Ultrasound Obstet Gynecol 2023; **62**: 94–105
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26178.

Congenital hypotonia: systematic approach for prenatal detection

T. WEISSBACH[1,2], M. HAUSMAN-KEDEM[2,3], Z. YANAY[2,4], R. MEYER[2,5], O. BAR-YOSEF[2,6], L. LEIBOVITCH[2,7], M. BERKENSTADT[2,8], O. CHORIN[2,8], H. SHANI[2,8], A. MASSARWA[1,2], R. ACHIRON[1,2], B. WEISZ[1,2], R. SHARON[2,9], S. MAZAKI-TOVI[2,5] and E. KASSIF[1,2]

[1]*Institute of Obstetrical and Gynecological Imaging, Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel;* [2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel;* [3]*Pediatric Neurology Institute, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;* [4]*Schneider Children's Medical Center, Petach Tikva, Israel;* [5]*Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel;* [6]*Pediatric Neurology, Safra Children's Hospital, Sheba, Tel Hashomer, Israel;* [7]*Neonatal Intensive Care Unit, Sheba Medical Center, Tel Hashomer, Israel;* [8]*Danek Institute of Genetics, Sheba Medical Center, Tel Hashomer, Israel;* [9]*Department of Neurology, Sheba Medical Center, Tel Hashomer, Israel*

KEYWORDS: congenital hypotonia; fetal motility; neuromuscular disease; polyhydramnios; reduced fetal movement

CONTRIBUTION

What are the novel findings of this work?
This is the first study to address the prenatal manifestation and diagnosis of congenital hypotonia as a single condition. The overall prenatal detection rate of congenital hypotonic conditions in our cohort was 38.5%. Only cases which underwent a targeted scan were detected and, among the cases which underwent this scan, the prenatal detection rate was 62.5%. A proposed diagnostic strategy that involved performing a targeted scan for a single non-specific ultrasound sign and carrying out a comprehensive genetic evaluation for any additional sign offered a theoretical detection rate of 88.5% in our cohort.

What are the clinical implications of this work?
Suggested is a semiotic strategy to improve the prenatal detection of congenital hypotonia. This is based on a list of sonographic signs that should be sought, some described herein for the first time.

ABSTRACT

Objectives *Congenital hypotonic conditions are rare and heterogeneous, and some are severely debilitating or lethal. Contrary to its prominent postnatal manifestation, the prenatal presentation of hypotonia is frequently subtle, inhibiting prenatal detection. We aimed to characterize the prenatal sonographic manifestation of congenital hypotonia throughout pregnancy, evaluate the yield of diagnostic tests and propose diagnostic models to increase its prenatal detection.*

Methods *This was a retrospective observational study of singleton pregnancies with congenital hypotonia, diagnosed either prenatally or immediately after birth, at a single tertiary center between the years 2012 and 2020. Prenatally, hypotonia was diagnosed if a fetus showed sonographic or clinical signs suggestive of hypotonia and had a confirmed underlying genetic condition, or in the absence of a known genetic abnormality if the fetus exhibited multiple prominent signs suggestive of hypotonia. Postnatally, it was diagnosed in neonates displaying reduced muscle tone leading to reduced spontaneous movement, reduced swallowing or feeding difficulty. We reviewed the medical records of pregnant patients carrying fetuses subsequently diagnosed with congenital hypotonia and assessed the yield of ultrasound scans, fetal magnetic resonance imaging, computed tomography and genetic tests. The detection rate of sonographic signs suggesting fetal hypotonia was calculated. The prevalence of non-specific signs, including polyhydramnios, persistent breech presentation, intrauterine growth restriction and maternal perception of reduced fetal movement, were compared between the study group and the local liveborn singleton population. Potential detection rates of different theoretical semiotic diagnostic models, differing in the threshold for referral for a targeted scan, were assessed based on the cohort's data.*

Correspondence to: Dr T. Weissbach, Institute of Obstetrical and Gynecological Imaging, Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel (e-mail: ferbyt@gmail.com)

Accepted: 19 January 2023

Results *The study group comprised 26 cases of congenital hypotonia, of which 10 (38.5%) were diagnosed prenatally, and the controls included 95 105 singleton live births, giving a prevalence of congenital hypotonia of 1:3658. Nuchal translucency thickness and the early anomaly scan at 13–17 weeks were normal in all 22 and 23 cases, respectively, in which this was performed. The mid-trimester scan performed at 19–25 weeks was abnormal in four of 24 (16.7%) cases. The overall prenatal detection rate of congenital hypotonic conditions in our cohort was 38.5%. Only cases which underwent a targeted scan were detected and, among the 16 cases which underwent this scan, the prenatal detection rate was 62.5% compared with 0% in pregnancies that did not undergo this scan (*$P = 0.003$*). An abnormal genetic diagnosis was obtained in 21 (80.8%) cases using the following modalities: chromosomal microarray analysis (CMA) in two (9.5%), whole-exome sequencing (WES) in 14 (66.7%) and methylation analysis in five (23.8%). CMA was abnormal in 8% (2/25) of the cases and WES detected a causative genetic mutation in 87.5% (14/16) of the cases in which these were performed. Comparison of non-specific signs in the study group with those in the local singleton population showed that hypotonic fetuses had significantly more polyhydramnios (64.0% vs 3.0%,* $P < 0.0001$*), persistent breech presentation (58.3% vs 4.2%,* $P < 0.0001$*), intrauterine growth restriction (30.8% vs 3.0%,* $P < 0.0001$*) and maternal perception of reduced fetal movement (32.0% vs 4.7%,* $P < 0.0001$*). Prenatally, the most commonly detected signs supporting a diagnosis of hypotonia were structural anomaly (62.5%, 10/16), reduced fetal movement (46.7%, 7/15), joint contractures (46.7%, 7/15) and undescended testes ≥ 30 weeks (42.9%, 3/7 males). Proposed diagnostic strategies that involved performing a targeted scan for a single non-specific ultrasound sign or two such signs, and then carrying out a comprehensive genetic evaluation for any additional sign, offered theoretical detection rates in our cohort of 88.5% and 57.7%, respectively.*

Conclusions *Congenital hypotonic conditions are rare and infrequently detected prenatally. Sonographic signs are visible from the late second trimester. A targeted scan increases prenatal detection significantly. Comprehensive genetic testing, especially WES, is the cornerstone of diagnosis in congenital hypotonia. Theoretical diagnostic models which may increase prenatal detection are provided.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Congenital hypotonia is defined as reduced resistance to passive range of motion that is present at birth[1,2]. The phenotypic spectrum of hypotonia is broad, including a range of severity, gestational age at onset and associated anomalies[2–6]. Marked hypotonia may appear prenatally or, if missed, immediately after birth[2,4,7], affecting basic functions, such as ambulation, feeding and breathing[8]. In one of its most severe forms, fetal akinesia deformation sequence (FADS) can present in early pregnancy with akinesia and multiple joint contractures (arthrogryposis)[9–11]. However, unequivocal signs, such as complete akinesia or joint contractures, are uncommon[3,9,10,12] and the manifestation of hypotonia is often gradual[2,13–15]. In contrast to rates in infancy, the prevalence and prenatal detection rate of congenital hypotonia are rarely reported[7]. This is mainly because hypotonia is not a single medical condition, but rather includes a range of conditions resulting from heterogeneous etiologies that include genetic disorders, infectious causes, exposure to toxins, metabolic errors and hypoxic encephalopathy[1,2,5,6,16]. Anatomically, hypotonia can result from abnormalities affecting one or more of the following loci: upper motor neuron, lower motor neuron, peripheral nerve, neuromuscular junction and muscle[5,17].

The prenatal detection of congenital hypotonia is challenging. First, contrary to structural anomalies, which are often apparent on ultrasound, hypotonia is a functional abnormality; thus, in routine prenatal screening, it frequently goes unnoticed[18,19]. Second, due to the possible antigravity effect of the amniotic fluid, severe hypotonia with explicit *ex-utero* manifestation may be masked *in utero*. Third, due to the characteristic gradual deterioration, repeated targeted ultrasound scans may be necessary[20]. Fourth, diagnosing hypotonia often requires a multidisciplinary approach, including systematic fetal motility assessment, a targeted scan for associated signs and anomalies, fetal magnetic resonance imaging (MRI), lab investigation and genetic tests[1–5,15,21–23]. Hence, the rate of prenatal diagnosis is low. Yet, prenatal diagnosis is imperative for counseling and management. As the current literature on the prenatal presentation of congenital hypotonia is meager, the aims of this study were to: characterize the sonographic manifestation of congenital hypotonia throughout pregnancy; report the yield of auxiliary diagnostic tests; and propose diagnostic models to increase its prenatal detection.

METHODS

This was a retrospective observational study of singleton pregnancies with congenital hypotonia, diagnosed either prenatally or immediately after birth, at a single tertiary center between the years 2012 and 2020. The study group included: fetuses with suspected hypotonia and a causative genetic abnormality; fetuses displaying multiple prominent signs suggestive of hypotonia without a confirmed genetic abnormality; and neonates displaying markedly reduced muscle tone, accompanied by one of the following: reduced spontaneous movement, reduced swallowing or sucking, or dysphagia, with or without a confirmed genetic abnormality. The control group included the population of singletons liveborn in our center between 2012 and 2020 which were not already in the study group.

The Israeli Guideline for Ultrasound in Pregnancy[24] recommends performing a routine early anomaly scan between 13 and 17 weeks of gestation and a mid-trimester anomaly scan between 19 and 25 weeks. This mid-trimester anomaly scan is similar to that described in the ISUOG Practice Guideline for performance of the routine mid-trimester fetal ultrasound scan[25]. Women are referred for a targeted scan if a structural anomaly or abnormal condition is suspected at any gestational age. These targeted scans are performed by experts in the field of fetal imaging.

Sonographic, imaging and clinical signs suggestive of hypotonia

The signs suggestive of hypotonia, classified as either 'non-specific' or 'supporting', have been described in studies reporting on hypotonic conditions[3,8–12,20,22,26–51]. Non-specific signs include findings that may appear in both hypotonic and normal fetuses, and do not require sonographic expertise for their demonstration: polyhydramnios[3,9,26–31], persistent breech presentation, defined as breech in the third trimester[3,8,27,28], and intrauterine growth restriction (IUGR)[27–29]. Maternal perception of reduced fetal movement is also considered a non-specific clinical sign[8,27,32–34,52].

Supporting signs[10,20,22,32] require a certain degree of sonographic expertise for their detection. These signs are further divided into overt supporting signs and subtle supporting signs. The overt supporting signs are complete akinesia and joint contractures, including clubfoot, arthrogryposis and fixed abnormal limb position (Figure 1)[8,28,29,35]. These signs are considered overt as they are relatively prominent on ultrasound examination. Subtle supporting signs are those that require particular awareness and expertise for their demonstration: small/absent stomach[46], reduced fetal movement[26,27,39,40], open/tent-shaped mouth[2,41] (Figure 2, Videoclip S1), reduced fetal swallowing, defined as absence of fluid propagation through the esophagus[42,43] for over 15 min[44,45], spine deformity with intact vertebrae[35] (Figure 3, Videoclips S2 and S3), thin ribs on chest X-ray[48–51] or on fetal bone reconstruction computed tomography (CT) (Figure 4), undescended testes (one or both, ≥ 30 weeks)[36–38] (Figure 5), short umbilical cord[47] (Figure 6) and other structural anomalies[3,53,54]. Of note, reduced fetal movement was determined subjectively; previously reported

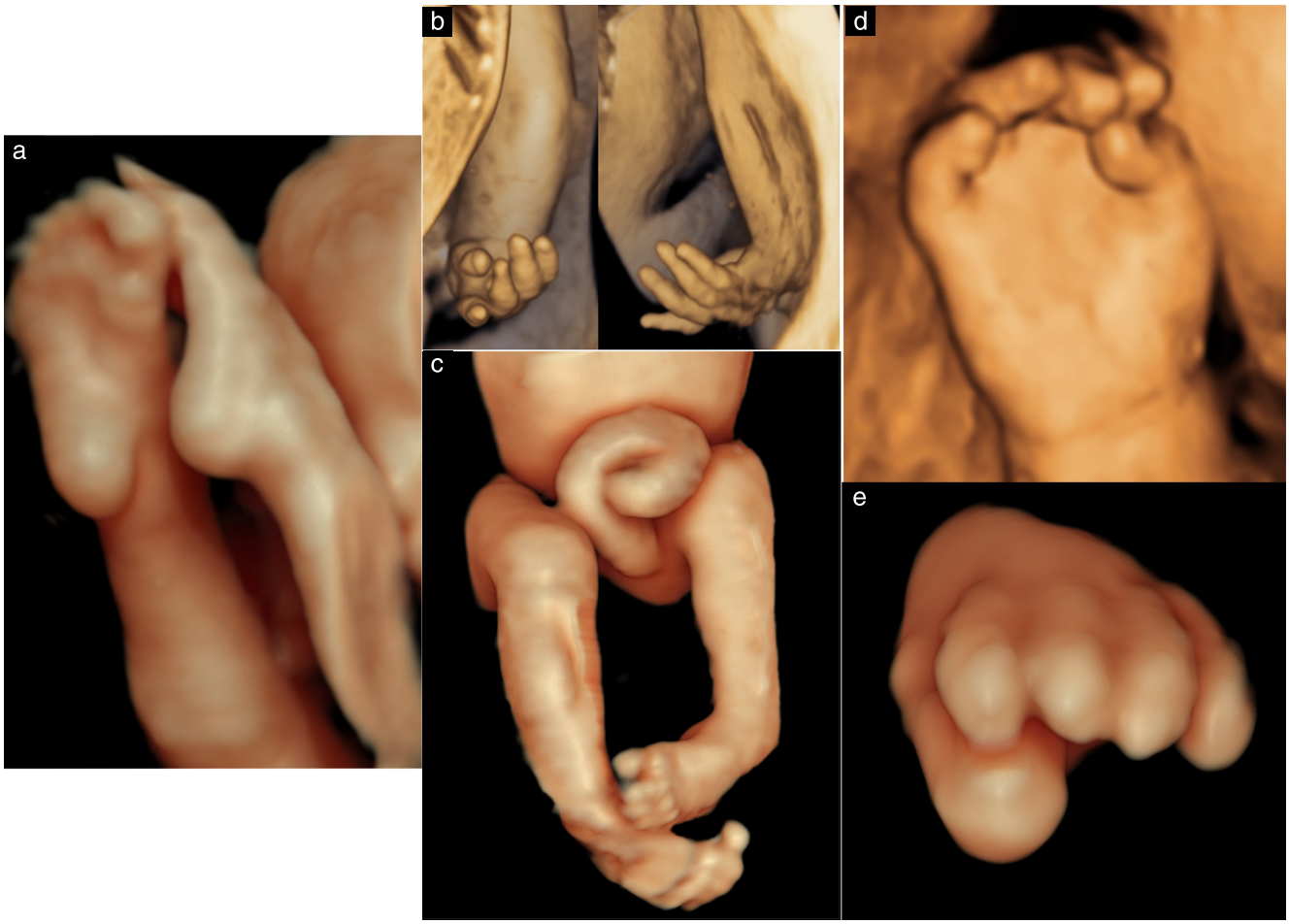

Figure 1 Overt signs of congenital hypotonia on ultrasound imaging: fetal joint contractures. (a) Plantar flexion in myotonic dystrophy, (b,c) waiter's tip sign (b) and bilateral clubfeet (c) in presumed hypotonia and (d,e) adducted thumb (d) and adducted toe (e) in nemaline myopathy Type 3.

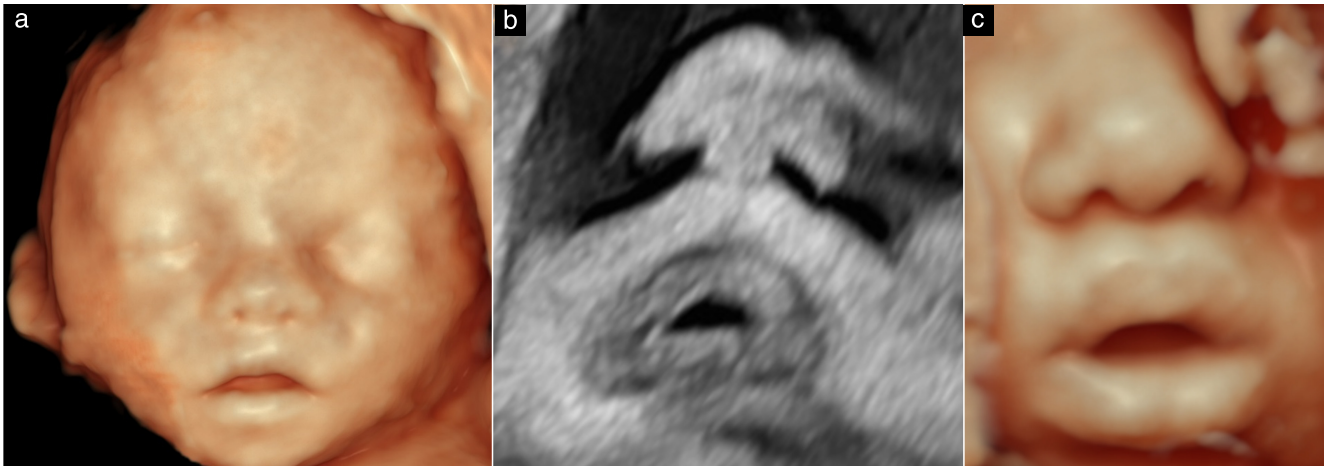

Figure 2 Subtle signs of congenital hypotonia on ultrasound imaging: open/tent-shaped mouth in cases of: (a) presumed hypotonia and (b,c) spinal muscular atrophy, subtype 'lower-extremity predominant', on two-dimensional (b) and three-dimensional (a,c) imaging (see also Videoclip S1).

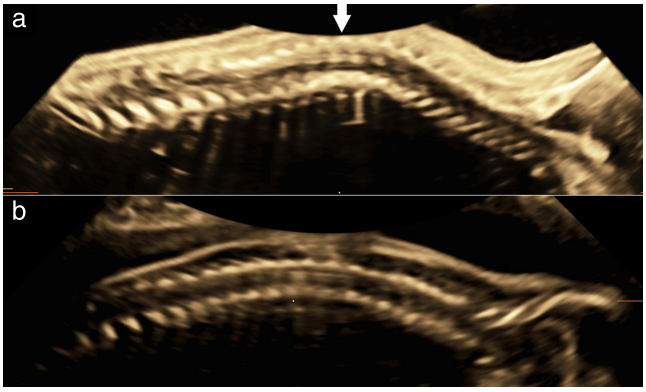

Figure 3 Subtle signs of congenital hypotonia on ultrasound imaging: spine deformity. (a) Thoracic kyphosis (arrow) in minicore myopathy (see also Videoclip S2), with (b) normal spine for comparison (see also Videoclip S3).

systematic assessment[15,20,22,23] was not employed in our study.

The medical records of all cases were retrieved and relevant data extracted, including maternal medical history, prenatal care, ultrasound scan findings (nuchal translucency, early anomaly, mid-trimester anomaly, biophysical, growth and targeted), fetal MRI and CT findings, genetic studies, neonatal intensive care unit records and postnatal hospital clinic follow-up visits. Three independent researchers reviewed all computerized medical records of pregnancies and neonates that met the inclusion criteria. The yield of each type of scan and the prevalence of sonographic and clinical signs suggestive of hypotonia, were calculated. We compared the prevalence of the non-specific signs between the study and control groups, to evaluate whether these signs were more common in hypotonic fetuses. In addition, based on the data of the study cohort, we evaluated the potential detection rates of three theoretical models, which differed with respect to the threshold for referral for a targeted scan (Figure S1).

Statistical analysis

Data are presented as median and interquartile range or percent and number. Chi-square and Fisher's exact tests were used to compare categorical variables. A one-sample proportion z-test was used to compare rates between the study group and the local liveborn population. Statistical significance was accepted at $P < 0.05$. Statistical analyses were conducted using IBM SPSS software v.25 (IBM Corp. Inc, Armonk, NY, USA). The study protocol was approved by the Institutional Ethics Committee at Chaim Sheba Medical Center (approval number 5345-18-SMC).

RESULTS

The study group comprised 26 cases of congenital hypotonia, of which 10 (38.5%) were diagnosed prenatally. The control group included 95 105 live births not affected by congenital hypotonia, rendering a prevalence of congenital hypotonia of 1:3658. Table S1 compares the demographic and perinatal characteristics of the study and control groups. In the study group, there was a 2:1 ratio of males:females, and approximately 70% of the 17 liveborn cases were delivered by Cesarean section, mostly (75% (9/12)) due to breech presentation. The parents opted for termination of pregnancy in nine (34.6%) cases and two neonates died shortly after birth.

Table 1 compares the prevalence of non-specific signs of congenital hypotonia between the study and control groups. All four non-specific signs, polyhydramnios, persistent breech presentation, IUGR and maternal perception of reduced fetal movement, were significantly more common in the study group ($P < 0.0001$ for each). Table 2 shows prenatal detection and overall (both pre- and postnatal) prevalence of supporting signs of hypotonia in affected cases. Structural anomalies, joint contractures, reduced fetal movement and undescended testes in males were the most common signs. Undescended testes (≥ 30 weeks) were also found to be significantly

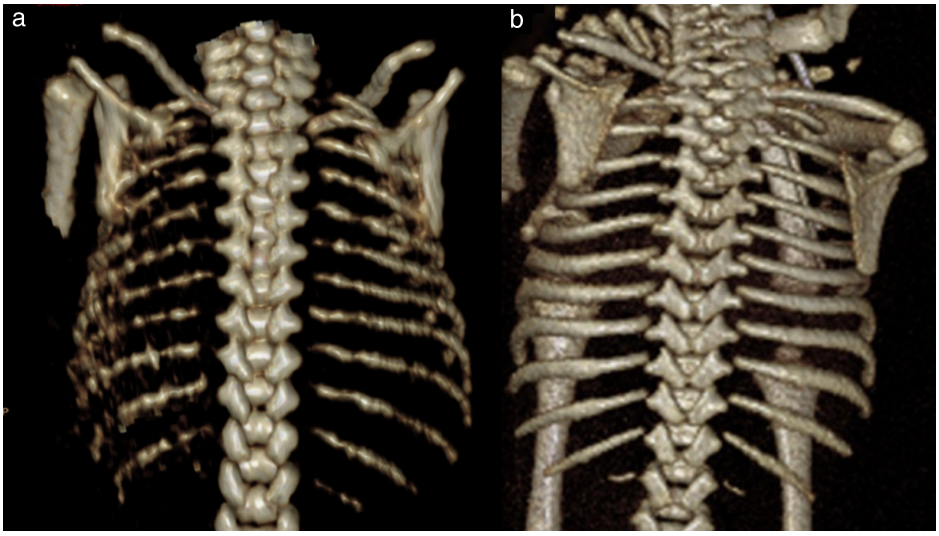

Figure 4 Subtle signs of congenital hypotonia on computed tomography: thin ribs. (a) Thin ribs detected prenatally in late third trimester in case of myotonic dystrophy. (b) Normal fetal ribs demonstrated in late third trimester in case of Prader–Willi syndrome.

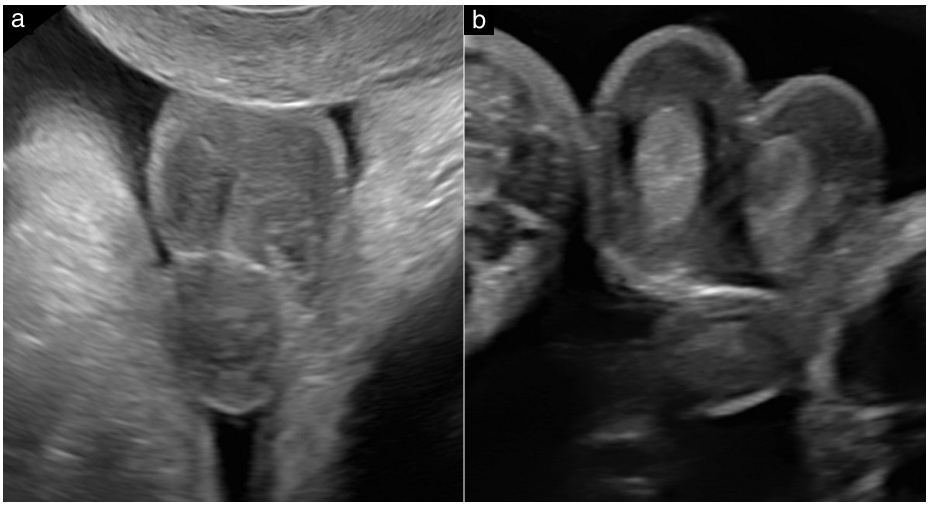

Figure 5 Subtle signs of congenital hypotonia on ultrasound imaging: undescended testes. (a) Undescended testes in nemaline myopathy at 35 weeks' gestation, with (b) normally descended testes at 31 weeks for comparison.

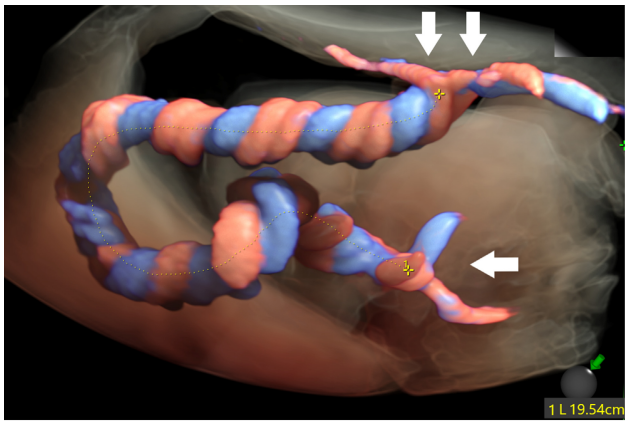

Figure 6 Subtle signs of congenital hypotonia on color Doppler imaging: short umbilical cord in case of minicore myopathy at 28 weeks' gestation. Cord measured < 20 cm from fetal end (arrow) to placental end (double arrows), i.e. < 5th centile.

increased in cases with hypotonia compared to the control group (73.3% (95% CI, 51–96%) *vs* 1.5%; $P < 0.0001$).

Table 3 illustrates the yield of the various diagnostic tests performed in the 26 cases with hypotonia. The nuchal translucency and early anomaly scans were reported as normal in all cases in which this was performed. The mid-trimester scan revealed abnormal findings in 16.7% (4/24) cases. In 16 of the cases, a targeted scan was performed, due to: polyhydramnios ($n = 7$), polyhydramnios and fetal abnormality ($n = 4$), fetal abnormality ($n = 3$), polyhydramnios and maternal perception of reduced fetal movement ($n = 1$) or small fetal stomach ($n = 1$). Of these, 81.25% ($n = 13$) had abnormal findings and, in 62.5% ($n = 10$), congenital hypotonia was diagnosed prenatally, at a median gestational age of 30.1 (interquartile range, 25.3–33.5) weeks. On biophysical assessment before delivery or termination of pregnancy, fetal tone was determined to be absent in only 8.0% (2/25) of cases. Other

Table 1 Non-specific signs of congenital hypotonia in 26 affected fetuses and neonates (study group) in comparison to control group

Non-specific sign	*Study group* (n = *26*)	*Controls* (n = *95 105*)	P
Polyhydramnios	16/25 (64.0 (43–82))	2849 (3.0)	< 0.0001
Persistent breech presentation	14/24 (58.3 (37–78))	3980 (4.2)	< 0.0001
Intrauterine growth restriction	8/26 (30.8 (14–52))	2891 (3.0)	< 0.0001
Maternal perception of reduced fetal movement	8/25 (32.0 (15–53))	4490 (4.7)	< 0.0001

Data are given as *n*/*N* (% (95% CI)) or *n* (%).

imaging studies were performed in a minority of cases: six had a fetal MRI and all reported normal findings, and three underwent fetal skeletal CT, which revealed thin ribs in one case. An abnormal genetic diagnosis was reached in 80.8% (21/26) of the cases. Chromosomal microarray analysis (CMA) was performed in 25 cases and found to be abnormal in 8.0% ($n = 2$) of these, and whole-exome sequencing (WES) detected a causative genetic mutation in 87.5% (14/16) of cases. Methylation analysis revealed a further five cases with Prader–Willi syndrome (PWS) caused by uniparental disomy or imprinting defect. In five cases, a genetic cause was either not found or not determined: two had normal CMA and WES results, two had normal CMA but WES was not performed and, in one, genetic testing was not required, as the diagnosis turned out to be transient congenital myasthenia gravis.

Table 4 provides details on all cases included in the study, giving their underlying etiology and clinical presentation. PWS was the most common underlying condition in the study cohort (23.1%, 6/26) and presented unique stigmata, including coexisting non-specific and supporting signs: polyhydramnios in three cases, persistent breech presentation in four, IUGR in four and undescended testes in all five male fetuses.

Table S2 compares the 16 cases that underwent a targeted scan with the 10 that did not. In both groups there was an indication for a targeted scan in a high proportion of cases (100% *vs* 70%, $P = 0.02$); however, not all patients were referred for, or agreed to undergo, a targeted scan. Only cases which underwent a targeted scan were detected prenatally and, among the cases which underwent this scan, the detection rate was 62.5%, compared with 0% in those that did not undergo this scan ($P = 0.003$). Cases that underwent a targeted scan also had statistically significantly higher detection rates of multiple sonographic supporting signs (three or more signs, 75% *vs* 10%, $P = 0.004$; four or more signs, 50% *vs* 0%, $P = 0.007$). Importantly, prenatal sonographic signs were missed more frequently in the group that did not undergo a targeted scan (80.0% *vs* 18.8%, $P = 0.004$), as in a case of Perrault syndrome harboring Sylvian polymicrogyria that was not observed on the routine mid-trimester scan.

Six cases remained undiagnosed despite a targeted scan. These cases and plausible factors hindering the diagnosis are presented in Table 5. Recurring factors were lack of assessment or underestimation of the significance of signs, especially undescended testes, a relatively common yet subtle sign of hypotonic conditions. Other reasons included unavailability of WES

Table 2 Overt and subtle signs supporting diagnosis of congenital hypotonia in 26 affected fetuses and neonates

Supporting sign	*Prenatal sign DR: targeted scan* (n = *16*)	*Overall prevalence (pre- and postnatal)* (n = *26*)
Overt signs		
Complete akinesia*	3/15 (20.0)	6/26 (23.1)
Joint contractures*	7/15 (46.7)	10/26 (38.5)
Subtle signs		
Small/absent stomach	1/16 (6.25)	N/A
Reduced fetal/neonatal movements*	7/15 (46.7)	26/26 (100)
Open/tent-shaped mouth*	3/15 (20.0)	4/25 (16.0)
Reduced swallowing	4/16 (25.0)	16/26 (61.5)
Spine deformity†	2/16 (12.5)	2/26 (7.7)
Thin ribs‡	1/3 (33.3)	3/13 (23.1)
Undescended testes§	3/7 (42.9)	11/15 (73.3)
Short umbilical cord	1/16 (6.25)	N/A
Other structural anomaly¶	10/16 (62.5)	15/26 (57.7)

Data are given as *n*/*N* (%). *In one case, severe oligohydramnios (following rupture of membranes) precluded assessment of joint position and fetal motility and masked the appearance of tent-shaped mouth. †Neuromuscular etiology, with intact vertebrae. ‡Confirmed by computed tomography prenatally or chest X-ray postnatally. §≥ 30 weeks; there were 17 male fetuses, of which 15 survived to 30 weeks' gestation, 11 with undescended testes; of these 15, seven women had a targeted scan. ¶Facial dysmorphism, fetal hydrops, umbilical-cord cyst, brachycephaly, ventriculomegaly, brain atrophy, hydronephrosis, hepatic cyst, choanal atresia, high-arched palate, retrognathia, small penis, congenital bone fracture. DR, detection rate; N/A, not applicable (because, postnatally, stomach size is not seen and cord was not assessed).

Table 3 Yield of prenatal tests in 26 cases with congenital hypotonia

Study type	*Rate of abnormal results**
Nuchal translucency	0/22 (0)
Early anomaly scan (14–17 weeks)	0/23 (0)
Mid-trimester anomaly scan (19–25 weeks)	4/24 (16.7)‡
Targeted scan	13/16 (81.25)
Fetal tone on biophysical scan†	2/25 (8.0)
Fetal brain MRI	0/6 (0)
Fetal skeletal CT (for thin ribs)	1/3 (33.3)
Abnormal genetic diagnosis	21/26 (80.8)
Chromosomal microarray analysis	2/25 (8.0)
Whole-exome sequencing	14/16 (87.5)
Methylation analysis	5

Data are given as *n*/*N* (%) or *n*. *Cases that received abnormal result/total number of cases that underwent test. †Abnormal result defined as absent tone. ‡Abnormalities noted on routine mid-trimester anomaly scan: small stomach, joint contractures, reduced fetal movement, club foot, prefrontal edema, mega cisterna magna and micro/retrognathia. CT, computed tomography; MRI, magnetic resonance imaging.

Table 4 Detailed genetic and phenotypic makeup of 26 cases diagnosed with congenital hypotonia

Disease group/condition	n	*Genetics, zygosity, inheritance*	*Prenatally detected*	*Prenatal presentation*	*Neonatal presentation*
Anterior horn cell disease					
SMA lower extremity, predominant	1	*DYNC1H1* AD *De novo*	Yes	Polyhydramnios, reduced fetal movements, absent swallowing, hypokinetic mouth movement, tent-shaped mouth, arthrogryposis (35 GW)	TOP
Neuromuscular junction disease					
Transient neonatal myasthenia	1	N/A	No	Uneventful	Transient hypotonia, reduced neonatal reflexes
Myopathy					
Nemaline myopathy type 3	3	*ACTA1* AD *De novo*	Yes ($n=1$)	Polyhydramnios, breech, reduced fetal movements, fetal hydrops, esophageal dysmotility, hypokinetic mouth movement, arthrogryposis, unilateral cryptorchidism (33 GW)	Breech presentation, extreme hypotonia, required mechanical ventilation and enteral feeding, facial diplegia, cryptorchidism
Nemaline myopathy type 10	1	*LMOD3* AR Compound heterozygote	Yes	Polyhydramnios, tent-shaped mouth, abnormal facies, fixed limb posture, abnormal finger position, reduced fetal movements (31 GW)	TOP
Minicore myopathy	1	*RYR 1* AR Compound heterozygote	Yes	Polyhydramnios, breech, small stomach, reduced fetal movements, short umbilical cord, thoracic kyphosis, reduced swallowing (27 + 6 GW)	TOP
X-linked myotubular myopathy	2	*MTM1* X-linked Hemizygote	No	Polyhydramnios, breech presentation, cryptorchidism, ventriculomegaly, hydronephrosis (33 GW)	Polyhydramnios, breech presentation, cryptorchidism, ventriculomegaly, brain atrophy, hydronephrosis, hypotonia
Myotonic dystrophy type 1, congenital	2	*DMPK* AD Trinucleotide repeat expansion	Yes	IUGR, small chest, polyhydramnios, absent swallowing, breech presentation akinesia/reduced fetal movements, joint contractures, fixed limb position (31 and 33 GW)	IUGR, small chest, polyhydramnios, akinesia/reduced movements, joint contractures, fixed limb position, severe hypotonia
Global developmental delay					
PWS	6	Uniparental disomy ($n=4$) 15q 11.2-12 imprinting disorder ($n=1$) 15q deletion ($n=1$)	No	Polyhydramnios (31, 35 + 6 and 41 GW), hypotelorism, brachycephaly, IUGR, reduced fetal movements (36 GW)	Cryptorchidism ($n=6$), generalized hypotonia ($n=6$), breech presentation ($n=4$), polyhydramnios ($n=3$), growth restriction ($n=4$), facial dysmorphism ($n=2$), high-arched palate ($n=1$)
Shukla–Vernon syndrome	1	*BCORL1* X-linked Hemizygote	No	Mild polyhydramnios (32 GW)	Hypotonia, cryptorchidism, down-slanting eyes
Kleefstra syndrome	1	EHTM1 AD *De novo*	Yes	Polyhydramnios (30 GW), reduced fetal movements, hydronephrosis	TOP
Aneuploidy					
Patau syndrome	1	Mosaic trisomy 13 *De novo*	Yes	Arthrogryposis and reduced fetal movements, short CC, hypoplastic cerebellum and vermis, MCM, dilated 4th ventricle, large echogenic kidneys, CDH, cardiac asymmetry, micro/retrognathia (22 GW)	TOP

Continued over.

Table 4 *Continued*

Disease group/condition	n	*Genetics, zygosity, inheritance*	*Prenatally detected*	*Prenatal presentation*	*Neonatal presentation*
Metabolic disease					
SAHHD	1	*AHCY* AR Compound heterozygote	No	Uneventful	Hypotonia, weak sucking, increased creatinine phosphokinase
Perrault (Zellweger spectrum) syndrome	1	*PRLTS1/HSD17B4* AR Compound heterozygote	No	Uneventful	Breech, polymicrogyria, convulsions, hypotonia
Presumed hypotonia					
Unknown	2	Normal CMA, normal WES	No	Normal routine anomaly scans	Ulnar deviation, breech, arthrogryposis, limb spasticity, joint stiffness, feeding intolerance, hypotonia, death at 1 month
			Yes	Polyhydramnios, reduced fetal movements, arthrogryposis, club feet, skin edema, upper spine kyphosis, brachycephaly, mouth slightly open (23 + 6 GW)	TOP
Unknown	2	Normal CMA, WES not performed	Yes	Severe polyhydramnios, akinesia, pleural effusion, pericardial effusion, skin edema cryptorchidism, arthrogryposis (29 + 2 GW)	TOP
			Yes	Persistent breech, arthrogryposis multiplex (24 + 4 GW)	Severe IUGR, arthrogryposis, unilateral clubfoot, hypotonia

Gestational weeks (GW) for prenatal presentation refers to age at scan in individual fetuses. AD, autosomal dominant; AR, autosomal recessive; CC, corpus callosum; CDH, congenital diaphragmatic hernia; CMA, chromosomal microarray analysis; IUGR, intrauterine growth restriction; MCM, mega cisterna magna; N/A, not available; PWS, Prader–Willi syndrome; SAHHD, S-adenosyl homocysteine hydrolase deficiency; SMA, spinal muscular atrophy; TOP, termination of pregnancy; WES, whole-exome sequencing.

at the time, oligohydramnios affecting visualization, and non-identification of PWS stigmata (reduced fetal movement, IUGR and polyhydramnios) despite the detection of each sign separately.

Theoretical diagnostic models (Figure S1)

In our cohort, at least one, two, three or four non-specific signs, potential indications for a targeted scan, were present in 88.5% ($n = 23$), 61.5% ($n = 16$), 15.4% ($n = 4$) and 3.8% ($n = 1$) of cases, respectively. Theoretically, by performing a targeted scan for a single non-specific sign and carrying out a comprehensive genetic evaluation for any additional sign, 88.5% (23/26) of the cohort would have been detected prenatally, while 11.5% (3/26) of cases would not have been referred for a targeted scan as they did not present an additional sign. Based on the prevalence of non-specific signs at our center, the number of scans that would need to be performed to detect one hypotonic case would be 178 (i.e. 2849/16) for polyhydramnios, 361 (2891/8) for IUGR, 284 (3980/14) for persistent breech presentation and 561 (4490/8) for maternal perception of reduced fetal movement.

By raising the threshold for a targeted scan to two non-specific signs and carrying out a comprehensive genetic evaluation for any additional sign, 57.7% (15/26) of the cohort would have been detected, 38.5% (10/26) of cases would have not been referred for a targeted scan and 3.8% (1/26) would have not undergone a genetic evaluation, as they did not present an additional sign. Data necessary to calculate the number needed to scan for a combination of non-specific signs were not available.

DISCUSSION

This study describes the prenatal manifestation of congenital hypotonia in a cohort of 26 cases. We report a prevalence of 1:3658 and a prenatal detection rate of 38.5%. As observed in our cohort, hypotonic conditions usually appear gradually, often manifesting only in the third trimester[13,22,27–29,39], explaining the low yield of the early and mid-trimester anomaly scans and the high yield of targeted scans, performed in later pregnancy.

Despite the prominent postnatal presentation of congenital hypotonia[2,5,6,17], its prenatal manifestation is considerably less obvious. Reduced fetal tone was observed in only 8% of cases on the biophysical scan. Therefore, non-specific signs, such as polyhydramnios, persistent breech presentation, maternal perception of reduced fetal movement and IUGR, may be the only opportunity to prompt a targeted scan. As in other fetal conditions[40,44,55–60], a targeted scan enhanced prenatal detection by identifying additional signs supporting a diagnosis; in those which underwent a targeted scan, the detection rate was 62.5%. However, a targeted scan without appropriate awareness of supporting signs was insufficient, as evidenced by the six cases that went

Table 5 Cases of congenital hypotonia undetected despite targeted scan

Condition	*GA at scan and scan findings*	*Postnatal presentation*	*Plausible factors hindering diagnosis*
Nemaline myopathy type 3	31 weeks Severe polyhydramnios, unilateral undescended testis, umbilical cord cysts, hypotelorism, breech	Hypotonia, rocker-bottom feet, thin ribs, reduced spontaneous movements, knee contractures, head lag, unilateral ptosis, reduced facial expression, absent spontaneous breathing, feeding difficulty	Exome sequencing not yet available
X-linked myotubular myopathy	33.2 weeks Polyhydramnios, normal fetal movements, unilateral undescended testis, mild ventriculomegaly, persistent breech	Severe hypotonia, unilateral undescended testis, absent spontaneous movements, requirement for mechanical ventilation, thin ribs, feeding intolerance, brain atrophy, ventriculomegaly, death at 2 months	Subtle and non-specific prenatal signs underestimated, rendering a low index of suspicion, fetal motility perceived normal
X-linked myotubular myopathy	18, 26 and 32 weeks Breech presentation, hepatic cyst	Severe hypotonia, reduced spontaneous movements, reduced eye opening, undescended testes, unilateral choanal atresia, feeding difficulty	Testicles not assessed and significance of breech presentation underestimated
Myotonic dystrophy 1	33.4 weeks Technical difficulty, no abnormality detected	Hypotonia, tent-shaped mouth, left knee contracture, right knee hyperlaxity, feeding difficulty	Technical difficulty on scan due to PPROM and oligohydramnios following polyhydramnios
PWS	36 weeks Hypotelorism, brachycephaly, IUGR, suspected hypotonia, polyhydramnios	Hypotonia, reduced facial expression, bradycardia events, weak cry, feeding difficulty	PWS stigmata not recognized, CMA performed, uniparental disomy not recognized
Shukla–Vernon syndrome	32 weeks Mild idiopathic polyhydramnios	Hypotonia, undescended testes, down-slanting eyes	Testicles and fetal motility not assessed

CMA, chromosomal microarray analysis; GA, gestational age; IUGR, intrauterine growth restriction; PPROM, preterm prelabor rupture of membranes; PWS, Prader–Willi syndrome.

undetected despite a targeted scan because existing signs were overlooked or underestimated. The targeted scan should include a neurosonogram to seek associated brain anomalies[3,53,54], as was observed in three patients in our cohort.

Theoretical diagnostic models showed that prenatal detection could potentially be increased to 88.5% or 57.7% by performing a targeted scan for one or two non-specific signs, respectively. These proposed diagnostic models demonstrate several important principles. First, it may be beneficial to employ a structured screening approach in which non-specific signs should raise suspicion and lead to referral for a targeted scan, at which supporting signs should be sought. Genetic investigation should be carried out for additional signs detected on the targeted scan. Second, a lower threshold for referral for a targeted scan would increase the likelihood of detecting congenital hypotonia. However, this approach would potentially result in hundreds of unnecessary scans, as evidenced by the calculated number of targeted scans required to detect one hypotonic case, ranging from approximately 180 for polyhydramnios to 600 for maternal perception of reduced fetal movement. Third, increased awareness of signs supporting a diagnosis of hypotonia, and comprehensive genetic investigation when more than one is observed, should aid in establishing the diagnosis.

A comprehensive genetic analysis provided a molecular diagnosis in 80.8% (21/26) of cases. Whereas CMA had a low yield for detecting hypotonic conditions (8.0%, 2/25), WES had a high yield (87.5%, 14/16), highlighting its essential role in the investigation of suspected hypotonia[1,21,61]. A recent study by AlBanji *et al.*[21] found CMA to be diagnostic in hypotonic conditions in 9% of cases and WES in 59%. Data on the contribution of WES to the diagnosis of various conditions are accumulating. Large-scale studies will aid in determining a more precise diagnostic yield for WES in hypotonia. PWS, a relatively common hypotonic condition, presents a diagnostic exception, as most cases are diagnosed by methylation analysis[38,62–64]. Recognizing the prenatal stigmata of PWS, i.e. IUGR, polyhydramnios, persistent breech presentation and undescended testes, is imperative for offering methylation analysis. Notably, in two cases presenting unequivocal signs of hypotonia, CMA and WES results were normal. This has been reported previously[3,9,10,12], suggesting that other genetic studies, such as whole-genome sequencing, may be required to reveal the underpinning genetics in these cases.

In addition to the more commonly described overt signs supporting a diagnosis of hypotonia, i.e. complete akinesia and joint contractures, one should consider several less-reported subtle supporting signs. Polyhydramnios, absent/small stomach and reduced swallowing all stem from impaired swallowing[40,42,46,65–68], manifesting postnatally as feeding difficulties[43,69,70]. Fetal swallowing can be assessed using dynamic esophageal patency assessment[44]. Normally, fetal swallowing occurs at intervals of up to 15 minutes, from the mid-trimester onwards[44,45]. Reduced fetal swallowing was noted in four cases. Polyhydramnios, frequently observed in pregnancies affected by hypotonia[9,26–31], occurred in 64% of our cases. As we observed, polyhydramnios usually appears in the third trimester[9,30,31,40,55]. Reduced fetal movement on ultrasound was determined subjectively in our study. However, a systematic fetal motility assessment has been described by De Vries and colleagues[23,71] and Sparling *et al.*[72]. This approach evaluates the quantity, quality, direction, velocity and amplitude of movements and recognizes specific movement patterns. Using this systematic assessment, abnormal fetal movement has been observed in various conditions[15,20,27]. Other studies have demonstrated the benefit of heightened awareness of fetal motility and associated anomalies in the prenatal detection of motility disorders[22,52,73,74]. An open/tent-shaped mouth, indicative of facial diplegia in neonates[2,75] has been demonstrated prenatally in myotonic dystrophy and nemaline myopathy[8,30,41], and in spinal muscular atrophy in our cohort. Spine deformity has been reported in FADS, myopathies and distal arthrogryposis[9,10,35,76]. It should be noted that kyphoscoliosis is usually caused by vertebral deformities[77,78]. However, in our current study, vertebral anomalies were excluded, suggesting a neuromuscular etiology. Thin ribs, suggestive of longstanding hypotonia, are well described in neonates[48–51], but not in fetuses. Rib width assessment is performed prenatally by reconstructive CT and postnatally by chest X-ray. In the current study, both thin and normal ribs were noted in fetuses with the same genetic mutations, demonstrating phenotypic heterogeneity. Undescended testes are associated with congenital hypotonic conditions[28,29,36–38], as seen in 73.3% (11/15) of the cohort's male fetuses, in PWS, nemaline myopathy, myotubular myopathy and Shukla–Vernon syndrome. Previous studies have noted an association between reduced fetal movement and a short umbilical cord, postulating that cord traction affects its lengthening[47,79]. In our series, a short cord was detected in minicore myopathy[47].

This study is not without limitations. The rarity of congenital hypotonia dictated a small cohort size, imposing statistical limitations. Moreover, fetuses were scanned by different sonologists of variable experience, affecting the detection of sonographic signs. Despite these limitations, this study adds novel and valuable information on a less well-studied condition, increasing awareness of some unique signs supporting a diagnosis of hypotonia, including tent-shaped mouth, spine deformity, short umbilical cord and reduced fetal swallowing.

In conclusion, congenital hypotonic conditions pose a diagnostic challenge, often going underdiagnosed prenatally. Definitive diagnosis relies on advanced genetic testing in most cases. This study describes signs that should raise concern for these conditions and proposes a diagnostic strategy that involves performing a targeted scan for a single non-specific ultrasound sign and carrying out a comprehensive genetic evaluation for any additional sign, which offered a theoretical detection rate of 88.5% in our cohort. While there is evidence to suggest that the proposed strategy is expected to increase prenatal detection, a cost-effective analysis may be required before its routine application.

REFERENCES

1. Zadeh N, Hudgins L. The genetic approach to hypotonia in the neonate. *Neoreviews* 2009; **10**: e600–e607.
2. Peredo DE, Hannibal MC. The floppy infant: evaluation of hypotonia. *Pediatr Rev* 2009; **30**: e66–76.
3. Niles KM, Blaser S, Shannon P, Chitayat D. Fetal arthrogryposis multiplex congenita/fetal akinesia deformation sequence (FADS) - Aetiology, diagnosis, and management. *Prenat Diagn* 2019; **39**: 720–731.
4. Dubowitz V. The floppy infant - a practical approach to classification. *Dev Med Child Neurol* 1968; **10**: 706–710.
5. Vawter-Lee MM, Seals SS, Thomas CW, Venkatesan C. Clinical reasoning: A neonate with micrognathia and hypotonia. *Neurology* 2016; **86**: e80–84.
6. Yozawitz E, Delfiner L, Moshé SL. Neonatal hypotonia. *Neoreviews* 2018; **19**: e445–e455.
7. Madhok SS, Shabbir N. *Hypotonia*. In: StatPearls [Internet]. StatPearls Publishing: Treasure Island (FL), 2022.
8. Yeung KS, Yu FNY, Fung CW, Wong S, Lee HHC, Fung STH, Fung GPG, Leung KY, Chung WH, Lee YT, Ng VKS, Yu MHC, Fung JLF, Tsang MHY, Chan KYK, Chan SHS, Kan ASY, Chung BHY. The KLHL40 c.1516A>C is a Chinese-specific founder mutation causing nemaline myopathy 8: Report of six patients with pre- and postnatal phenotypes. *Mol Genet Genomic Med* 2020; **8**: e1229.
9. Cao Q, Yang Y, Pan M, Han J, Yang X, Li D-Z. Fetal akinesia: The application of clinical exome sequencing in cases with decreased fetal movement. *Eur J Obstet Gynecol Reprod Biol* 2021; **260**: 59–63.
10. Reischer T, Liebmann-Reindl S, Bettelheim D, Balendran-Braun S, Streubel B. Genetic diagnosis and clinical evaluation of severe fetal akinesia syndrome. *Prenat Diagn* 2020; **40**: 1532–1539.
11. Romero NB, Monnier N, Viollet L, Cortey A, Chevallay M, Leroy JP, Lunardi J, Fardeau M. Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. *Brain* 2003; **126**: 2341–2349.
12. Witters I, Moerman P, Fryns J-P. Fetal akinesia deformation sequence: a study of 30 consecutive in utero diagnoses. *Am J Med Genet* 2002; **113**: 23–28.
13. Parra J, Martínez-Hernández R, Also-Rallo E, Alias L, Barceló MJ, Amenedo M, Medina C, Senosiain R, Calaf J, Baiget M, Bernal S, Tizzano EF. Ultrasound evaluation of fetal movements in pregnancies at risk for severe spinal muscular atrophy. *Neuromuscul Disord* 2011; **21**: 97–101.
14. Pearn JH. Fetal movements and Werdnig-Hoffmann disease. *J Neurol Sci* 1973; **18**: 373–379.
15. de Vries JIP, Fong BF. Changes in fetal motility as a result of congenital disorders: an overview. *Ultrasound Obstet Gynecol* 2007; **29**: 590–599.
16. Kiefer J, Hall JG. Gene ontology analysis of arthrogryposis (multiple congenital contractures). *Am J Med Genet C Semin Med Genet* 2019; **181**: 310–326.
17. Harris SR. Congenital hypotonia: clinical and developmental assessment. *Dev Med Child Neurol* 2008; **50**: 889–892.
18. Filges I, Hall JG. Failure to identify antenatal multiple congenital contractures and fetal akinesia–proposal of guidelines to improve diagnosis. *Prenat Diagn* 2013; **33**: 61–74.
19. Filges I, Hall JG. We are failing to identify disorders of fetal movement - why? *Prenat Diagn* 2012; **32**: 919–920.
20. Donker ME, Eijckelhof BHW, Tan GMB, de Vries JIP. Serial postural and motor assessment of Fetal Akinesia Deformation Sequence (FADS). *Early Hum Dev* 2009; **85**: 785–790.
21. AlBanji MH, AlSaad AN, AlAnazi RF, Aleisa ZA, Alam DS, Alhashim AH. Utility of hypotonia diagnostic investigations: a 12-year single center study. *Mol Genet Metab Rep* 2020; **25**: 100665.
22. Tjon JK, Tan-Sindhunata GM, Bugiani M, Witbreuk MM, van der Sluijs JA, Weiss MM, van de Pol LA, van Weissenbruch MM, van der Knoop BJ, de Vries JI. Fetal akinesia deformation sequence, arthrogryposis multiplex congenita, and bilateral clubfeet: Is motor assessment of additional value for in utero diagnosis? A 10-year cohort study. *Prenat Diagn* 2019; **39**: 219–231.
23. de Vries JIP, Fong BF. Normal fetal motility: an overview. *Ultrasound Obstet Gynecol* 2006; **27**: 701–711.
24. Malinger G, Eisenberg V, Shpiegel E, Gilboa Y, Valsky D, Yanai N, Shrim A. Israeli Guidelines for Performing Ultrasound in Pregnancy. Israeli Medical Association [Internet]. 1 Jun 2021 https://ima-contentfiles.s3.amazonaws.com/Ne172_UltrasoundinPregnancy.pdf

25. Salomon LJ, Alfirevic Z, Berghella V, Bilardo CM, Chalouhi GE, Da Silva Costa F, Hernandez-Andrade E, Malinger G, Munoz H, Paladini D, Prefumo F, Sotiriadis A, Toi A, Lee W. ISUOG Practice Guidelines (updated): performance of the routine mid-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2022; **59**: 840–856.
26. Esplin MS, Hallam S, Farrington PF, Nelson L, Byrne J, Ward K. Myotonic dystrophy is a significant cause of idiopathic polyhydramnios. *Am J Obstet Gynecol* 1998; **179**: 974–977.
27. Fong BF, De Vries JIP. Obstetric aspects of the Prader–Willi syndrome. *Ultrasound Obstet Gynecol* 2003; **21**: 389–392.
28. Geysenbergh B, De Catte L, Vogels A. Can fetal ultrasound result in prenatal diagnosis of Prader–Willi syndrome? *Genet Couns* 2011; **22**: 207–216.
29. Bigi N, Faure J-M, Coubes C, Puechberty J, Lefort G, Sarda P, Blanchet P. Prader–Willi syndrome: is there a recognizable fetal phenotype? *Prenat Diagn* 2008; **28**: 796–799.
30. Zaki M, Boyd PA, Impey L, Roberts A, Chamberlain P. Congenital myotonic dystrophy: prenatal ultrasound findings and pregnancy outcome. *Ultrasound Obstet Gynecol* 2007; **29**: 284–288.
31. Yee C, Choi S-J, Oh S-Y, Ki C-S, Roh C-R, Kim J-H. Clinical characteristics of pregnancies complicated by congenital myotonic dystrophy. *Obstet Gynecol Sci* 2017; **60**: 323–328.
32. Grotto S, Cuisset J-M, Marret S, Drunat S, Faure P, Audebert-Bellanger S, Desguerre I, Flurin V, Grebille AG, Guerrot AM, Journel H, Morin G, Plessis G, Renolleau S, Roume J, Simon-Bouy B, Touraine R, Willems M, Frébourg T, Verspyck E, Saugier-Veber P. Type 0 spinal muscular atrophy: further delineation of prenatal and postnatal features in 16 patients. *J Neuromuscul Dis* 2016; **3**: 487–495.
33. Macleod MJ, Taylor JE, Lunt PW, Mathew CG, Robb SA. Prenatal onset spinal muscular atrophy. *Eur J Paediatr Neurol* 1999; **3**: 65–72.
34. Chen CP, Lin SP, Chern SR, Tsai FJ, Wang TY, Lin HH, Wang W. Prenatal diagnosis of X-linked myotubular myopathy. *Prenat Diagn* 2010; **30**: 177–179.
35. Busack B, Ott C-E, Henrich W, Verlohren S. Prognostic significance of prenatal ultrasound in fetal arthrogryposis multiplex congenita. *Arch Gynecol Obstet* 2021; **303**: 943–953.
36. Arora V, Ferreira CR, Dua Puri R, Verma IC. Primrose Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa GM, Grip KW, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993.
37. Cherik F, Reilly J, Kerkhof J, Levy M, McConkey H, Barat-Houari M, Butler KM, Coubes C, Lee JA, Le Guyader G, Louie RJ, Patterson WG, Tedder ML, Bak M, Hammer TB, Craigen W, Démurger F, Dubourg C, Fradin M, Franciskovich R, Frengen E, Friedman J, Palares NR, Iascone M, Misceo D, Monin P, Odent S, Philippe C, Rouxel F, Saletti V, Strømme P, Thulin PC, Sadikovic B, Genevieve D. DNA methylation episignature in Gabriele-de Vries syndrome. *Genet Med* 2022; **24**: 905–914.
38. Zhou Y, Ma MS, Li GY, Zhang ZJ, Ding J, Xu YW, Qiu ZQ, Song HM. [Analysis of the clinical perinatal characteristics of 226 patients with Prader-Willi syndrome in China]. *Zhonghua Er Ke Za Zhi* 2021; **59**: 466–470.
39. Murata T, Fukuda T, Kanno A, Kyozuka H, Yamaguchi A, Shimizu H, Watanabe T, Fujimori K. Polyhydramnios and abnormal foetal heart rate patterns in a foetus with Prader-Willi syndrome: A case report. *Case Rep Womens Health* 2020; **27**: e00227.
40. Kollmann M, Voetsch J, Koidl C, Schest E, Haeusler M, Lang U, Klaritsch P. Etiology and perinatal outcome of polyhydramnios. *Ultraschall Med* 2014; **35**: 350–356.
41. Mashiach R, Rimon E, Achiron R. Tent-shaped mouth as a presenting symptom of congenital myotonic dystrophy. *Ultrasound Obstet Gynecol* 2002; **20**: 312–313.
42. Jaradeh S. Muscle disorders affecting oral and pharyngeal swallowing. *GI Motility online*. 2006. 10.1038/gimo35.
43. Modolell I, Mearin F, Baudet JS, Gámez J, Cervera C, Malagelada JR. Pharyngo-esophageal motility disturbances in patients with myotonic dystrophy. *Scand J Gastroenterol* 1999; **34**: 878–882.
44. Kassif E, Elkan Miller T, Tsur A, Trozky Y, Gur T, De Castro H, Hadi E, Yulzari V, Weissmann-Brenner A, Messing B, Yoeli-Ullman R, Sharon R, Mazaki-Tovi S, Achiron R, Weisz B, Weissbach T. Dynamic esophageal patency assessment: an effective method for prenatally diagnosing esophageal atresia. *Am J Obstet Gynecol* 2021; **225**: 674.e1–12.
45. Malinger G, Levine A, Rotmensch S. The fetal esophagus: anatomical and physiological ultrasonographic characterization using a high-resolution linear transducer. *Ultrasound Obstet Gynecol* 2004; **24**: 500–505.
46. McKenna KM, Goldstein RB, Stringer MD. Small or absent fetal stomach: prognostic significance. *Radiology* 1995; **197**: 729–733.
47. Naeye RL. Umbilical cord length: clinical significance. *J Pediatr* 1985; **107**: 278–281.
48. Tsai CH, Huang WS, Tsai FJ, Lee CC, Chen SS. X-linked recessive myotubular myopathy proven by muscle biopsy. *J Formos Med Assoc* 1996; **95**: 153–156.
49. Osborne JP, Murphy EG, Hill A. Thin ribs on chest X-ray: a useful sign in the differential diagnosis of the floppy newborn. *Dev Med Child Neurol* 1983; **25**: 343–345.
50. Fried K, Pajewski M, Mundel G, Caspi E, Spira R. Thin ribs in neonatal myotonic dystrophy. *Clin Genet* 1975; **7**: 417–420.
51. Chassevent J, Sauvegrain J, Besson-Leaud M, Kalifa G. Myotonic dystrophy (Steinert's disease) in the neonate. *Radiology* 1978; **127**: 747–749.
52. Dahan-Oliel N, van Bosse HJP, Bedard T, Darsaklis VB, Hall JG, Hamdy RC. Research platform for children with arthrogryposis multiplex congenita: Findings from the pilot registry. *Am J Med Genet C Semin Med Genet* 2019; **181**: 427–435.
53. Adamo L, Kassif E, Achiron R. Arthrogryposis, Visual Encyclopedia of Ultrasound in Obstetric and Gynecology [Internet]. ISUOG. 2019 [cited 2022 Oct 17]. Available from: https://www.isuog.org/education/visuog/obstetrics/extremities/arthogryposis.html
54. Nemec SF, Höftberger R, Nemec U, Bettelheim D, Brugger PC, Kasprian G, Amann G, Rotmensch S, Graham JM Jr, Rimoin DL, Prayer D. Fetal akinesia and associated abnormalities on prenatal MRI. *Prenat Diagn* 2011; **31**: 484–490.
55. Kassif E, Weissbach T, Kushnir A, Shust-Barequet S, Elkan-Miller T, Mazkereth R, Weissmann-Brenner A, Achiron R, Weisz B. Esophageal atresia and tracheoesophageal fistula: prenatal sonographic manifestation from early to late pregnancy. *Ultrasound Obstet Gynecol* 2021; **58**: 92–98.
56. Committee on Practice Bulletins—Obstetrics and the American Institute of Ultrasound in Medicine. Practice bulletin no. 175: ultrasound in pregnancy. *Obstet Gynecol* 2016; **128**: e241–e256.
57. International Society of Ultrasound in Obstetrics & Gynecology Education Committee. Sonographic examination of the fetal central nervous system: guidelines for performing the "basic examination" and the "fetal neurosonogram". *Ultrasound Obstet Gynecol* 2007; **29**: 109–116.
58. Paladini D, Malinger G, Birnbaum R, Monteagudo A, Pilu G, Salomon LJ, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 2: performance of targeted neurosonography. *Ultrasound Obstet Gynecol* 2021; **57**: 661–671.
59. Lazebnik N, Many A. The severity of polyhydramnios, estimated fetal weight and preterm delivery are independent risk factors for the presence of congenital malformations. *Gynecol Obstet Invest* 1999; **48**: 28–32.
60. Simpson J, Hornberger LK. What does fetal echocardiography add beyond the anomaly scan? *Circ Cardiovasc Imaging* 2022; **15**: e014168.
61. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med* 2013; **369**: 1502–1511.
62. Shubina J, Barkov IY, Stupko OK, Kuznetsova MV, Goltsov AY, Kochetkova TO, Trofimov DY, Sukhikh GT. Prenatal diagnosis of Prader-Willi syndrome due to uniparental disomy with NIPS: Case report and literature review. *Mol Genet Genomic Med* 2020; **8**: e1448.
63. Fermin Gutierrez MA, Mendez MD. Prader-Willi Syndrome. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2022.
64. Cheon CK. Genetics of Prader-Willi syndrome and Prader-Will-Like syndrome. *Ann Pediatr Endocrinol Metab* 2016; **21**: 126–135.
65. Dashe JS, McIntire DD, Ramus RM, Santos-Ramos R, Twickler DM. Hydramnios: anomaly prevalence and sonographic detection. *Obstet Gynecol* 2002; **100**: 134–139.
66. Brumfield CG, Davis RO, Owen J, Wenstrom K, Kynerd PM. Pregnancy outcomes following sonographic nonvisualization of the fetal stomach. *Obstet Gynecol* 1998; **91**: 905–908.
67. Millener PB, Anderson NG, Chisholm RJ. Prognostic significance of nonvisuali zation of the fetal stomach by sonography. *AJR Am J Roentgenol* 1993; **160**: 827–830.
68. McKelvey A, Stanwell J, Smeulders N, Nasr R, Curry J, Pandya P. Persistent non-visualisation of the fetal stomach: diagnostic and prognostic implications. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**: F439–42.
69. Vasta I, Kinali M, Messina S, Guzzetta A, Kapellou O, Manzur A, Cowan F, Muntoni F, Mercuri E. Can clinical signs identify newborns with neuromuscular disorders? *J Pediatr* 2005; **146**: 73–79.
70. Leonard RJ, Kendall KA, Johnson R, McKenzie S. Swallowing in myotonic muscular dystrophy: a videofluoroscopic study. *Arch Phys Med Rehabil* 2001; **82**: 979–985.
71. Lüchinger AB, Hadders-Algra M, van Kan CM, de Vries JIP. Fetal onset of general movements. *Pediatr Res* 2008; **63**: 191–195.
72. Sparling JW, Van Tol J, Chescheir NC. Fetal and neonatal hand movement. *Phys Ther* 1999; **79**: 24–39.
73. Dicke JM, Piper SL, Goldfarb CA. The utility of ultrasound for the detection of fetal limb abnormalities–a 20-year single-center experience. *Prenat Diagn* 2015; **35**: 348–353.
74. Filges I, Tercanli S, Hall JG. Fetal arthrogryposis: Challenges and perspectives for prenatal detection and management. *Am J Med Genet C Semin Med Genet* 2019; **181**: 327–336.
75. Cabrera Viteri MI, Acosta Farina D, Morales Mayorga H, Cabrera Johnson M, Albán Castro S. Splenogonadal fusion associated with Moebius and Poland syndromes: first case reported. *Cir Pediatr* 2021; **34**: 219–222.
76. Punetha J, Monges S, Franchi ME, Hoffman EP, Cirak S, Tesi-Rocha C. Exome sequencing identifies DYNC1H1 variant associated with vertebral abnormality and spinal muscular atrophy with lower extremity predominance. *Pediatr Neurol*. 2015; **52**: 239–244.
77. Marks DS, Qaimkhani SA. The natural history of congenital scoliosis and kyphosis. *Spine* 2009; **34**: 1751–1755.
78. Mackel CE, Jada A, Samdani AF, Stephen JH, Bennett JT, Baaj AA, Hwang SW. A comprehensive review of the diagnosis and management of congenital scoliosis. *Childs Nerv Syst* 2018; **34**: 2155–2171.
79. Ryo E, Kamata H, Seto M, Morita M, Yatsuki K. Correlation between umbilical cord length and gross fetal movement as counted by a fetal movement acceleration measurement recorder. *Eur J Obstet Gynecol Reprod Biol* 2019; **1**: 100003.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Theoretical diagnostic flowchart for congenital hypotonia, comparing detection rate following targeted scan indicated by at least one, two or three non-specific signs, and comprehensive genetic investigation being carried out for any additional sign. Numbers are based on our study cohort data.

Table S1 Demographic and perinatal characteristics of study groups

Table S2 Yield of targeted scan

Videoclip S1 Videoclip showing open/tent-shaped mouth.

Videoclip S2 Videoclip showing thoracic kyphosis in minicore myopathy.

Videoclip S3 Videoclip showing normal spine for comparison.