

Microphthalmia and Anophthalmia in Chuuk state, Federated States of Micronesia

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Abstract

Microphthalmia ('small eye') and anophthalmia ('no eye') are rare congenital defects of eye development. Previous studies utilizing a variety of methodologies have estimated their combined incidence at anywhere from 4 to 30 cases per 100,000 live births. In Chuuk, Federated States of Micronesia, there have been 42 cases detected since 1988, yielding an estimated incidence of 140 cases per 100,000. A number of putative genetic and environmental causes have previously been associated with microphthalmia and anophthalmia, including vitamin A deficiency. To date, it is unclear which of these factors may play a role in the alarmingly high rates observed in Chuuk. The Chuuk Division of Public Health has proposed a study to explore these potential causes, which will hopefully shed light on the prevention of these rare but debilitating conditions.

Introduction

Microphthalmia (possession of an abnormally small globe; also referred to as microphthalmos) and anophthalmia (complete absence of the globe; also called anophthalmos) are rare congenital conditions. Various studies (all conducted in developed countries) have estimated their prevalence at ranging from 4 to 30 cases per 100,000 births.^{1,2} Microphthalmia and anophthalmia (M/A) can be considered as being two ends of a spectrum of ocular malformation, on one end characterized by simple microphthalmia, in which the eye is anatomically normal but has a total axial length less than two standard deviations below the age-adjusted mean. Patients with simple microphthalmia may have vision in the affected eye, albeit usually with severe hyperopia (>8 diopters). On the other end of the spectrum is complete anophthalmia, with no histologic evidence of eye tissue. Most cases lie in-between. M/A may occur in isolation, as in two-thirds of cases, or can occur, in one-third of cases, with other anomalies or as part of a well-characterized syndrome.³ Management of patients with M/A requires a multidisciplinary approach, involving pediatricians, ophthalmologists, plastic surgeons, neurologists, geneticists, psychologists, nutritionists, nurses and health educators.

The putative causes of M/A can be broadly grouped into two categories: genetic and environmental. Genetic causes may be due to major chromosomal abnormalities, such as duplications, deletions, translocations, or trisomies; or monogenic causes, primarily de novo mutations to the SOX2 gene.³ The strongest evidence for environmental causes is for congenital infections, such as rubella, toxoplasmosis, cytomegalovirus, varicella,



parvovirus B19, influenza, and Coxsackie A9. Other environmental causes that have been postulated include maternal vitamin A deficiency (which can itself predispose the mother to infections; conversely, infections can predispose a person to VAD), hyperthermia, solvent abuse, x-rays, alcohol, and medicines such as thalidomide and warfarin. Other associated factors may include maternal age over 40, multiple births, low birth weight, and low gestational age; a protective effect was seen in one study when mothers had greater than 12 years of education, even after adjustment for confounding factors.³ Finally, it has been postulated that there may be an interaction between genetics and environment: mutations in a recessive gene involved in cellular access to vitamin A, which normally protects an embryo from natural variation in maternal vitamin A intake, could render the embryo intolerant of conditions of VAD.⁴

For the past seven years, the Chuuk Children with Special Health Care Needs (CSHCN) clinic at the Chuuk Division of Public Health (Chuuk State, Federated States of Micronesia) has been seeing a startling number of children born with severe microphthalmia or anophthalmia, occurring either unilaterally or bilaterally. According to records, as far back as 1988, there have been children detected with these problems; however, this was not known to the program until early 2000, when several of these cases presented to the CSHCN clinic. This dramatic increase in incidence alarmed the CSHCN physician and the staff at the public health clinic, prompting them to research the history of the problem.

Burden of M/A in Chuuk and the possible role of vitamin A deficiency

Review of the CSHCN registry revealed that there are, on average, one or two cases of M/A seen per year, with the greatest number of cases occurring in 2003; in this year, 10 children with M/A were seen at the clinic. Between 1988 and 2008, there were a total of 42 children born with M/A. Using Chuuk State Census data from 1994 and 2000,⁵ we can estimate the total number of births over this 20-year time period to be approximately 30,000, resulting in an M/A incidence of approximately 140 per 100,000 live births. There has not been a discernible temporal trend in the incidence of cases. We have found cases of M/A throughout the islands of Chuuk state, with the greatest number of cases (15) in the islands of the Northern Namoneas group.

One of the authors conducted informal interviews with the case-patients' mothers regarding their diets, lifestyles, and activities during their pregnancies, with emphasis on the first trimester. The questions sought to compare behaviors and experiences during the gestation of the child with M/A, as compared with previous pregnancies, in order to identify any common factors that would suggest some possible causes of M/A in this population. The results of these informal interviews were uninformative; there was nothing unusual noted that the mothers did or experienced in comparison with their previous pregnancies. No control group of unaffected mothers was interviewed.

Because of the postulated association of M/A with maternal vitamin A deficiency (VAD), we conducted a review of the burden of VAD in Chuuk.

Previous studies done in Chuuk on VAD were primarily conducted on children. For example, a clinic-based study conducted in 1987 on 60 systematically sampled 38- to 83-month-old children found that 17% had xerophthalmia, and 57% showed evidence of subclinical VAD.⁶ A population-based study⁷ conducted the following year on 455 randomly selected 38- to 83-month-old children showed that 14% had night blindness



and 6% had Bitot's spots, which far exceed the WHO cutoffs of 1% and 0.5%, respectively.⁸ Only one study, conducted in 2002, assessed both child and maternal VAD; there was widespread VAD in both populations, the.⁹ Compared with other countries globally, the Federated States of Micronesia is estimated by WHO to have a moderate^a burden of VAD.¹⁰

Other possible causes of M/A in Chuuk

This relatively rare medical condition has occurred at a frighteningly high rate on these small tropical islands, much higher than has previously been reported in developed countries. The central question, of course, is: why is this the case? Present research suggests that heritable genetic defects play only a minor role in the epidemiology of M/A, suggesting that environmental causes (or environmental triggers of occult genetic defects) play the more central role in Chuuk. Nevertheless, the possibility of a heritable genetic trait unique to this population must not be overlooked, as isolated island populations are prone to rare genetic disorders (for example, achromatopsia, i.e., total colorblindness, on the island of Pingelap in nearby Pohnpei state).¹¹

Of the environmental causes, those most likely to be relevant to Chuuk are maternal VAD and infection, hyperthermia, and alcohol. Little is known about the role of infection and hyperthermia during pregnancy in Chuuk. Alcohol abuse is epidemic in Chuuk, though its relevance in women of childbearing age has not been studied. The one study of VAD in mothers showed a degree of VAD in this study population overall; however, it will be crucial to determine whether VAD is present specifically in mothers of M/A-affected children. The interaction of a genetic predisposition with maternal VAD must also be explored. The obstetric parameters associated with M/A (e.g., advanced maternal age, low birth weight) are also worth exploring, though they do not easily lend themselves to making causal inferences.

Next Steps

While the etiology of M/A in Chuuk is far from certain, it is clear that the problem is considerable. Because so little is known about the etiologic factors, the CSHCN has submitted a grant proposal to UNICEF to conduct a study of both genetic and environmental factors; the study would employ a survey tool administered to mothers and a blood sample collection for genetic, serologic (for infectious etiologies), and VAD testing of the affected children and their parents. Without a greater understanding of the possible etiologies of M/A in Chuuk, the CSHCN will continue to face challenges in educating patients and families about its cause and prevention, or providing genetic counseling for future pregnancies.

A future question is whether the exceptionally high burden of M/A is limited to Chuuk, or whether the problem is widespread within this region of the world, or developing countries in general. One of the authors recently encountered a child with microphthalmia in Ebeye, Republic of the Marshall Islands, while conducting unrelated research. This suggests that the high burden of this rare but debilitating condition may not be limited to Chuuk, but may rather be common to other Pacific areas with similar environments and risk factors.

a. Compared globally, the Federated States of Micronesia public health burden of VAD-associated indicators is estimated as follows: a 'mild' problem with night blindness in preschool-aged children; 'no' problem of night blindness among pregnant women; a 'severe' problem with serum retinol levels in preschool-aged children; and a 'mild' problem with serum retinol levels in pregnant women.¹⁰



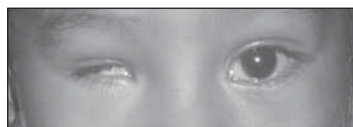


Figure 1:
A Chuukese child with unilateral clinical anophthalmia



Figure 2:
A Chuukese child with bilateral clinical anophthalmia

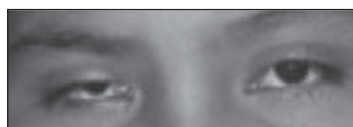


Figure 3:
A Chuukese child with unilateral (right-sided) microphthalmia

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