

Patient Name: MAX A CORTEZ**MRN:** 30421403**DOB:** 04/30/2009**Date of Visit:** 06/05/2009**Division of Genetics****1717 South Orange Avenue****Suite 100****Orlando, FL 32806**

Mr. and Mrs. and Cortez
2324 Academy Cir W
Kissimmee, FL 34744

Dear Mr. and Mrs. Cortez:

I had the pleasure of seeing you in my Genetics Clinic on 06/05/2009. As you know, we sat down and discussed possible explanations for the problems that your son, Max, was born with.

The pregnancy with Max was pertinent for no early problems for the mother during the pregnancy. Ultrasound around 18 to 20 weeks' gestation raised the concern for possible hydrocephalus with a very large head. The family was seen by Dan Riconda, a genetic counselor with a prenatal diagnostic group out of Orlando Health. Amniocentesis was done which came back normal male 46,XY. Followup ultrasounds showed again significant hydrocephalus and also concern for possible contractures. Mother was healthy and well during the pregnancy with no high blood pressure or high blood sugar. She took no medications except for prenatal vitamins. There were no significant illnesses or infections. There were no reports of any tobacco, alcohol or drug use. Mom went into preterm labor around 32 weeks' gestation and Max was delivered at that time via C-section for hydrocephalus.

Max immediately required respiratory support after delivery and was ventilated. He survived only for 17 days. He remained on the ventilator the whole time with no attempts to over breathe the ventilator. From a neurological standpoint, a head MRI done postnatally showed marked dilation of the lateral ventricles. There was also mild-to-moderate dilation of the third ventricles. The cerebellar hemispheres were diminutive. The brainstem was dysmorphic in appearance with thinning of the anterior-to-posterior dimension of the pons, focal angulation of the pons and buckling of the medulla. There was marked thinning of the cerebral hemispheres likely related to ventricular dilation. The basal ganglia was not seen. There were multicystic structures in the area that should be occupied by the basal ganglia. I had a colleague of mine in Chicago, a pediatric neurologist, look at Max's MRIs. Unfortunately, my colleague was unable to look at the MRI until after Max had passed on. My colleague believes that the MRI findings are consistent with a condition called Walker-Warburg syndrome. From a cardiac standpoint, no major cardiac abnormalities were reported. From a renal ultrasound standpoint, there was mild left-sided hydronephrosis. From a GU standpoint, ambiguous genitalia was noticed at birth with a phallus but no scrotum. A pelvic ultrasound raised concern that the testes were intraabdominal. Extremities were found to have multiple fixed contractures involving arms and legs. Max's gut never worked and he developed severe edema early in his hospital course. Ophthalmology evaluation done during the course of his hospital stay reported clouded corneas and microphthalmia. There was a concern for possible increased intraocular pressure.

Patient Name: MAX A CORTEZ
MRN: 30421403

Testing done in the newborn period from a genetic standpoint, includes a CK level done right after birth, which was elevated at 531 but a repeat done a few days later had normalized. Cholesterol level was 48 which is actually normal for a child of 32 weeks gestation. A 7-dehydrocholesterol test was sent and was negative.

Family history is pertinent for Max being the first child for his parents. Max's mother is 26 years old and 5 feet 8 inches tall. She is healthy and well. She is the only child for her parents. Her parents are both in their 60s with concern for possible cancer in her father. That side of the family is of European descent. Max's father is 26 years old and 6 feet 1 inches tall. He reports no health problems. He has 2 brothers and 3 sisters, all healthy and well who have not yet had children. Paternal grandfather has a history of diabetes. That side of the family is from Mexico. There are no reports of any individuals with multiple joint contractures or hydrocephalus in either mother or father's side of the family.

On physical exam, when I evaluated him shortly after birth, Max was intubated and had minimal spontaneous movement. He had a large head circumference with widely split anterior fontanelle and posterior fontanelle and third fontanelle. There was bruising on the forehead. His eyes were tightly shut. I could not open them. His ears were low set and had reasonable architecture. His neck was short and broad with sloping shoulders. Chest had good aeration with ventilation. Heart had a regular rate and rhythm without a murmur. Abdomen was soft and nontender. There was no significant hepatosplenomegaly. GU exam showed hip pterygia. Phallus was present but no scrotum was detectable and no testes were palpable. Back was straight. Extremities showed decreased flexion of elbows with mild pterygia at the shoulders. There were bilateral severe finger contractures with overlapping fingers. He had markedly adducted thumbs bilaterally. There were diminished creases of the fingers. Knees were bent and contracted in an Indian sitting position and he had bilateral club feet. It was difficult to visualize the genitalia due to the crossing of his legs. Skin showed no abnormalities although there were multiple areas of bruising consistent with a difficult delivery. From a neurological standpoint, there was minimal spontaneous movement.

In summary, Max was born at 32 weeks' gestation and died at about 17 days of age. I spent about half an hour talking to the family about what may have caused Max's problems. Initially, when I saw him, my first thoughts were Smith-Lemli-Opitz syndrome and muscle-eye-brain disease. Smith-Lemli-Opitz was ruled out by the normal 7-dehydrocholesterol testing. Muscle-eye-brain disease was still a possibility, although the fact that his CK normalized made it a little less likely because, classically, people with muscle-eye-brain disease do have elevated CK. My colleague in Chicago does think that the CNS findings are classic for Walker-Warburg syndrome, which is one of the muscle-eye-brain diseases. It may be that normalized CK in Max's case is simply that he really had no muscle tissue left to make CK and that would go along with the severity of his condition. I explained to the family that muscle-eye-brain disease is a general term for individuals who have abnormalities of the muscle, eye and the brain and there are multiple different subheadings in muscle-eye-brain disease and Walker-Warburg is one of them. Walker-Warburg syndrome is one of the more severe types of muscle-eye-brain disease. Individuals with Walker-Warburg syndrome classically have significant brain abnormalities such as we are seeing in Max with dilated ventricles, often have cobblestone and lissencephaly, which

Patient Name: MAX A CORTEZ

MRN: 30421403

we really could not see in Max because he had such ventricular dilation. They also can have very classic abnormalities at the brainstem that Max had. Individuals with this condition may also be born with significant contractures we are seeing with Max. They can have genital abnormalities in males and they can have eye abnormalities including cloudy cornea and small eyes; so from the clinical standpoint, Walker-Warburg seems a very appropriate diagnosis for him. It is a difficult diagnosis to confirm. Genetic testing for Walker-Warburg is very limited. There are 2 genes, POMT1 and POMT2 and, when they do not work correctly, can lead to Walker-Warburg syndrome, but only a small number of people with Walker-Warburg syndrome who have been evaluated have had mutations in those genes, probably less than 20%. This is not a very good way to confirm the diagnosis of Walker-Warburg. Unfortunately, we were not able to send testing for him before he passed on.

Whether or not he had Walker-Warburg, I am comfortable saying he has muscle-eye-brain disease as the greater category and, basically, all forms of muscle-eye-brain disease including Walker-Warburg are autosomal recessive in nature. This would mean if the parents were to have any further children, there would be in 1:4 or 25% chance of each pregnancy to have another child with problems similar to what we are seeing in Max, and I would expect the problems would be potentially as severe as what we were seeing in Max. Prenatal testing is limited. If another child of the Cortez's were to inherit this condition, then I would expect to see early abnormalities on the ultrasound; so likely we would be able to make a diagnosis based on ultrasound exam by 16 to 20 weeks' gestation. Genetic testing is somewhat limited from the standpoint that we do not have the affected person to test. It is possible to test one or both parents to see if they both have a detectable mutation in one of their POMT1 or POMT2 genes. There are 2 groups in the United States who do this testing. One is Prevention Genetics in Wisconsin and another group is University of Iowa Hospitals and Clinics Department of Pathology. I was able to give the parents information on both groups. Prevention Genetics tests for multiple different genes that can fall under the heading of muscle-eye-brain disease. The testing for POMT2 and POMT1 would be about \$1300.00 or \$1400.00 dollars. Again, if we test the parents and we do not find a mutation, it does not rule out Max having Walker-Warburg syndrome. It is clear that there are many different genes that when they do not work correctly can lead to Walker-Warburg syndrome. Right now, we can only test for a small number of them. Thus, the genetic testing is very limited here. We also talked about what we would do with the test results if, indeed, we found a mutation in both parents. We could offer them testing during a pregnancy to see if the pregnancy would be affected. This would require invasive testing.

Prenatal testing can be done as early as 11 weeks gestation by chorionic villus sampling (CVS). This involves removing a tiny piece of the placenta, and testing those cells for a chromosome abnormality or a known genetic disorder. This procedure has an approximately 1:200 risk for pregnancy loss. Testing can also be done later in pregnancy at or after 14 weeks gestation by amniocentesis. This involves removing a small amount of fluid from around the fetus. Fetal cells are harvested from this fluid and then tested for a chromosome abnormality or a known genetic disorder. The risk for pregnancy loss with this procedure is approximately 1:300. Noninvasive testing can also be done during a pregnancy such as fetal ultrasounds or maternal blood testing, but these tests may not allow a definitive diagnosis of a genetic condition.

COPY

Page 3 of 5

Patient Name: MAX A CORTEZ
MRN: 30421403

Preimplantation genetic diagnosis (PGD) is a process by which a embryo can be tested for certain chromosomal anomalies or genetic disorders prior to implanting the embryo. This process requires in vitro fertilization (IVF), which is the fertilization of an egg in the laboratory. The resultant embryos then have a single cell removed early in development. The DNA from that single cell can then be tested for chromosomal or genetic disorders. IVF can be an expensive procedure and may not be covered by insurance if a couple is not infertile.

The parents, at this time, said they would not consider ending a pregnancy. Thus, any testing we would do would simply be for information purposes from a genetic standpoint, which would be helpful but, frankly, we could get that same information 2 weeks later by ultrasound; so from that standpoint, the testing would not have as much of an impact on this.

Should the parents wish to pursue PGD, the only way for that to be of assistance to them would be if we could find a mutation in both parents; so the chance of us finding something that would be helpful that might be changed, how they might pursue future pregnancy is small but it is a possibility and should the family wish to pursue to see if either one is a carrier for POMT1 or POMT2, we would be happy to help them work on getting coverage for the testing.

The family seemed to have a good understanding of what we talked about. They asked good questions throughout our discussion. They had previously seen a genetic counselor prenatally, Dan Riconda, and had gone over some of the issues related to possible autosomal recessive inheritance. The family has my card and, if they have any further questions, I would be happy to assist them. I gave them information on the genetic testing to be done for the POMT1 and POMT2 gene. Again, we would be happy to help them if there are any further questions or concerns.

Thank you for allowing me to share in the care of your son. If you have any questions or concerns, or I can be of any further help, please contact me.

Sincerely,

Dictation electronically signed by
Patricia Wheeler, MD
on 06/08/2009 16:17:56

Patricia Wheeler, MD
Division of Genetics

PW/jm

DD: 20090605153619

DT: 20090607113233

CN: 126096

DID: 234200

cc: Mr and Mrs Cortez, 2324 Academy Cir W, Kissimmee, FL, 34744 Fax:

Patient Name: MAX A CORTEZ
MRN: 30421403

Copy to Referring: ,