Lethal congenital contracture syndrome: further delineation and genetic aspects

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Abstract
In a national morphology based study of lethal arthrogryposis between 1979 and 1992, 40 fetuses and infants with lethal congenital contracture syndrome (LCCS, McKusick 253310) were found in Finland. The incidence of LCCS in Finland was 1:19 000 births. There were 20 affected males and 20 affected females in 26 families. In 16 cases the pregnancy was terminated after the prenatal diagnosis of total akinesia and fetal hydrops on ultrasound. There were 19 stillborn infants and five were born showing signs of life, but died within one hour. The segregation analyses yielded 0.45 affected by the “singles” method and 0.34 by the “sib” method. The birthplaces of the grandparents were located in the sparsely populated north east of Finland. This finding supports the existence of an autosomal recessive LCCS gene in Finland, particularly in the north eastern part.

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The lethal congenital contracture syndrome (LCCS) is an autosomal recessive syndrome (McKusick 253310) leading to perinatal death. Affected fetuses present a typical phenotype with hypoplastic jaw, low set ears, hypoplastic lungs, and contractures of the extremities, with overextended knees. Similar features always occur when a fetus does not move and the phenotype is called the fetal akinesia deformation sequence. In LCCS the abnormalities are very severe and typically there is also fetal hydrops which can be detected by ultrasound from the 14th gestational week. The fetal akinesia in LCCS is caused by the degeneration of descending tracts and anterior horn motor neurones of the spinal cord.

LCCS was originally described in 10 families from north eastern Finland. As far as we know, no familial cases have been reported elsewhere. However, a few sporadic cases similar to LCCS have been published. As part of the classification of lethal arthrogryposis, an epidemiological and genealogical study on LCCS was carried out in Finland.

Materials and methods
Cases of lethal arthrogryposis in Finland have been collected since 1979. A prospective study was begun in 1988 with a request for information about cases with lethal arthrogryposis and instructions for necropsy in the Journal of the Finnish Medical Association in 1988. A personal visit was made to the five university hospitals (Helsinki, Kuopio, Oulu, Tampere, and Turku) in Finland, in which complicated deliveries are treated and genetic counselling and paediatric pathology are performed. The material comprised 91 cases of which 40 met the diagnostic criteria of LCCS: early hydrops and fetal akinesia, lethality, the Pena-Shokeir phenotype, and specific neuropathology with the degeneration of anterior horn of the spinal cord and an extreme skeletal muscular atrophy.

Necropsies were performed in the local central hospitals. In prospective cases the brain and spinal cord were fixed in entirety and skeletal muscle samples were frozen. The fixed CNS and frozen muscle samples were sent to the Department of Pathology of the Oulu University Hospital with photographs, x rays, necropsy records, family data, and clinical history. Postmortem study consisted of routine necropsy and neuropathological investigation. The specimens were fixed in phostate buffered 10% formalin. After washing, dehydration, and embedding in paraffin, serial 6 μm sections were cut and stained with eosin and haematoxylin. Skeletal muscle samples were frozen in isopentane, cooled with liquid nitrogen, and stored at −70°C. Serial frozen sections were routinely processed.

To determine pulmonary hypoplasia, lung weight or radial alveolar count were used as the criteria for diagnosis. Intraterine growth was compared to the latest Finnish standards in cases older than 24 gestational weeks and to international standards in the rest of the cases. Clinical data were collected from hospital records. The abortion frequency was compared with that in the normal population.

Differences in regional gene frequencies were assessed by the grandparents’ birthplaces. The birthplaces were confirmed from the population register. For the incidence calculation the number of annual births until 1990 was obtained from the Statistical Yearbook of Finland, and those during 1991 and 1992 by personal communication from Statistics Finland. Segregation analysis was performed with the singles methods and the a priori method, which both assume truncate complete ascertainment, and with the sib method, which assumes single incomplete ascertainment.

Results
Clinical details are summarised in table 1. The material included a total of 40 LCCS cases, 20 males and 20 females in 26 families (fig 1). The incidence of LCCS calculated for the period studied (1979–1992) was 1:19 000 births. This means five new cases in Finland yearly.
Table 1 Summary of the clinical features and necropsy findings

| Case  | 1a | 1b | 1c | 1d | 2a | 2b | 2c | 3a | 4a | 4b | 5a | 5b | 6 | 7 | 8 | 9 | 10a |
|-------|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|
| Sex   | F  | F  | M  | M  | F  | F  | M  | F  | M  | M  | F  | M  | F  | F  | M  |
| Age of the mother (y) | 34 | 35 | 37 | 39 | 24 | 26 | 27 | 25 | 32 | 33 | 21 | 22 | 32 | 20 | 24 | 23 |
| Gestational age (w) | 28 | 30 | 18 | 17 | 21 | 20 | 19 | 26 | 28 | 17 | 35 | 32 | 31 | 34 | 33 | 27 | 26 |
| Survival (minutes, hours, days) | 0  | 0  | ia | ia | 0  | ia | ia | 0  | 0  | ia | min 0 | 0 | 0 | 0 | 0 | 0 |
| Apgar score (at 1/5/10 minutes) | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| Diminished fetal movements | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Prenatal diagnosis | -  | +  | +  | -  | +  | -  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Hydrops | -  | +  | +  | -  | +  | -  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Polycladraminos | +  | -  | -  | +  | -  | +  | -  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  |
| Birth weight (g) | 820 | 1140 | 90 | 3900 | 440 | 310 | 1040 | 430 | 880 | 1250 | 560 | 550 |
| Birth CH length (cm) | 36 | 36 | 18 | 16 | 24 | 24 | 22 | 24 | 35 | 31 | 34 | 40 | 39 | 22 |
| Birth CR length (cm) | 13 | 11.5 | 18 | 19 | 16 | 16 | 13 | 13 |
| Pterygia | n  | n  | e  | n  | e  | n  | e  | n  | e  | e  | e  | e  | e  | e  | e  | e  | e  |
| Lung hypoplasia | +  | +  | +  | -  | +  | -  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Fractures of long bones | H,F | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  | F  |
| Spinal cord pathology | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Muscle pathology | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |

is = induced abortion, n = neck, e = elbow, H = humerus, F = femur. Families 1–6 have been reported previously.

PREGNANCY AND DELIVERY
The mother reported diminished fetal movements in 13 cases. Prenatal diagnosis was done on the basis of total fetal akinesia and hydrops on ultrasound in 24 cases. In 16 of these, the family chose termination of pregnancy, and in the rest of the cases the pregnancy continued.

Of these eight pregnancies seven ended before term with abortion or stillbirth, and one with the birth of a male infant in the 33rd gestational week. He died at the age of one minute. In the rest of the 16 pregnancies without prenatal diagnosis, there were 12 stillborn and four infants showing signs of life at birth. The outcome of the infants was fatal in one hour. The mean gestational age was 27 weeks from the last menstrual period.

Besides the affected fetuses, there were 26 healthy sibs, seven spontaneous abortions, one extraterine pregnancy, five stillborn fetuses, and four induced abortions, which were not studied and were excluded from the segregation analysis. The latter included one genetic termination (trisomy 21), and three terminations for social indications. The frequency of spontaneous abortion was 8.3%, which is no higher than the abortion frequency in the normal population.

CLINICAL FINDINGS
Twenty fetuses were small (under 2 SD) for gestational age. Normal intrauterine growth was detected in all cases but one below 22 gestational weeks. Hydrops was verified in 37 fetuses, even in the severely autolysed. The face of all fetuses was peculiar with ocular hypertelorism, apparently low set and sometimes posteriorly angulated ears, and hypoplastic jaw. The limbs were of normal proportion, but looked stick-like because of the extreme muscle atrophy. Multiple joint contractures with a similar pattern was seen in all cases (fig 2). There were flexion contractures in the elbows, wrists, and hips. The knees were in marked hyperextension, the shoulders were adducted, and severe bilateral club foot was present. Pterygia were observed in 18 cases, most often in the elbows.

NECROPSY FINDINGS
Pulmonary hypoplasia was verified in 20 cases and muscle atrophy was macroscopically present in all cases and histologically verified in 19 cases. The spinal cord was available in 19 cases. It showed a marked reduction of the ventral part and a paucity of motor neurones (fig 3). Fractures of the long bones, most often the femur, were seen in six cases.

![Figure 1](http://jmg.bmj.com/ June 21, 2017 - Published by group.bmj.com)
Lethal congenital contracture syndrome

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Figure 2 Typical cases of LCCS: (A) a 38 week old fetus and (B) a prenatally diagnosed 17 week old fetus from family 18.

Figure 3 The spinal cord showed a marked reduction in the ventral part, a paucity of anterior motor neurones, and hydropic degeneration of descending tracks. (H and E stain).

Genetic aspects

The segregation analysis of the pedigrees showed a ratio of affected sibs of 0.45 (SE 0.08) by the "singles method" and 0.34 (SE 0.07) by the "a priori" method. The observed number of patients (40) was higher than expected on the basis of recessive inheritance (32, SE 2.34) by the "singles method". The birthplaces of the grandparents were used to illustrate the geographical distribution of LCCS in Finland. They were localised in the sparsely populated north eastern area of Fin-
land (fig 4), the same region as those of the 10 original families. The gene frequency for northern Finland, the provinces of Oulu and Lappi, was 0.016 and for the whole country was 0.0089, and the carrier frequency was 1:31 and 1:57, respectively, calculated by the Hardy-Weinberg coefficient.

Discussion
Lethal congenital contracture syndrome (LCCS) is part of the fetal akinesia phenotype (FADS). The pathological mechanism of FADS was well documented by Moessinger. He curarised pregnant mice and the fetuses showed a classic picture of FADS with hypoplastic lungs and contractures of the extremities. It is understood that any disorder which leads to immobility in utero causes the FADS phenotype. The phenotype has been called "arthrogryposis multiplex congenita", and it originally applied to multiple flexed joints present at birth. Nowadays, it is used in the more specific meaning of a phenotype in which there are joint contractures present in at least two areas of the body at birth with evidence of muscle wasting, but no evidence of progressive neurological disease. The overlapping term Pena-Shokeir syndrome, or more recent Pena-Shokeir I phenotype, was introduced after Pena and Shokeir reported two sisters who had severe camptodactyly, club feet, knee and hip ankylosis, facial anomalies, and pulmonary hypoplasia. Arthrogryposis multiplex congenita

Figure 4  The birthplaces of the grandparents were in north eastern Finland. The map shows the distribution of a respective number of marks arranged according to the population density of Finland.
Lethal congenital contracture syndrome

and Pena-Shokeir phenotype are descriptive terms that cover several separate entities with fetal akinesia.

In the London Dysmorphology Database, LCCS is part of the Pena-Shokeir-multiple ankyloses-pulmonary hypoplasia syndrome. As stated in the abstract of the Database, Pena-Shokeir-multiple ankyloses-pulmonary hypoplasia covers a number of separate entities. We consider LCCS as a distinct entity within it. In LCCS there is a constant neuropathological finding with severe reduction of anterior horn of the spinal cord and total or nearly total absence of large motor neurons. Above the decussation of the pyramids, the CNS is normal.

However, most reports of perinatally lethal cases referred to in the Database refer present with abnormal brain development, such as immaturity, cortical ectopia, polymicrogyria or hypoplasia of the optic nerves and optic chiasma, multicystic encephalophaty, hemiatrophy of the temporal lobe, hydrencephaly, or present with brain damage, or with a well preserved spinal cord, or with brain damage, or with a well preserved spinal cord, or with brain damage, or with a well preserved spinal cord, or with brain damage, or with a well preserved spinal cord. LCCS also has a unique, severe clinical picture. It is always fatal during the fetal period, and it presents with hydrodrops, severe intrauterine growth retardation, and extreme hypoplasia of skeletal muscle.

The prenatal diagnosis can be achieved as early as the 13th gestational week. In families with recurrent cases, the affected fetuses have been detected by sonography without exception before the 20th week of gestation. The fetuses have shown joint contractures, hydrops, and no movement. As discussed later, LCCS is an autosomal recessive syndrome with a recurrence risk of 25%, which is higher than the 10 to 15% risk in the Pena-Shokeir syndrome, as stated in the London Dysmorphology Database.

There are only a few studies on the incidence of arthrogryposis. In a Finnish study of 36 711 live born infants, it was found to be 1:3000.

The material included four perinatally lethal cases in one family. The same incidence of arthrogryposis was found in a Canadian series of 350 affected newborns, of which 29 (8%) died in the first year of life. According to these two studies, lethal arthrogryposis is estimated to occur once in every 37 500 births, which is about half the incidence calculated for LCCS in the present study. The increased occurrence can be explained by the recognition of the FADS phenotype and growing interest in perinatally lethal cases. Complicated pregnancies are treated nowadays in university hospitals, in which paediatric pathology services and more exact diagnosis are available.

The present study confirms the original clinical findings of LCCS. Both male and female fetuses were equally affected. Prenatal diagnosis could be made by ultrasound even in the 14th week of gestation when hydrodrops appeared and fetal movements diminished. In the present cases prenatal diagnosis was achieved in 60% of cases, whereas in the original study the frequency was 25%. Prenatal diagnosis is also reliable in sporadic cases. Polyhydramnios was usually found in the third trimester of pregnancy, whereas the fetal hydrodrops appeared earlier and was detected even in severely macerated cases. The mean gestational age in the present cases was a little less than in the original study. A few pregnancies continued, instead of the earlier 33 weeks, until the 36th week from the last menstrual period. The outcome was still very poor and all pregnancies ended fatally before term. The longest survival was 50 minutes. Intrauterine growth retardation of the fetuses was not seen in cases terminated before the 23rd gestational week, but appeared in most older cases.

The original study of 10 families suggested autosomal recessive inheritance of LCCS, but the number of affected fetuses was too high. In the siblings there were 16 affected fetuses, eight unaffected children, six spontaneous abortions of unknown type, and five stillborn fetuses, which were not studied. In the present study the number of affected fetuses was again high in comparison to that expected for autosomal recessive inheritance. This can be explained by the small size of siblings and the youth of the mothers, who had not yet passed their fertile age. The family planning possibilities might also have affected the results of segregation analysis. Three of the families had chosen sterilisation and one couple was divorced after having an affected fetus. It is possible that a few sporadic cases in families with healthy sibs could have gone undiagnosed or misdiagnosed.

The gene and carrier frequencies of LCCS in Finland and especially in northern Finland are high. This is in line with the specific pattern of hereditary diseases in Finland, over-representation of some, mostly autosomal recessive disorders, and lack of diseases which are common in other countries. This specific pattern of hereditary diseases is the result of the national and regional isolation of the small population which is especially pronounced in sparsely populated north eastern Finland.

Most of the ancestors of the LCCS families originated from this area.

The modern methods of molecular genetics can provide further understanding of LCCS. The second generation linkage mapping in multigenic polygenic diseases, of which containing short tracks of (C-A) repeats has made gene mapping of rare genetic diseases more effective. As the pathogenesis of LCCS is interpreted to be the degeneration of anterior horn motor neurones and the autosomal recessive form of childhood onset SMA has been mapped to chromosome 5q12-2-13, the 5q region is the first object of the study. The locus has been refined to the interval between D5S435 and MAP1B, and recently the region 5p-12-D5S76-D5S812-SMA-A (5′MAP1B-3′MAP1B)/D5S112-JK53CA1/2-(D5S39-D5S127)-5qter. However, the diagnostic criteria for spinal muscular atrophy proposed by the International SMA Consortium include arthrogryposis as an exclusion criterion. Linkage studies on lethal SMA cases with arthrogryposis have so far shown no confirmation of the 5q location.

The second locus which needs to be excluded is 21q21.1-22.1, the locus for familial amyotrophic lateral sclerosis, in which anterior horn cells in the spinal cord are also affected. The exaggeration of naturally occurring
motor neurone death was proposed to be a part of the anterior horn damage in SMA.54 In LCCS this mechanism could play an important role, because the degeneration of anterior horn motor neurones in LCCS overlaps the time of naturally occurring death of the motor neurones during fetal development.48 Recently, motor neurone survival has been shown to be promoted by neurotrophins.49-52 Thus, this family of growth factors, their receptors, or mediators may be involved with the pathogenesis of LCCS. The neurotrophins have been mapped in the human genome as shown in table 2, giving hints for linkage analysis. On a purely speculative basis the candidate genes could be located in chromosomes 1p, 5q, 9q, 11p, 17q, and 21q. A linkage study on the present cases is in progress.

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