Bifid uvula and familial Stickler syndrome diagnosed prenatally before the sonographic “equals sign” landmark

Mario Lituania · Gabriele Tonni

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Abstract

Purpose The prenatal ultrasound visualization of the soft palate and especially the uvula may be technically difficult due to its anatomy and presence of surrounding structures. A cleft involving the soft palate and the uvula is one of the clinical features of Stickler syndrome, a rare connective tissue disorder.

Materials and methods Third trimester scan performed at 30 weeks' gestation in a pregnant woman with a familial history of Stickler syndrome using conventional 2D ultrasound.

Results Transabdominal scan performed with the fetal head in oblique plane and following fetal swallowing movements enabled a previously unrecognized median cleft at the level of the uvula. Molecular biology analysis allowed a precise prenatal diagnosis of Stickler syndrome and excluded overlapping syndrome.

Conclusions The prenatal ultrasound diagnosis was achieved time before the “equals signs” was proposed as a useful sonographic marker of a normal uvula. The identification of a bifid uvula by conventional 2D ultrasound led to a prenatal diagnosis of Stickler syndrome in this affected Family and allowed the neonatologist team to be available at the time of birth. Moreover, postnatal multispecialist

follow up could be timely planned for targeted organ examination and appropriate management.

Keywords Stickler syndrome · Bifid uvula · 2D ultrasound · Prenatal diagnosis · Molecular biology

Introduction

The Stickler syndrome or hereditary progressive arthroophthalmopathy is a rare connective tissue disorder estimated to affect approximately 1/7,500 newborns [1]. The syndrome was first described by Stickler in 1965 [2] and phenotype includes degeneration of the vitreous gel and retina, myopia, craniofacial dysmorphisms, hearing impairment, skeletal dysplasia and progressive arthropathy. Mutations at three collagen loci COL2A1, COL11A1 and COL11A2 were found in Stickler syndrome patients [3, 4], with about two-thirds of investigated familial cases found to be associated to COL2A1 gene mutations [5]. An association between Stickler syndrome and Pierre-Robin sequence was reported [6, 7].

Cleft or bifid uvula, a small division or split in the midline of the uvula, is considered as a partial cleft palate (CP) of the smallest degree [8]. The prevalence of some form of uvular cleft was observed in 2.26 % of 709 children with the highest prevalence among Caucasian, in agreement with a previous incidence of 1.44 % on 9,701 adult Caucasians as reported by Meskin et al. [9].

Visualization of the soft palate was particularly problematic because of its curved anatomical arrangement, shadowing by neighboring tissues and difficulty in its discrete recognition on ultrasound examination due to lack of a landmark [10]. In a series by Cash et al. [11], 67 % of the cases were isolated cleft lip, 93 % were cleft lip and palate (CLP) while only 22 % were isolated CP.

M. Lituania
Preconceptional and Prenatal Physiopathology Center,
Department of Obstetrics and Gynecology, Galliera Hospital,
IRCCS, Genoa, Italy

G. Tonni (✉)
Maternal-Fetal Medicine, Department of Obstetrics and
Gynecology, Guastalla Civil Hospital, AUSL Reggio Emilia,
Via Donatori di Sangue, 1, 42016 Guastalla (Reggio Emilia),
Italy
e-mail: Tonni.Gabriele@ausl.re.it

The fact that the prenatal detection rate of CP is very low (0–1.4 %) demonstrates that the difficulty of visualizing CP during routine examination [11–16] and that there are no satisfactory indicators of an isolated CP [10]. The palate cannot be visualized in its entirety in a single conventional plane by 2D ultrasound as the soft palate lays at 30° to the primary. The secondary palate gradually increases in its curvature (in both sagittal and coronal planes) as the uvula lengthens with advancement of gestation. The uvula is a good landmark for directing the examination plane to the soft palate. The optimal time for visualization of the soft palate is beyond 20 weeks' gestation, possibly at around 23–24 weeks, when the uvula could be identified consistently as a definitive structure and the palatal arch is present but not very marked. Nevertheless, as the soft palate can be seen also before 20 weeks' gestation, especially in the sagittal plane, a sonographic search of this anatomical structure should be sought at the time of routine second trimester scan. 3D ultrasound has provided evidences to represents a new technical approach to the study of fetal palate and different techniques were developed [17–20]. However, actually 3D ultrasound is not systematically used during routine second trimester scan as it requires specific operators training and quality imaging is dependent upon acquisition of excellent volume data sets for offline analysis.

In a work by Wilhelm and Borgers [10], visualization of either the uvula or the soft palate was successful in 98.4 % of the cases using 2D ultrasound. A case of an isolated CP in a normal fetus was diagnosed while in one case with CLP, the CP and the completely split uvula were detected. Wilhelm and Borgers [10] concluded that absence of the “equals sign” indicates CP and should prompt further examination of the soft palate in a median sagittal section.

Case report

A 37-year-old woman, G5P4, was referred to our tertiary Prenatal Diagnostic Center at 30 weeks of gestation for detailed scan following an unremarkable second trimester scan performed elsewhere. The woman had a positive familial history of Stickler syndrome, as shown in the genealogical tree (Fig. 1).

The ultrasound examination was carried out in 2004 using a Technos MPX (Esaote, Genoa, Italy) equipped with a 3.5–5 MHz transabdominal probe. With the fetus lying in supine position, a normal hard and soft palate could be seen by means of 2D- and Doppler sonography. A scanning section of the fetal head in oblique plane allowed the operator to detect a previously undiagnosed median cleft at the level of the uvula (Fig. 2).

Fig. 1 Genealogical tree of the Family affected by Stickler syndrome

Amniocentesis was performed after genetic counseling and signed informed consent for fetal karyotyping and molecular biology analysis. Linkage polymorphism of the 3-prime-VNTR (variable-number tandem repeat) COL2A1 gene located on chromosome 12q13.11 was performed and showed normal 46, XY with mutation of the allele 3. No other congenital malformations could be demonstrated. Genetic and multispecialist counseling to the couple was undertaken and pediatric and neonatologist team were available at the time of delivery.

A baby weighing 3,760 g with normal 1- (9) and 5-min (10) Apgar score was born at term by normal vaginal delivery. The boy underwent serial follow up examination by a pediatric surgical team, with confirming of the prenatally 2D ultrasound diagnosis (Fig. 3).

Fig. 2 Transabdominal scan performed at 30 week's gestation with the fetal head in oblique plane showing a previously undiagnosed median cleft at the level of the uvula (red arrows)

Surgical correction of the bifid uvula was performed at 4 year postnatal life. The updated outcome comprises a mild to moderate deafness partially corrected by acoustic implants, a right blindness by the age of 6 following a severe retinal detachment and left eye cerclage due to vitreoretinopathy.

Discussion

Different geno- and phenotypes of Stickler syndrome were recognized and reported in Table 1. This connective tissue disorder has a variable expression.

In our studied Family, the patient number 2 (female) of the third generation shows postnatally the following congenital anomalies: cleft of the soft palate, myopia, right retinal detachment, muscle-skeletal disorders, mild deafness, dental anomalies, and mitral valve prolapsed. The patient number 3 (female) of the third generation shows postnatal a cleft of the soft palate, myopia of high degree, hypotonia, psychomotor impairment, and complicated dental anomalies. The patient number 5 of the third generation (male) was studied prenatally with Level II sonographic examination that was initially performed elsewhere. The certificate referred to “a presumptive normal hard and soft palate” by means of 2D and Doppler ultrasound. When the patient was scanned at 30 weeks of gestation at our prenatal diagnostic tertiary care center, the favourable supine fetal position and the swallowing movements enabled the operator to detect, in an oblique coronal plane, a previous unrecognized bifid uvula.

In recent years, 3D ultrasound has provided evidences to represents a new technical approach to the study of fetal palate and different techniques were developed [17–20]. Nevertheless, 3D ultrasound is not systematically used

Table 1 Phenotype, Mendelian inheritance in man (MIM), gene locus, chromosome location and mode of inheritance of Stickler syndrome

Phenotype	MIM number	Gene/locus	Chromosome	Inheritance
Type I	108300	COL2A1	12q13.11	AD
Type II	604841	COL11A1	1p12	AD
Type III	184840	COL11A2	6p21	AD
Type IV	120210	COL9A1	6q12-q14	AR
Type V	120260	COL9A2	1p33-p32.2	AR

AD autosomal dominant, AR autosomal recessive

during routine second trimester scan as it requires specific operators training and quality imaging is dependent upon acquisition of excellent volume data sets for offline analysis.

Nonetheless, when skill operators and ultrasound machine equipped with commercially software are available, 3D–4D ultrasound may aid the prenatal visualization and thus detection of CP, especially those involving the soft palate and the uvula. Of course, yawning and swallowing movements resulting in a fluid-filled pharynx physiologically improve the visualization of these structures [21].

Although this useful “visualization window” cannot be captured with only one volume, 3Dlive/4D may be applied.

Chosack and Eidelman [22] defined a cleft uvula as a distinct bifurcation of at least one-fourth of the total uvula length and reported prevalence of only 0.44 % among a population of 70.359 children ages 6–18 residing in Israel.

In a series of 667 singleton pregnant women referred for detailed anomaly scan between 20 and 25 weeks of gestation, Wilhelm and Borgers [10] were able to visualize the uvula during routine 2D ultrasound examination as an “equals sign” in 90.7 % and the soft palate in 85.3 %, respectively, in a median sagittal section. Visualization of either the uvula or the soft palate was successful in 98.4 % of the cases. A case of an isolated CP in a normal fetus was diagnosed while in one case with CLP, the CP and the completely split uvula were detected. These authors [10] concluded that absence of the “equals sign” indicates CP and should prompt further examination of the soft palate in a median sagittal section.

In our “historical” case diagnosed before the “equals sign” was proposed as a useful ultrasound landmark of the fetal uvula, the 2D ultrasound diagnostic cluster was a cleft involving medially and almost completely the uvula. The good snapshot of the bifid uvula was captured in an oblique plane and was aided by fetal swallowing movements.

Moreover, the ultrasound diagnosis of bifid uvula elicited a late amniocentesis with molecular biology analysis that could demonstrate a 3-prime-VNTR COL2A1

Fig. 3 Anatomical details of the bifid uvula (U), adenoid tissue (AT) and palatine crura (PC) before surgical correction

Table 2 Overlapping disorders involving mutation on COL2A1, COL11A1, COL11A2 with MIM number, gene locus and clinical phenotype

Disease/inheritance	MIM number	Gene/locus	Phenotype
Achondrogenesis type II/AD	200610	COL2A1	Absent ossification of the column, marked shortening of trunk and limbs, IUFD or early neonatal death
SEMD/AD	184250	COL2A1	Severe short stature, CP, retinal detachment, “dappled” metaphyses of the long bone at Rx
Spondyloperipheral dysplasia/AD	271700	COL2A1	Short stature, spondyloepiphyseal dysplasia, brachydactyly
ARDD/AD		COL2A1	Severe myopia and vitreoretinal degeneration
Marshall syndrome/AD	154780	COL11A1	Flat facial profile, isolated CP and/or Pierre Robin sequence, high myopia, early-onset cataracts, sensorineural hearing loss
OSMED/AR	215150	COL11A2	Flat face, CP, severe hearing loss
WZS/AR	277610	COL11A2	Midface hypoplasia, micrognathia, hearing loss, rhizomelic limb shortening
DFNA13/AR	601868	COL11A2	Middle-frequency nonsyndromic hearing deafness

AD autosomal dominant, AR autosomal recessive, ARDD autosomal dominant rhegmatogenous retinal detachment, CP cleft palate, DFNA nonsyndromic sensorineural hearing loss, IUFD intrauterine fetal death, OSMED autosomal recessive otospondylometaphyseal dysplasia, SEMD spondyloepiphyseal dysplasia congenital, WZS Weissenbach–Zweymuller syndrome

mutation on chromosome 12q13.11 enabling a prenatal diagnosis of Stickler syndrome.

The genetic investigation further revealed that the sibling had inherited the allele 3 from the mother that in this Family is responsible for the Stickler syndrome. The molecular biology investigation could also excluded overlapping autosomal dominant disorders involving mutation in the COL2A1 gene and including achondrogenesis type II, spondyloepimetaphyseal dysplasia Strudwick type, spondyloperipheral dysplasia, platyspondylic lethal skeletal dysplasia Torrence type, osteoarthritis with mild chondrodysplasia and rhegmatogenous retinal detachment; autosomal disorders involving mutation in the COL11A1 such as Marshall syndrome or those involving COL11A2 mutation such as otospondylometaphyseal dysplasia, Weissenbach–Zweymuller syndrome and nonsyndromic sensorineural hearing loss (Table 2).

Furthermore, the prenatal diagnosis allowed appropriate genetic and multispecialist counseling with estimation of recurrence risk and made pediatric and neonatologist team assistance at the time of birth available. This is extremely importance in case of autosomal dominant type of Stickler syndrome as in our reported case because affected individuals have a 50 % chance of passing on the mutation to each offspring.

Beside maxillo-facial surgery, that in our case occurred at the age of four, affected individuals should undergo annual examination by a vitreoretinal specialist, audiologic evaluations every 6 months through age of 5 years, then annually thereafter, screening for mitral valve prolapse on routine examination.

Conflict of interest Mario Lituania and Gabriele Tonni declare that they do not have a financial relationship with any organization or

company. They had full control of all primary data and agree to allow the Journal to review their data if requested.

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