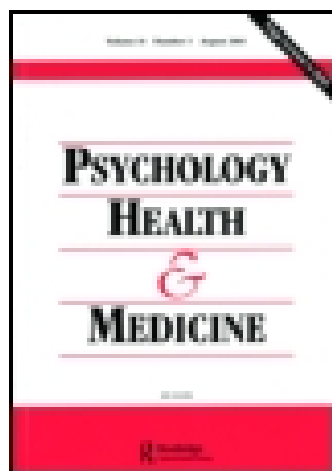




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Perinatal stress and food allergy: a preliminary study on maternal reports

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Perinatal stress and food allergy: a preliminary study on maternal reports

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Maternal stress in fetal and early life has been associated with the development of respiratory allergies, but no studies exist about food allergy. Stressful events and the quality of caregiving provided, as they affect the emotional and physiologic regulation of the infant, could alter the hypothalamic–pituitary–adrenal and immune system, facilitating an increased allergic response. This study aimed to investigate the influence of perinatal stress, as perceived by mothers, on developing food allergy in childhood. A survey on pregnancy and the first three months after giving birth was submitted to 59 Italian mothers of at least one child suffering from severe food allergy and one completely healthy child, for a total of 118 children examined. The presence of stressful events and the quality of perinatal period for each child were assessed retrospectively. The food allergic children's data were compared to siblings' data through inferential statistics. The results showed a significantly higher number of stressful events occurred during patients' perinatal period, compared to siblings, in particular bereavements in pregnancy and parenting difficulties in postpartum. Mothers reported harder pregnancies and more stressful, harder, and, in general, worse postpartum when referring to their food-allergic children, in comparison with their siblings ($p < .05$). Psychological aspects are demonstrated to be involved in the development of allergic diseases. This study constitutes the first step to examine the role of early stress and perinatal psychosocial factors in the pathogenesis of food allergy; further studies are necessary to understand individual psychological impact and its relations with genetic and biological factors.

Keywords: food allergy; perinatal stress; postpartum; pregnancy; stress events

Introduction

Food allergy is an adverse health effect arising from a specific immune response to dietary antigens that includes acute, potentially fatal reactions (Boyce et al., 2010; Muraro et al., 2014). It constitutes the primary cause of anaphylaxis presenting to emergency departments (Sampson, 2004) and represents a common disease, especially among children, with studies suggesting a cumulative prevalence of 3–6% and a worrying increase in its incidence (Sicherer, 2011). The limits imposed by the strict diet and the constant risk of anaphylaxis make food allergy a burden for patients and their families, affecting

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considerably their quality of life and psychological well-being (Bollinger et al., 2006; Cummings, Knibb, King, & Lucas, 2010).

The causes of food allergy are still unknown and, although the occurrence of the pathology appears to be strongly influenced by genetics, the basis of the genetic predisposition to food allergy has not been differentiated from that for atopy in general. There are still no measures for general recommendations in order to prevent food allergy and no particular genes have been linked conclusively to the disease. In addition, genetic susceptibility alone does not explain the prevalence of food allergy satisfactorily, leaving ample room to consider the importance of environmental influences and interactions between the host and the environment. The mother not only transfers her genes to her baby, but she is also the environment during gestation and continues to be a major environmental factor during early infancy of her child (Björkstén, 2005; Dreskin, 2006; Kimber & Dearman, 2002). Ecological variables may include also psychological factors: it was found that stress may influence the neuroendocrine system and then the immune system (Morgan & Martinez, 1992; Van Lieshout & MacQueen, 2008; Wright, Rodriguez, & Cohen, 1998). Maternal stress in fetal and early life has been associated with the development of asthma in children (Cookson, Granell, Joinson, Ben-Shlomo, & Henderson, 2009; Lin, Wen, Lee, & Guo, 2004; Pincus-Knackstedt et al., 2006; Salk, Grellong, Strauss, & Dietrich, 1974): Sustained excessive cortisol secretion could affect the developing immune system, especially T-helper Th1 and Th2 cell differentiation, and further increase the susceptibility to asthma and atopy in genetically predisposed individuals (Von Hertzen, 2002). Stressful events and the quality of caregiving provided, as they affect the emotional and physiologic regulation of the infant, could alter the hypothalamic–pituitary–adrenal (HPA) system or the immune functioning, facilitating an increased allergic response (Klennert et al., 2001; Wright, 2007). However, mechanism for a stress effect is still unclear. The reason why some children develop allergy and others do not is still unknown (Busse et al., 1995).

Although the significance of the psychological aspects has been demonstrated relating to respiratory allergy (Busse et al., 1995; Cookson et al., 2009; Klennert et al., 2001; Lin et al., 2004; Morgan & Martinez, 1992; Pincus-Knackstedt et al., 2006; Salk et al., 1974; Van Lieshout & MacQueen, 2008; Von Hertzen, 2002; Wright, 2007; Wright et al., 1998), no studies have been held concentrating on food allergy.

The aim of this study was to investigate the possible influence of perinatal stress, as reported by mothers, on the development of severe food allergy in childhood, comparing pregnancy and postpartum period of patients and their siblings.

Methods

Participants

Fifty-nine Italian mothers (mean age = 41.20; SD = 6.26) having at least one child suffering from severe food allergy and one completely healthy child took part in the study. Forty-six mothers (78%) reported allergies in their and/or their husbands' family.

The sample of allergic children consisted of 34 male and 25 female attending a Referral Centre for Food Allergy Diagnosis and Treatment, Italy. Patients were confirmed suffering from severe immunoglobulin E (IgE)-mediated food allergy by an allergology and immunology specialist on the basis of a clinical history with evidence of sensitization and positive skin prick test and/or serum-specific IgE results and/or a positive food challenge; all participants developed food allergy in early childhood, had a

prescription for self-injectable adrenalin, and did not suffer from serious concomitant non-allergic disease.

The sample of healthy children consisted of 29 male and 30 female not suffering from allergic or other diseases.

The mean age at the time of the study was 8.3 (SD = 4.7) for allergic children and 10.6; (SD = 7.1) for healthy siblings. Forty-nine percent (29) of the patients and 42% (25) of the siblings were first born. It is worth noting that no significant differences were found in our sample relating to children's sex and age at the time of the study, birth order, pregnancy length, use of drugs, delivery, and breast feeding ($p < .05$). In particular, about the use of drugs during pregnancy, the same frequency of 27.1% (16) was found among allergic children and their siblings. Drugs were mostly tocolytics and anti-hypertensive medications. Socioeconomic factors and genetic background are obviously the same for the patients and their siblings.

Instruments

An ad hoc survey about pregnancy and the first three months after the birth of the child suffering from severe food allergy and the completely healthy child was submitted. It assessed retrospectively maternal perceptions concerning stressful events and the quality of perinatal period for each child. Pregnancy: mothers were asked to state the presence or absence of some events or conditions during pregnancy in a list of stressful situations. Participants could also add stressful events, which occurred and were not present in the list. They were asked as well to estimate their pregnancy basing on some positive and negative adjectives (e.g. happy, hard) on a Likert scale from 1 to 5 (1 = not at all; 5 = very much). Moreover, they were asked to evaluate their physical condition, the fetus' condition (based on regular medical visits carried out during pregnancy), and social support received in that period by partners, relatives, or people close to them, on a Likert scale from 1 to 5.

Postpartum: mothers were asked to state the presence or absence of some events or conditions during the first three months after birth in a list of stressful situations. Participants could also add stressful events which occurred and were not present in the list. They were asked to evaluate postpartum based on the same positive and negative adjectives on a Likert scale from 1 to 5 (1 = not at all; 5 = very much). Then they were asked to evaluate their physical condition, the child's physical condition, and social support received in that period by partners, relatives, or people close to them, on a Likert scale from 1 to 5.

The survey was created by authors basing it on clinical experience and literature (Cassidy, 1999) Questions are shown in Tables 1 and 2.

Procedure

Sixty-seven mothers of food allergic patients were contacted sequentially during clinical visits, during a period of 10 months, at a Referral Centre for Food Allergy Diagnosis and Treatment, in Italy, considering the inclusion and exclusion criteria. Fifty-nine women accepted to take part in the study giving their informed consent and completing the survey on pregnancy and the first three months after the birth for the child suffering from severe food allergy and the completely healthy child. Information about pregnancy length, complications, threat of miscarriage, use of drugs, mother and fetus pathology,

type of delivery, and birth complications were collected through a cross-check between mothers' report and medical records.

The study was performed in respect of the Italian regulation regarding potential sensitive data and according to World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Statistical analysis

The food allergic children's collected data were compared to siblings' data through inferential statistics. The McNemar test was used to analyze differences in the frequency of stressful events; the Wilcoxon test was used to analyze differences in the quality of pregnancy and postpartum, in the total number of stressful events occurred and in the quality of physical conditions and social support, as felt by mothers.

Findings were analyzed using the SPSS 17 statistical software package. The level of significance was set at .05.

Results

Pregnancy

As shown in Table 1, a significant difference in the number of bereavements occurred during food allergic children pregnancy compared to siblings ($p = .039$). Bereavements included the death of the mother's parents or other relatives occurred in prevalence in the last months of pregnancy.

Furthermore, a significantly higher number of 'other' answers were registered for food allergic children ($p = .031$): These responses indicated a stressful event not present in the list of the questionnaire. Investigating this variable and analyzing what mothers reported, the presence of four typologies of stressful events emerged: managing parents or parents in law; managing other children; absence of the husband (e.g. for work); and managing the house, as shown in Figure 1. These factors constitute low/middle but daily and long-lasting stressors. The main frequency of stress (37%) was related to relational difficulties with mothers' parents or parents in law.

A significant difference in the total number of stressful events occurred during food allergic children pregnancy was found, compared to siblings ($p = .003$).

The pregnancy of food allergic children was felt by mothers as significantly harder than the siblings' one ($p = .033$).

Postpartum

Concerning the three months after the birth, as reported in Table 2, the findings illustrate for food allergic children, a higher frequency of birth complications, need of incubator, feeding and sleeping difficulties, mother's and child's pathology, bereavements, economic troubles, and 'other.' Nevertheless, only this last variable ($p = .017$) and the variable 'feeding difficulties' ($p = .001$) showed a significant difference between allergic patients and their healthy brothers or sisters. Analyzing what mothers reported as 'other,' the presence of five typologies of stressful events emerged: parenting difficulties, family tension, managing parents or parents-in-law, managing other children, and absence of the husband, as shown in Figure 2. These factors constitute low/middle but daily and prolonged stressors. The main frequency of stress (70%) was related to parenting difficulties including problems with newborn caregiving and 'maternity blues.' Food

Table 1. Investigated variables in pregnancy: comparison between food allergic children and siblings.

Variables	Food allergic children		Siblings		TEST $p < .05$ McNemar
	Frequency	%	Frequency	%	
Presence of stressful events					
Threat of miscarriage	11	18.6	8	13.6	
Bed rest	12	20.3	9	15.3	
Mothers' pathology	17	28.8	11	18.6	
Fetus' pathology	3	5.1	1	1.7	
Pregnancy complications	8	13.6	4	6.8	
Bereavements	8	13.6	1	1.7	.039
Relatives' severe illness	9	15.3	9	15.3	
Economic troubles	6	10.2	4	6.8	
Relocations	8	13.6	5	8.5	
Other	11	18.6	5	8.5	.031
Total number of stressful events	93	–	57	–	Wilcoxon .003
<i>How was your pregnancy?</i>	M	SD	M	SD	Wilcoxon
Long	38.67	1.87	38.76	2.10	
Untroubled	3.53	1.02	3.58	.88	
<i>Difficult</i>	<i>1.95</i>	<i>1.06</i>	<i>1.68</i>	<i>.75</i>	<i>.131</i>
Happy	3.98	.86	3.97	.85	
Stressful	1.76	.86	1.81	.84	
Calm	3.07	1.048	3.20	.87	
Hard	1.92	1.04	1.63	.61	.033
Positive (sum of positive variables)	10.58	2.59	10.61	2.47	
Negative (sum of negative variables)	5.63	2.67	5.10	1.90	
Total score (positive–negative)	4.93	4.82	5.61	3.64	
Social support	3.41	1.15	3.49	1.15	
Mother's health conditions	3.93	.79	4.07	.61	
Fetus' health conditions	4.47	.60	4.49	.60	

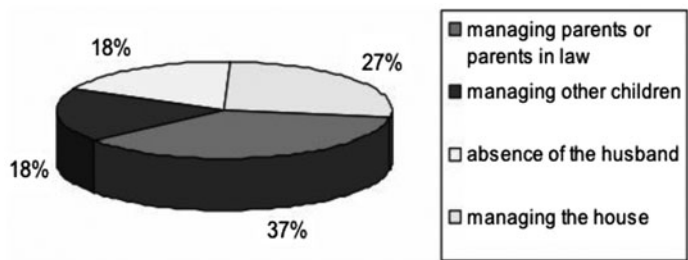


Figure 1. "Other variable": other stressors occurred in food allergic children pregnancy reported by mothers.

allergic children, postpartum was felt by mothers as significantly less untroubled ($p = .008$), more stressful ($p = .025$), harder ($p = .017$), and in total, more negative ($p = .008$) compared to siblings. The first three months after birth showed, in general, a lower quality (score postpartum) for patients than siblings ($p = .008$).

Table 2. Investigated variables in postpartum: comparison between food allergic children and siblings.

Variables		Food allergic children		Siblings		TEST $p < .05$ McNemar
		Frequency	%	Frequency	%	
Delivery	Natural	47	79.7	43	72.9	.017
	Caesarean	12	20.3	16	27.1	
Breastfeeding		57	96.6	57	96.6	
Birth complications		9	15.3	3	5.1	
Incubator		7	11.9	3	5.1	
Feeding difficulties		18	30.5	6	10.2	
Sleeping difficulties		20	33.9	13	22	
Mother's pathology		12	20.3	6	10.2	
Child's pathology		12	20.3	6	10.2	
Bereavements		5	8.5	3	5.1	
Relatives' severe illness		5	8.5	6	10.2	
Economic troubles		9	15.3	4	6.8	
Relocations		3	5.1	2	3.4	
Other		17	28.8	4	6.8	
Total number of stressful events		110	–	56	–	.001 Wilcoxon .0001
<i>Ordinal variables</i>		M	SD	M	SD	Wilcoxon
Weight at birth		3345 g	558.65	3394 g	385.15	.008
Length of breastfeeding		8.38 months	4.40	7.95 months	3.35	
Weaning age		6.90 months	2.48	6.69 months	1.88	
How untroubled was your postpartum?		2.95	.92	3.36	.92	
Difficult		2.37	.95	2.08	.99	
Happy		3.73	1.03	3.85	.96	
Stressful		2.68	1.04	2.34	.92	
Calm		2.66	.92	2.86	.84	
Hard		2.53	1.04	2.14	.94	
Positive (sum of positive variables)		9.34	2.45	10.02	2.27	
Negative (sum of negative variables)		7.58	2.78	6.56	2.62	.008
Total score (positive–negative)		1.76	4.73	3.56	4.34	.008
Social support		3.39	1.23	3.42	1.16	.025
Mother's health condition		3.97	.67	3.93	.72	
Child's health condition		4	.77	4.44	.68	

Discussion

Comparing mothers' report of pregnancies with food allergic children and healthy children, a significant higher total number of stressful events emerged, especially bereavements. In accordance with these findings, pregnancies with allergic children were reported by mothers as significantly harder than with their healthy children ($p < .05$).

It has been already demonstrated that severe life events such as the death of a relative during pregnancy can expose the child to increased risk of developing health

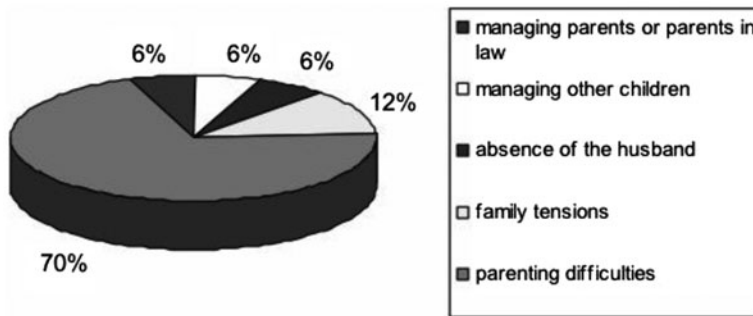


Figure 2. “Other variable”: other stressors occurred in food allergic children postpartum reported by mothers.

problems (Khashan et al., 2008; Li et al., 2009; Virk et al., 2010). The bereaved present altered cortisol levels (Pfeffer, Altemus, Heo, & Jiang, 2009) and this could affect perinatal outcome (Seng, Low, Ben-Ami, & Liberzon, 2005). A number of studies associated stress in prenatal life with early and long-term developmental effects linked to altered maternal glucocorticoid exposure. Maternal stress stimulates placental secretion of corticotrophin-releasing hormone that may kindle the fetal HPA axis to amplify glucocorticoid overload, influencing the development of the immune and nervous systems. It has been proposed that maternal-altered cortisol levels may influence the developing fetal immune system through a direct impact of stress hormones on cytokine production and Th2 cell prevalence, contributing to an increased susceptibility for atopic diseases in later life (de Weerth & Buitelaar, 2005; Pincus-Knackstedt et al., 2006; Von Hertzen, 2002; Wright, 2007; Wright & Bosquet Enlow, 2008).

Maternal responses on the postpartum questionnaire also demonstrated a significantly higher total number of stressful events and feeding difficulties, compared to siblings'. It should be noted that feeding difficulties could be also interpreted as an early sign of vulnerability to food allergy. However, the three months after the birth were felt to be by mothers as considerably less tranquil, more stressful, harder, and in total, more negative for patients than for healthy children. Non-optimal environment and caregiving experiences in early childhood are believed to affect biological vulnerabilities: Stress may disrupt the delicate balance of the interrelated systems (autonomic, neuroendocrine and immune system) increasing susceptibility to allergic sensitization (Wright, 2007; Wright & Bosquet Enlow, 2008). In particular, the HPA axis has been found to be highly responsive to child-caregiver interactions, so that insensitive caregiving may endorse altered HPA responses; on the other hand, children who experienced supportive and sensitive caregiving in early life may result better equipped to cope with environmental stressors and, therefore, less likely to manifest troubled HPA and autonomic reactivity that may set them at risk for immune-based diseases, such as allergies (Gunnar, 1998; Lyons-Ruth & Block, 1996). It is reasonable to consider that a mother involved in coping with stressful events can be less available, cognitively and emotionally, in taking care of her baby; therefore, it is possible that stress and the quality of caregiving provided, as they affect the emotional and physiologic regulation of the infant, could alter the HPA system or immune functioning, facilitating an increased allergic response.

A significant higher number of low/middle (although daily and prolonged) stressors were reported for children with food allergy than for children without food allergy, in

both pregnancy and postpartum questionnaires. This can be noted particularly with regard to ‘troubles with relatives’ and ‘parenting difficulties.’ Some authors have suggested that an accumulation of daily ‘hassles’ could reach the levels of a life event (Kanner, Coyne, Schaefer, & Lazarus, 1981). Moreover, parenting difficulties rated in the first year of life were found to be associated with developing asthma in childhood (Klinnert et al., 2001).

It is worth underlying that no significant differences were found in our sample relating to birth order, pregnancy length, type of delivery, sex, age, and breastfeeding; although most of the mothers reported allergies in their and/or their husbands’ family, only one of their children developed severe food allergy. Differential exposure to stress and variability in stress responses in early critical periods may enhance the chance of developing allergies by potentiating the cascade of biological events that increase susceptibility for atopy (Mäntymaa et al., 2003; Wright, 2007; Wright et al., 1998). This could support the hypothesis of a perinatal programming, which proposes that non-genetic factors acting in early life may permanently organize or imprint physiological system (de Weerth & Buitelaar, 2005; Wright & Bosquet Enlow, 2008); findings suggest that psychological stress can be included in the list of potential programming agents.

This is a preliminary research and it shows many limits, first of all its retrospective nature and the fact that it is mainly based on mothers’ self-report. The absence of significance differences in the sample related to children’s age at the time of the study and birth order states a balance of the duration of the retrospective recall period, eliminating some possible bias. Much information (e.g. pregnancy length, treat of miscarriage, mother and fetus pathology, use of drugs, type of delivery, and birth complications) were collected through a cross-check between mothers’ report and medical records. Moreover, a number of studies confirmed that maternal recall of perinatal issues has to be considered reliable (Buka et al., 2000; Mackenzie & Lippman, 1989; Quigley, Hockley, & Davidson, 2007). About the subjectivity of the assessment, considering that the response to stress is personal, an ad hoc self-report seemed useful, as a first step, to know mother’s personal perception about perinatal stress. Further researches, using validated psychological and physiological measures, are needed to confirm these preliminary data. The selection of the population for this study has both merit and problem: the problem relates to the size of the sample. On the merit side, many confounding factors which may occur in a survey of unrelated mothers of food allergic and non-food allergic children are eliminated using families with one healthy child and one food allergic child so that factors such as genetic background, environmental and socioeconomic aspects are unchanged.

The findings showed a higher number of stressful events in the perinatal period among those who developed food allergy: it can represent a first significant step to assess the complex etiology of the pathology in a multidisciplinary perspective. It also emphasizes the meaning of considering disease as a result of the interaction of multiple factors (genetic, immunological and psychosocial) at different levels (cellular, interpersonal and environmental).

The present study was the first, as far as we know, to investigate the relation between perinatal stress and the development of severe food allergy in childhood, comparing patients to their siblings. Further prospective researches assessing psychophysiological stress reactivity in gestation and early childhood are obviously needed to clarify the role of stress and perinatal psychosocial factors in the pathogenesis of food allergy and its relation with genetic and biological factors.

Competing interest

No financial support was awarded relating to this paper. None of the aforementioned authors has any 'Conflicts of interest' relevant to the work of this publication.

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