Diabetes, Body Mass Index, Vitamin Supplementation and Anotia/Microtia

Martha M. Werler
Jane E. Sheehan
Allen A. Mitchell

Slone Epidemiology Center
Boston University

Presented at Teratology Society Annual Meeting

Vancouver, BC

June 30, 2004

What do we know about the epidemiology of anotia/microtia?

What do we know about the epidemiology of anotia/microtia?

Not much!

Anotia/Microtia

The epidemiology of anotia and microtia. Harris, J, Kallen B, Robert E. J Med Genet 1996;33:809-13.

Mastroiacovo P, Corchia C, Botto LD, Lanni R, Zampino G, Fusco D. Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. J Med Genet 1995;32:453-7.

Report from International Clearinghouse for Birth Defects Monitoring Systems. Congenital Malformations Worldwide. 1991. Elsevier.

Anotia/Microtia

What we do know:

Prevalence is ~1-2 per 10,000 births

Anotia/Microtia

Highest in:

Mexico	6.4
So. America	4.6
China	4.6
Calif – Hispanics	3.2
Calif – Asians	2.2
Ariz – Nat. Amer.	17.5

per 10,000 births

Anotia/Microtia

What we do know:

More common in males

Sex ratio: 1.6

~ 63 male : 37 female

Anotia/Microtia

Known causes:

Thalidomide

Isotretinoin

Genetic

Risk factor:

? Diabetes

Anotia/Microtia

Laterality:

35% bilateral
65% unilateral

Bilateral more likely to have associated malformations than unilateral

Anotia/Microtia

Associated malformations:

34-39% with associated major malformations, after excluding known chrom. anomalies

Anotia/Microtia

Associated malformations:

Facial cleft
Cardiac defect
Goldenhar S.
An/microphthalmia
Limb reduction defect
Renal anomaly
Holoproscencephaly

Anotia/Microtia

Associated defects occurring together:

Anotia/microtia + holoproscencephaly + an/microphthalmia

Anotia/microtia + neural tube defect + facial cleft

Holoproscencephaly – diabetes

Neural tube defects – diabetes

– body mass index

– vitamin use

Facial clefts – ?vitamin use

Are – diabetes

– body mass index

– vitamin use

associated with anotia/microtia risk?

Hemifacial Microsomia Study

Objective:

To identify vasoactive and other risk factors for hemifacial microsomia (HFM)

Hemifacial Microsomia Study

- 1997-2002
- Retrospective study
- Multicenter study – U.S. and Canada
- Cases from craniofacial centers
- Controls from case's pediatrician's office

Hemifacial Microsomia Study

- Cases diagnosed with
  - Hemifacial microsomia
  - Facial asymmetry
  - Unilateral anotia/microtia
- < 3 years of age

Hemifacial Microsomia (HFM) Study

268 cases

- **238 with HFM**
  - **122 without an/microtia**
  - **116 with an/microtia**
- **39 with unilateral an/microtia**

{ **155 anotia/ microtia cases**

854 non-malformed controls

Anotia/Microtia Study

Race/ethnicity	Cases n=155	Controls n=854
White, non-Hisp.	45.2%	65.2%
Hispanic	41.3%	18.5%
African-Amer.	5.2%	11.7%
Asian-Amer.	7.5%	3.6%
Native Amer.	1.9%	0.9%

Anotia/Microtia Study

Sex:

Sex ratio: 1.9
65% male vs. 52% male controls

Associated malformations:

75% with HFM
35% with defect other than HFM

Hemifacial Microsomia Study

- Mothers were interviewed by telephone
- Questions on
  - Demographic factors
  - Reproductive factors
  - Behaviors
  - Illnesses, medications, vitamins

Anotia/Microtia Study

Diabetes: pre-existing or
gestational (lunar months 1 -5)

Body mass index: prepregnancy
height/meters^2

Vitamin supplementation: Folic acid-
containing vitamin
1st use in lunar month 1
1st use in lunar months 2 or 3

Anotia/Microtia Study

Diabetes	Cases n=155	Controls n=854
Overall	**16 (10.3%)**	**12 (1.4%)**
pre-preg.	**8 (5.2%)**	**4 (0.5%)**
dx LM1-3	**3 (1.9%)**	**2 (0.2%)**
dx LM 4-5	**5 (3.2%)**	**6 (0.7%)**

Anotia/Microtia Study

Body mass index (kg/m^2)	Cases n=155	Controls n=854
<19	19 (12.3%)	54 (6.3%)
19-23.9	64 (41.3%)	446 (52.2%)
24-27.9	27 (17.4%)	175 (20.5%)
28-31.9	21 (13.5%)	87 (10.2%)
≥32	13 (8.4%)	72 (8.4%)
Unknown	11 (7.1%)	20 (2.3%)

Anotia/Microtia Study

F.A. 1st use in	Cases n=155	Controls n=854
LM 1	44 (28.4%)	275 (32.2%)
LM 2 or 3	70 (45.2%)	454 (53.2%)
Later or none	41 (26.5%)	125 (14.6%)

Anotia/Microtia Study

Risk factor	Odds ratio@	95% CI
Diabetes	6.3	2.7-14.9
BMI: <19*	2.3	1.2-4.3
BMI: ≥28*	1.2	0.7-2.1
F.A. LM 1-3	0.7	0.4-1.1

@Adjusted for maternal age, education, income, race, and # gestations.

*ref. category 19-23.9

Does vitamin use modify the effect of diabetes on anotia/microtia risk?

Does vitamin use modify the effect of diabetes on anotia/microtia risk?

Diabetes and vitamins?	No	Yes
Birth defects	3.9*	0.15
Hydrocephaly	2.5	0
Heart defects	4.5*	1.0
Respiratory tract	6.8	0
Pyloric stenosis	4.0	0

*p<.05

Anotia/Microtia Study

Diabetes	Cases	Controls
+ F.A. use	11 (7.1%)	10 (1.2%)
OR (95% CI)*	5.5 (2.0-15.0)	
- F.A. use	5 (12.8%)	2 (1.7%)
OR (95% CI)*	9.8 (1.1-87.0)	

*Adjusted for maternal age, education, income, race, and # gestations

Anotia/Microtia Study

Limitations:

- **Study designed to capture HFM cases**
- **Bilateral cases not ascertained**
- **Ascertainment of anotia/microtia cases is not likely to be complete**

Anotia/Microtia Study

Limitations:

Would cases born to women with

diabetes

high or low BMI

vitamin supplementation

be more or less likely to be in the study?

Anotia/Microtia Study

Strengths:

- **Ethnic/race and sex distributions in present study were similar to CBDMP**

Anotia/Microtia Study

Limitations:

- **Retrospective recall**
- **Imperfect measure of diabetes**

Anotia/Microtia Study

Conclusions:

Our findings confirm those from Italy: diabetes appears to increase anotia/microtia risk

Anotia/Microtia Study

Conclusions:

Our findings suggest that, unlike NTDs, obesity does not increase anotia/microtia risk

Rather, our findings suggest women with low pre-pregnant BMI might have an increased risk

Anotia/Microtia Study

Conclusions:

Our findings suggest that folic acid-containing vitamin supplementation does not attenuate the effects of diabetes on anotia/microtia risk.

Anotia/Microtia

Sideness:

65% are unilateral

61% are right-sided

Anotia/Microtia Study

Body mass index (kg/m^2)	Cases n=155	Controls n=854
<19	(12.3%)	(6.3%)
19-23.9	(41.3%)	(52.2%)
24-27.9	(17.4%)	(20.5%)
28-31.9	(13.5%)	(10.2%)
≥32	(8.4%)	(8.4%)
Unknown	(7.1%)	(2.3%)

www.emedicine.com/ped/topic3003.htm

www.emedicine.com/ped/topic3003.htm