters. This is because complications occurring during pregnancy and at delivery have a high familial recurrence and have a stronger relationship with maternal factors. Prenatal complications such as anemia or pre-eclampsia have a high rate of recurrence in different pregnancies of the same mother [13], and the same is true for delivery complications due to uterine anomalies [11, 14]. The importance of maternal factors is also shown by the relationship we found between maternal psychiatric morbidity and presence/number of perinatal complications in AN subjects. In the literature, mothers with psychiatric disorders are considered more at risk for perinatal events [24], and similar findings have been reported for mothers with a lifetime eating disorder [25]. Although it is not easy to disentangle the genetic and environmental effects of the presence of maternal psychiatric disorders, data from the literature seem to suggest that health risk behaviors (such as malnutrition or smoking) might mediate between maternal diagnosis and perinatal outcome [25–27]. Unfortunately, we have no data available about possible mediators of risk, such as malnutrition or smoking, in our sample of mothers of AN subjects.

Our study has strengths and limitations that should be considered. The use of obstetric records completed at the time of subjects' birth is one of the strengths of the present study. In addition, all obstetric records were from the same Hospital, and only in few cases did we rely on both discharge letters and parental recall. Most patients were recruited among outpatient referrals and cannot be considered to be representative of all affected subjects of the general population. However, in our previous studies about perinatal complications [7, 22], we did not find any significant difference between subjects recruited in the community and those recruited in a clinical setting concerning perinatal characteristics. Similarly, although the control group of the present study cannot be considered representative of the general female population because of our recruitment method, it did not significantly differ from the representative control group of our previous study [7] as regards the rate and number of perinatal complications. Although all sisters were assessed after the mean age of onset for anorexia nervosa, we cannot rule out that some sisters might develop an eating disorder after our assessment. In addition, we had not the possibility to directly interview most sisters. However, since we found no differences between sisters and controls, this type of bias, if it exists, is of a conservative nature. The fact that we had no data available about maternal psychiatric morbidity in control subjects is another limitation. Finally, although our number of siblings is similar or greater than those used in similar studies in the literature [9–11], the study needs replication because it is the first to explore this issue and because the power of the statistical analyses is difficult estimate, depending on the average sharing of the disease-promoting genes between affected and unaffected sisters [8].

In conclusion, the present study is the first to provide evidence against a gene-environment covariation model for explaining the role of familial and perinatal factors in the pathogenesis of AN. These findings have implications for future studies on the etiopathogenesis of AN which should explore whether perinatal complications play an additive or interactive role with familial/genetic factors to increase the risk for the illness. In addition, the evidence against a covariation model has important implications for prevention [8]. If perinatal complications are not due to the genetic risk factors for AN, but represent an independent environmental risk factor, any intervention that is effective in reducing perinatal complications may have a positive effect in terms of decreasing the incidence of AN. Particular attention should be paid to high-risk subjects such as mothers with a lifetime history of psychiatric or eating disorders.

Conflict of interest The authors declare no conflict of interest. The present study was performed without any external funding.

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