

Arthrogryposis multiplex congenita

Search for prenatal factors in 66 sporadic cases

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Wynne-Davies, R., and Lloyd-Roberts, G. C. (1976). *Archives of Disease in Childhood*, **51**, 618. **Arthrogryposis multiplex congenita: search for prenatal factors in 66 sporadic cases.** In a family and epidemiological survey of 66 cases of arthrogryposis multiplex congenita all cases were found to be sporadic and no family association with clubfoot, congenital dislocation of the hip, or hereditary neuromuscular disease was found. The mothers were significantly older than average. Oligohydramnios was noted in only one-third of cases but many other complications of pregnancy, including probable attempts at abortion, had occurred. It is likely that most cases of arthrogryposis are nongenetic and result from a defective intrauterine environment, whether hormonal, vascular, mechanical, or possibly infective.

At present arthrogryposis multiplex congenita is only a clinical definition of what is probably a heterogeneous group of congenital disorders which are similar in having extreme stiffness and contracture of joints with absence of muscle development around them. The normal contours of affected limbs are lost, skin creases are absent, and the limbs appear nearly cylindrical. Structural (that is, fixed, uncorrectable) deformities are common and include dislocation of the hip, clubfoot, scoliosis, and flexion contractures of knees, elbows, wrists, or other joints, though some may be in extension. Similar deformities can be produced in the lower limbs by obvious spinal cord disease, such as myelomeningocele or myelodysplasia, but these are clearly paralytic in origin and have been excluded from this survey. 'Arthrogryposis' also occurs in Potter's syndrome, where there is agenesis of the kidneys and severe oligohydramnios: these stillborn infants have also been excluded.

True arthrogryposis multiplex congenita is present at birth and neither improves nor worsens with age, though untreated deformities will progress with the growth of the child. The cause is unknown, though a variety of hypotheses have been suggested. It is likely that a rare primary *myogenic* type exists which is of autosomal recessive inheritance. This has been regarded as a nonprogressive congenital

muscular dystrophy. However, most cases of arthrogryposis are sporadic, and evidence suggests a primary disorder of the anterior horn cells causing a *neurogenic* disorder (Adams, Denny-Brown, and Pearson, 1962; Sharrard, 1971; Tachdjian, 1972). Patchy destruction or failure of development of these cells may cause characteristic deformities observed in these children, for example the 'waiter's tip' position of the upper limbs, perhaps due to absence of anterior horn cells at the 5th and 6th cervical level (Fig.). However, this neurological pattern of deformity is not often seen.

Many electromyographic studies have been reported (Banker, Victor, and Adams, 1957; Swinyard and Magora, 1962; Pearson and Fowler, 1963; Villanueva, 1968; Bharucha, Pandya, and Dastur, 1972). Though a 'myopathic' or 'neuropathic' type of lesion has sometimes been recorded, these studies, as well as the examination of biopsy and necropsy material, have often been inconclusive because of the absence of muscle (Kanof, Aronson, and Volk, 1956; Drachman and Banker, 1961; Vestermark, 1966; Dastur, Razzak, and Bharucha, 1972). Amick, Johnson, and Smith (1967) noted one patient with electromyographic changes indicative of a myopathy who also had increased serum creatinine phosphokinase and aldolase activity. Ionasescu, Zellweger, and Filer (1970) reported increased synthesis of collagen in 2 cases of arthro-

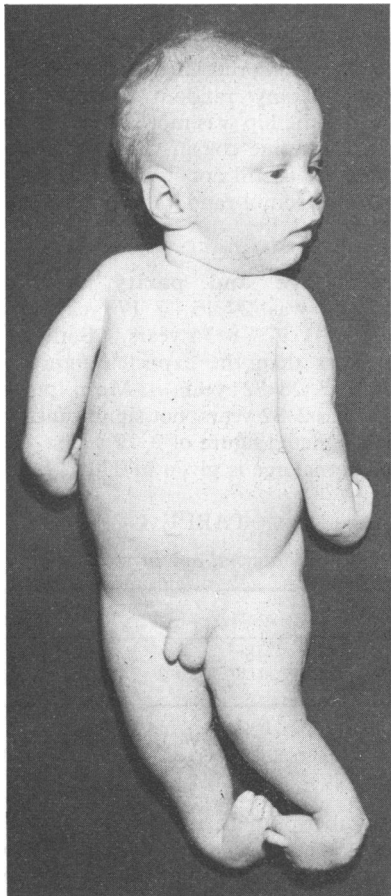


FIG.—An infant showing arthrogryposis multiplex congenita involving all four limbs. The 'waiter's tip' position of the upper limbs perhaps indicates destruction or failure of development of the anterior horn cells at the 5th and 6th cervical level.

gryposis and speculated that various causes could all lead to a common metabolic defect.

An arthrogryposis-like deformity in chicks occurring after curare injection into chick embryos was described by Drachman and Coulombre (1962) and Fuller (1975). Paralysis and subsequent growth resulted in a condition similar to arthrogryposis. Jago (1970) reported a woman treated over several days with muscle relaxants for tetanus at 10–12 weeks of pregnancy who delivered an arthrogrypotic child.

Arthrogryposis is sometimes associated with mechanical factors such as prolonged intrauterine immobilization of the fetus with oligohydramnios (Browne, 1955; Dunn, 1969), the theory being that

severe compression of the fetus (for whatever reason) results in total failure of muscle development. Reduced amounts of amniotic fluid and fetal malposition (usually breech presentation) have also been reported (Mead, Lithgow, and Sweeney, 1958; Lamy, Jammot, and Ajjan, 1965; Laitinen and Hirvensalo, 1966; Friedlander, Weston, and Wood, 1968; Gibson and Urs, 1970), as well as the mother's observation of little or no fetal movement. Since these reports merely state that the baby was stiff or paralysed, one can only note that oligohydramnios, malpresentation, and arthrogryposis are sometimes associated, not that one causes the other.

Aim

A group of arthrogrypotic patients and their families were reviewed in an attempt to identify any genetic or prenatal aetiological factors. Secondly, an attempt was made to determine whether there was a high familial incidence of possibly related deformities, such as clubfoot or congenital dislocation of the hip, which (if present) would indicate a similar aetiology for the whole group.

Population incidence

A survey from Helsinki (Laitinen and Hirvensalo, 1966) noted 11 cases in 36 900 births (3/10 000), considerably higher than the incidence recorded in the Edinburgh Register of the Newborn (1964–68) of only 1 in 56 029 births (0·19/10 000). There are, however, reports of a much higher frequency elsewhere, notably Uganda. No figures are available, but patients with the disorder 'appeared in each clinic' (R. Huckstep, personal communication, 1973). In Tasmania and South Australia, Williams (1973; personal communication, 1974) has recorded that the Royal Children's Hospital in Melbourne (serving a population of about 3½ million) treated 100 patients in the 15 years between 1957 and 1972, whereas only 28 patients have been treated in Edinburgh in the 38 years 1936–1974. (The orthopaedic hospital serves a population of about 1¼ million.) Thus, the frequency of arthrogryposis in South Australia, with an essentially European-derived population, is approximately three times that in Scotland and probably in the whole of Great Britain, where it is generally recognized to be a very rare disease.

Material

A total of 98 records were studied, but 32 patients were excluded from the survey (21 were abroad or untraceable, in 9 the diagnosis was not accepted after

visiting the patient, and 2 families refused to co-operate). The 66 index patients investigated had attended one of four orthopaedic centres: Hospital for Sick Children, London 28 patients; Princess Margaret Rose Orthopaedic Hospital, Edinburgh 25 patients; Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry 8 patients; Royal Hospital for Sick Children, Glasgow 5 patients.

Those from the Hospital for Sick Children had been included in a clinical survey reported by Lloyd-Roberts and Lettin (1970). Because of the possibility of undiagnosed myelodysplasia, only patients with both upper and lower limb involvement, or upper limbs only, were included.

Method

Particular care was taken to ensure as far as possible that the arthrogryposis patients formed a homogeneous group and all patients were examined personally by one of us.

The families of all patients were visited and data obtained (from the mother in most cases) of the pregnancy history, including maternal illness, drugs taken, threatened abortion, oligohydramnios, fetal movements, gestation length, and birthweight. Parental age, the parity of the patient, and social class, based on the father's occupation, were recorded. Associated anomalies in the index patients were noted, as well as developmental defects occurring among first, second, and third-degree relatives. Since many of the patients were now adult, their current work and activities were noted. Control figures for parental age, parity, gestation length, and other aspects of the pregnancy and social history were obtained from the figures of the Registrars General for Scotland (1962), and England and Wales (1963), and from the Edinburgh Register of the Newborn (1964-68).

Results

Sex ratio. There were slightly more males (39) than females (27), giving a sex ratio of 1.4.

Associated anomalies. 4 of the 66 patients were mentally retarded (6%). 4 had an inguinal and 1 a hiatus hernia. One patient had an absent toe and another absent toenails: one an absent radius, fibula, and a cleft palate. There was one case of ventricular septal defect. All other associated anomalies, such as dislocation of hips and knees, clubfeet, and scoliosis, were likely to be secondary to absent musculature and joint contractions.

Genetic factors. All 66 cases were sporadic, no other family case being known among 272 first-degree relatives, 785 second-degree, and 781 third-degree (a total of 1838 individuals). The occurrence of muscular dystrophy or neuromuscular disease in the families was not confirmed in any

instance. There were no cases of talipes equinovarus among the first or second-degree relatives, and only one among the third-degree—the expected frequency for any random survey. Congenital dislocation of the hip was more common, one sister, two nieces, and one cousin being affected. However, the figure is still not significantly greater than that expected from a random survey of the normal population.

Parental age and parity. Mean (\pm SD) maternal age was 29.15 ± 7.17 years and mean paternal age 31.97 ± 8.34 years. Both are significantly greater than the expected figures (mother 26.03, father 28.82 years). Mean parental age difference was 2.82 years, not significantly different from the predicted figure of 2.79 years. Distribution of maternal age is given in Table I, showing a

TABLE I
Maternal age in years

Incidence	15-19	20-24	25-29	30-34	35 +	Total
Observed	7	16	13	16	14	66
Expected*	4.09	20.29	20.7	12.66	8.26	66

$$\chi^2_{(4)} = 10.71 \quad 0.05 > P > 0.02.$$

*From the Registrar General: Annual Reports for the United Kingdom (1961).

greater number of mothers over the age of 30 years; there are also more mothers in the 15-19 years age group, or fewer mothers in the 20-29 years age group than expected. No significant effect was observed in the parity of the index patient; the effect of maternal age is a direct one, unrelated to parity.

Other epidemiological findings. There were no significant findings with regard to social class, the observed and expected figures being almost equal. The number of births in the winter and summer were equal. In 37.5% of cases the mother thought that fetal movements were reduced compared with other pregnancies, or were absent altogether. However, 7 mothers (10.9%) thought that fetal movements were much increased.

Data were available on length of gestation in 63 cases and in 9 of them (14.3%) gestation was less than 38 weeks. In 16 cases (25.4%) it was 42 weeks or over. Both these proportions were significantly different in comparison with the control data from the Edinburgh Register of the Newborn (6.4 and 12.3% respectively). There was a preponderance of breech births or version late in

pregnancy (21 of 66 cases, 33%), greater than an expected figure of 2-3%. The patients were significantly below the expected weight of 3376 g (7.44 lb), the mean being 2994 g±680 SD (6.6 lb±1.5). This is probably related to the absent musculature.

Complications of pregnancy.

Possible oligohydramnios. There was a history of possible oligohydramnios in 19 cases (29.7%), but medical confirmation could not generally be obtained. A typical remark made by these mothers was, 'I wore normal clothes throughout pregnancy'.

Bleeding during pregnancy. A history was available for 64 patients and bleeding was noted during the first trimester in 9 of them and at a later stage in 3 others (18.8% in all). This is significantly higher than in the normal population (6.7%) but it is known that a mother who has had an abnormal baby is more likely to give such a history and the apparent increase is not necessarily reliable. Data from the Edinburgh Register of the Newborn were used, therefore, to note the proportion of pregnancies in which the mother recollected bleeding in the first trimester or later when the child was born with clubfoot or congenital dislocation of the hip alone (similar deformities to arthrogryposis). There were 39 of 277 mothers who gave such a history (14.1%), which is not significantly different from the arthrogryposis figures.

Other complications. There were a number of other adverse factors or complications of pregnancy (Table II), which taken as a whole, are considerably greater than those found in any other congenital malformation survey completed from the Orthopaedic Department in Edinburgh. Almost certainly there were three instances of ineffectual attempts at abortion, perhaps more.

Deaths. 6 patients died either during or shortly before the period covered by this survey. (2 of gastroenteritis aged 9 and 16 years; 4 of pneumonia aged 9 months, 16, 20, and 39 years, the latter being also a chronic alcoholic.)

Activities. It has been stressed by many authors (Mead, *et al.*, 1958; Lloyd-Roberts and Lettin, 1970) that these patients are often highly intelligent and make courageous attempts to overcome their deformities, and this was confirmed in the present survey. Only 4 of the 66 patients were mentally retarded; the great majority were

TABLE II
Complications of pregnancy in mothers of infants with arthrogryposis

Record no.	Mother's age	
1	16	Bleeding at 30 w, leaking liquor for last 2 months, ? attempted abortion
6	38	Very anaemic throughout pregnancy; cyanocobalamin injections; retained placenta
8	31	Bleeding at 5 m; severe toxæmia and in hospital from 10 w to end of pregnancy; oligohydramnios confirmed
24	36	Previous operation for a bicornuate uterus, 3 previous abortions; bleeding at 12 and 16 w; taking stilboestrol from 8 w onwards
29	29	Threatened abortion at 12 w; probable oligohydramnios; retained placenta
30	30	Severe oligohydramnios; given large doses of diuretics at 20 w (because of a previous stillbirth associated with severe toxæmia of pregnancy)
38	20	Toxæmia—in hospital for last 6 w
40	35	Continuous bleeding for first 12 w, oligohydramnios confirmed: mother took several 'abortion drugs'
44	21	Threatened abortion at 30 w; probable hydramnios; leaking liquor for last 2 w
46	36	Oligohydramnios; 'a lot of medication for migraine'
47	40	Threatened abortion at 14 w; hormone injections; hydramnios at 30 w
49	20	Threatened abortion twice at 8 and at 16 w
56	35	Bleeding around 8 w, after injections 'to bring period on'; bleeding again at 16 weeks
57	30	Menstruation only once a year after birth of first child—index patient was third
68	41	Continuous bleeding for first 3 m of pregnancy and on 'tablets'; subsequently found she was pregnant; hysterectomy for fibroids within a year of birth of patient

attending, or had attended, normal school and were noted as bright and intelligent. A favourite out-of-school activity was swimming, some patients being surprisingly expert. 18 patients over the age of 18 years were not mentally retarded, and all but 3 were employed full-time. One of those 3 died at the age of 20 years from bronchopneumonia after being completely bedridden and suffering from appalling contractures. He did not attend for treatment until he was fully grown. A woman of 24 years was unemployed, but helped her mother with housework. Only one male, aged 43 years, lived in an institution, but was in good health and able to do handiwork. He had only had occasional lessons from a teacher at home or while in hospital.

Discussion

Since only clinical diagnosis is possible in arthrogryposis multiplex congenita, there is no certainty that this survey is of a homogeneous group, in

spite of the care taken to ensure this. Clearly most cases of this disease must be nongenetic in origin. The 'myogenic' type described in published reports was not seen and must therefore be very rare in clinical practice, and of different aetiology since it is reported as of autosomal recessive inheritance. One must accept quite a large body of evidence describing lack of anterior horn cells at necropsy, though it is not often possible to confirm or refute this in any one patient, and none of the patients who died in this survey had a post-mortem examination. Also, it is not known whether this absence of anterior horn cells is a primary defect, or only secondary to the absence of muscles supplied by these nerves. The similarity of these findings to those caused by postnatal infection with the poliomyelitis virus may be significant, particularly in view of the high incidence of arthrogryposis in South Australia. The population there is essentially European-derived and it is likely there is some local environmental factor giving rise to the disorder.

If arthrogryposis were aetiologically related to other structural deformities, such as talipes equinovarus and congenital dislocation of the hip (which are of multifactorial inheritance), one would expect to find an excess of these conditions in the families of patients. This was not so, and it is concluded that arthrogryposis multiplex congenita is an aetiological separate group.

This survey confirmed others in finding some examples of oligohydramnios, reduced fetal movement, and breech presentations—three factors likely to be linked—but such a history could only be obtained in less than one-third of cases and was not medically confirmed even in all of these. It is likely that arthrogryposis can be caused by whatever factors produce oligohydramnios, but apparently more often occurs without clinical evidence of this.

Other complications of pregnancy occurred and it seems that many arthrogryptic fetuses have a very unfavourable start to life for many different reasons. Retrospective history taking is notoriously unreliable when a mother has had an abnormal baby, but where possible medical confirmation was obtained. Taken as a whole there were many more adverse types of pregnancy history in this survey than expected, including a significant excess of older than average mothers. There are probably many different causes of arthrogryposis, and it may be that the unfavourable intrauterine environment is hormonal, is related to an inadequate fetal blood supply or to mechanical factors and oligohydramnios only, or perhaps sometimes to ineffectual attempts at abortion and (or) some prenatal viral infection similar to poliomyelitis.

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