THE 1960s EPIDEMIC OF ARTHROGRYPOSIS MULTIPLEX CONGENITA

A SURVEY FROM THE UNITED KINGDOM, AUSTRALIA AND THE UNITED STATES OF AMERICA

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Arthrogryposis multiplex congenita is believed to be a specific clinical entity which is aetiologically unrelated to the "arthrogryposis-like" deformities of known neurological diseases such as myelomeningocele and myelodysplasia. The observation that the condition appeared to be three times as common in Melbourne, Australia, as in four centres in the United Kingdom (Wynne-Davies and Lloyd-Roberts 1976), prompted this survey of 132 patients: 73 from the United Kingdom, 34 from Australia and 25 from Wilmington, Delaware, USA. The survey aimed to establish the same criteria for diagnosis in the three countries and to search for prenatal and genetic aetiological factors. It was shown that all centres treated more newborn children with this disorder during the 1960s than either before or after that period. All cases were sporadic and there was no family association with talipes equinovarus, congenital dislocation of the hip or hereditary neuromuscular disease. "Environmental" findings from all three centres were similar and it was concluded that arthrogryposis multiplex congenita is a non-genetic disease of early pregnancy, associated with a variety of unfavourable intra-uterine factors. In addition, an unknown but possibly viral environmental agent may have been present to a significant extent only during recent decades and is now declining.

It is unfortunate that the term "arthrogryposis" is frequently used to mean virtually any skeletal dysplasia, syndrome or developmental disorder in which there is contracture or stiffness of joints. Arthrogryposis multiplex congenita as defined here is believed to be a specific clinical disorder in which there is extreme stiffness and contracture of joints with absence of muscle development around them. It is present at birth and neither improves nor worsens with age, though untreated deformities progress with the growth of the child (Figs 1 to 3). The normal contours of affected limbs are lost, skin creases are absent and the limbs appear to be nearly cylindrical. Associated deformities are common and include dislocation of the hip, club foot and scoliosis, as well as flexion contracture of some joints, though others may be fixed in extension.

The term "arthrogryposis-like" is reserved for similar deformities resulting from recognised neurological disease such as myelomeningocele and myelodysplasia, in which the limb disorders are clearly paralytic in

origin. Such patients have been excluded from the survey. An arthrogryposis-like condition also occurs in Potter's syndrome where there is agenesis of the kidneys and severe oligohydramnios. These infants are stillborn and have also been excluded.

Clinicians dealing with children suffering from arthrogryposis multiplex congenita over many years of growth and development are firmly convinced of the existence of a distinct and separate clinical entity, even though minor degrees of the condition may be indistinguishable from other disorders such as the Freeman-Sheldon syndrome. This survey therefore includes only severely affected individuals in whom the condition was clearly defined and unmistakable.

Theories of causation. It is likely that there is a rare primary *myogenic* type of arthrogryposis multiplex congenita which is a congenital non-progressive muscular dystrophy of autosomal recessive inheritance (Banker, Victor and Adams 1957), though no case has been observed by any of the present authors. The great

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Fig. 1

Fig. 2

Fig. 3

Photographs of patients suffering from arthrogryposis multiplex congenita in infancy, childhood and as an adult. The adult patient did not present at hospital until he was 21 years of age, and shows the appalling increase in deformity that can occur in the untreated patient during growth.

majority of cases are sporadic and some reports suggest a primary *neurogenic* disorder of the anterior horn cells. However, evidence is usually incomplete, electromyographic studies being inconclusive because of the absence of muscle (Kanof, Aronson and Volk 1956; Drachman and Banker 1961; Vestermark 1966; Bharucha, Pandya and Dastur 1972; Dastur, Razzak and Bharucha 1972).

Arthrogryposis is sometimes associated with prolonged intra-uterine immobilisation of the foetus with oligohydramnios, a theory being that severe compression results in total failure of muscle development (Browne 1955; Dunn 1969). Reduced amounts of amniotic fluid and foetal malposition have frequently been reported in this condition. It can be noted only that they are sometimes associated, but not necessarily causative. Casey and Ger (1979) have noted dermatoglyphic abnormalities in arthrogryposis, suggesting there must be an early prenatal pathogenesis.

Jago (1970) reported a child born with arthrogryposis following treatment of maternal tetanus with muscle relaxants. More recently Smith, Clarren and Harvey (1978) have suggested hyperthermia in early pregnancy as a possible teratogenic agent, and Edwards (1971) has produced the disorder experimentally in guinea-pigs by inducing maternal hyperthermia during gestation.

It is of interest that an apparently identical condition occurs in sheep (Roberts 1929), cattle, and

horses, with good circumstantial evidence that it is caused by infection of the mother by the Akabane virus during early pregnancy quoted by Williams in 1978. This virus was first isolated in Japan and has since been recovered from affected animals in Israel and Australia. Definite confirmation of the relationship between the virus and the disease awaits experimental production of the disease in cattle, but the virus has been inoculated into ewes and does and affected offspring have resulted. Whittem (1957) studied the disease in calves and suggested that the primary abnormality, whatever its cause, was degeneration of the anterior horn cells in the early months of gestation. This results in destruction of muscle fibres in the foetus, with some muscles being affected earlier or more severely than others. Muscle tone is lost and there is failure to balance the normal tone of antagonists. This restricts the movement of muscles and joints during the intra-uterine period of rapid growth, leading to partial fixation of joints and the development of shortened ligaments and other peri-articular tissues, thus producing the typical clinical changes of arthrogryposis.

A search for prenatal factors in 66 cases of arthrogryposis multiplex congenita was reported by Wynne-Davies and Lloyd-Roberts (1976). All cases were found to be sporadic and there was no family association with club foot, congenital dislocation of the hip or hereditary neuromuscular disease. It was concluded that most cases were non-genetic and

resulted from a defective intra-uterine environment which could be hormonal, vascular, mechanical or possibly infective. It was noted during this survey that the population frequency in Melbourne, Australia, appeared to be about three times as high as that in each of four different centres in the United Kingdom.

The aims of this survey were to investigate the Australian patients and their families, to add a further group from the USA and to establish that the same criteria for diagnosis were being used in all centres. It was also hoped that the finding of differing prenatal or genetic factors in Australia would throw some light on the aetiology of the disorder.

MATERIAL AND METHOD

A total of 132 patients were included in the survey, 73 were from five orthopaedic centres in the United Kingdom, 66 of them having been previously reported (Wynne-Davies and Lloyd-Roberts 1976). There were 27 from the Hospital for Sick Children, Great Ormond Street, London, 25 from Princess Margaret Rose Orthopaedic Hospital, Edinburgh, nine from the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, seven from Harlow Wood Orthopaedic Hospital, Nottingham and five from the Royal Hospital for Sick Children, Glasgow. Twenty-five patients were from the Alfred I. duPont Institute, Wilmington, Delaware, USA, and 34 from Australia, comprising 25 from Melbourne, Victoria, five from Adelaide, South Australia and four from Tasmania.

Several patients at first diagnosed as having arthrogryposis multiplex congenita were excluded on further investigation. The main difficulties arose in myelodysplasia, muscular dystrophies of postnatal

onset, the Freeman-Sheldon syndrome, and both metatropic and diastrophic dwarfism. To exclude the possibility of undiagnosable myelodysplasia, all patients included in the survey had involvement of three or four limbs or of both upper limbs.

Great care was taken to ensure as far as possible that the patients formed a homogeneous clinical group. All have been recently examined by one of the authors and the Melbourne patients by two of the authors (PFW and RWD). Information relating to the pregnancy, including illness, drugs, threatened abortion, oligohydramnios, gestation length and birth weight was obtained from the mother in most cases. The parental age and position of the index patient within the family were noted, as were seasonal incidence and social class and income group based on the occupation of the father. Associated anomalies in the patient and developmental anomalies in first, second and third-degree relatives were recorded. Results from the different centres were compared with each other and where possible with local control figures.

RESULTS

Numbers attending orthopaedic clinics. It is difficult to establish the true population incidence of arthrogryposis multiplex congenita. A survey from Helsinki (Laitinen and Hirvensalo 1966), noted 11 cases in 36 900 total births (3 per 10 000) which is a considerably higher incidence than that recorded in the Edinburgh Register of the Newborn (1964-68), of only one case in 56 029 total births (0.19 per 10 000). It is considered likely in such a severe and difficult congenital disorder that the orthopaedic centres concerned would be treating all patients in their area and that, with the exception of deaths during the first year of life, ascertainment is likely

Fig. 4

Histogram showing the number of patients with severe arthrogryposis presenting at five centres in the United Kingdom, at Wilmington, Delaware, USA, and in Melbourne, Australia, from 1940 to 1976. The figures can only be minimum ones but the increased frequency between 1955 and 1970, with a subsequent decrease, is well shown.

to be nearly complete. There is no evidence for a reduced life span after the first year (Hansen 1968). It was thought that the numbers presenting at clinics over the years since hospital disease indexing systems were established would be of interest, although they must be considered to be minimum figures. For this reason hospital records were searched from the 1940s to the end of 1976, and cases which satisfied the criteria used for the main survey are added in Figure 4.

These histograms show few cases in the early years, a sharp increase in the late 1950s and 1960s, with a subsequent decline in numbers during the 1970s. The peak years for the United Kingdom centres started in about 1957 and included the next 12 years, whereas in Melbourne, and among fewer cases in Wilmington, the peak started two years later in 1959. Epidemiological and possible prenatal environmental factors were analysed separately for these peak periods (1957–69 for the United Kingdom and 1959–71 for the other two centres), and for the periods before and after the peak years, in a search for any differences.

Sex ratio. There were 79 males and 53 females affected in all centres—with a sex ratio for the United Kingdom and Australia of 1.4 and for Wilmington 2.0.

Associated anomalies. The associated anomalies of dislocation of the hip and knee, club foot and scoliosis in the involved patient are likely to be secondary to the joint contractures and absent musculature, and were not noted. Other anomalies were found. Ten patients had inguinal herniae, four of them also with undescended testicles. Seven patients showed micrognathos, five had a lateral and one a central cleft palate, this latter deformity being of autosomal dominant inheritance in that patient's family. Two patients had a high arched palate, six had mental retardation and four showed minor absence defects at the ends of the fingers or toes with deformed nails. Ventral septal defect, absent radius and fibula, vaginal cyst, and multiple narrowed intervertebral disc spaces with fused vertebrae were recorded, each in only one patient.

Genetic factors. All 132 cases were sporadic, no other case being known amongst 532 first-degree relatives. There was one possibly affected second-degree relative—the 48-year-old maternal aunt of a Melbourne patient had mild involvement of both upper limbs but no other defects, and in whom the diagnosis must be in doubt. There was no affected third-degree relative among first cousins only. Thus the survey revealed only one doubtfully affected second-degree relative amongst a total of 3266 individuals. There was no instance of consanguinity in the survey.

The occurrence of muscular dystrophy or inherited neuromuscular disease was not confirmed in any family, though one paternal uncle of an Australian patient had died at the age of two years allegedly with muscular dystrophy and "some sort of hydrocephalus". The father of one American patient had contractures of the fingers

Table I. Maternal age distribution in arthrogryposis multiplex congenita

	Maternal age in years				Total numbers
	15–19	20–24	25–29	30+	
<i>United Kingdom</i>					
Observed	7	20	14	32*	73
Expected†	4.52	22.44	22.90	23.14	73
<i>Australia</i>					
Observed	2	6	13	13	34
<i>Wilmington</i>					
Observed	1	5	7	12	25
Total—number per cent	10 7.6	31 23.5	34 25.8	57 43.2	132

* $\chi^2=8.48$; d.f.=3; $0.05>P>0.025$. Probably significant.

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

which were also reported in three paternal uncles. This minor isolated deformity is known to occur as an autosomal dominant, as it appears to be in this family. There was no case of talipes equinovarus amongst first- or second-degree relatives and only one amongst the third-degree relations, which corresponds with the expected frequency for a random population survey. Congenital dislocation of the hip occurred in one first-degree, two second-degree and one third-degree relative, again not a significantly greater incidence than that expected from a random survey.

Other developmental disorders in the families showed no particular pattern, nor was any one anomaly of greater frequency than might be expected from a survey of over 3000 individuals. There was only one twin pair in the whole survey—an unexpectedly small number. Both twins were female, but they were dizygous and only one was affected.

Parental age. The United Kingdom, Australian and American figures were very similar, with no significant differences between them. There was a mean maternal age of 29.11 ± 0.58 years and a mean paternal age of 32.08 ± 0.67 years. Precise comparison with controls is only available for the United Kingdom centres, but the fewer cases in Australia and Wilmington follow a similar pattern, and it is likely that the maternal age is significantly higher than in the general population. The distribution of maternal ages is shown in Table I, and it is seen that 43 per cent of the mothers were over 30 years old at the time of the birth of the affected child, while the expected figure for the United Kingdom is only 31 per cent. The mean parental age difference was 2.97 ± 0.33 years which is not significantly different from the expected United Kingdom figure. No significance was observed in the position of the index patient within the family. There were no significant findings from any

centre with regard to family income group or seasonal incidence. Previous abortions (15 per cent) and stillbirths (two per cent) of all conceptions corresponded to the expected figures for the general population.

Gestation period. This differed from normal figures, with an excess both of premature infants and of postmature infants. The three countries again showed very similar figures. Fourteen per cent had a gestation of under 38 weeks and 24.8 per cent had a gestation of 42 weeks and over. The latter period is likely to be associated with the low birth weight of the child and with reduced foetal movement. Index patients had a mean birth weight of 2973 ± 57 grams (6.56 ± 0.125 pounds) which is significantly below the expected mean birth weight of 3376 grams (7.44 pounds). This is probably related to the absent musculature.

Presentation and pressure effects. There was an excess of malpresentation, again approximately equal in the three countries. This was usually a breech presentation, which was recorded in 36.9 per cent of patients, as against an expected figure of two to four per cent. There was a history of possible oligohydramnios in 25.7 per cent of patients from the United Kingdom and Australia but this information was not available from Wilmington. Medical confirmation could not generally be obtained, but a typical remark made by the mothers was "I wore normal clothes throughout pregnancy". It was, however, quite clear that oligohydramnios did not invariably accompany arthrogryposis. The maximal incidence in this survey could only be about one in four cases.

Other complications of pregnancy. A history was available for the mothers of 130 patients. Bleeding was noted during the first trimester in 24 of them (18.5 per cent), with no significant difference between the three countries. This figure is greatly in excess of that expected for the normal population (about seven per cent), but the retrospective history taken some time after the pregnancy concerned may not be wholly reliable. Four mothers reported leaking of liquor throughout pregnancy. There was an unusually high incidence of other adverse factors or complications in all three centres and these are listed in Table II in order of the year of birth of the child. Accounts of drugs taken during the early weeks of pregnancy are only recorded where the information is thought to be accurate.

DISCUSSION

Arthrogryposis multiplex congenita can only be a clinical diagnosis and it must remain uncertain that this survey is of a homogeneous group of patients. However, by restricting it to severely involved individuals it seems likely that a fairly definite clinical group has been obtained. The findings of the 1976 United Kingdom survey were confirmed both in Wilmington, Delaware, and in the Australian patients. With the doubtful

exception of one second-degree relative, all cases were sporadic, and there was no family association with congenital talipes equinovarus, dislocation of the hip or hereditary neuromuscular disease. Arthrogryposis multiplex congenita as here defined must clearly be a non-genetic disorder unrelated to the "myogenic" type which is reported to be of autosomal recessive inheritance. If arthrogryposis were aetiologically related to the congenital structural deformities of talipes equinovarus and dislocation of the hip, which are of multifactorial inheritance, one would expect to find an excess of these in the families of patients. Since this was not so, it is concluded that patients with arthrogryposis multiplex congenita belong to a separate aetiological group.

In the absence of genetic factors, search must be made for intra-uterine environmental abnormalities, and here there was considerable evidence. The findings were much the same in all three centres, in that the mothers were older than average and nearly one in three of them reported some abnormality or complication of the pregnancy, often in association with hormone therapy. It seems likely that without the aid of hormones many of these children would have aborted in early pregnancy. This could account in part for the "bulge" of cases seen in the late 1950s and 1960s when such treatment was common.

It is difficult to know how relevant, or even reliable, are the maternal histories; but the complications reported are remarkably consistent: elderly mothers, threatened abortions, leaking liquor, hormone therapy and instances of obvious uterine disease or deformity sometimes followed by hysterectomy within a year of the birth of the affected child. There were three or four instances of ineffectual attempts at abortion early in the pregnancy. It is often stated that retrospective history taking from the mother is unreliable in that she is likely to remember wrongly or to give undue importance to minor incidents, because she has had a deformed child. However, some of the complications over-enthusiastically remembered in this type of survey were conspicuously absent; to give examples, no statements were obtained relating to high blood pressure, toxæmia of pregnancy, pyelitis, or to upper respiratory tract or other infections.

Reliable statistical evaluation is impossible but it should be noted that nearly one in three mothers reported some abnormality of pregnancy. Even allowing for retrospective history-taking and errors of memory, this is a remarkably high proportion in comparison with that found in the maternal histories of children with other congenital malformations. Only about one in 14 of these mothers gives such a history (RWD, unpublished data).

The particularly high number of patients from the Melbourne area (25) was analysed separately, but there were no differences in the epidemiological findings

Table II. Complications of pregnancy in mothers of infants with arthrogryposis

Year of birth of patient	Age of mother	Complications of pregnancy
1942	46	Leaking liquor early in pregnancy
1947	28	Bicornuate uterus
1950	40	Bleeding at 14 weeks. Hormone injections. Hydramnios at 30 weeks
1951	33	Oligohydramnios. "A lot of medication for migraine"
1957	20	Bleeding at 8 and at 16 weeks
1958	38	Very anaemic throughout pregnancy. Cyanocobalamin injections. Retained placenta
1959	26	Bleeding throughout pregnancy which was mostly spent in bed. Bicornuate uterus. Hormones from 2 months onwards
1960	31	Bleeding at 5 months. Severe toxæmia, in hospital from 10 weeks to end of pregnancy. Oligohydramnios confirmed.
1960	35	Bleeding around 8 weeks after injections "to bring period on". Bleeding again at 16 weeks
1961	30	Severe oligohydramnios. Large doses of diuretics at 20 weeks because of a previous stillbirth associated with severe toxæmia of pregnancy
1961	35	Continuous bleeding for first 2 months. Bicornuate uterus.
1962	30	Menstruation only once a year after birth of first child. Index patient was third child
1963	16	Bleeding at 30 weeks, leaking liquor for last two months. Possible attempted abortion
1963	29	Bleeding at 12 weeks. Probable oligohydramnios. Retained placenta
1963	35	Continuous bleeding for first 12 weeks. Oligohydramnios confirmed. Mother took several "abortion drugs"
1963	28	Bleeding at 10 weeks
1963	39	Bleeding at 2 months. Hormones throughout pregnancy
1963	28	Bleeding in first trimester
1963	25	18 weeks in hospital for severe asthma with much medication
1964	36	Previous operation for bicornuate uterus. Three previous abortions. Bleeding at 12 and 16 weeks. Hormones from 8 weeks onwards. Retained placenta
1965	21	Bleeding at 30 weeks. Probable hydramnios. Leaking liquor for last 2 weeks
1965	33	Bleeding from 2 to 6 months. In bed until 7th month. Hormone injections twice a week from 2 months.
1965	44	Treated with hormones for the menopause before discovering she was pregnant
1966	24	Bleeding at 8 to 12 weeks
1967	27	Bleeding continuously throughout pregnancy. Hysterectomy for fibroids within a year of birth of child
1967	41	Continuous bleeding for first 3 months of pregnancy while on hormones. Pregnancy diagnosed later. Hysterectomy for fibroids within a year of the birth of child
1968	25	Bleeding at 8 weeks
1968	34	Appetite depressants for first 4 to 5 months
1968	22	Bleeding at 18 weeks
1968	32	Bleeding at 3 months. Given hormones
1970	28	Bleeding at 12 weeks followed by leaking liquor. Hormone injections for the next 3 months. Bleeding again at 6 months and in hospital for 6 weeks
1970	25	Bleeding at intervals throughout pregnancy which was mostly spent in bed. Hormone injections early. Before pregnancy was diagnosed nasal sinuses were drained, followed by severe secondary haemorrhage, readmission to hospital and "injections for bleeding"
1971	20	Bleeding at 6 to 8 weeks
1972	28	Bleeding and hormones for first 4 months
1972	31	Bleeding throughout pregnancy. Bicornuate uterus
1973	30	Partial hysterectomy 2 months after birth of child
1974	25	Hysterectomy for infected ovaries and excessive bleeding one year after birth of child
1975	27	Leaking liquor from 18 weeks
1976	30	Bleeding continuously up to 5 months. Hormones for whole of pregnancy

between these and the other Australian patients, or the patients from Wilmington or the United Kingdom. The only figures which approached statistical significance were the numbers of mothers with threatened abortions and associated hormone therapy in the Melbourne area which were nearly twice the number of Wilmington patients and three times the number of United Kingdom patients. There was no evidence to implicate hyperthermia, associated with either maternal infection or with the climate, since there was no seasonal variation in incidence. No significant differences could be found in epidemiological factors either preceding or succeeding the years of peak incidence.

The theory that the disorder is caused by, or is always associated with, oligohydramnios is not borne out by this survey. There were some instances of this, but in three-quarters of the mothers there was no evidence of any pressure abnormality. It is likely that arthrogryposis *can* be caused by some factors which may also produce oligohydramnios, but apparently in most cases there is no evidence of this.

It seems that arthrogryposis multiplex congenita must be a disorder of fairly recent origin. Even allowing for the inadequacy of hospital disease indexing systems in the earlier years, it is remarkable that no middle-aged or elderly patients are seen in present-day adult clinics. This agrees with Davidson and Beighton's (1976) observation from South Africa that the great majority of their patients were under the age of 24 years—that is, that the South African "epidemic" started in about 1952. This apparently "new" onset of the disorder, or at least the excessive numbers reported, is not accounted for, but speculation must include prenatal, possibly viral, infection. All that is certain is that arthrogryposis multiplex congenita is an environmental disease of early pregnancy, associated with one or more of a variety of unfavourable intra-uterine factors which include structural uterine deformity, vascular abnormality, hormonal imbalance, increased pressure and possibly intra-uterine infection; and that an unknown environmental agent has probably been present to a significant extent only during recent decades, and that it is currently declining.

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