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## Maternal risk factors for severe microtia/atresia in China: A case-control study

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## ABSTRACT

**Objective:** Microtia/atresia is a severe malformation of the external ear. Previous studies have reported the potential risk factors on microtia, whereas few focused on severe microtia/atresia. The aim of the study was to investigate the effects of maternal exposure to environmental risk factors in patients with severe microtia/atresia in China.

**Methods:** A case-control study was conducted. Cases were patients with severe microtia/atresia who presented to PUMCH between January 2014 and October 2017. A total of 322 patients with severe microtia/atresia were enrolled and 322 normal controls matched 1:1 with the patients by sex, age and nationality were enrolled. The designed questionnaires were completed and data were gathered. Odds ratios were estimated with logistic regression models along with 95% confidence intervals in severe microtia/atresia.

**Results:** Most cases were males (68.6%), and the cases were observed more common in unilateral (80.7%), right-sided (54.0%). Multivariate logistic regression analysis showed that threatened abortion (OR 4.066, 95% CI = 2.360–7.007), NSAIDs (OR 2.576, 95% CI = 1.079–6.148), virus infection (OR 1.933, 95% CI = 1.148–3.256), anemia (OR 1.902, 95% CI = 1.026–3.526), miscarriages (OR 1.804, 95% CI = 1.425–2.285), maternal age (OR 1.079, 95% CI = 1.015–1.148) and paternal age (OR 1.061, 95% CI = 1.003–1.122) were associated with a higher risk of severe microtia/atresia.

**Conclusion:** These results support that some maternal risk factors could be associated with severe microtia/atresia.

## 1. Introduction

Microtia/atresia is a congenital malformation of the external ear, often involving the pinna, tragus, lobe, and external auditory canal, and ranging in severity from minimally abnormal to the complete absence of the auricle [1]. The incidence of microtia/atresia in China has been estimated to range from 0.83 to 1.53 per 10,000 births [2]. Approximately 10% of patients with congenital microtia/atresia are affected bilaterally [3]. Microtia has been classified into four grades [4]: Grades I and II, minor or mild deformity with the auricle structures being fully or partially distinguishable; Grade III, severely malformed auricle with no definable structures; and Grade IV (anotia) [5], total absence of the

external ear. Microtia/atresia often presents as a rudimentary auricle, atresia of the auditory canal and middle ear abnormalities, resulting in conductive hearing loss [6]. Moreover, these patients experience higher rates of psychosocial burden and social stigma than the general population [7].

Although hereditary factors, such as chromosomal abnormalities and genetic mutations, have been reported to play an important role in the occurrence of microtia, environmental risk factors have also been associated with microtia. These risk factors may include prenatal exposure to maternal medications [8], maternal illness [9], advanced parental age [9–11], high parity [9–12], race/ethnicity [10,11,13], high altitude [14], urban area [15], low maternal education [13,16],

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multiple births [10,13] and low birth weight [9,10,12].

Despite studies assessing the environmental risk factors for microtia in various populations, potential risk factors remain unclear. Although previous studies have examined patients with microtia with different levels of severity, little attention was given to describing malformations of the auricle and external auditory canal. However, a retrospective study found that maternal exposure to several factors was linked to a greater likelihood of severe microtia in infants [17], making it necessary to assess the association of severe malformation with environmental factors. In addition, factors evaluated in previous investigations of microtia, especially prenatal factors affecting embryonic development, have been limited and insufficient. To investigate the effects of exposure to environmental factors in patients with severe microtia/atresia, we performed a case-control study to evaluate maternal risk factors for severe microtia/atresia in China.

## 2. Materials and methods

### 2.1. Study population

This is a hospital-based case-control study. The present study involved patients with severe microtia/atresia who presented to the Otorhinolaryngology Department of Peking Union Medical College Hospital (PUMCH) in Beijing, China, between January 2014 and October 2017. Because syndromic microtia may have hereditary origins, only patients with non-syndromic microtia were included in this study. Since microtia is recognized as a minimal phenotype of hemifacial microsomia, patients with hemifacial microsomia were also included. Patients with a family history of microtia and those with other major malformations, such as cardiac, renal and limb defects were excluded.

All patients with microtia enrolled in this study underwent detailed physical examinations performed by experienced clinicians. The grade of microtia was determined using the Marx classification [4]. Considering severe microtia was more likely to be affected by maternal factors than mild microtia [17], only patients with microtia grades III and IV accompanied by atresia were defined as having severe microtia/atresia and included in this study. This study included 322 patients with severe microtia/atresia. The mother of each patient was subsequently asked to fill out a detailed questionnaire, either by interview in the hospital or on the telephone, under the guidance of a clinician. A total of 322 normal controls matched 1:1 with the patients by sex, age and nationality were enrolled by field investigation. All the controls were recruited from healthy children in schools nearby PUMCH and those who came to the hospital for other reasons. None of the controls and their parents had any birth defects, including pre-auricular fistula and tags. The study protocol was approved by the Institutional Review Board of PUMCH, and written informed consent was obtained from the parents of all patients.

### 2.2. Questionnaire survey

After reviewing previous studies concerning risk factors for birth defects, including microtia, and evaluating responses of patients' parents, potential environmental risk factors that may contribute to the occurrence of microtia by directly affecting embryonic development during pregnancy were selected. Because auricle development is usually completed by the twelfth week of gestation, potential environmental risk factors occurring during the first trimester of pregnancy were investigated. Thus, 21 questions related to selected environmental exposure were included in the questionnaire administered to patients and controls. The questionnaire consisted of five sections: demographic information, history of miscarriage, maternal health history, maternal habits and exposure to environmental factors during the first trimester of pregnancy. The detailed questions included name, sex, age, geographic region, living environment, history of miscarriage, threatened

abortion and preventive treatments, prenatal illness, medication history, alcohol consumption, smoking, and exposure to chemicals and ionizing radiation. For inclusion, the evaluated diseases must have been diagnosed by physicians during pregnancy. Women who had smoked at least one cigarette per day or were exposed to passive smoke during pregnancy were defined as having a history of smoking. Women who had consumed alcohol at least once per week during pregnancy were defined as having a history of alcohol consumption, with these women further subdivided into sporadic and regular alcohol drinkers according to their frequency of alcohol consumption. Women who had been frequently exposed during pregnancy to harmful chemicals, such as pesticides or formaldehyde, at home or at work, were defined as having a history of chemical exposure. Women who had received medical X-rays at least once or who worked at a computer for at least 10 h per day without protective measures during pregnancy were defined as having a history of ionizing radiation.

### 2.3. Statistical analysis

All statistical analyses were performed using SPSS software, version 22.0 (IBM, USA). Quantitative variables were compared using Student's t-tests and categorical variables were compared using the Pearson chi-square and Fisher's exact tests. Univariable associations between proposed risk factors and microtia were estimated by calculating odds ratios (OR) and 95% confidence intervals (CIs) compared with matched controls, with variables having p-values less than 0.05 considered statistically significant. Variables found to be significant on univariate analysis were included in multivariate analysis by logistic regression. Cochran-Armitage tests for trend were performed to analyze ranked data in risk factors.

## 3. Results

### 3.1. Demographic data

A total of 322 patients with severe microtia/atresia were enrolled in this study. Of these 322 patients, 221 (68.6%) were boys and 101 (31.4%) were girls; 174 (54.0%) were affected on the right side, 86 (26.7%) on the left side, and 62 (19.3%) on both sides. According to the Marx classification, 319 (99.1%) and three (0.9%) patients were categorized as having Grades III and IV microtia respectively (Table 1).

### 3.2. Univariate analysis

Among mothers of children in the severe microtia/atresia group, 79 (24.5%) experienced threatened abortion, which characterized by vaginal bleeding and intermittent uterine cramping while the cervix is closed, 72 (22.4%) had viral illnesses (including the common cold,

**Table 1**  
Characteristics of the patients with severe microtia/atresia.

	Severe microtia/atresia		Total Cases
	III	IV (Anotia)	No. (%)
<b>Gender</b>			
Male	218 (67.7%)	3 (0.9%)	221 (68.6%)
Female	101 (31.4%)	0	101 (31.4%)
<b>Laterality</b>			
<b>Unilateral</b>	257 (79.8%)	3 (0.9%)	260 (80.7%)
Left side	85 (26.4%)	1 (0.3%)	86 (26.7%)
Right side	172 (53.4%)	2 (0.6%)	174 (54.0%)
<b>Bilateral<sup>a</sup></b>	62 (19.3%)	0	62 (19.3%)
<b>Total Cases</b>	319 (99.1%)	3 (0.9%)	322 (100%)

<sup>\*</sup>The severity of ears were evaluated according to Marx classification.

<sup>a</sup> Bilateral patients were classified according to the more severe ears.

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