Arthrogryposis multiplex congenita: Analysis of twelve cases

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Summary

Objective: The term arthrogryposis multiplex congenita (AMC) refers to multiple joint contractures present at birth. AMC is not a specific disorder but is the consequence of neurological, muscular, connective tissue, and skeletal abnormalities or intrauterine crowding, which may lead to limitation of fetal joint mobility and the development of contractures. *Methods*: Cases referred to our perinatology department for detailed examination were retrospectively analyzed. *Results*: Twelve cases with AMC were detected during the antenatal period. The ultrasound features related to the "lack of movement" included limb abnormalities (multiple contractures, clenched hands, and clubbed feet), short umbilical cord, polyhydramnios, pulmonary hypoplasia, camptodactyly, and micrognathia. Five of the early detected cases (71%) were found to have increased nuchal translucency or nuchal fold. All of the cases at the third trimester resulted in neonatal death. *Conclusion*: First trimester screening may be useful for early diagnosis of AMC. Sonographic findings in late pregnancy might be helpful in predicting the prognosis. Due to the high recurrence risk, a specific screening program should be performed for the following pregnancies by examination of the fetus several times for movement and position of the limbs.

Key words: Arthrogryposis multiplex congenita; Nuchal edema; Contractures; Polyhydramniosis; Hydrops; Fetal akinesia.

Introduction

Arthrogryposis multiplex congenita (AMC) is defined as multiple joint contractures. The incidence of this condition is 1/3,000 births [1, 2]. Antenatally diagnosed arthrogryposis is often lethal. In a recent Finnish study the total incidence (selective terminations, stillbirths, and infant deaths included) of lethal arthrogryposis was reported to be 1/6,985 [3]. The joint contractures occur because of decreased fetal movement (fetal akinesia). Neurogenic processes affecting either the peripheral or the central nervous system are the most common causes. Other causes of fetal akinesia include muscle or connective tissue abnormalities, uterine anomalies or fibroids, intrauterine vascular compromise after bleeding, and maternal diseases such as diabetes mellitus, multiple sclerosis and myotonic dystrophy [2]. AMC may be associated with a number of different syndromes.

Prenatal diagnosis of AMC is focused on diminished fetal movement and the presence of joint contractures or skeletal deformities. The classic sonographic findings include clenched hands, clubfeet and often polyhydramnios [4]. We describe the sonographic findings, clinical courses and postmortem examinations of 12 cases.

Materials and Methods

Cases referred to our perinatology department for detailed examination for different reasons were retrospectively analyzed. Data on obstetric history and ultrasound (US) findings were recorded at the time of sonographic examination. Arthrogryposis was defined as joint contractures present in at least two regions of the body as seen at US, postmortem examination or autopsy. The clinical, laboratory, autopsy, and US data were re-evaluated.

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Result

During the 3-year period (2004-2007) we found 12 cases which had been diagnosed prenatally as having multiple contractures of different etiologies. Of these 12, five were in the third trimester and all of these cases suffered neonatal death. Eight cases between 16-30 weeks of gestation resulted in selective pregnancy termination. The second trimester screening was unremarkable in all cases in the third trimester. Six of the 12 cases (50%) had a history of a previous baby with various anomalies. All of the cases had severe bilateral talipes and fixed flexion deformities of the wrists and elbows (Figure 1). Either fixed flexion or extension of the knees was detected in 11 of the cases (Figures 2, 3); the case with muscle dystrophy had only distal arthrogryposis. Other findings and prognoses are presented in Table 1. Nuchal edema (2 had cystic hygroma) was detected in 71% (5 of the 7) of the cases in the first and second trimesters. In four cases, amniocentesis and in one case fetal umbilical cord blood sampling was performed uneventfully. In one case chorionic villus sampling was performed for specific immunstaining of collagen type VI due to the sonographic findings and a previous child with Ullrich type muscle dystrophy.

Postnatal examination of the fetal muscle revealed dystrophic changes. Chromosomal analysis was normal in six cases. Specific diagnosis could be made in seven (58%) of the cases based on the necropsy findings, previous history, sonographic findings, and immunstaining of the chorionic villi (Table 2). Five cases were autosomal recessive forms of AMC and one case had X linked recessive inheritance. Necropsy of case number one revealed occult spina bifida at the cervical region.

Fig. 1

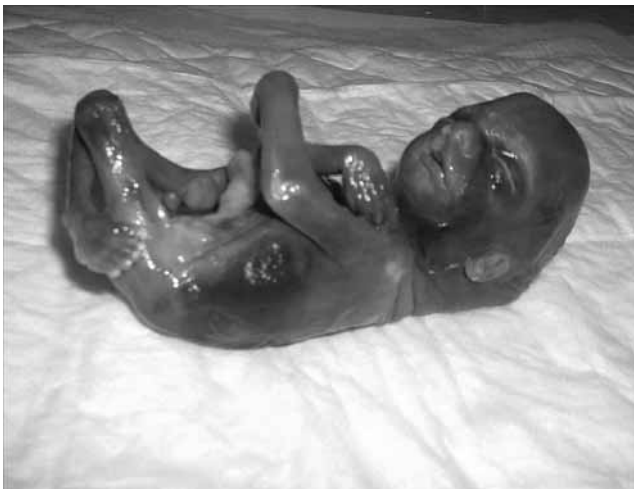

Fig. 2

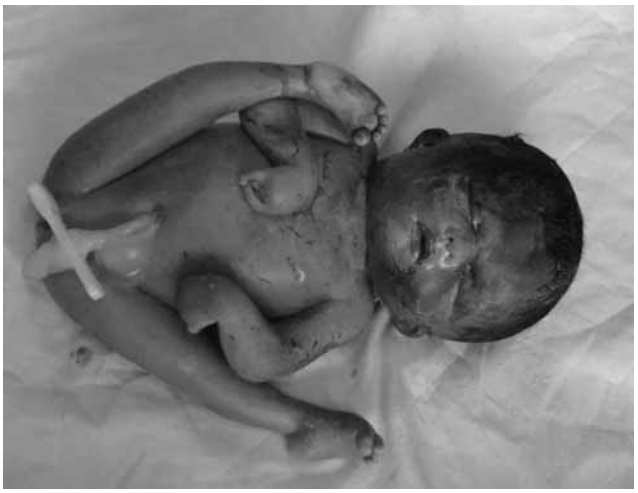

Fig. 3

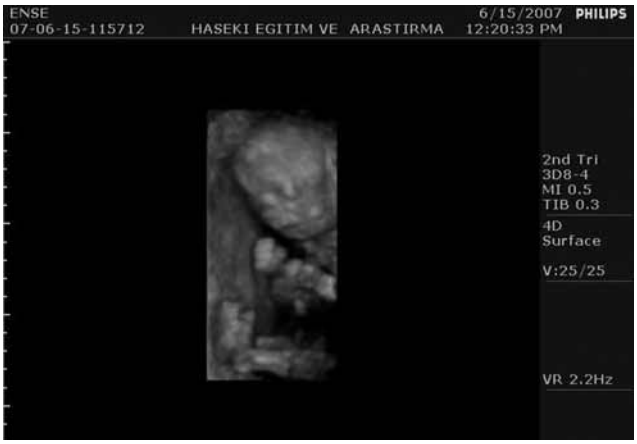

Fig. 4

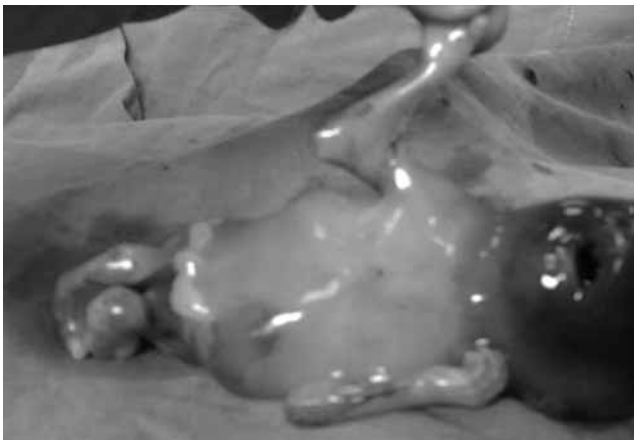

Figure 1. — Fixed flexion in all of the extremities in the case of X linked hydrocephaly.
Figure 2. — Fixed position of the joints at 3D sonographic examination (case 12).
Figure 3. — Fixed extantion of the legs (case 11).
Figure 4. — Fixed flexion and webbing (case 6).

Discussion

The term arthrogryposis (arthron: joint, gryposis: bent), which implies that the contractures are in flexion, appeared in 1923. Another term 'multiple congenital contractures' was proposed after that because the contractures were fixed in extension in some cases. AMC is another synonym. Moessinger proposed the most recent name 'fetal akinesia deformation sequence' (FADS), in 1983 [5]. Decreased fetal movements in utero may lead to a sequence of anomalies. FADS is characterized by multiple joint contractures, pulmonary hypoplasia, short umbilical cord, craniofacial anomalies and micrognathia.

There have been a number of case reports of prenatal diagnoses of arthrogryposis between 16 weeks to term [6-8]. Depending on the onset and the severity of the pathology sonographic findings and the prognosis of the fetus may vary. AMC due to a neuropathic lesion may not be sonographically detected until 20 weeks, as neurogenic atrophy typically manifests late in gestation and is often progressive. This may be the reason for unremarkable second trimester scans in our cases. The need for diagnostic neuroimaging of the craniocervical junction in patients with AMC has already been stressed by some authors [9]. In our first case the presence of the neural tube defect at the cervical region could not be detected by sonographic examinations. The necropsy of the fetus provided the specific diagnosis.

Early diagnoses of AMC have been based on an abnormal nuchal translucency in the late first trimester, rather than abnormalities in limb positioning and contractures [10-12]. However, our cases, which were detected by first trimester scanning, had contractures (case numbers 5 and 6), suggesting very early onset of the pathology.

Fetal hydrops and polyhydramnios are mentioned as poor prognostic signs [13]. It has been suggested that immobility causes accumulation of subcutaneous fluid and atony in the diaphragm, leading to a change in thoracic pressure and a disturbance in lymphatic circulation [14, 15]. It is still not clear why hydrops was not seen in all cases. Scalp edema and nuchal edema were detected in seven of our cases (58%). One of these cases in the third trimester also had ascites and hydrothorax. In this case, at 30 weeks of gestation the parents were counseled

Table 1. — *Sonographic, macroscopic findings, history and prognosis of the cases*.

Number	Findings	Ankles	Knees	Elbows and wrists	History	Prognosis
1	PHA, MG, Short umb. cord, CS, AOM	PE	Extended	Flexed	1 NND at term	NND at 35 weeks
2	PHA, MG, camptodactly, scalp edema, hypertelorism, AOM	PE	Extended	Flexed	1 NND at term	NND at 38 weeks
3	Microftalmy, hypertricosis, clenched hands	PE	Extended	Flexed		NND at 38 weeks
4	AOM	PE	Extended	Flexed	1 NND at term	NND at 39 weeks
5	Cystic hygroma, webbing, hydrops, Short umb. cord	PE	Flexed	Flexed		TOP at 16 weeks
6	Cystic hygroma, webbing, hydrops, Short umb. cord	PE	Flexed	Flexed		TOP at 17 weeks
7	Ventriculomegaly, adducted thumb, NE, short umb. Cord	PE	Flexed	Flexed	1 TOP, hydrocephaly	TOP at 18 weeks
8	MG, NE, diaphragmatic hernia	PE	Extended	Flexed		TOP at 22 weeks
9	Scoliosis, MG, webbing, NE	PE	Flexed	Flexed		TOP at 20 weeks
10	Clenched hands, AOM	PE	–	Flexed	1 child with CMD	TOP at 22 weeks
11	Hydrops, PHA, Short umb. cord, clenched hands	PE	Extended	Flexed		TOP at 30 weeks
12	NE, clenched hands	PE	Extended	Flexed	2 TOP, AMC	TOP at 22 weeks

PHA: Polyhydramnios, CS: Collapsed stomach, PE: Pes ekinovarus, MG: Micrognathia, AOM: Absence of fetal movement, NE: Nuchal edema, NND: Neonatal death, TOP: Termination of pregnancy, CMD: Congenital muscle dystrophy, Umb: umbilical.

Table 2. — *Chromosome analysis and specific diagnosis of the cases*.

Number	Chromosomal analysis	Specific diagnosis
1	–	Spina bifida at the cervical region
2	Normal (CS)	–
3	–	Cerebro-oculo-facio-skeletal-syndrome (AR)
5	Normal (AS)	Lethal multiple pterygium syndrome (AR)
6	Normal (AS)	Lethal multiple pterygium syndrome (AR)
7	Normal (AS)	X-linked hydrocephalus
8	Normal (AS)	Pena Shokeir (AR)
10	Normal (CVS)	Ullrich type muscle dystrophy (AR)

AS: Amniocentesis, CVS: Chorionic villus sampling, CS: Cordosentesis, AR: Autosomal recessive.

regarding the dismal prognosis and opted to terminate the pregnancy. The baby was born with an Apgar score of 0.

In the cases with cystic hygroma associated with multiple contractures, the diagnosis of lethal multiple pterygium syndrome was considered. This is an autosomal recessive condition characterized by soft tissue webbing between contracted joints (Figure 4). This disorder is uniformly lethal and pathological assessment of fetuses suggests delayed cannalation between the jugular lymphatic sacs and the internal jugular vein, which leads to an accumulation of lymphatic fluid around the fetal neck [16]. Our cases also had hydrothorax and the pregnancies were terminated after amniocentesis (cases 5, 6).

Polyhydramnios, due to impaired swallowing, was present in about 20% of cases in a series after 26 weeks of gestation [11]. Polyhydramnios was found in three of the cases in the third trimester (60%). Frequently, in severe cases of AMC, the umbilical cords are short because the infants have not been moving and stretching the cord as occurred in four of our cases (33%). This might also be a sign of early onset.

Micrognathia is also a common finding in fetuses with lethal arthrogryphosis, since fetal muscle movement is required for the normal growth of craniofacial bones. The reported frequency is 41% in AMC cases [11]. Micrognathia was also detected in two of our cases in the third trimester (40%) as a possible consequence of neuromuscular dysfunction.

In AMC cases pulmonary hypoplasia was probably present due to absent or decreased fetal respiratory activity [17, 18]. Four of the cases above 26 weeks (80%) failed to inspire, while one case (case 4) had weak respiratory activity that lasted 24 hours.

Distal arthrogryposis (DA), which affects distal joints, can also result from various cerebral, neuromuscular and connective tissue lesions, and may occur as part of a number of congenital syndromes [2]. In one of the cases (case 9), after detection of DA by serial US examinations, chorionic villus sampling was performed. The diagnosis of Ullrich type muscle dystrophy was made based on the weak staining of collagen VI.

AMC is a component of a number of genetic syndromes. In one series of 350 AMC cases, 14% exhibited autosomal dominant inheritance, 7% autosomal recessive inheritance, and 2% X-linked recessive inheritance [1]. In our series, specific diagnoses could be made in seven cases: five cases had autosomal recessive (41.6%), and one case had X linked recessive (8.3%) inheritance. The recurrence form of the lethal anomaly in additional three cases (cases 2, 4, 12) pointed out also an autosomal recessive form of inheritance.

Four genetic loci associated with autosomal recessive AMC syndromes have been described [19-23]. In a recent study the findings suggested that there was genetic heterogeneity of congenital arthrogryposis in the same population: the same phenotype was caused by mutations in different genes and the authors concluded that AMC is of even greater genetic heterogeneity than previously known [24].

Conclusion

Despite new findings the availability of early prenatal diagnosis is critical. A case specific screening program should be planned for the following pregnancies of the affected families. Since increased nuchal translucency has been found in fetuses with lethal arthrogryposis before contractures become apparent, first trimester screening should be carried out. Scanning the fetus at 16, 20, 24, and 32 weeks to evaluate fetal movements and characteristic fetal positions could reveal congenital contractures. If the diagnosis is made after viability, US findings of poor prognosis may be helpful in obstetric management.

References

[1] Hall J.G.: "Genetic aspects of arthrogryposis". *Clin. Orthop. Relat. Res.,* 1985, *194*, 44.
[2] Hall J.G.: "Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach and general aspects". *J. Pediatr. Orthop.,* 1997, *159*, 66.
[3] Pakkasjarvi N., Ritvanen A., Herva R., Peltonen L., Kestila M., Ignatius J.: "Lethal congenital contracture syndrome (LCCS) and other lethal arthrogryposes in Finland - An epidemiological study". *Am. J. Med. Genet. A.*, 2006, *140,* 1834.
[4] Bui T.H., Lindholm H., Demir N., Thomassen P.: "Prenatal diagnosis of distal arthrogryposis type I by ultrasonography". *Prenat. Diagn.*, 1992, *12,* 1047.
[5] Moessinger A.C.: "Fetal akinesia deformation sequence: an animal model". *Pediatrics.,* 1983, *72*, 857.
[6] Baty B.J., Cubberly D., Morris C., Carey J.: "Prenatal diagnosis of distal arthrogryposis". *Am. J. Med. Genet.,* 1988, *29*, 501.
[7] Madazlı R., Tuysuz B., Aksoy F., Barbaros M., Uludag S., Ocak V.: "Prenatal diagnosis of arthrogryposis multiplex congenital with increased nuchal translucency but without any underlying fetal neurogenic or myogenic pathology". *Fetal. Diagn. Ther.,* 2002, *17,* 29.
[8] Sepulveda W., Stagiannis K.D., Cox P.M., Wigglesworth J.S., Fisk N.M.: "Prenatal findings in generalized amyoplasia". *Prenat. Diagn.,* 1995, *15*, 660.
[9] Luedemann W.O., Tataqiba M.S., Hussein S., Samii M.: "Congenital arthrogryposis associated with atlantoaxial subluxation and dysraphic abnormalities'. Case report". *J. Neurosurg.*, 2000, *93,* 130.
[10] Ajayi R.A., Keen C.E., Knott P.D.: "Ultrasound diagnosis of the Pena Shokeir phenotype at 14 weeks of pregnancy". *Prenat. Diagn.,* 1995, *15*, 762.
[11] Hyett J., Noble P., Sebire N.J., Snijders R., Nicolaides K.H.: "Lethal congenital arthrogryposis presents with increased nuchal translucency at 10-14 weeks of gestation". *Ultrasound. Obstet. Gynecol.,* 1997, *9*, 310.
[12] Scott H., Hunter A., Bedard B.: "Non-lethal arthrogryposis multiplex congenita presenting with cystic hygroma at 13 weeks gestational age". *Prenat. Diagn.*, 1999, *19,* 966.
[13] Herva R., Leisti J., Kirkinen P., Seppanen U.: "A lethal autosomal recessive syndrome of multiple congenital contractures". *Am. J. Med. Genet.,* 1985, *20*, 431.
[14] Machin G.A.: "Hydrops revisited: literature review of 1,414 cases published in the 1980s". *Am. J. Med. Genet.*, 1989, *34*, 366.
[15] Vuopala K., Leisti J., Herva R.: "Lethal arthrogryposis in Finland-A clinico- pathological study of 83 cases during thirteen years". *Neuropediatrics.,* 1994, *25,* 308.
[16] Hammond E., Donnenfeld A.E.: "Fetal akinesia". *Obstet. Gynecol. Surv.,* 1995, *50,* 240.
[17] Moerman P., Fryns J.P.: "The fetal akinesia deformation sequence-A fetopathological approach". *Genet. Couns.*, 1990, *1*, 25.
[18] Vardon D., Chau C., Sigodi S., Figarella-Branger D., Boubli L.: "Congenital rapidly fatal form of nemaline myopathy with fetal hydrops and arthrogryposis. A case report and review". *Fetal. Diagn. Ther.*, 1998, *13,* 244.
[19] Makela-Bengs P., Jarvinen N., Vuopala K., Suomalainen A., Ignatius J., Sipila M. *et al.*: "Assignment of the disease locus for lethal congenital contracture syndrome to a restricted region of chromosome 9q34, by genome scan using five affected individuals". *Am. J. Hum. Genet.,* 1998, *63*, 506.
[20] Shohat M., Lotan R., Magal N., Shohat T., Fischel-Ghodsian N., Rotter J.I. *et al.*: "A gene for arthrogryposis multiplex congenita neuropathic type is linked to D5S394 on chromosome 5qter". *Am. J. Hum. Genet.,* 1997, *61*, 1139.
[21] Gissen P., Johnson C.A., Morgan N.V., Stapelbroek J.M., Forshew T., Cooper W.N. et al.: ''Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis-arthrogryposis- renal dysfunction-cholestasis (ARC) syndrome''. *Nat. Genet.,* 2004, 36, 400.
[22] Narkis G., Landau D., Manor E., Elbedour K., Tzemach A., Fishelson M *et al.*: "Homozygosity mapping of lethal congenital contractural syndrome type 2 (LCCS2) to a 6 cM interval on chromosome 12q13". *Am. J. Med. Genet. A.,* 2004, *130*, 272.
[23] Tanamy M.G., Magal N., Halpern G.J., Jaber L., Shohat M.: "Fine mapping places the gene for arthrogryposis multiplex congenita neuropathic type between D5S394 and D5S2069 on chromosome 5qter". *Am. J. Med. Genet.,* 2001, *104*, 152.
[24] Narkis G., Landau D., Manor E., Ofir R., Birk O.S.: "Genetics of Arthrogryposis". *Clin. Orthop. Relat. Res.,* 2006, *456*, 30.

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