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Prenatal Profile of Cornelia de Lange Syndrome (CdLS): A Review of 53 Pregnancies

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Abstract

Cornelia de Lange Syndrome (CdLS) is a multisystem developmental disorder characterized by growth retardation, cognitive impairment, external and internal structural malformations, and characteristic facial features. Currently, there are no definitive prenatal screening measures that lead to the diagnosis of CdLS. In this study, documented prenatal findings in CdLS syndrome were analyzed towards the development of a prenatal profile predictive of CdLS. We reviewed 53 cases of CdLS (29 previously reported and 24 unreported) in which prenatal observations/findings were available. The review of these cases revealed a pattern of sonographic findings, including obvious associated structural defects, growth restriction, as well as a more subtle, but strikingly characteristic, facial profile, suggestive of a recognizable prenatal ultrasonographic profile for CdLS. In addition the maternal serum marker, PAPP-A, may be reduced and fetal nuchal translucency may be increased in some pregnancies when measured at an appropriate gestational age. In conclusion, CdLS can be prenatally diagnosed or readily ruled out in a family with a known mutation in a CdLS gene. The characteristic ultrasonographic profile may allow for prenatal diagnosis of CdLS in 1) subsequent pregnancies to a couple with a prior child with CdLS in whom a mutation has not been identified or 2) when there are unexplained pregnancy signs of fetal abnormality such as oligo- or polyhydramnios, a low maternal serum PAPP-A level and/or increased nuchal translucency, fetal growth retardation, or structural anomalies consistent with CdLS.

Keywords

PAPP-A; IUGR; Cornelia de Lange Syndrome; CdLS; Prenatal screening

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INTRODUCTION

Cornelia de Lange Syndrome (CdLS) (OMIM# 122470, 300590, 610759) is a genetically heterogeneous dominant multi-system developmental disorder characterized by growth and cognitive retardation; abnormalities of the upper limbs; gastroesophageal dysfunction; diaphragmatic, cardiac, ocular, palatal, and genitourinary anomalies; hirsutism; and characteristic craniofacial features. Facial findings include synophrys with high arched eyebrows, thin lips with a characteristic protrusion of the maxilla, long and smooth philtrum, small nose with anteverted nostrils, long eyelashes, low-set and posteriorly angulated ears, and micrognathia. There is a wide spectrum of limb abnormalities starting with small hands with subtle changes in the phalanges and metacarpal bones, increasing in severity to include varying degrees of oligodactyly, syndactyly, and limb contractures and as severe as almost complete absence of the upper extremities. Complex congenital heart defects and diaphragmatic hernia are common, and have been reported in prenatal diagnosis of CdLS. Intrauterine growth retardation (IUGR) is almost universal in classic CdLS, but often absent in milder cases. Neurologic function is abnormal, including variable degrees of intellectual disability, behavioral difficulties, and delayed or absent speech.

CdLS is genetically heterogeneous. Three genes in the cohesin pathway have been implicated, with mutations in *NIPBL* causing approximately 60% of cases and mutations in *SMC1A* and *SMC3* being responsible for an additional 5% [Krantz et al., 2004; Musio et al., 2006; Deardorff et al., 2007]. Prevalence is estimated to be as high as 1 in 10,000 [Opitz, 1985], with most cases being sporadic resulting from *de novo* dominant mutations. Recurrence in siblings has been reported, usually resulting from germline mosaicism. Recurrence risk is estimated at 1% when neither parents has discernible findings of CdLS [Gillis et al., 2004]. While no proven biochemical marker exists to screen for an increased risk of CdLS prenatally, isolated reports of growth delay, characteristic ultrasound findings, and abnormal biochemical markers suggest that there may exist a particular profile of findings that could lead to a prenatal diagnosis of CdLS, especially in families known to be at risk because of a prior affected child.

Twenty-nine cases with prenatal observations have been reported in the literature. Only nine of these were given a prenatal clinical diagnosis of CdLS, based mainly on a pattern of ultrasound findings that included IUGR, limb anomalies, characteristic facial findings, congenital diaphragmatic hernias (CDH) or congenital heart defects (CHD) [Goolsby et al., 1995; Manouvrier et al., 1996; Ackerman and Gilbert-Barness, 1997; Ranzini et al., 1997; Boog et al., 1999; Urban and Hartung, 2001; Lee et al., 2002; Le Vaillant et al., 2004; Price et al., 2005]. Twenty additional cases describe pregnancies with abnormal findings that resulted in a child diagnosed with CdLS at birth [Lacourt et al., 1977; Bruner and Hsia 1990; Drolshagen et al., 1992; Cunniff et al., 1993; Jelsema et al., 1993; Manouvrier et al., 1996; Sekimoto et al., 2000; Huang and Porto, 2002; Marino et al., 2002; Applewhite et al., 2003; Arbuzova et al., 2003; Hulinsky et al., 2005; Niu et al., 2006; Kennelly and Moran, 2007]. While IUGR is almost universal in classic CdLS [Kliewer et al., 1993], it may not occur until late gestation, or be absent. Upper limb reduction defects are seen in nearly a third of patients, and are often associated with a more severe presentation of CdLS [Jackson et al., 1993; Kennelly and Moran, 2007]. Mid-trimester pregnancy associated plasma protein A (PAPP-A) has been shown to be significantly reduced in pregnancies affected by CdLS [Westergaard et al.,1983; Aiken et al., 1999].

In this report, we review the prenatal findings in 29 literature and 24 previously unreported CdLS cases in order to develop a prenatal profile predictive of CdLS.

MATERIALS AND METHODS

Under an IRB-approved protocol of informed consent, information on pregnancies which resulted in the birth or termination of an infant with CdLS was collected from several centers. For cases diagnosed outside of our institution, clinical details, photographs, and in some cases, blood samples, were obtained to confirm the diagnosis of CdLS. Twenty-four previously unreported cases from the USA, Canada, and Australia were identified, in which CdLS was diagnosed clinically and prenatal ultrasound images, reports, and/or biochemical screening markers were available. Findings identified through ultrasound imaging were reviewed. When possible, nuchal translucency (NT), growth parameters for gestational age, structural anomalies, and facial profiles were evaluated from available ultrasonographic images. PAPP-A level for the patient described in CDL-141-AF was obtained at the Foundation for Blood Research, Scarborough, Maine. Fetal biometric measurements were assigned percentiles for gestational age (GA) based on the data in Diagnostic Images of Fetal Anomalies [Nyberg et al.,2003].

Review of the literature resulted in 29 prenatal cases reported between 1977–2009.

CASE REPORTS

In addition to the 29 literature cases, we summarized the clinical findings in the 24 newly identified patients, including six diagnosed prenatally with CdLS, 15 pregnancies with abnormal findings that resulted in a diagnosis of CdLS at or after birth and three unremarkable pregnancies resulting in an infant born with CdLS. (see Supplemental Case Reports in Supporting Information online).

RESULTS

Data from the 53 patients are summarized in Table I, and clinical synopses of the 24 newly reported cases are documented in the Supporting Information online in Supplemental Case Reports. Prenatals suggestion of CdLS was based on a constellation of abnormalities on second trimester ultrasound, including IUGR, limb anomalies, characteristic facial findings, and major organ anomalies. In eight cases (15%), an abnormally elevated NT and/or low PAPP-A contributed to the diagnosis.

Intra-uterine growth retardation was the most common ultrasound finding, affecting 43/53 pregnancies. Although IUGR was detected on average at 25 weeks (late in the second trimester) and was identified as early as 16 weeks [Bruner and Hsia, 1990], it was minimal in its early appearance (Fig 1). Not until later gestation did it become significant enough in itself to warrant investigation. IUGR was generally symmetric, affecting all measurements, and progressive throughout the late second and third trimester. Table II documents the growth parameters and centiles/standard deviations when detailed sonographic measurements were available. Although IUGR was often not formally diagnosed until growth parameters were below the 5^{th}–10^{th} centiles, growth parameters were below the 50^{th} centile for the majority of scans performed earlier in pregnancy.

Limb anomalies were the finding most suggestive for CdLS, and the most helpful finding leading to a prenatal diagnosis. In total, 35/53 patients had limb abnormalities, ranging in severity from small hands or flexed forearms to complete absence of the upper limbs, evident as early as fourteen weeks, and generally reported on the first ultrasound during the pregnancy. Of the 15 prenatally diagnosed patient, fourteen had limb abnormalities (93%) evident on ultrasound between 13 and 34 weeks (Case 1, Case 2, Case 3, Case 4, Case 5, Case 6 and [Manouvrier et al., 1996; Ackerman and Gilbert-Barness, 1997; Ranzini et al., 1997; Boog et al., 1999; Urban and Hartung, 2001; Lee et al., 2002; Le Vaillant et al., 2004;

Price et al., 2005]). In contrast, of the 38 cases without a prenatal diagnosis, only 20 (53%) had significant upper extremity abnormalities noted on ultrasound (Case 10, Case 14, Case 15. Case 16, Case 19, Case 21 and [Drolshagen et al., 1992; Manouvrier et al., 1996; Sekimoto et al., 2000; Huang and Porto 2002; Marino et al., 2002; Applewhite et al., 2003; Arbuzova et al., 2003; Le Vaillant et al., 2004; Hulinsky et al., 2005; Lemire 2006; Lalatta et al., 2007].

Characteristic facial features were reported in 26 of 53 (49%) individuals. This profile was evident by 19–20 weeks. Reports generally described micrognathia with prominent maxilla, prominent skin of the forehead, prominent eyelashes, depression of the nasal root or small nose with anteverted nares, and a long smooth philtrum with prominent convexity. When described, the facial profile became a critical finding in narrowing the differential diagnosis to CdLS. Characteristic ultrasound findings are summarized in Figure 2.

Surprisingly, life-threatening anatomic defects, such as CDH and CHD, led to prenatal suggestion of CdLS in only 23/53 pregnancies. In two, CDH on prenatal ultrasound led to a clinical diagnosis of Fryns syndrome, which was amended after characteristic CdLS features were identified at birth. Indeed, the prenatal finding of CDH often led to a wide differential diagnosis of genetic disorders. Of the 23 cases with congenital abnormalities, 16 described CDH and 10 CHD (3 had both). Cardiac abnormalities included VSD (4), ToF (3), ASD (1), tortuous aortic arch (1), and one complex, previously undescribed cardiac abnormality (Case 5).

Increased NT/NF (nuchal fold) was described in 6 of 13 cases with measurement (46%). Two additional patients had cystic hygroma, which in one resulted in redundant nuchal skin. Elevated NT/NF was seen in the first and second trimester and ranged from 3.3 mm to 8 mm, with an average of 6.2 mm.

PAPP-A was measured in six pregnancies. Four had a normal value of PAPP-A (Case1, Case 18, Case 22, and Case 24). One had a low PAPP-A value at 0.20 MoM at 11 weeks [Arbuzova et al., 2003] and another had a PAPP-A of 0.16 MoM at 14 weeks (Case 6).

Fifteen pregnancies provided data on maternal serum screening. Seven had completely normal results, with low risk for aneuploidy and neural tube defect. Of the remaining, two had a neural tube defect risk of 1 in 227 (Case 20) and 1 in 260 [Applewhite et al., 2003]; one had a AFP level at 0.4 MoM [Bruner and Hsia, 1990]; one had a trisomy risk greater than 1:10 with AFP at 2.02 MoM, uE3 at 0.47 MoM, and hCG at 0.22 MoM [Marino et al., 2002]; one had a trisomy 18 risk of 1:40 with AFP at 1.02 MoM, uE3 at 0.60MoM, hCG at 0.23MoM, and amniotic AFP 1.58MoM (Case 13); Case 6 had an increased risk for Down syndrome; and Case 7 had an increased risk for Trisomy 18 of 1 in 19 with an AFP at 1.20 MoM, uE3 at 0.73 MoM, hCG at 0.48 MoM, and inhibin A at 1.53 MoM.

Karyotype, generally via amniocentesis, CVS, or skin fibroblast sampling, was reported in 36 individuals. Three were found to have chromosomal abnormalities. One case reported a translocation between chromosomes 3 and 5 (46,XX,t(3;5)(q21;p13)), which was thought to lead to a severe CdLS phenotype [Price et al., 2005]. A second case detected a large deletion on chromosome 5 involving the entire *NIPBL* region (46,XY,del(5)(p13.1p14.2)) [Hulinsky et al., 2005]. A third, unreported case, detected a balanced reciprocal translocation between chromosomes 16 and 20 (46,XX,t(16;20)(p13.1;p11.2)). This patient also had a postnatally detected *NIPBL* truncating mutation, and though the translocation is *de novo*, it is likely not responsible for the CdLS phenotype (Case 13).

In addition to the findings reported above, these cases described a number of other ultrasound abnormalities. Four patients had neurologic findings on sonogram, including

cerebellar vermis hypoplasia, agenesis of the cerebellar vermis, ventriculomegaly, dangling choroid plexus, and agenesis of the corpus callosum. In addition, several had umbilical artery abnormalities, including a two-vessel cord in five, and abnormal uterine artery Doppler with middle cerebral artery sparing in one, and absent to reverse diastolic flow in another. Cardiac anomalies included heart displacement, cystic structure behind the heart, tortuous aortic arch, pericardial effusion, left ventricular hypertrophy, and persistent left superior vena cava. Other findings included absent nasal bone, fisting/skin webbing, pleural effusion, fetal edema, renal pyelectasis, echogenic kidneys, premature ossification of the sternum, dilated loops of bowel, and omphalocele. Eight cases reported oligohydramnios and six cases reported polyhydramnios during the course of the pregnancy.

DISCUSSION

Growth

Although IUGR is a nearly universal sign in CdLS, it is mild in early gestation, becoming significant only later. It often appears between 20 and 25 weeks of gestation, and is symmetrical affecting all measurements. Estimated fetal weight is often below the fifth centile by the end of gestation [Kliewer et al., 1993]. In cases that reported normal growth, one pregnancy was terminated at 22 weeks, and the other three resulted in infants with normal birth weights for their gestational age. It is possible that IUGR would have developed later during the pregnancy which ended in termination. Although IUGR is one of the most frequent findings in CdLS, it is non-specific, and must be considered along with other findings for a prenatal diagnosis.

PAPP-A

Several reports showed low PAPP-A levels during the second and third trimester of CdLS pregnancies [Westergaard et al., 1983; Aitken et al., 1999; Arbuzova et al., 2003]. In their retrospective review of 19 pregnancies resulting in a child with CdLS, Aitken et al. [1999] reported PAPP-A values below the median in 18/19. Notably, these PAPP-A values were measured during the second trimester, at 15–19 weeks. The one pregnancy with a normal PAPPA value was sampled at 11 weeks. In the current study Cases 1, 18, 22, and 24 had normal PAPP-A values and one showed a low PAPP-A at 14 weeks (Case 7). These data suggest that PAPP-A may be a more reliable predictor of CdLS in the second trimester. Only once was a low PAPP-A described in early pregnancy, at 11 weeks [Arbuzova et al., 2003]. This limited data prevents us from drawing conclusions about this tool in prenatal diagnosis, and remains an area for further research.

Nuchal Translucency

Increased NT has been reported in CdLS pregnancies. Huang and Porto [2002] described a fetus with a NT of 6.4 mm at 11 weeks. Follow-up ultrasounds revealed other anatomic abnormalities. Sekimoto et al. [2000] described an 11 week fetus with an increased NT of 8 mm in whom other anatomic abnormalities typical for CdLS were subsequently noted. However, 46% of the cases described in the current paper had a normal NT. This suggests that NT alone is not sensitive enough as a prenatal CdLS screening tool, but that fetuses with increased NT should be examined carefully, especially in the setting of IUGR. Since NT is increasingly measured as a routine first trimester risk screening parameter, more data on the relationship of low NT values and CdLS will be valuable.

Limb Abnormalities

Limb abnormalities were commonly detected in prenatal sonographic evaluation of CdLS. Most were asymmetric defects in the distal upper extremities, including micromelia and

oligodactyly. While severe upper limb defects were correlated with a prenatal CdLS diagnosis, these severe defects were present in only approximately 1/3, and subtle limb involvement should be looked for. Ulnar aplasia and a flexed elbow are typical of the syndrome and were detected on ultrasound examination. Finger abnormalities included syndactyly, short metacarpals, phalangeal hypoplasia, and clinodactyly of the fifth finger. Hypoplasia of the medial phalanx of the fifth finger and hypoplasia of the first metacarpal combined with deformation of the proximal radial metaphysis and subluxation of the radial head is very specific for CdLS, and affects 90% of postnatally evaluated patients [Braddock et al., 1993]. Thus, careful sonographic evaluation of the upper extremities, in the context of IUGR and other suggestive signs, could facilitate early detection of CdLS.

Facial Profile

Its unique sonographic facial profile is not yet an established prenatal marker for CdLS. However, it was reported in many reviewed cases, and often appreciated retrospectively. Postnatally, the prominent hyperconvex featureless philtrum, micrognathia, and depressed nasal root, especially when accompanied by long eyelashes, thin lips, low-set ears, and hirsutism of the forehead, suggest CdLS. Although these signs can be subtle, many may be recognized on a prenatal ultrasound by persons experienced in the detection of fetal CdLS.

Conclusion

The vast majority of infants born with CdLS are sporadic and recurrence in families with unaffected parents is rare. Recurrence due to germ line mosaicism in such families has been estimated to be 1% [Gillis et al., 2004]. For families with documented germ line mosaicism (recurrence of CdLS in a subsequent pregnancy to unaffected parents who do not carry the familial mutation in their studied DNA samples), the risk for subsequent recurrence is as high as 50%. For these families, and especially for those in whom a causative mutation has not been identified, a diagnostic prenatal profile would be useful and reassuring in subsequent pregnancies. Even for families with a single child or prior pregnancy affected by CdLS, the value of reassurance should not be underestimated. Every effort should be made to document a mutation in the affected child in order to allow for testing of future pregnancies.

Anxiety may be high during subsequent pregnancies in families in which a causative mutation cannot be identified. Our study suggests that IUGR and facial differences may be evident earlier than clinically reported. A retrospective review of the initial ultrasound in Case 14 showed micrognathia and upper limb deformities that could have prompted an earlier diagnosis, and IUGR was evident from 18 weeks. Case 11 is instructive for early prenatal diagnosis of CdLS. Ultrasonographic anatomic evaluation should begin early and be repeated frequently. NT can be measured at 11 weeks, and PAPP-A can be assessed from 9 weeks to early mid trimester. As these two measures are increasingly performed routinely for aneuploidy screening in the first trimester, reporting of these values from CdLS pregnancies would allow construction of CdLS risk figures for future pregnancies based on this screening. Early ultrasounds should assess upper limb abnormalities, and later ultrasounds should evaluate facial profile for the characteristics described above. As ultrasound technology advances, three-dimensional sonography could become a useful diagnostic tool for early detection of CdLS. Le Vaillant et al. [2004] described a case detected at 28 weeks via traditional ultrasound with IUGR, VSD, very mild limb abnormalities, and facial findings. Three-dimensional sonography allowed a more detailed look at the facial dysmorphia, and revealed the bulging forehead, depressed nasal root, large philtrum, severe micrognathia, and hirsutism characteristic of CdLS. In addition, they utilized three-dimensional computed tomography of the fetal skeleton to further characterize the upper limb defect as hypoplasia of the radial head and shortened first metacarpal. While

in this case the diagnosis likely could have been made based on the 2-D findings, use of 3-D ultrasound and CT could be useful in narrowing a differential diagnosis or estimating the disease severity. Figure 3 provides a flow chart suggesting an algorithm for the prenatal diagnosis of CdLS in families with and without a prior CdLS pregnancy.

In a recent publication by Pajkrt et al. [2010], seven CdLS cases were retrospectively reviewed for prenatal findings. In four CdLS was considered prenatally and confirmed shortly after birth. All seven had asymmetrical upper limb defects, five had IUGR, and five had facial features suggestive of CdLS identified by ultrasound. An additional 28 previously reported cases were reviewed as well. Their analysis of the 35 cases concluded that IUGR was identified in 80%, and upper limb anomalies in nearly half. Characteristic facial features, internal organ defects and increased nuchal translucency were commonly seen and aided in diagnosis confirmation.

Many families at average risk undergo prenatal screening tests. Prenatal diagnosis must be made during the mid-trimester to allow for possible termination. Diagnoses made later in pregnancy can be helpful for anticipatory guidance and newborn management. Early signs of fetal difficulty, such as IUGR and increased NT, should suggest a potential CdLS diagnosis after more common causes have been excluded, and the proposed algorithm may be followed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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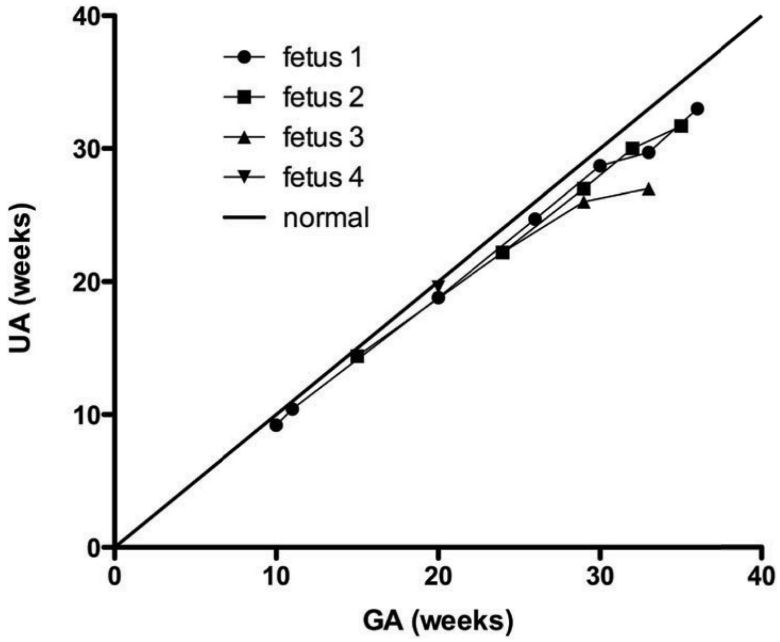

Figure 1.
Plot of fetal growth measurements of four patients with CdLS in whom multiple measurements were available. UA, ultrasound age; GA, gestational age.

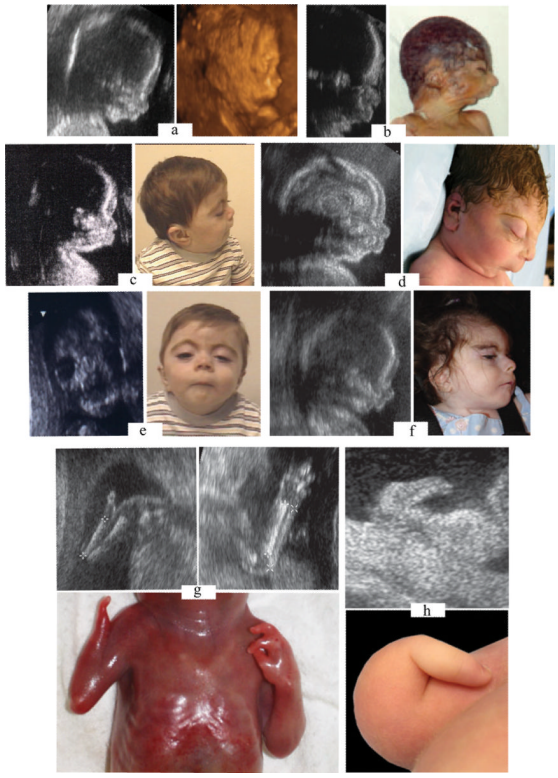

Figure 2.

Ultrasound findings from select cases with postnatal correlation. a-f) Facial profiles in CdLS pregnancies: a) Facial features at 21 weeks and subsequent 3-D ultrasound (“Case 20” in supplementary digital content); b) Facial features at 28 weeks and postnatal facial features at 28 2/7 weeks (“Case 21” in supplementary digital content); c) Facial profile, ultrasound at 19 weeks, postnatal profile at 1 year (“Case 8” in supplementary digital content); d) Prenatal ultrasound profile at 23 weeks and immediate postnatal profile (“Case 2” in supplementary digital content); e) Prenatal ultrasound of full face at 19 weeks and postnatal full face at 1 year (“Case 8” in supplementary digital content); f) Prenatal ultrasound profile at 18 weeks and postnatal profile at 16 months (“Case 13” in supplementary digital content); g-h) Limb findings in CdLS pregnancies: g) Prenatal ultrasound at 19 weeks showing oligodactyly of upper limbs and 20 week autopsy images (“Case 19” in supplementary digital content); h) Prenatal ultrasound at 23 weeks of right limb showing severe oligodactyly with postnatal conformation (“Case 2” in supplementary digital content).

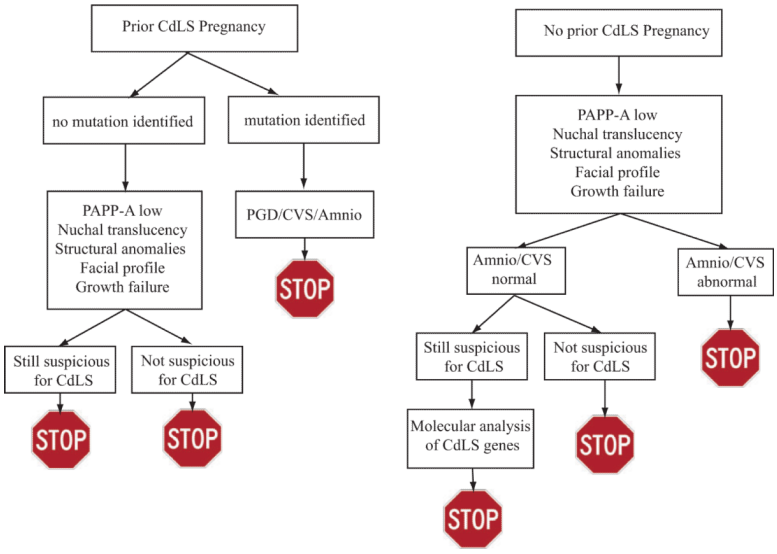

Figure 3.
Flow chart of recommended approach to prenatal diagnosis of CdLS for families with or without a prior CdLS pregnancy.

Table I

Prenatal findings in 53 cases from our cohort and the literature.

Case	IUGR	Limbs	Face	CDH	CHD	Inc NT/NF	Low PAPP-A
Ackerman and Gilbert-Barness, 1997	+ (20)	+ (20)	+ (20)	+ (20)			
Boog et al., 1999	+ (20)	+ (20)	+ (20)				
Goolsby et al., 1995	+ (17)			+ (17)			
Le Vaillant et al., 2004	+ (20)	+ (20)	+ (20)		VSD (28)	− (10)	
Lee et al., 2002	+ (19)	+ (19)	+ (19)		ToF (19)		
Manouvrier et al., 1996 (Case 1)	+ (32)						
Manouvrier et al., 1996 (Case 2)	+ (32)	+ (32)		+ (32)			
Manouvrier et al., 1996 (Case 3)	+ (33)	+ (33)	+ (33)				
Price et al., 2005	+ (21)	+ (21)	+ (21)				
Ranzini et al., 1997	+ (34)	+ (34)	+ (34)				
Urban and Hartung, 2001	− (22)	+ (22)	+ (22)				
Applewhite et al., 2003		+ (21)	+ (21)	+ (21)	VSD (21)	+ (21)	
Arbuzova et al., 2003	+ (22)	+ (22)				− (22)	+ 0.20 MoM (11)
Bruner and Hsia, 1990	+ (16)						
Cunniff et al., 1993	+ (27)			+ (27)			
Drolshagen et al., 1992		+ (14)	+ (27)		ToF (27)		
Hulinsky et al., 2005	+ (26)	+ (20)		+ (20)		+ (20)	
Jelsema et al., 1993	+ (28)	+ (28)		+ (18)			
Lacourt et al., 1977	+ (27)						
Marino et al., 2002 (Case 1)	+ (19)	+ (19)	+ (19)	+ (19)			
Marino et al., 2002 (Case 2)	− (18) + (28)	+ (18)		+ (18)			
Sekimoto et al., 2000	+ (21)	+ (21)				+ 8mm (11)	
Huang and Porto, 2002	+ (19)	+ (22)	+ (22)			+ 6.4mm (11)	
Lemire, 2006	+ (23)	+ (23)	+ (32)	+ (19)			
Lalatta et al., 2007 (Case 1)	− (22)	+ (22)	+ (22)	+ (22)			
Lalatta et al., 2007 (Case 2)	+ (34)						
Kennelly and Moran 2007 (Case 1)		+(20)		+(20)	+(20)		

Case	IUGR	Limbs	Face	CDH	CHD	Inc NT/NF	Low PAPP-A
Kennelly and Moran 2007 (Case 2)	+(22)	+(22)					
Niu et al., 2006	+(28)					− 0.7 mm (13)	
Case 01*	-	+ (19)	+ (17)	-	-		− (11)
Case 02*	+ (23)	+ (23)	+ (23)	+ (23)	-		
Case 03*	+ (20)	+ (20)	+ (20)	-	VSD/ASD (20)		
Case 04*	+ (19)	+ (33)	-	+ (33)	-		
Case 05*	+ (27)	+ (27)	+ (27)	-	Complex CHD (27)		
Case 06*	+ (24)	+	-	-	-		
Case 07*	− (18) + (32)	− (32)	-	-	-	− 1.1mm	+ 0.16 MoM (14)
Case 08*	− (20)	-	-	-	-	+ 6.7mm (20)	
Case 09*	− (17) + (23)	-	-	-	-		
Case 10*	+ (20)	+ (20)	+ (20)	+ (20)	ToF (20)		
Case 11*	+ (19)	-	-	-	-		
Case 12*	+ (30)	-	-	-	Tortuous aortic arch (30)		
Case 13*	− (18) + (33)	-	+ (18)	-	-	−(19)	
Case 14*	+ (18)	+ (28)	+ (28)	-	-		
Case 15*	+ (23)	+ (20)	+ (20)	+ (20)	-		
Case 16*	+ (35)	+ (15)	+ (32)	-	VSD (21)	+ 3.3mm (12)	
Case 17*	+ (20)	+ (20)	-	-	-		
Case 18*	-	-	-	-	-	− 1.56 mm	− 1.24 MoM
Case 19*	+(19)	+(19)	+(19)	-	-		
Case 20*	+(21)	-	+ (21)	-	-		
Case 21*	+(19)	+(28)	+(28)	-			
Case 22*	− (19) + (30)	-	-	-	-	− (12)	− 0.81 MoM (11)
Case 23*	− (18)	− (18)	-	-	-		

Case	IUGR	Limbs	Face	CDH	CHD	Inc NT/NF	Low PAPP-A
Case 24*	-	-	-	-	-		-

Number in parentheses represents gestational age.

'+' indicates presence of feature;'−' indicated absence of feature. Blank spaces indicated findings that were not reported (although in many cases, such as diaphragmatic hernias, it can be presumed that the finding not being mentioned is likely to indicate that it was not present).

PAPP-A, pregnancy associated plasma protein-A; IUGR, intrauterine growth retardation; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; MoM, multiples of the median; NT, nuchal translucency (1st trimester); NF, nuchal fold (2nd trimester); ASD, atrial septal defect; VSD, ventricular septal defect.

*All new cases reported in this paper also have individual case synopses that can be found in Supplemental Digital Content 1.

Table II

Prenatal Ultrasound Growth Measurements and Centiles.

	GA (weeks)	BPD (cm)	HC (cm)	AC (cm)	FL (cm)	EFW (grams)
Case 2	23.9	5.9 (50th)	20.9 (21st)	17 (−2.5 SD)	3.6 (2nd)	
	28.7	7.2 (37th)	25.3 (11th)	20 (−3.5 SD)	4.4 (−4.1 SD)	
	32.6	7 (−4.3 SD)	25.7 (−3.3 SD)	21.8 (−3.4 SD)	4.8 (−5 SD)	
Case 3	20.1	4.49 (36th)	16.6 (29th)	15.0 (21st)	2.9 (25th)	
Case 5	27.0	6.5 (16th)	23.6 (14th)	19.7 (5th)	4.4 (2nd)	
Case 7	18.7	4.1 (25th)	15.5 (30th)	12.6 (3rd)	2.5 (11th)	212 (25th)
	32.7	Not reported	25.8 (−3.24 SD)	22.8 (−2.91 SD)	5.0 (−4.29 SD)	1049 (−2.44 SD)
Case 8	19.8	4.4 (25th)	16.2 (19th)	14.3 (4th)	3.0 (37th)	
	25.3	6.0 (25th)	22.3 (27th)	20.4 (68th)	4.4 (50th)	726 (39th)
Case 12	20.3	4.7 (63rd)	15.8 (13th)	13.5 (−2.9 SD)	3.0 (37th)	300 (13th)
	26.3	6.7 (75th)	23.1 (23rd)	20.5 (8th)	4.6 (37th)	805 (34th)
	30.0	7.4 (25th)	26.6 (17th)	24.4 (34th)	5.5 (34th)	1308 (23rd)
	33.3	8.4 (63rd)	30.6 (52nd)	27.1 (15th)	6.0 (16th)	1817 (13th)
	36.0	8.7 (25th)	30.0 (5th)	29.4 (23rd)	6.4 (5th)	2192 (6th)
Case 13	18.4	3.9 (50th)	14.4 (32nd)	12.1 (31st)	2.5 (50th)	
	22.1	5.0 (16th)	18.9 (27th)	15.6 (11th)	3.7 (63rd)	406 (19th)
	33.3	6.9 (−4.7 SD)	25 (−3.8 SD)	23.6 (−2.6 SD)	5.2 (−3.6 SD)	1123 (1st)
Case 14	28.0	5.7 (−4.66 SD)	21.2 (−3.44 SD)	17.2 (−4.4 SD)	4.3 (−3.0 SD)	
Case 16	15.0	2.9 (48th)	10.4 (27th)	8.6(12th)	1.4 (15th)	100 (69th)
	32.6	8.0 (16th)	28.2 (6th)	25.6 (4th)	5.7 (2nd)	1514 (5th)
	35.0	8.4 (16th)	30.6 (19th)	28.4 (16th)	5.7 (−3.3 SD)	1874 (4th)
Case 19	19.3	4.7 (91st)	16.3 (50th)	14.4 (72nd)	2.9 (63rd)	296 (50th–90th)
	31.0	7.7 (37th)	26.9 (9th)	24.6 (5th)	5.2 (1st)	1300 (11th)
Case 20	18.2	4.2 (84th)	14.8 (42nd)	12.9 (60th)	2.6 (63rd)	227 (50th–75th)

GA, gestational age; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight. Centile or standard deviation of measurement is in parentheses.