Fetal damage after accidental polio vaccination of an immune mother

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SUMMARY. Irreparable damage to the anterior horn cells of the cervical and thoracic cord was found in a 20-week-old fetus whose mother was immune to poliomyelitis before conceiving but who was inadvertently given oral polio vaccine at 18 weeks gestation. Polio neutralizing antibody titres in sera, taken before and after pregnancy, were identical and were at levels normally regarded as providing protection. Unsuccessful attempts were made to isolate poliovirus from extracts of fetal brain, lung, liver and placenta. Fluorescent antibody tests were performed on various levels of the central nervous system and on the left and right extensor forearm muscles. Specific positive fluorescence to poliovirus 2 and 3 antigens was detected at dorsal spinal cord level only. One positive result was seen with Coxsackie A9 antiserum and fresh guinea-pig complement in the inflammatory cells in the right extensor forearm muscles.

This experience, as yet unexplained, underlines the importance of ensuring that women are not pregnant prior to oral polio vaccination.

Introduction

Manufacturers of live polio vaccines advise against their use in pregnancy although there is no evidence to suggest that intrauterine infection occurs. A leading article in the *British Medical Journal* stated that it was advisable to withhold vaccine in the first four months of pregnancy, but added that there was no evidence that live polio vaccine affected the fetus adversely,[1] a view which was endorsed by Levine and colleagues.[2] The British National Formulary (1981) recommends the use of inactivated polio vaccine in pregnancy. We have failed to discover any reference to fetal infection after oral polio vaccine in pregnancy. We describe a fetus with irreparable damage to the anterior horn cells of the spinal cord whose mother was immune to poliomyelitis prior to conceiving but who was accidentally given oral polio vaccine early in pregnancy.

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Case report

The patient was a 19-year-old unmarried girl, employed as a student nurse. She first consulted on 7 May 1980 because of six weeks amenorrhoea, her last menstrual period being 26 March 1980. She had previously taken the oral contraceptive Eugynon 30. Vaginal examination was not carried out at this visit, but a Gravindex pregnancy test was negative. She next consulted on 18 June 1980 because of continuing amenorrhoea. On vaginal examination the uterus was found to be cystic, and a repeat pregnancy test was arranged. She did not keep her next appointment but returned on 11 August 1980, by which time the size of the uterus indicated about 18 weeks gestation. She requested termination of the pregnancy, which was carried out on 21 August 1980 by the extra-amniotic prostaglandin method, the labour lasting 12 hours. During the counselling interview it was discovered that she had been given oral polio vaccine on 1 August 1980, as part of the routine immunization programme for student nurses. At a later interview she denied having been ill at any time during the pregnancy. When the initial pathological examination of the fetus revealed polio-like histological changes, an attempt was made to determine the immune status of the patient before her pregnancy. The patient was unsure of her previous immunizations in childhood, so efforts were made to check the school medical records, but these had been destroyed. By chance, a frozen blood sample, taken in November 1979, was available, and a specimen of blood was withdrawn on 5 January 1981 for comparison. The immune titres of both samples were determined.

Pathological features

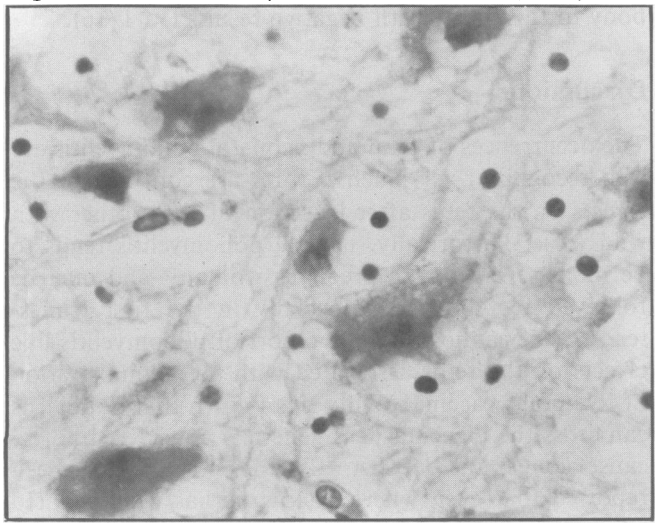
The specimen received was a 10 × 7 × 2 cm placenta with membranes, a 12 cm cord and a female fetus whose crown–rump length was 14 cm with right foot length of 31 mm, more compatible with around 18–19 weeks gestation than with the 20–21 weeks suggested by the history and clinical examination. The left foot length

was only 26 mm, more compatible with 17.5 weeks gestation. By all criteria therefore, the fetus was rather small-for-dates.[3] Full necropsy showed no gross abnormality. Extensive histological study of the major organs and tissues, including the olfactory bulbs,[4] showed abnormalities confined to the spinal cord and to the lungs, where there was a patchy 'pneumonia' of some peripheral bronchial buds.

The spinal cord showed subtle extensive damage to more than half of the anterior horn cells at cervical and dorsal levels, but the neurones of the lumbar area had virtually escaped. In the former areas, extensive loss of Nissl substance, rather extensive cytolysis of neurones, focal cytoplasmic vacuolation and extensive karyolysis were seen, affecting both lateral and medial groups of neurones but more especially the medial group. Type B intranuclear inclusion bodies were absent. This damage had not aroused any acute inflammatory cellular response but there was a subtle glial reaction over the whole area and patchy satellitosis was also evident (Figures 1 and 2). The medulla oblongata was normal and there was no encephalitis or aseptic meningitis.

Since these features were unexpected, their significance had to be assessed. This was done firstly by studying the various muscle groups in both forelimbs. Although neuronal damage affected both anterior horns of the cervical and dorsal cord, skeletal muscle changes of significant degree were seen only in the extensor muscles of the right hand and in the biceps of the right arm, presenting as numerous zigzag fibres, focal degeneration with coagulative necrosis and loss of striations, patchy fragmentation of fibres with atrophy and patchy staining, interstitial oedema and an early inflammatory reaction of neutrophil polymorphs and macrophages.

Figure 1. *Spinal cord. Lumbar area. Left anterior horn. Several stellate anterior horn neurones with reasonably normal features. Minimal central chromatolysis and cytoplasmic vacuolation in one or two. Prominent oligodendroglia. Compare with Figure 2. (Haematoxylin and eosin, × 1,400.)*



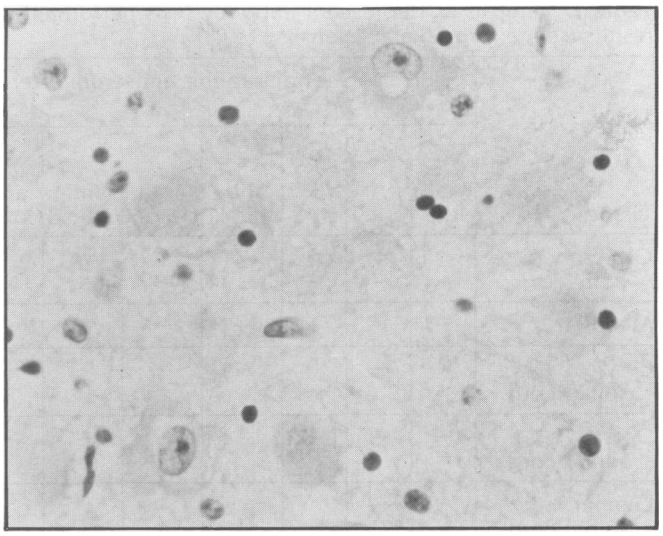


Figure 2. *Cervical area. Left anterior horn. Several ghost anterior horn neurones with total loss of Nissl substance, many with loss of nucleus or various degrees of karyolysis, and occasional cytoplasmic vacuoles. Oligodendroglial cells are as abundant as in Figure 1 but perinuclear halos are less prominent. The lack of the customary neutrophil polymorph response and astrocytic reaction may be due to the time interval between receiving vaccine and the therapeutic abortion (20 days). (Haematoxylin and eosin, ×1,400.)*

Minimal zigzag muscle fibres were seen in the right triceps muscle. The biceps, triceps and extensor muscles of the left arm and hand were essentially normal. The combination of more extensive spinal cord damage with more limited secondary skeletal muscle degenerative changes is a classical situation in the old literature on poliomyelitis.

A second attempt to corroborate the initial histological observations was made by applying fluorescent antibody tests to paraffin-embedded tissue by adapting well-recognized methods.[5,6] Although interest was centred on the cervical and dorsal levels of the spinal cord, other tissues were used as negative controls, namely one olfactory bulb, medulla, lumbar spinal cord, and extensor forearm muscles of the right and left hands. Fourteen sections of each tissue were stained. The indirect fluorescent antibody staining procedure was employed, using monovalent rabbit antisera to poliovirus types 1, 2, and 3, and to Coxsackie virus A9, as well as negative control rabbit serum. The tests were repeated, incorporating fresh guinea-pig complement into the first step of the staining procedure, which was followed by a search for complement fixation using fluorescein-isothiocyanate (FITC) conjugated goat antiguinea-pig serum,[7,8] and there was a complement control test. Another control test employed buffer alone in the first step, and the final sets of sections were stained to search for fixation of the C_3 component of human complement and/or human gamma globulin at

Table 1. Synopsis of fluorescent antibody tests performed, the formalin-fixed paraffin-embedded tissues tested, and the results (see text for explanations).

	FITC—Goat anti-rabbit antiserum after:							FITC—Goat anti-guinea-pig antiserum after:						
Tissue	PBS	NRS	NRS + GPC	anti-polio 1	anti-polio 2	anti-polio 3	anti-Cox A9	GPC	anti-polio 1 + GPC	anti-polio 2 + GPC	anti-polio 3 + GPC	anti-Cox A9 + GPC	FITC anti-human C_3	FITC anti-human gamma globulin
Olfactory bulb	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Medulla	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cervical spinal cord	–	–	–	–	–	–	–	–	–	–	–	–	± (d)	± (e)
Dorsal spinal cord	–	–	–	–	+ (a)	+ (b)	–	–	+ (c)	–	–	–	–	–
Lumbar spinal cord	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Left forearm extensors	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Right forearm extensors	–	–	–	–	–	–	–	–	–	–	–	+ (f)	–	–

Abbreviations: FITC, fluorescein isothiocyanate; PBS, phosphate-buffered saline; NRS, normal rabbit serum; GPC, guinea-pig complement. (a)–(f): see under Pathological features.

any points. Positive results were obtained in only six of 98 sections examined (Table 1), namely:

(a) positive staining of the cytoplasm of some anterior horn cells of the dorsal spinal cord with polio 2 antiserum;

(b) a more strongly positive result at the same site with polio 3 antiserum and resembling the result which Kovács and colleagues[9] obtained in monkeys infected with poliovirus type 3;

(c) a wisp of cerebrospinal fluid over the dorsal spinal cord stained for complement fixation in association with poliovirus type 1 antiserum;

(d) some anterior horn cells of the cervical spinal cord showed a weak positive result for the C_3 component of complement;

(e) at the same site there was a weak positive result for human gamma globulin;

(f) four to six inflammatory cells in the interstitial oedema of the extensor muscles of the right hand were strongly positive with Coxsackie virus A9 antiserum, the skeletal muscle fibres being negative.

Virological features

Twenty per cent extracts each of brain, lung, liver and placenta were prepared as described elsewhere.[10] These extracts were examined for the presence of virus by inoculation into baboon monkey kidney, human embryo lung and human rhabdomyosarcoma (RD) cell cultures, and incubated at 37°C for 21 days. Although baboon kidney and RD cells are particularly sensitive for the isolation of polioviruses, none was detected.[11] We also failed to detect any other of the enterovirus, adenovirus or herpes group of viruses.

Tests for neutralizing antibodies to the three types of polioviruses and the six group B Coxsackie viruses were carried out using the modified micro metabolic inhibition test described by Kyriazopoulou and Bell.[12] The results were identical in the two serum specimens for polio type 1 (1/256), polio type 2 (1/32) and polio type 3 (1/64), normally indicating good protection against poliovirus infection. In addition, there was no evidence of recent Coxsackie virus B infection; the titres for each of types B1, 2, 3, 5 and 6 were $\leq$ 1/16 and for B4 a titre of 1/32 only was detected in both specimens. Because of the anomalous result with Coxsackie A9 virus fluorescent antibody test reported above, the patient's serum taken five months after operation was tested for antibody to this virus, with negative results ($<$ 1/16).

Discussion

The occurrences of fetal and neonatal poliomyelitis are well recognized.[13-15] Such reports are confined to the effects on the fetus after infection of the mother with wild virus. Historically, natural poliomyelitis tends to be more severe in the pregnant woman[15] and may be followed by abortion, especially in the first trimester.[14-16] We cannot find any report of poliomyelitis-like effects on the fetus associated with the administration of live polio vaccine. While it is known that poliovirus can cross the placenta, it is generally considered not to cause congenital defects.[17] Furthermore, it has been reported that even where poliovirus has been isolated

from a fetus following maternal infection, histological changes in the central nervous system have not been common,[4] but occasionally there is histological poliomyelitis.[18,19] The histological features of the case described are those of irreparable damage to anterior horn cells which could be overlooked easily because of the lack of an acute inflammatory response, no doubt owing to the short time interval between vaccine administration and abortion (20 days). The findings are similar to those of Töndury.[19] The cord damage is accompanied by secondary skeletal muscle changes in the extensor muscles of the right hand and in the biceps of the same arm. A report[18] on a case of fetal poliomyelitis with 'rag doll' flaccidity at birth and death half an hour later in a non-immune mother illustrates widespread inflammatory changes, but gestation was 35 weeks at delivery and either 20 or 25 days after the onset of maternal symptoms. The lack of inflammatory reaction in our case is not incompatible with that report or with our patient's history, and is to be expected according to Töndury,[19] Bodian,[20] Johnson and Mims.[21]

We were fortunate to have sera available to compare antibody levels before and after vaccine administration. The antibody titres for each of the three serotypes were identical before and after vaccine administration and were at a level which is considered to provide protection,[22] but recent evidence suggests that antibody protection of the fetus may not be as complete as was formerly considered.[23] In endemic areas, poliovirus type 3 maternal antibody does not appear to cross the placenta as readily as antibodies to poliovirus types 1 and 2. Indeed, fetuses which are less than 17 weeks gestation are negative for poliovirus type 3 antibody even although the mother possesses it.[23] This aspect was not examined in our case. The administration of oral polio vaccine would not normally be expected to result in viraemia. Colonization of the gut would be the only expected result. However, Partridge and colleagues recently described congenital rubella in a baby born to a mother who was immune to rubella before conceiving.[24] We may have observed a similar phenomenon in respect of oral (live) polio vaccine. In retrospect, a sample of spinal cord for attempted virus isolation might have proved more helpful in establishing the cause of the damage detected on histology, but then there would have been less cord for histological study and it would have shown secondary effects of trauma.

It may be important to note that the infant was small-for-dates, and with the rather excessive differences in the lengths of the feet there may be subtle evidence of selective muscle wasting and secondary osseous trophic changes in the legs and feet. These observations together with the evidence of muscle damage lend support to the histological features of poliomyelitis. Poliomyelitis, however, may be due to viruses other than polioviruses. The distinct though weak positive results for polioviruses 1, 2 and 3 in cervical and dorsal cords should not be interpreted too liberally, but be accepted as suggestive evidence that poliovirus antigen was present in the sites described. How poliovirus antigen reached there must remain speculative, but there remains much ignorance about the pathogenesis of poliomyelitis.[25]

We had two reasons for selecting antiserum to Coxsackie A9 virus as a negative control for the poliovirus antisera; firstly, the Coxsackie viruses are part of the enterovirus group, as are the polioviruses; and secondly, recent articles have linked this virus with various chronic myopathies.[26-29] These reports indicate that virus particles are often in crystalline form in the skeletal muscle fibres on electron microscopy and sometimes in regenerating fibres only; but our positive result does not involve the muscle fibres (which show varying degrees of degeneration), only some of the reactive inflammatory cells in the oedematous interstitial tissue. This solitary positive result was unexpected. Since it affects only one muscle group in the fetus, and has not been accompanied by any illness in the mother who did not mount an antibody response in the ensuing five months, we consider this result to be a false positive one. While Coxsackie A9 virus has been cultured from the muscle in one case of chronic myopathy,[28] Green and colleagues caution that glycogen crystals can mimic enterovirus crystals unless precautions are taken to test for this possibility.[30]

While the mechanism of the results described here is not explained, this experience underlines the need to exclude pregnancy before administering live polio vaccine.

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Occasional Paper 24

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Social class analysis—an embarrassment to epidemiology

Every aspect of society has profound effects on public health yet one of the principal tools epidemiologists have adopted to examine these is wholly inappropriate. The Registrar General's social class classification is an empiricist methodology which has been engineered to conform to the prejudices of narrow minded professionals and blatantly manipulated to produce smooth mortality gradients. It obscures much that would be of value and interest and should be abandoned for scientific enquiries.

Source: Jones IG. Social class analysis—an embarrassment to epidemiology. *Com Med* 1984; **6:** 37-46.