Ultrasonographic Prenatal Diagnosis of Treacher Collins Syndrome : A Case Report

PORNPIMOL RUANGVUTILERT, MD, PhD*,
PRASERT SUNSANEEVITHAYAKUL, MD*,
ANUWAT SUTANTAWIBUL, MD*,
CHANIN LIMWONGSE, MD**

Abstract

A case of Treacher Collins syndrome (TCS) diagnosed prenatally using ultrasonography is reported. The pregnant woman was gravida 2, para 0. Her husband had stigmata of the syndrome. Ultrasonography revealed polyhydramnios, abnormal fetal ears and marked micrognathia. Abortion occurred spontaneously at 26 weeks of gestation. The abortus bore clinical features of the syndrome.

Key word : Treacher Collins Syndrome, Mandibulofacial Dysostosis, Prenatal Diagnosis

RUANGVUTILERT P, SUTANTAWIBUL A, SUNSANEEVITHAYAKUL P, LIMWONGSE C
J Med Assoc Thai 2003; 86: 482-488

Treacher Collins syndrome (TCS) is inherited as an autosomal dominant disorder. The incidence is 1 : 50,000 livebirths[1-3]. As many as 60 per cent of cases have no family history and are thought to be a new mutation[1-4]. This disorder is also known as mandibulofacial dysostosis and Franceschetti-Zwahlen-Klein syndrome[5]. It involves abnormal development of tissues derived from the first and second branchial arches. Normally, the first branchial arch splits into a larger mandibular process and a smaller maxillary prominence[6]. The mandibular process gives rise to the mandible, the incus and malleus of the middle ear, and muscles of mastication. The maxillary prominence gives rise to the maxilla, the zygoma, the squamous portion of the temporal bone, the cheek, and portions of the external ears. The second branchial arch forms the remaining structures of the external ear, the stapes of the middle ear, and the

* Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology,
** Division of Medical Genetics, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

muscles of facial expression. Affected individuals usually have mandibular hypoplasia, abnormal ears, pinna, auditory tubes and middle ear ossicles leading to conductive hearing loss, cleft palate, downward slanting palpebral fissures and coloboma of lower eyelid[2-3,7]. Some cases also have preauricular skin tags or fistulas, abnormal hair growth on the cheeks and absence or hypoplasia of zygomatic arch[4-6]. Mental retardation is uncommon. There is also a wide range of severity. While some cases hardly have abnormalities detectable, this condition is sometimes life threatening in others because of difficulty in airway maintenance[1,8-10]. This occurs because the midface hypoplasia results in a shallow nasopharyngeal air space and the micrognathia causes the posterior displacement of the tongue into the oropharyngeal airway[6]. In a milder case, several reconstruction or surgical corrections may be offered to improve hearing or to ameliorate the facial deformities[11,12]. Detection of a fetus affected with this condition is, therefore, beneficial in the light of preparation for the birth of such a child. Here, the authors report a prenatal diagnosis using ultrasound in a Thai pregnant woman whose husband was affected with the disease.

CASE REPORT

A 20 year-old Thai woman, gravida 2, para 0, had her first visit at the antenatal care at 9 weeks 5 days of gestation. The first pregnancy had spontaneously aborted a year earlier at a gestational age of approximately 3 months without an obvious cause. Her nephew was affected with maple syrup urine disease. In addition, her husband had a hypoplastic mandible and no auditory canals. Other history and physical examination were unremarkable. A routine dating ultrasound scan showed an intrauterine pregnancy with a living fetus of 8 weeks 4 days. Consultation with the geneticist revealed the pedigree and the risk estimation for each disease in the current pregnancy as illustrated in Fig. 1. An ultrasound scan was planned for 18 week's gestation. However, the patient did not attend and presented 18 weeks later at the gestational age of 26 weeks. Ultrasonography revealed polyhydramnios with an amniotic fluid index

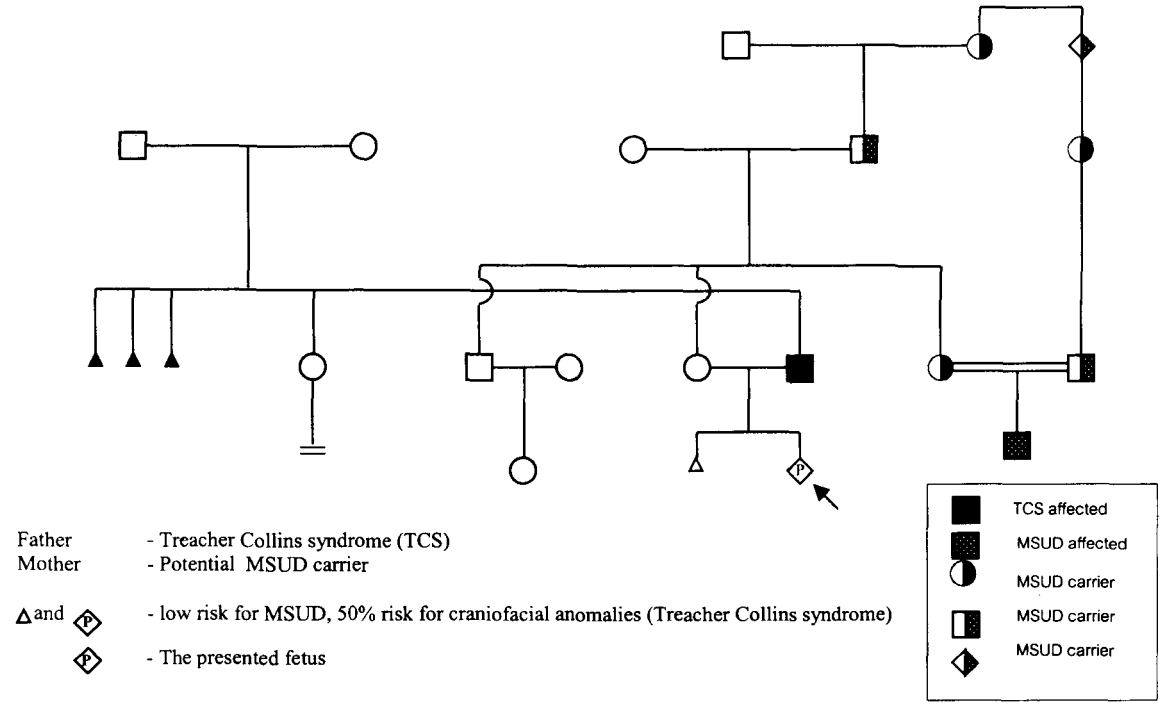

Fig. 1. Pedigree of the family.

of 30 centimeters, mandibular hypoplasia compared to the normal range[13] and anomaly of the right ear as shown in Fig. 2-3. Fetal perimetry was consistent with a gestational age of 25 weeks 6 days without obvious growth retardation (estimated fetal weight 771 grams).

The patient developed premature uterine contractions 4 days later. The uterine cervix was 4 cm dilated with 100 per cent effacement and intact membranes at the first examination. An 840-gram male fetus was delivered 8 hours later with the appearance illustrated in Fig. 4 including malar hypoplasia,

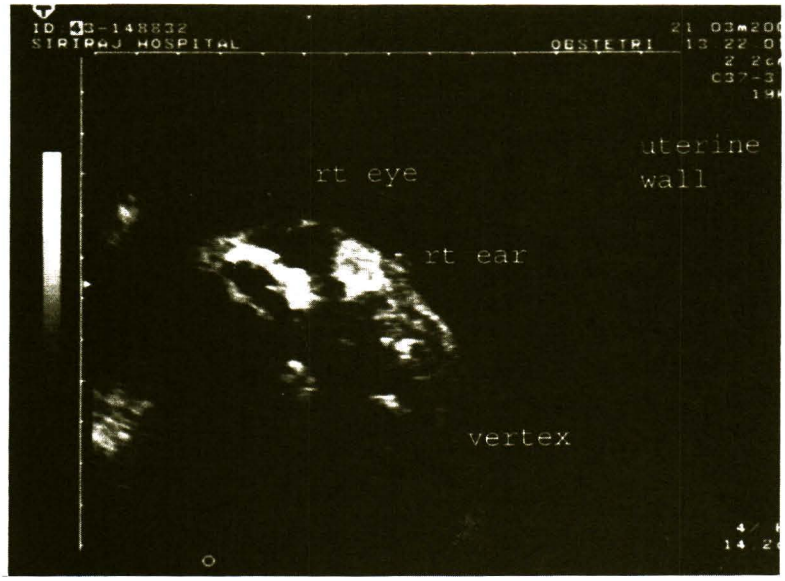

Fig. 2. Abnormal formation of right ear. Note the polyhydramnios.

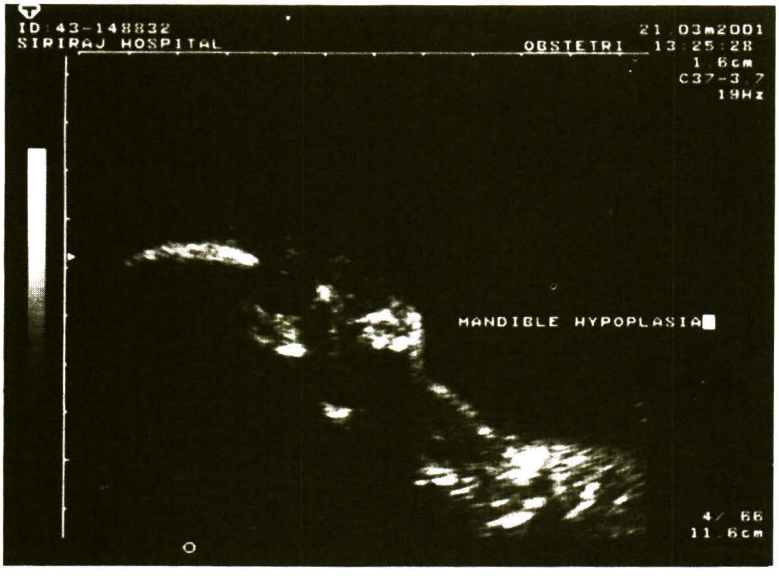

Fig. 3. Fetal profile showing mandibular hypoplasia.

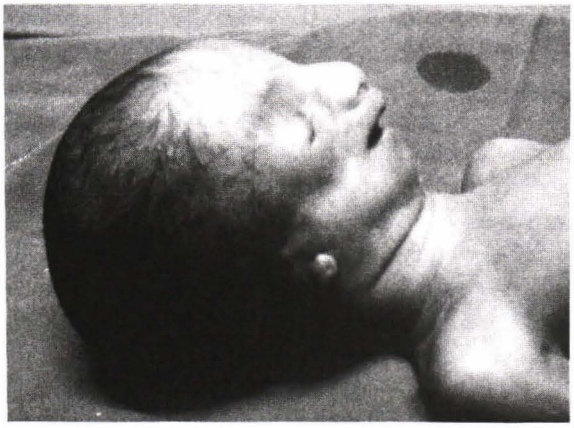

Fig. 4. Appearance of the abortus. Facial profile compared to the ultrasound in Fig. 3. Note the downward slanting of palpebral fissures, malar hypoplasia, receding chin, and anomalous low-set right ear. Preauricular pit is also visible.

downslanting palpebral fissures, mandibular hypoplasia, and preauricular skin pits consistent with TCS. Additional findings revealed at the autopsy were external ear canal defect and unexpanded lungs.

Postabortal course was uneventful and the patient was advised of the recurrence risk and decided upon a contraceptive method.

DISCUSSION

This family presented with a possible genetic disease on the maternal side. However, it was in fact a disorder from the paternal side that affected the fetus. The father had obvious manifestations of TCS which is a developmental disorder of the first and second branchial arches. There are some other disorders in the differential diagnosis[2,5-6]. Nager syndrome and Miller syndrome may have facial features similar to TCS but they have additional limb abnormalities. Usually they are sporadic, albeit, some Mendelian patterns have been reported. Goldenhar syndrome or other disorders in the oculoauriculovertebral (OAV) spectrum usually have vertebral involvement. While mode of inheritance of OAV disorders is not clear, most cases are sporadic.

To the authors' awareness, this is the first report of prenatal diagnosis of TCS in Thailand. Because this condition is sometimes fatal, prenatal recognition of the affected fetus is beneficial so that some problems may be anticipated. For example, preparation may be made for the possible serious difficulty of respiration[8,10,14,15]. Also, possible treatment can be discussed with the parents in non-fatal cases[11,16]. As far back as 1984, prenatal diagnosis of this condition was reported by Nicolaides et al [7]. They used fetoscopy to visualize the fetal face and head in the second trimester. With this, they assessed four fetuses at risk and correctly identified two affected and two normal ones. In the abnormal fetuses, mandibular hypoplasia and abnormalities of the palpebra and auricles were seen by fetoscopy. Later, fetal micrognathia and abnormal ears were documented on ultrasonography by Crane and Beaver and several other groups[8,17-20]. Antimongoloid slant of palprebral fissures was observed in one study [18]. Growth restriction has been reported in some cases[6]. Polyhydramnios can occur as a result of abnormal swallowing possibly due to marked micrognathia or tracheo-esophageal abnormalities[9,17-19]. The presented case also showed some of these fetal features and polyhydramnios on ultrasound scanning.

The gene responsible for TCS has been mapped to 5q31.3-32 and is designated *TCOF1*[21]. The coded protein, called treacle, exhibits peak expression in the branchial arches and may be a phosphorylation-dependent nucleolar protein[22]. The majority of mutations of the gene results in a premature termination codon suggesting that the mechanism of the disease is haploinsufficiency, i.e., the quantity of functioning protein is halved[21]. Also, the resulting truncated treacle is shown to be mislocalized within the cell[23]. Alternatively, dominant-negative effects can occur whereby the abnormal protein affects the function of the normal one[24]. In an experimental study, mice with a mutation in Tcof1, the murine *TCOF1* orthologue, showed massive apoptosis in the prefusion neural folds, leading to severe craniofacial anomalies, indicating that correct dosage of treacle is essential for survival of cephalic neural crest cells [25]. In one study, the amount of full-length treacle in fibroblasts and lymphoblasts varied less than twofold and this was observed in both the cells from TCS patients and healthy individuals. The investigators postulated that the correct dosage of normal treacle is needed at the specific time during development and may be in the specific cell type[24]. Other possible mechanisms of TCS are abnormal neural crest migra-

tion or anomalies in the extracellular matrix[2]. To date, at least 51 disease-causing mutations have been found [26]. Linkage analysis has been utilized along with ultrasonography for prenatal diagnosis[1,27]. This may improve the accuracy of the diagnosis as, due to the wide variable expression of the disorder even within the family, subtle cases can be missed using ultrasound study alone. Linkage analysis has detected individuals with TCS with no clinical features in one study[4]. In the presented case, this was not performed since ultrasonography was able to reveal the anomalies of the fetus.

Another aspect to consider is whether this condition justifies pregnancy termination. This condition is not always lethal due to the varying severity. Various reparative interventions on affected organs have been reported as well as a special anesthetic technique tailored for effective airway maintenance and oxygenation. On the other hand, some affected pregnancies may be so severe that termination of pregnancy may be considered. The presented case terminated spontaneously probably due to the severity of the anomalies. In addition, polyhydramnios might have contributed to the risk of premature uterine contraction. This might reflect the severity of the disease due to reduction in swallowing. The first pregnancy of the presented case was not available to determine whether it had been affected by the disease.

Maple syrup urine disease (MSUD) appeared not to be relevant with this case as the risk was very low. It is an autosomal recessive disorder. From the pedigree (Fig. 1), her nephew was affected and her sister and brother-in-law were related, with her being at worst a carrier of the disease. Since her marriage was not consanguinous, the chances of her offspring being affected with MSUD were very low.

In summary, a case of TCS fetus was diagnosed using prenatal ultrasound. This can be a useful tool in an obvious case. Linkage analysis may be added in large families at risk where the manifestation is mild or minimal, both post and prenatally.

ACKNOWLEDGEMENTS

The authors wish would like to thank the patient and her family for allowing us to report and illustrate the relevant findings. We also wish to thank Professor Charles H Rodeck, Head of the Department of Obstetrics and Gynaecology, Royal Free and Univerisity College Medical School, University College London, UK, for reviewing the manuscript.

(Received for publication on December 1, 2002)

REFERENCES

1. Edwards S, Fowlie A, Cust M, Liu D, Young I, Dixon M. Prenatal diagnosis in Treacher Collins syndrome using combined linkage analysis and ultrasound imaging. J Med Genet 1996; 33: 603-6.
2. Dixon M. Treacher Collins syndrome. J Med Genet 1995; 32: 806-8.
3. Jahrsdoerfer R, Jacobson J. Treacher Collins syndrome: Otologic and auditory management. J Am Acad Audiol 1995; 6: 93-102.
4. Marres H, Cremers C, Dixon M, Huygen P, Joosten F. The Treacher Collins syndrome. A clinical, radiological, and genetic linkage study on two pedigrees. Arch Otolaryngol Head Neck Surg 1995; 121: 509-14.
5. Herman T, Siegel M. Special image case book. Treacher Collins syndrome. J Perinatal 1996; 16: 413-5.
6. Wagner R, Koenigsberg M, Goldberg R. US case of the day. Mandibulofacial dysostosis (MFD). Radiographics 1996; 16: 1517-20.
7. Nicolaides K, Johansson D, Donnai D, Rodeck C. Prenatal diagnosis of mandibulofacial dysostosis. Prenat Diagn 1984; 4: 201-5.
8. Carlson D. Case of the day. Treacher-Collins syndrome. J Ultrasound Med 1995; 14: 322-33.
9. Milligan D, Harless F, Duff P, Kopelman J. Recurrence of Treacher Collins' syndrome with sonographic findings. Mil Med 1994; 159: 250-2.
10. Shah F, Ramakrishna S, Ingle V, Dada J, Khabori M, Murty P. Case report. Treacher Collins syndrome with acute airway obstrsuction. Int J Pediatr Otorhinolaryngol 2000; 54: 41-3.
11. Granstrom G, Jacobsson C. First and second branchial arch syndrome: Aspects on the embryogenesis, elucidations, and rehabilitation using the osseointegration concept. Clin Implant Dent Relat Res 1999; 1: 59-69.
12. Posnick J. Treacher Collins syndrome: Perspectives in evaluation and treatment. J Oral Maxillofac Surg 1997; 55: 1120-33.
13. Chitty L, Campbell S, Altman D. Measurement of the fetal mandible-feasibility and construction of a centile chart. Prenat Diagn 1993; 13: 749-56.
14. Bryden D, Remington S, Mason C. Treacher Collins syndrome and difficult intubation. Br J Hosp Med 1995; 53: 419.
15. Bahk J, Kim J, Kim C. Use of the laryngeal mask airway to preoxygenate in a paediatric patient with Treacher-Collins syndrome. Paediatr Anaesth 1998; 8: 274-5.
16. Posnick J, Ruiz R. Treacher Collins syndrome: Current evaluation, treatment, and future directions. Cleft Palate Craniofac J 2000; 37: 434.
17. Meizner I, Carmi R, Katz M. Prenatal ultrasonic diagnosis of mandibulofacial dysostosis (Treacher Collins syndrome). J Clin Ultrasound 1991; 19: 124-7.
18. Ochi H, Matsubara K, Ito M, Kusanagi Y. Prenatal sonographic diagnosis of Treacher Collins syndrome. Obstet Gynecol 1998; 91: 862.
19. Cohen J, Ghezzi F, Goncalves L, Fuentes J, Paulyson K, Sherer D. Prenatal sonographic diagnosis of Treacher Collins syndrome: A case and review of the literature. Am J Perinatol 1995; 12: 416-9.
20. Crane J, Beaver H. Midtrimester sonographic diagnosis of mandibulofacial dysostosis. Am J Med Genet 1986; 25: 251-5.
21. Dixon M. Treacher Collins syndrome. Hum Mol Genet 1996; 5: 1391-96.
22. Jones N, Farlie P, Minichiello J, Newgreen D. Detection of an appropriate kinase activity in branchial arches I and II that coincides with peak expression of the Treacher Collins syndrome gene product, treacle. Hum Mol Genet 1999; 8: 2239-45.
23. Marsh K, Dixon J, Dixon M. Mutations in the Treacher Collins syndrome gene lead to mislocalization of the nucleolar protein treacle. Hum Mol Genet 1998; 7: 1795-800.
24. Isacc C, Marsh K, Paznekas W, et al. Characterization of the nucleolar gene product, treacle, in Treacher Collins syndrome. Mol Biol Cell 2000; 11: 3061-71.
25. Dixon J, Brakebusch C, Fassler R, Dixon M. Increased levels of apoptosis in the prefusion neural folds underlie the craniofacial disorder, Treacher Collins syndrome. Hum Mol Genet 2000; 9: 1473-80.
26. Splendore A, Silva E, Alonso L, et al. High mutation detection rate in TCOF1 among Treacher Collins syndrome patients reveals clustering of mutations and 16 novel pathogenic changes. Hum Mutat 2000; 16: 315-22.
27. Dixon M. Treacher Collins syndrome: From linkage to prenatal testing. J Laryngol Otol 1998; 112: 705-9.

การวินิจฉัยก่อนคลอดของกลุ่มอาการทรีเชอร์ คอลลินส์ ด้วยการตรวจคลื่นเสียงความถี่สูง : รายงานผู้ป่วย 1 ราย

พรพิมล เรืองวุฒิเลิศ, พบ, ปรด, อนุวัฒน์ สุตัณฑวิบูลย์, พบ*,*
ประเสริฐ ศันสนีย์วิทยกุล, พบ, ชนินทร์ ลิ่มวงศ์, พบ***

รายงานการใช้การตรวจคลื่นเสียงความถี่สูงในการวินิจฉัยก่อนคลอดของภาวะ Treacher Collins syndrome ผู้ป่วยตั้งครรภ์ที่สอง ครรภ์แรกแท้ง สามีมีการแสดงออกของภาวะนี้ การตรวจคลื่นเสียงความถี่สูงพบว่ามีภาวะครรภ์แฝดน้ำ ทารกมีหูผิดปกติ และมีคางสั้นชัดเจน การตั้งครรภ์ลงเอยด้วยการแท้งเองเมื่ออายุครรภ์ 26 สัปดาห์ ทารกที่แท้งออกมามีสิ่งตรวจพบของภาวะ Treacher Collins syndrome

คำสำคัญ : กลุ่มอาการทรีเชอร์ คอลลินส์, แมนดิบูโลเฟเชียล ดิสออสโตสิส, การวินิจฉัยก่อนคลอด

พรพิมล เรืองวุฒิเลิศ, อนุวัฒน์ สุตัณฑวิบูลย์,
ประเสริฐ ศันสนีย์วิทยกุล, ชนินทร์ ลิ่มวงศ์
จดหมายเหตุทางแพทย์ ฯ 2546; 86: 482–488

* สาขาวิชาเวชศาสตร์มารดาและทารก, ภาควิชาสูติศาสตร์-นรีเวชวิทยา,
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700