Genetic Evaluation for Craniofacial Conditions

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KEYWORDS

• Genetic evaluation • Genetic counseling • Family history • Teratogens • Dysmorphology • Genetic testing • Cleft lip • Cleft palate

KEY POINTS

- Every child born with a craniofacial disorder should be evaluated by a clinical geneticist.
- Many craniofacial disorders have a genetic etiology, and large variety of genetic testing is available for testing affected individual and family members.
- Although many genetic disorders are common, many patients present with rare or unique conditions requiring specialized genetics evaluations and tests.
- All children with craniofacial disorders should be managed by an interdisciplinary craniofacial or cleft team.

INTRODUCTION

Congenital anomalies and disorders are those conditions that are present at birth and that require some level of medical intervention. These conditions occur in approximately 3% to 5% of all live births.[1] Craniofacial conditions, including orofacial clefts, craniosynostoses, the mandibulofacial dysostoses, and craniofacial macrosomia, are among the most common birth congenital anomalies. Many of these conditions have a genetic etiology (chromosomal, single-gene disorders, or epigenetic mutation) or may be caused by teratogens. Because of this, it is important for each child born with a craniofacial condition to be evaluated and followed by a medical geneticist. The American Cleft Palate-Craniofacial Association in their Standards for Cleft Palate and Craniofacial Teams states, "The Team also must demonstrate access to refer to a neurosurgeon, an ophthalmologist, a radiologist, and a geneticist."[2] The role of the medical geneticist is to assist in making a diagnosis of any known genetic disorder or syndrome, assist families and craniofacial team members in understanding the natural history of any syndrome, and ensure that additional medical evaluations and interventions are performed as indicated. There are thousands of different causes for craniofacial conditions. Identifying the etiologies is important for understanding the cause of a particular condition and influencing the management of a particular disorder. Also, craniofacial conditions are chronic conditions and follow-up evaluations with a medical geneticist should be encouraged.

THE GENETICS EVALUATION

The purpose of the genetics evaluation is to

- Make a diagnosis
- Characterize natural history
- Establish appropriate follow-up evaluations and testing
- Determine recurrence risk and potential genetic testing for family
- Provide genetic counseling for family

Disclosure: Dr H.M. Saal is a member of the Medical Advisory Board and the Speakers Bureau for Alexion Pharmaceuticals.

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Facial Plast Surg Clin N Am 24 (2016) 405–425
http://dx.doi.org/10.1016/j.fsc.2016.06.001
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Ideally, the genetics evaluation should be performed as early as possible, often soon after birth. Given the technical advances in prenatal diagnosis, prenatal genetic evaluation has become a common occurrence. The genetics evaluation differs from the typical medical evaluation with greater emphasis on prenatal and family histories.

Prenatal Evaluation

Congenital craniofacial conditions begin in utero. Therefore, obtaining a comprehensive pregnancy history is essential to understanding etiology, especially with regard to teratogen exposure, maternal illness, and prenatal testing. Teratogens are substances that interfere with normal embryologic and fetal development. Teratogens include medications and drugs, high-dose radiation, viruses, and maternal illnesses.

Maternal illnesses that are known to cause craniofacial anomalies are diabetes and maternal phenylketonuria. Women with diabetes, both type 1 diabetes mellitus and type 2 diabetes mellitus, have least a 2-fold risk for having a child with birth defects, the greatest risks associated with type 1 diabetes mellitus.[3] The major birth defects are renal, vertebral, brain, and craniofacial anomalies. Craniofacial anomalies include cleft lip, cleft palate (CP), and Pierre Robin sequence (PRS). In my institution, maternal diabetes is among the most common causes of cleft lip with or without CP (CLP) and CP. Women who have phenylketonuria are unable to properly metabolize the amino acid phenylalanine. If an affected woman does not follow a phenylalanine-restricted diet, the elevated levels of the metabolites of phenylalanine can cause multiple anomalies, including microcephaly, ear anomalies, congenital heart defects, and CP.[4] Maternal hyperthyroidism and Graves disease have been associated with neonatal craniosynostosis.[5]

Prenatal testing is commonly performed, especially fetal ultrasound. Ultrasound is performed in midtrimester in most pregnancies in the United States. Cleft lip can be identified with routine ultrasound in approximately 75% of cases[6] and diagnosis approaches 100% with high-resolution ultrasound.[7] It is more difficult to diagnose CP by ultrasound; however, micrognathia and PRS can be diagnosed prenatally.[8] For more complex cases, especially with those with multiple anomalies, fetal MRI scans are performed at several high-risk centers and can be useful for assessing severity of fetal structural and brain anomalies and have a direct impact on pregnancy management (**Fig. 1**).[9]

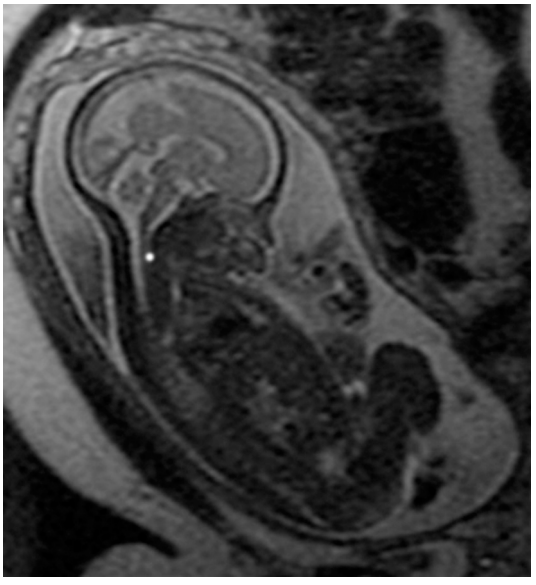

Fig. 1. Fetal MRI scan demonstrating severe micrognathia in a fetus with PRS.

If fetal anomalies are suspected, prenatal genetic testing should be considered. Invasive testing includes amniocentesis, which can be performed from 14 weeks' gestation to term, and chorionic villus sampling can be performed at 12 weeks' gestation. These procedures are usually

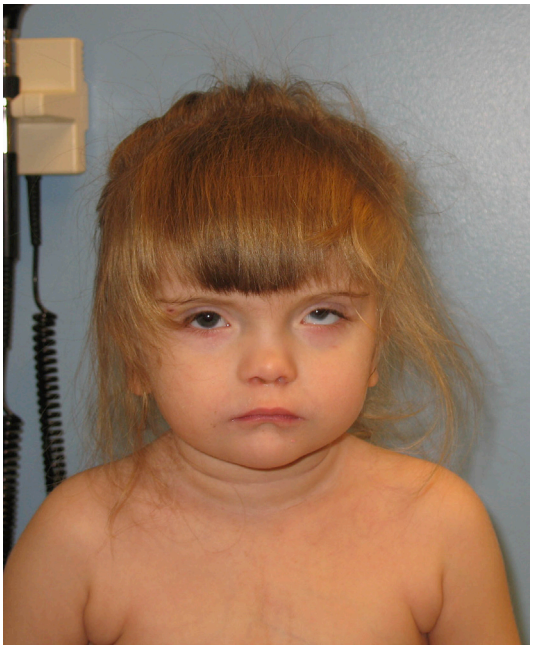

Fig. 2. Young girl with fetal valproate syndrome. Note the short nose, long philtrum, and up-slanting palpebral fissures.

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