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Arthrogryposis Following Treatment of Maternal Tetanus with Muscle Relaxants

Case Report

A 29-year-old woman was admitted to the University College Hospital of the West Indies, on 3 February 1966, nine days after an attempted instrumental abortion, suffering from severe generalized tetanus, with a continuing intrauterine pregnancy of from 10 to 12 weeks' duration. The disease ran a severe course, necessitating curarization and prolonged mechanical ventilation. The details of the drugs administered are summarized in the Table.

The patient was readmitted to the obstetrical unit on 6 September 1966, and the next day was delivered spontaneously of a living male infant, weighing 3·56 kg., after a first stage labour of 5 hours 30 minutes, and a second stage labour of 20 minutes. At no time were there signs of fetal distress. The placenta and membranes were delivered intact; the placenta showed some calcification and a few small infarcts, but was of normal weight.

The infant was examined on 30 September. The posture and over-all appearance are shown in the Fig. Head circumference 36 cm., crown heel length 48 cm. A normally active male baby within the limits of the rigidities. Low forehead, small lower jaw, and short neck and lateral webbing. Right sternomastoid tumour. Bilateral gynaecomastia. Chest, heart, and lungs normal. Both flanks bulge paradoxically on straining, more so on the left. Left indirect inguinal hernia. No abnormality of the back.

Over-all limb proportions normal. The abnormal joints showed typical arthrogrypotic features, with flail movement over a given range, limited by solid, slightly springy blocks to further movement. Both scapulae high. Glenohumeral abduction to 70°, further scapular movement 20°. Flexed webbed elbows, extension to within 80° of full range. Wrists and fingers held flexed, but normal ranges of joint movement against tight flexor muscles. Fingers normally developed. Thumbs held opposed and adducted across the palms.

Normal pelvis. Both hips irreducibly anteriorly dislocated, in 70° external rotation and slight flexion, further flexion range 20°, other movements very limited. Stable knees held slightly flexed, no skin creases, extension to within 5° of full range, flexion to 90°.

Severe talipes equinovarus, lateral skin dimples, forefoot and toes fully developed. Radiographs confirmed the dislocations of the hips. The number of cervical vertebrae was normal. The bone morphology was normal.

Discussion

This infant showed the deformities of arthrogryposis multiplex congenita, of the so-called, and more common, 'neurogenic' variety. Opinion is now hardening to the view that this condition is the end result of a number of pathological processes which immobilize the fetal limb at some period during, or shortly after, the formation of the joints (Drachman and Banker, 1961), and arthrogryposis has been produced in chicks by intravenous curarization *in ovo* for periods of 24–28 hours between the 7th and 15th day of incubation (Drachman and Coulombre, 1962). Necropsies in the 'neurogenic' cases have shown lesions in the central nervous system which all interrupt the final motor pathway, the most common being a selective depopulation of the anterior horn cells of the spinal cord and brain-stem, at levels appropriate to the muscles and joints affected. This is thought to be

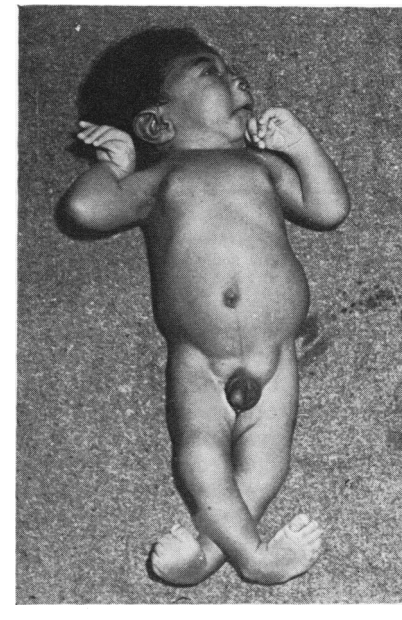

FIG.—*Posture and appearance of infant.*

TABLE

Daily Total Doses of Drugs Administered to the Mother (mg.)

Day No.	d-Tubocurarine	Diazepam	Chlorpromazine	Digoxin	Hydrochlorothiazide	Antibiotics†	Sedatives‡	Ventilation	Spasms	Conscious Level§
1	125 iv					a	z	Continuous	Numerous	3
	60 im									
2	240 im					a	z		Numerous	
3	210 im	40 oral				a			Moderate	4
4	150 im	200 oral				a			Moderate	
5	90 im	240 oral				a	z′		Moderate	
6	180 im	120 oral		0·5 iv	100 oral	a			Moderate	5
	15 iv	20 im								5
7	90 im	40 im		0·125 iv		b			Moderate	5
				0·125 im						
8	30 im	40 im		0·25 im		b			Few	2
		10 iv								
9	1	10 im		0·25 im		b			Nil	
10	30 im	10 im		0·25 im		b			Few	
	60 im	40 oral								
11		120 oral	100 oral	0·25 oral	100 oral	c			Few	
12		160 oral	200 oral	0·5 oral		c			Few	
		40 im							Few	
13		120 oral	300	0·5	100	c			Few	
14		240 oral	200	0·75		c			Few	
15		240	200	0·75	100	c			Few	
16		240	200	0·75		c			Few	
17		200	200	0·75	100	c			Few	
18		180	200	0·75		c		Weaning	Few	
19		120	200	0·75	100	c			Nil	
20		120	200	0·75		c			Nil	
21		120	200	0·75	100				Nil	
22		60	200	0·75					Nil	
23		60	200	1·0	100			50%	Nil	
24		60	200	0·5						
25		60	200	0·5				Night only		1
26		60	100	0·5						
27		60	100	0·5						
28		60	50	0·5						
29		60		0·5			y	Off		
30		60		0·5			y			
31		50	50	0·5						
		10 im								
32		50 oral	50	0·5						
		10 im								
33		50 oral		0·5						
34		40 oral		0·5			y			
35		40	50	0·5						
36				0·5*				Tube out		

*Discontinued 13 March.
†a, crystalline penicillin 4 megas; b, a + streptomycin 1 g.; c, tetracycline 1 g.
‡z, sodium amytal 750 mg.; z′ sodium amytal 250 mg.; y, chloral hydrate grains 30.
§1, fully conscious; 2, sleeping but rouses to answer questions; 3, responds to simple commands; 4, responds to stimulation; 5, unconscious.

due to a degenerative process which begins after the formation of the nervous tissue, but which has largely burnt out by term. Muscle biopsies in surviving cases have been interpreted as showing the changes of denervation atrophy. This form of the disease is not inherited, and is associated with no retrospectively recognizable disease in the mother.

This same degenerative process, though rare, may have occurred in this fetus unconnected with the events of the pregnancy, and would be distinguished in a muscle biopsy at future surgery. In this case, however, there are other possible causes.

Maternal insults. The mother suffered several episodes of severe hypoxia during the course of her illness, as well as bronchopneumonia and myocarditis.

Tetanus toxin. The principal tetanus toxin is a protein of a molecular weight of about 72,000, whose main action is to reduce the likelihood of the release of transmitter substance (which is probably acetylcholine) on the arrival of the spike impulse at the endings of the inhibitory neurones acting in the motor pool of the spinal cord. A similar, though clinically less apparent, effect has been

demonstrated at myoneural junctions. Though proteins of this size can be transmitted to the fetus intact, the process is usually selective. However, absorption of tenanus toxin by the fetus from the uterine lumen has been shown in some species, and direct infection of the fetus, though almost certainly incompatible with fetal survival, cannot be entirely excluded. Nevertheless, it is unlikely that a toxin of this physiological specificity, even if it reached the fetus, would have any effects additional to those seen in the adult. There are several published reports of pregnancies surviving maternal tetanus in one of which the tetanus occurred at the end of the first trimester and in no case did an abnormal fetus result.

Drug-induced paralysis. The evanescence of effect of a single dose of d-tubocurarine depends on the diffusion of the drug away from the end-plate and its redistribution throughout the extracellular space, from which it is slowly removed. Repeated administration of the drug may saturate this space, and the duration of action come to depend on the rate of its excretion and destruction. Furthermore, in these circumstances, considerable fetal accumulation of the drug is to be expected, whereupon the same factors prolonging paralysis would operate.

This view is confirmed by a recent case report (Older and Harris, 1968), in which a mother, under treatment for status epilepticus with curarization and controlled ventilation, was delivered of a 28-week fetus which was heavily curarized. In the current case the mother required continuous ventilation for 19 days, and it is probable that the fetus was paralysed for a comparable period, due to the action of d-tubocurarine, supplemented by diazepam and chlorpromazine.

Conclusions

While there are several possible causes for this infant's arthrogryposis, drug-induced immobilization of the fetus at the time of or shortly after the development of the joint cavities seems the most probable.

The severity of the deformities of this infant, and ubiquity of the drugs that may have caused them, would probably justify a review of the prolonged administration of relaxant drugs to women in the first trimester of pregnancy.

Summary

An infant with arthrogryposis was born to a mother who had been treated with d-tubocurarine in early pregnancy. The arthrogryposis is attributed to immobilization of the fetus at the time of joint formation.

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R. H. JAGO*

St. George's Hospital, Tooting Grove, London S.W.17

*Formerly Registrar, Department of Orthopaedic Surgery, University College Hospital of the West Indies, Mona, St. Andrew, Jamaica.

Dermatitis Herpetiformis in a Treated Coeliac Child

The relation between dermatitis herpetiformis (DH), structural and functional abnormalities of the small intestine, and coeliac disease with gluten sensitivity remains uncertain. It is well established that DH may be accompanied by malabsorption, and that such cases have abnormalities of the small intestinal villi of variable degree (Marks, Shuster, and Watson, 1966; Fraser, Murray, and Alexander, 1967; Fry *et al.*, 1967; van Tongeren, van der Staak, and Schillings, 1967; Marks *et al.*, 1968). Furthermore, malabsorption may precede the characteristic eruption of DH by several years (Fraser, Ferguson, and Murray, 1968). The importance or even relevance of these observations to gluten sensitivity is less clear, since the degree of villous atrophy found in DH may fall far short of subtotal villous atrophy which is the diagnostic essential in gluten sensitive coeliac disease. Nevertheless, gluten withdrawal may benefit the malabsorption syndrome of DH (van Tongeren *et al.*, 1967; Marks *et al.*, 1968; Fraser *et al.*, 1968), and gluten sensitivity has been demonstrated in the small intestinal mucosa (Shuster, Watson, and Marks, 1968). In addition, improvement in the skin manifestations of DH has been noted in some patients on a gluten-free diet (van Tongeren *et al.*, 1967; Marks *et al.*,