Archives of Disease in Childhood, 1977, **52**, 176–182

Neurological sequelae in children surviving mechanical ventilation in the neonatal period

K. J. MARRIAGE AND PAMELA A. DAVIES

From the Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London

SUMMARY The incidence of mental defect, visual and hearing disability, major neurological handicap, and such minor neurological handicap as can be detected on examination at 2–9 years without formal intelligence testing, is presented among survivors of neonatal mechanical ventilation at Hammersmith Hospital between the years 1966–1973 inclusive. 77 (21%) of 367 children survived, over three-quarters of them being born elsewhere. 3 died before the age of 6 months, 2 suddenly and unexpectedly at home, the third accidentally. 1 child was lost to follow up. 11 (15%) of the remaining 73 children had neurological sequelae as defined. In two-thirds this was moderate to severe. Spastic diplegia may no longer be the commonest form of cerebral palsy among those of low birthweight, particularly those surviving severe neonatal illness.

The application of mechanical ventilation to the newborn since the mid-1960s has presumably allowed survival of seriously ill infants who would previously have died, and who have had a variety of illnesses, not necessarily primarily respiratory. Neurological handicap among survivors could be due to the underlying illness or its complications, or even to complications of the treatment itself. Thus however caused, it could represent a new source of childhood handicap, and it seems important to determine its extent and severity in a neonatal intensive care referral unit as artificial ventilation becomes widely used, and survival rates improve. This paper describes such neurological sequelae, and correlates their occurrence as far as possible with perinatal events in an effort to identify early those children likely to be affected.

Patients and methods

Selection. The children studied were all born in or admitted shortly after birth to the neonatal unit at Hammersmith Hospital and had survived mechanical ventilation between the years 1966, when the technique was first successfully used, and 1973 inclusive. This treatment was given to infants who, though they had established spontaneous respiration after birth, later became seriously hypoxic in high concentrations of oxygen (Pao_2 3·9–5·3 kPa (30–40 mmHg) in 100% oxygen), or were having recurrent apnoeic episodes of a severity to require hand ventilation for longer than 10 minutes. This meant in effect that infants rarely died in the unit—in the latter 4 years of the study at least—without a period of ventilation, which was withheld initially only from some very immature babies of less than 1000 g birthweight and others with severely disabling congenital malformations. Thus 77 of 376 ventilated infants (21%) survived the neonatal period, 59 (77%) of these having been born elsewhere and transferred because of serious illness and/or very low birthweight.

Perinatal data. Details of the mothers' pregnancy, labour, and delivery were abstracted from the maternal notes. Details of the infants' birthweight, gestational age, condition at birth, illness necessitating ventilation, and neurological state were ascertained from notes made by the neonatal residents at the time. No systematic neurological examination was carried out on all infants by one observer during the 8-year period; and the abnormalities noted, which were essentially gross, included hyper- or hypotonia, abnormalities or asymmetry of posture, fits, and inappropriately absent reflexes such as the Moro, and sucking and swallowing reflexes in the mature.

Follow-up. An attempt was made to follow or keep in touch with all infants regularly after their discharge from the unit. In a few cases this failed, but all but

Received 11 June 1976

one (see below) were later traced and either re-examined by us, or if they had left the area, details were kindly supplied by other paediatricians or family doctors. Full clinical examinations were made at each visit, and delayed developmental progress assessed using items of Sheridan's and the Denver Developmental Screening Tests (Sheridan, 1960; Frankenburg and Dodds, 1967); neurological examination was carried out on all as appropriate to the age of the child (Paine and Oppé, 1966). Any children suspected as a result of these examinations of having visual or auditory handicap were referred for the appropriate expert assessment. Some of the children did have formal intelligence testing, either because they also formed part of a follow-up study of very low birthweight infants (Francis-Williams and Davies, 1974) or because they were considered to be retarded, but this was not done as a routine, many of them still being under school age.

Results

Composition of survivors, neonatal details, and mortality. The birthweights of the 77 infants ranged between 840 and 5340 g (mean 1921 g, median 1760 g), and gestational ages between 27 and 40 weeks (mean and median 33 weeks). 13 were small for dates (i.e. birthweight was below the 10th centile for gestational age, using a combination of standards (see Davies *et al.*, 1972). 24 (31%) of the infants weighed 1500 g or less; 28 (36%) weighed 1501–2000 g; 16 (21%) weighed 2001–2500 g, and 9 (12%) >2500 g. 41 (53%) of the 77 infants were male, and 36 (47%) female.

The illnesses requiring ventilation could be divided into three broad groups. The largest group of 38 infants (49·3%) had respiratory distress (see Davies *et al.*, 1972, for definition) presumed to be due to hyaline membrane disease; several of this group had recurrent episodes of apnoea in the course of their illness. The second group of 28 (36·4%) had recurrent apnoea of immaturity without any evidence of respiratory disease; and the third group, comprising 11 children (14·3%), had a miscellany of conditions leading to hypoxia or respiratory failure such as meconium aspiration, pulmonary infection, or metabolic disease. The time of onset of mechanical ventilation of the whole group and duration is shown in Table 1.

Table 1 *Details of mechanical ventilation in 77 survivors*

	Range	*Mean (h)*	*Median (h)*
Age at onset	15 min–28 d	27	12
Duration	2 h–48 d	83	38

The overall survival rate was 21%, as stated above. Survival doubled between the first year (1966) and the last (1973), but survival from 1966–69 inclusive at 16% was not significantly different from that of 1970–73 inclusive at 24%.

Later follow-up and correlation of handicap with perinatal events. 3 of the infants surviving the neonatal period died after discharge from the unit and before the age of 6 months; 2 died suddenly and unexpectedly at home, and the third was killed in a road traffic accident. A fourth child could not be traced after leaving the country unexpectedly. All weighed between 2000 and 2500 g at birth, and had been making apparently normal progress until these events. The following details therefore refer to the 73 remaining survivors.

Eleven of the 73 (15%) survivors proved to have neurological abnormality, details of which are given in Table 2. 3 of the 11 are now dead. The first of these (Case 10), severely microcephalic, mentally retarded, and spastic, later developed *Escherichia coli* meningitis and died. A second child (Case 11), developmentally retarded, died of the metabolic illness, propionic acidaemia, which had originally necessitated ventilation. The third (Case 7) with spastic quadriplegia, microcephaly, and mental defect died aged 3¼ years at home. The coroner's necropsy report did not reveal the cause of death, and no detailed examination of the brain was made. Of the remaining 8 handicapped children, one is incapable of any independent existence, 4 are moderately handicapped, and 3 are leading reasonably normal lives, though one is physically limited by cyanotic congenital heart disease.

Later neurological handicap was found in 4 of the 38 children (10%) with presumed hyaline membrane disease, in 4 of the 28 children with recurrent apnoea (14%), and in 3 of the 11 children (27%) with other illnesses (see Table 2). It occurred in 3/24 (12%) of those weighing 1500 g and less at birth, in 6/40 (15%) of those weighing 1501–2500 g, and in 2/9 (22%) of those >2500 g. Handicap at gestations up to and including 32 weeks (5/35 or 14%) was the same as that at gestations 33–36 weeks (4/30 or 13%), but involved one-quarter (2/8) of those of 37 weeks or more. The tally of handicap in the last 4 years of the study (1970–73) was nearly double that (16%) for the first 4 years (9%), but this may have been because of increasingly wide application of ventilation. Infants born in the hospital had a marginally lower incidence of later handicap (2/17, 12%) than those born elsewhere (9/56, 16%).

Further correlation with perinatal data was made though full details will not be given for the sake of brevity; they are available from the authors. There

Table 2 *Details of 11 children with later neurological handicap*

Case no.	*Year of birth*	*Birthweight (g)*	*Sex*	*Gestation (d)*	*Age first ventilated (h)*	*Duration of ventilation (h)*	*Neurological abnormality in neonatal period*		*Later neurological handicap*	*Reason for ventilation*
							Fits	*Other*		
1*	1971	1700	F	214	31	22	>1	+	Spastic diplegia	Respiratory distress
2†	1972	1800	M	242	63	12	—	—	Mental retardation with autistic features (sib autistic)	,, ,,
3	1973	1560	M	214	3	96	1	+	Severe sensorineural deafness	,, ,,
4	1973	1590	F	233	59	57	>1	—	Spastic diplegia	,, ,,
5†	1967	1730	M	251	59	48	>1	—	Ataxic diplegia, retardation, IQ 67	Recurrent apnoea
6†	1970	2200	M	266	6	5	—	+	Spastic quadriplegia, microcephaly, severe mental defect	,, ,,
7‡	1971	1180	M	196	79	92	>1	+	Spastic quadriplegia, microcephaly, severe mental defect, deafness	,, ,,
8*	1973	1440	M	203	12	52	—	+	Spastic diplegia	,, ,,
9	1966	1100	F	203	28 d	48 d	—	—	Minor neurological disability, clumsy gait, unable to hop on one foot; full scale IQ 99 (performance 86, verbal 111)	Pneumonia
10‡	1971	3120	M	280	8 d	5	>1	+	Spastic quadriplegia, microcephaly, severe mental defect	Cardiac arrest after accidental pneumomediastinum
11‡	1973	3600	M	280	11 d	48	>1	+	Developmental retardation	Propionic acidaemia

*Born at Hammersmith Hospital.
†Small-for-dates.
‡Now dead.

was no significant association between later neurological handicap and a maternal history of previous or threatened miscarriage, antepartum haemorrhage, prolonged (more than 24 hour) membrane rupture, or breech delivery. Similarly, no significant correlation could be found between later neurological handicap and the following neonatal events: birth asphyxia, defined crudely as failure to establish spontaneous respirations within 2 minutes of birth; hypoglycaemia, defined as blood glucose of 1·1 mmol/l (20 mg/100 ml) or below; severe acidosis, defined as a negative base excess, calculated from arterial blood gas measurements, of more than 10 mmol/l (10 mEq/l); alkali therapy, either total amount or expressed per g birthweight; and hyperbilirubinaemia, defined as total bilirubin of 255 μmol/l (15 mg/100 ml) or above, though severe sensorineural deafness in one child *was* associated with a total bilirubin of 391 μmol/l (22·9 mg/100 ml) for which an exchange transfusion was performed. On the other hand, the correlation between later neurological handicap and fits in the neonatal period occurring before, during, or after ventilator therapy was significant ($P < 0.05$). 21 children had such fits, 7 of whom were among the later handicapped. In 14 of the 21 children fits were multiple, and 6 children were later abnormal, while in the remaining 7 children who had a single fit only one became abnormal. In only 2 of the 11 handicapped children was no neurological abnormality of any kind detected in the neonatal period, whereas this was true of 39 of the 66 later apparently normal children ($P < 0.05$). Distribution of growth centiles for height, weight, and head circumference at later follow-up was normal for those who had been appropriately grown in the uterus. A handful of children had further admissions for respiratory infections, and in 2 these were severe and required a further period of ventilation. No fewer than 8 of the 73 survivors later developed asthma.

Discussion

Controlled trials of mechanical ventilation using endotracheal intubation and intermittent positive pressure ventilation in the neonatal period have been few, have been concerned with the treatment of hyaline membrane disease only, and have not had neurological assessment of survivors as their prime concern. Reid *et al.* (1967) showed a significantly lower mortality among ventilated infants 1000–2000 g compared with controls, though numbers particularly of very low birthweight infants (<1500 g), were small. Murdock *et al.* (1970) on the other hand were only able to show such benefit for infants over 2000 g. Since these early studies were published refinements in ventilator technique have been made (Reynolds, 1975), means of ventilation which can sometimes avoid endotracheal intubation such as the use of a tightly fitting face mask, or a negative pressure respirator have been devised, and continuous positive airway pressure (Gregory *et al.*, 1971) has been introduced. The latter may reduce the need for mechanical ventilation both in hyaline membrane disease and in recurrent apnoea. Nevertheless, mechanical ventilation is now widely applied in many neonatal units, and several recent reports give follow-up details of the survivors. These are summarized in Table 3, but though listed in this way for brevity and convenience, critical comparison of

Table 3 *Details of some mechanically ventilated newborn survivors (listed by year ventilation started)*

Author	*No. of cases*	*Year of birth*	*Birthweight (g) (range & mean)*	*Indication*	*Neurological sequelae (%)*	*Length of follow-up (yr)*
Johnson *et al.* (1974)	54	1962–1969	870–4337 2319	Various	19	2–9
Hof & Weisser (1969)	29	1963–1966	1100–3300 1605	RDS	17	1–4
Dinwiddie *et al.* (1974)	50	1964–1968	? 2010	Various	12	4–8
Present study	73	1966–1973	840–5340 1920	Various	15	2–9
Reynolds & Taghizadeh (1974)	32	1967–1972	1020–2890	RDS	6	1–7
Brown *et al.* (1973)	27	1968–1971	1070–3000 1966	Various	30	1–5
Harrod *et al.* (1974)	22	196?–1971	1070–3440 2070	RDS	4 (32% 'suspect')	1–5
Fitzhardinge *et al.* (1976)	73	1970–1973	ALL ⩽1500 g	Various	18	1–3
Outerbridge & Stern (1972)	84	?	1050–4360 ?	Various	16	1–6

Note: Populations often very different, thus comparison of results difficult—see text.
RDS=respiratory distress syndrome.

the differing results is invidious and of little value when the populations reported may differ in their indications for ventilation, in numbers of referred cases, in birthweight range, underlying illness, year of birth, sample size, duration of follow up, and socio-economic circumstances. It is undoubtedly more profitable for us to consider briefly the implications of our results.

Among the 15% neurologically handicapped children in our study we found two-thirds to be moderately or severely afflicted. Though formal intelligence testing has only been carried out on a few of the children, we feel confident that those with visual or hearing handicap of moderate to severe degree, and those with an IQ less than 70 as well as all those with a major neurological handicap have been identified. Some further minor neurological disability, and especially learning difficulties, may become more evident with time. The incidence of a similar tally of handicaps among 165 infants weighing $\leqslant$1500 g at birth and cared for in our unit between the years 1961–70 inclusive was 18% (Davies, 1976), of whom only one-third could be said to be moderately or severely disabled. 11 of the present ventilator survivors are also included in the group of 165 children, but all save one (Case 9, Table 2) who has a minor disability, appear normal.

Spastic diplegia was the commonest neurological handicap in the very low birthweight group (Davies and Tizard, 1975), and has generally been considered so in earlier studies, However, Fitzhardinge *et al.* (1976), reporting on 73 ventilator survivors all weighing 1500 g or less at birth, showed that hydrocephalus often needing shunt treatment, spastic quadriplegia, and hemiplegia occurred as commonly, if not more commonly, and the majority of the children had moderate to severe disability. A changing pattern of cerebral palsy therefore seems to have emerged among seriously ill very low birthweight infants surviving mechanical ventilation when compared to other children in this weight group. Fitzhardinge *et al.* (1976) thought the most common underlying cause of their neurological handicap was intraventricular haemorrhage (this being the commonest cause of death in the ventilated in their study), and it seems likely that this could be so where hydrocephalus, hemiplegia, and even perhaps spastic quadriplegia are concerned. However, spastic diplegia has become much less common in recent years (Davies and Tizard, 1975; Hagberg *et al.*, 1975), and an iatrogenic cause, now largely being avoided but as yet unidentified with certainty, now seems likely for this particular form of cerebral palsy. Intraventricular haemorrhage probably was not the cause of handicap in the mature infants in our study. Failure of cerebral perfusion associated with profound hypotension seems to be a possibility in some, such as Cases 6 and 10, one of whom at least had a well documented cardiac arrest.

Neuropathological studies of the brains of immature infants, some of whom had undergone prolonged mechanical ventilation, have shown varying lesions and degrees of periventricular leucomalacia (Brand and Bignami, 1969; Grunnet *et al.*, 1974; Smith *et al.*, 1974; Armstrong and Norman, 1974; Schneider *et al.*, 1975). Armstrong and Norman (1974) believed the latter to be areas of infarction secondary to perfusion failure in border zones of circulation. Schneider *et al.* (1975) in particular stressed the wide spectrum of lesions in the hemisphere white matter ranging from periventricular leucomalacia and subcortical necrosis to diffuse glial proliferation and impaired myelin formation, with excessive vascularization in meninges and white matter. They also felt that the fibrillary gliosis of brain stem and cerebellar structures represented a disorder of glial differentiation, related to the hemisphere changes, but were uncertain of its significance. They believed the findings, ranging as they did from distinct necrosis to diffuse gliosis and impaired myelination, suggested that compensation should be possible in surviving children.

Analysis of perinatal data did not clearly differentiate children at risk from later handicap. With the exception of a significant association with fits in the early neonatal period particularly when multiple, and with other abnormal neurological signs, analysis was unhelpful, perhaps because of the small numbers. Both of these features are now well recognized to be associated with later abnormality. It must be pointed out though that at least as many children who had multiple fits turned out apparently normal, and we certainly cannot yet state categorically in the neonatal period that a given infant will turn out normal or abnormal. We cannot be sure either that all these 77 children would have died without ventilation, though by definition they were all seriously ill when it was begun. If we assume they would have died in the past, then we have to say that 11 children now survive, most with moderate to severe handicap, as a result of neonatal intensive care. We feel it is encouraging that 85% of the survivors are apparently normal, though it must be emphasized they are still very young and this must be considered a provisional estimate.

There is little significant difference in outcome between those born in hospital (a small number only) and those referred from elsewhere. The latter had been fetched in nearly every case from the referring hospital and were attended on the journey by a neonatal resident and a nurse from the intensive

care unit (Storrs and Taylor, 1970). Thus though delivery of the mothers in Hammersmith Hospital would have been preferable and would have entailed for them less separation from their infants after birth, it seems clear that given skilled attendance on the journey, the outlook for later morbidity in the child is not greatly different in our hands. We believe there is much to be said for all such infants being cared for in centres where the necessary nursing, medical, and ancillary services can be provided throughout the 24 hours. Infants on ventilators need constant and unremitting attention to ensure maintenance as far as possible of normal blood gas measurements, temperature, nutrition, and blood pressure. Given these, results among survivors should improve in the future.

We are most grateful to all staff who cared for the children in the neonatal period; and to those paediatricians and family doctors who have sent us later details of their progress. We also thank Professor J. C. McClure Browne for permission to abstract maternal details, and Mr. Ian Keith for his help with the statistical analysis.

P.A.D. is greatly indebted to the Nuffield Foundation for continuing support.

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Correspondence to Dr. P. A. Davies, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, 150 Du Cane Road, London W12 0HS.

Addendum

Since this article was submitted, one child, previously considered 'apparently normal', has been found to have a mild spastic monoplegia, bringing the tally of obvious handicap to 12/73 (16%). He weighed 1900 g at 247 days' gestation, and was ventilated from 2 hours of age for 96 hours, for severe respiratory distress syndrome.