Clinical factors associated with adverse outcome for babies weighing 2000 g or less at birth

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SUMMARY Using clinical factors, the probabilities of survival with and without major handicap were separately calculated by multiple logistic regression for 988 children who weighed 2000 g or less at birth and who were born in the period 1976–1980. For survivors weighing 501–1250 g in whom incidence of serious handicap was 21%, neonatal fits and the need for mechanical ventilation carried significantly increased risks of later serious handicaps. In contrast, for survivors weighing 1251–2000 g in whom the incidence of serious handicap was 6%, significant factors were spontaneous, uncomplicated preterm delivery, recurrent apnoea, and abnormal neonatal neurological findings. The probability of dying was assessed in two ways—firstly, using seven clinical factors available on admission to the neonatal unit, and secondly, using 10 perinatal and neonatal factors. Handicapped survivors had a perinatal risk between that of those babies who survived and that of those who died. Of the handicapped survivors, those with spastic diplegia and hemiplegia had been extremely low risk babies (medians 1.4% and 1.6%, respectively), whereas those with other impairments had much higher risks (range 17.5–38.1%). We postulate that certain impairments arise independently of clinical events, although most occur in children who had complicated perinatal courses.

The aetiology of the neurodevelopmental handicaps that occur in children with low birth weights who survive is poorly understood. Such handicaps comprise several different impairments affecting motor, sensory, and intellectual function. The many different combinations of impairment that are found suggest common predisposing factors. It has been postulated that those perinatal events that lead to a child being handicapped may be similar to those that culminate in death,¹ but similar impairments may be found among other children who have had no perinatal problems. This paper examines the hypothesis that handicap may be predicted from the clinical course of a low birthweight baby. Clinical factors associated with adverse perinatal outcome are defined in a group of babies who were born weighing 2000 g or less and who were managed in one perinatal referral centre during a five year period.

Subjects and methods

We studied 1034 consecutive babies weighing 2000 g

or less, born between 1 January 1976 and 31 December 1980 who were cared for on the neonatal medical unit at this hospital. Seven hundred and nineteen were born here, and 315 were neonatal referrals. Details of the neurodevelopmental outcome of the survivors had been discussed elsewhere.^{2,3} For the purposes of this study a neurodevelopmental handicap was defined as one or more of the following: cerebral palsy, developmental retardation (Griffiths quotient or Wechsler pre-school and primary intelligence quotient (IQ) <71), blindness or deafness sufficient to warrant special education and hydrocephalus. The outcome was known at a median age of 39 months (range 24–81) for 702 of 724 babies who had been discharged (97%). Twenty had died (eight with considerable pre-existing handicaps), and 57 long term survivors had handicaps.

Patients were excluded if a serious congenital abnormality was clearly the cause of death (n=40) or handicap (n=10).³ Factors associated with survival were therefore analysed for 270 babies who died in hospital and 714 survivors. The follow up data for

65 survivors was incomplete; these were excluded and factors associated with handicap were analysed for 594 healthy survivors and 55 with handicaps.

Information about the perinatal events and necropsy findings was retrospectively abstracted from the clinical records and coded for computer analysis. Preliminary analysis was done with the Statistical Package for the Social Sciences (SPSS). Thirty seven clinical factors were selected for further study. The incidence of perinatal death and handicap for children with each clinical factor is shown in table 1. Birth weight and gestational age were included as continuous variables in each analysis.

To examine the associations between each of these 37 factors, firstly with survival, and secondly with the presence of severe handicap among the survivors, a series of multivariate logistic regression analyses were carried out using the Genstat statistical package. These models associated the log odds (logit) of death or handicap with the factors under consideration and determined the strongest associations. To remove factors that were not significant from the models we adopted a 'backwards stepwise' approach; at each step the factors that contributed least to the 'fit' of the model were dropped as long as the actual difference made was not significant ($p > 0.05$, according to the change in 'deviance'). Only babies with complete data could be included in this analysis. Once a final list of factors had been obtained, all babies with complete data on the final list of factors were included and the significance of each factor in turn was obtained by deleting it and examining the change in deviance.

It was not practicable to look for associations with individual impairments among the survivors, because of the small numbers, and so the log odds of severe handicap of any form were modelled. This was done for birth weights of 500–1250 g and 1251–2000 g so that we could compare the findings with our previous studies in which patients were divided into two groups—very low birth weight with high mortality and morbidity, and low birth weight with low mortality and morbidity.

A final analysis was performed to model log odds of death, firstly using data available at the time of admission to the neonatal medical unit, and secondly using neonatal variables as well. From the final model the predicted probability of death was calculated for each baby, separating those who died from those who survived, with and without handicap.

Results

FACTORS ASSOCIATED WITH NEURODEVELOPMENTAL HANDICAP AMONG SURVIVORS

Of the 124 children weighing from 500–1250 g at

birth, 93 had complete records for all clinical factors and a further 20 were added at the final step; the incidence of handicap was 24 of 113 (21%). Two factors were significantly associated with subsequent handicap—neonatal fits and the need for mechanical ventilation ($p < 0.005$ and $p < 0.025$, respectively). Both were associated with increased risks of handicap with odds ratios of 5.7:1, 95% confidence interval (CI) 1.4 to 23, and 4.4:1, CI 1.5 to 13, respectively.

Of the 590 children weighing from 1251–2000 g at birth, 466 had complete records and a further 70 were added at the final step. The incidence of handicap in these children was 31 of 536 (6%). The factors most significantly associated with handicap were an uncomplicated spontaneous delivery, (odds ratio 2.9:1, CI 1.3 to 6.6, $p < 0.025$), neonatal neurological abnormality (odds ratio 6.1:1, CI 2.3 to 16 $p < 0.001$) and recurrent apnoea ($p < 0.005$). Children with recurrent apnoeic spells were grouped by the time of onset and presence of respiratory distress (table 1), each group being compared with a group of children without apnoea. There were no impairments among the children who developed apnoea in the presence of established respiratory distress. Children who had early apnoea (within 3 days) had an increased risk (odds ratio 2.2:1, CI 0.6 to 7.8), as did children with late apnoea (odds ratio 4.3:1, CI 1.6 to 11.3).

CLINICAL FACTORS ASSOCIATED WITH DEATH

We analysed the data available up to the point of admission to the neonatal medical unit for 803 children with complete records. These comprised antenatal factors, details of delivery and resuscitation, birth weight, and gestational age, and including those babies who died in the delivery room. At the final step 146 children were added log odds of dying were calculated for those factors significantly associated with death (table 2). Decreasing birth weight was the factor with the strongest and most significant association, each 100 g below 2000 g increasing the risk of dying by a factor of 1.35. Neonatal transfer was associated with a three times increased risk, but this referred group is highly selected and the reasons for high mortality have been discussed elsewhere.⁴ The small number of black babies in the study have less risk than white babies. Suppression of labour with sympathomimetic drugs was associated with a considerably reduced risk, but paradoxically those pregnancies complicated by more than one episode of preterm labour had an increased risk. It would therefore seem that merely delaying labour may be beneficial, but that stopping premature labour is not. Delay in the establishment of spontaneous respiration and the need for alkali at resuscitation (both indicative

Table 1 Perinatal factors selected for multiple regression analysis

Clinical factor	Total No	No (%) who died	No (%) of healthy survivors	No (%) handicapped
Preconceptional:	988	274 (28)	659 (67)	55 (6)
Ethnic group:				
White	871	243 (28)	579 (67)	49 (6)
Black	28	3 (11)	22 (79)	3 (11)
Asian	84	26 (31)	55 (66)	3 (4)
Social class:				
I+II	170	46 (27)	112 (66)	12 (7)
III	351	72 (21)	262 (75)	17 (5)
IV+V	154	42 (27)	102 (66)	10 (7)
Single mother	172	41 (24)	125 (73)	6 (4)
Previous obstetric loss:				
First trimester only	300	90 (30)	193 (64)	17 (6)
Any (including neonatal deaths;	122	23 (19)	88 (72)	11 (9)
Investigated for infertility	49	17 (35)	31 (63)	1 (2)
Antenatal:				
Pre-eclampsia	186	36 (19)	142 (76)	8 (4)
Antepartum haemorrhage (requiring intervention)	63	24 (38)	37 (59)	2 (3)
Preterm rupture of membranes (primary event)	265	69 (26)	178 (67)	18 (7)
Duration of ruptured membranes:				
12-24 hours	52	14 (27)	31 (60)	7 (14)
>24 hours	188	54 (29)	124 (66)	10 (5)
Multiple episodes of preterm labour	291	97 (33)	177 (61)	17 (6)
β agonists (>12 hours before delivery)	272	62 (23)	190 (70)	20 (7)
Steroids (>24 hours before delivery)	130	25 (19)	98 (75)	7 (5)
Preterm labour only (no recorded intervention or complication)	182	59 (32)	106 (58)	17 (9)
Antenatal referral to St Mary's Hospital	88	21 (24)	61 (69)	6 (7)
Delivery details:				
Route of delivery:				
Breech	140	64 (46)	64 (46)	12 (9)
Caesarean section	340	69 (20)	257 (76)	14 (4)
Intubated at delivery	383	152 (40)	211 (55)	20 (5)
Alkali given	229	101 (44)	117 (51)	11 (5)
Spontaneous respirations established after 10 minutes	70	30 (43)	37 (53)	3 (4)
Ventilated to neonatal unit (no respiratory effort)	109	82 (75)	24 (22)	3 (3)
Apgar score at 1 minute <7	533	192 (36)	311 (58)	30 (6)
Apgar score at 5 minutes <7	243	118 (49)	112 (46)	13 (5)
Small for dates (<10 th percentile)	320	58 (18)	250 (78)	12 (4)
Multiple pregnancy (No of babies)	173	45 (26)	116 (67)	12 (7)
Female	458	131 (29)	307 (67)	20 (4)
Neonatal transfer	306	139 (45)	143 (47)	24 (8)
Neonatal factors:				
Hyaline membrane disease	358	119 (33)	209 (58)	30 (8)
Apnoea:				
<72 hours old (no respiratory distress)	67	16 (24)	41 (61)	10 (15)
>72 hours old	110	21 (19)	72 (66)	17 (16)
With respiratory distress	122	63 (52)	54 (44)	5 (4)
Mechanical ventilation (>4 hours)	409	246 (60)	134 (33)	29 (7)
Pulmonary airleak	161	113 (70)	40 (25)	8 (5)
Pulmonary haemorrhage	34	30 (88)	4 (12)	0 —
Positive blood cultures	357	98 (28)	227 (64)	32 (9)
Meningitis	17	14 (82)	1 (6)	2 (12)
Symptomatic hypoglycaemia	66	26 (39)	37 (56)	3 (5)
Fits	85	50 (59)	23 (27)	12 (14)
Other neurological abnormality	146	87 (60)	43 (30)	16 (11)
Exchange transfusion:				
n=1	93	28 (30)	58 (62)	7 (8)
n=2-11	113	44 (39)	57 (50)	12 (11)

of perinatal asphyxia) were also associated with increased risk.

For the next analysis neonatal factors were included, but babies who died in the delivery suite were excluded. One hundred and sixty eight children were added at the final step making a total of 971. The factors most strongly associated with death are shown in table 3. Birth weight, recurrent preterm labour, and drug suppression of labour with drugs were again important, but the introduction of neonatal factors reduced the significance of the markers of asphyxia given above. Of the neonatal factors, mechanical ventilation conferred the highest risk, followed by neonatal meningitis, pulmonary haemorrhage, neurological abnormality, and pulmonary air leaks. Conversely, recurrent apnoea and septicaemia diagnosed microbiologically were associated with decreased risks of death. Because these latter variables are found among older neonates, the data set was re-examined controlling for age at death (grouped as less than 4 days and more than 3 days); the same factors remained associated with death.

Finally the predicted probability of death was calculated (based on the modelled log odds described in table 3) for the 971 babies admitted to the neonatal medical unit on whom complete data was available. This included 54 handicapped survivors, there being inadequate clinical records for one handicapped child who was born in 1977 with severe developmental delay and who had had a complicated neonatal course. The distribution of risks expressed as the percentage probability of dying is shown in table 4. The handicapped children have

Table 4 Predicted probabilities of death for all patients with complete information

	No	% Probability of death	
		Median	Quartiles
Babies who died	268	81.4	58.5-99.6
Survivors:			
No handicap	584	3.6	1.8-7.6
Handicap	54	11.7	2.9-40.0

Table 2 Clinical factors associated with death: data available on admission to Neonatal Medical Unit (n=949)

	p Value	Odds ratio	95% Confidence interval
Birth weight*	<0.001	1.35:1	1.3 to 4.0
Delayed onset of respirations:	<0.001		
>10 minutes		1.5:1	0.8 to 2.9
Ventilated from birth		7.7:1	4.2 to 14
Several episodes of preterm labour	<0.001	5.3:1	3.1 to 9.4
Neonatal transfer to St Mary's Hospital	<0.001	3.2:1	2.1 to 4.7
Alkali given at resuscitation	<0.01	1.9:1	1.2 to 3.2
β agonist given	<0.001	1.6:9	3.7 to 12.7
Ethnic group:	<0.025		
Black		1.9:5	1.3 to 68
Asian		1:1.3	0.7 to 2.5

*Risk increases at each decrease of 100 g.

Table 3 Perinatal and neonatal factors associated with death (n=971)

	p Value	Odds ratio	95% confidence interval
Birth weight*	<0.001	1.5:1	1.4 to 1.6
Mechanical ventilation	<0.001	32:1	17 to 62
Meningitis	<0.001	28:1	4.7 to 166
Pulmonary haemorrhage	<0.001	10:1	2.2 to 47
Neurological abnormality	<0.001	3.7:1	2.0 to 6.7
Multiple episodes of preterm labour	<0.001	4.2:1	2.1 to 8.4
Pulmonary air leak	<0.005	2.0:1	1.1 to 3.4
β agonist given	<0.005	1.3:1	1.5 to 6.5
Apnoeic spells:	<0.001		
After third day		1.5:9	3.0 to 11
Before third day, with respiratory distress syndrome		1:1.8	0.9 to 3.6
Pathogen isolated on blood culture	<0.001	1.5:1	3.1 to 9.5

*Risk increases at each decrease of 100 g.

Table 5 Predicted probabilities of death: individual impairments

	No	% Probability of death	
		Median	Quartiles
Spastic diplegia	14	1.4	0.5-3.6
Spastic hemiplegia	7	1.6	0.8-34.0
Spastic quadriplegia	10	17.5	3.2-44.0
Developmental retardation*	9	12.8	0.7-55.1
Blindness	7	20.6	20.6-55.1
Hydrocephalus	9	34.0	17.5-48.9
Deafness	7	38.1	12.4-87.6

*As only impairment.

predicted probabilities between those of the non-handicapped survivors and those of the babies who died, but with considerable overlap among the survivors. When individual impairments are considered (table 5), this overlap is mainly among the children with diplegia and hemiplegia. Children with either of these two cerebral palsies have lower probabilities than those children with quadriplegia (Mann-Whitney U test: $p=0.003$ and $p>0.1$, respectively). All other groups have comparatively high predicted probabilities of death when compared with non-handicapped survivors, or with those with either diplegia or hemiplegia.

Discussion

Although the origins of most neurodevelopmental impairments among survivors with low birth weights remain obscure, these data show that most impairments were found in children who had complicated perinatal courses. Small numbers in each group precluded multivariate analysis of associated factors with individual impairments, but the high frequency and similarity of neonatal problems encountered by children with such diverse impairments (such as blindness or cerebral palsy) and the frequent coexistence of such impairments³ encouraged us initially to analyse the 'handicap' group as one.

Neonatal referrals, who comprised of those with handicaps 24 (44%), were included because almost all had been delivered in district general hospitals and stabilised before transport. When allowance was made for the need for mechanical ventilation, survival and incidence of handicap were similar in patients born here and those who had been referred.⁴

Although dividing the survivors into two groups according to birth weight (less than 1251 g and more than 1250 g) seems an artificial distinction, analysis

of the associates of handicap among the survivors in the two groups was suggested by our finding of different ranges of impairments in the two groups,³ differing individual associations with handicaps,² and—most importantly—a considerable increase in mortality and handicap in those who weighed less than 1251 g.³

The association between impairment of the neurological and respiratory systems and outcome is to be expected. They are the systems most frequently compromised in the neonatal period, and among the 222 (72%) of the babies in the study who died and had necropsies, 180 (81%) had hyaline membrane disease and 162 (73%) had intraventricular haemorrhages (unpublished observations). Most of these children were born before cerebral ultrasound scanning became standard in this hospital and thus the association of impairment with such findings could not be explored.

The small number of factors associated with handicap was disappointing but confirmed other reports, mainly from studies of babies weighing less than 1000 g, which have variously associated low Apgar scores,⁵ mechanical ventilation,^{6,7} fits,^{5,8} and clinical or ultrasound evidence of intraventricular haemorrhage.⁸ A further study attempted to correlate cerebral palsy or developmental retardation with clinical factors in babies weighing less than 1501 g from two separate hospitals.⁹ No common associated factors were found. Furthermore, it was observed that only half of the 30 children with cerebral palsy had been ventilated and only two (7%) had an Apgar score at five minutes of less than four. Thus children with cerebral palsy were not necessarily the illest babies. In a case control study of 18 preterm children with diplegia, an Apgar score of less than four at one minute was found more often among diplegic children, who were also more likely to have had symptomatic intracranial haemorrhages or neonatal fits.¹⁰ Fourteen diplegic children (78%) had little or no respiratory distress, however, and similar proportions had no evidence of intracranial haemorrhage (72%), or seizures (78%).

In this study 11 handicapped children (20%) did not need neonatal intensive care. These were four children with diplegia, four with hemiplegia—both impairments with a low calculated risk of death—one with tetraplegia, and two with developmental retardation. Low Apgar scores at one minute were, however, found in six of 14 children with diplegia (43%) and three of seven children with hemiplegia (43%). In contrast, only one of 10 children with quadriplegia had an uncomplicated neonatal course (he later developed infantile spasms) and only two had low Apgar scores at one minute. Babies who developed diplegia and hemiplegia later were not, there-

fore, necessarily ill in the neonatal period. These unexplained impairments may have their origin in the antenatal or perinatal periods, as indicated by depressed Apgar scores at birth and a low incidence of perceived perinatal complications. In contrast, in this study, quadriplegia was found mainly in children who developed serious postnatal illness and who had seemed to be in good condition at birth.

Certain impairments that often coexist—quadriplegia, blindness, and deafness—are more common among the smallest babies and occur in those needing intensive care and mechanical ventilation, often with associated neurological abnormality. A similar distribution of birth weights and incidence of neonatal factors is found in posthaemorrhagic hydrocephalus, which we also defined as a serious impairment. Recent developments in neonatal care resulting in improved survival for the smallest babies may therefore be associated with the presence of severe multiple handicaps in survivors.

The sole antenatal factor that could be associated with later handicap was an otherwise uncomplicated spontaneous delivery in the group weighing 1251–2000 g at birth. Surprisingly, antepartum haemorrhage, pre-eclampsia, preterm rupture of the membranes, or antenatal transfer seemed to have no effect. When factors associated with death were examined, however, a beneficial effect of delaying labour for more than 12 hours with sympathomimetic drugs was found but there was an adverse effect if there was more than one isolated episode of preterm labour. The use of sympathomimetic drugs is controversial¹¹; it has been claimed that β receptor agonists may reduce the subsequent incidence of hyaline membrane disease in the baby.^{12 13} A reduction in mortality, such as is implicit here, would be the logical result. The aim of tocolytics, however, is to stop preterm labour. These data suggest that delayed delivery may be beneficial, whereas more than one discrete episode of preterm labour seems to be undesirable.

Birth weight was more important in predicting outcome in these babies than either gestational age itself or being small for gestational age, neither of which exerted any significant extra effect. In addition, neither gender nor route of delivery had any effect on outcome, as previously reported.

Although the condition of the baby at delivery was not associated with later handicap, asphyxia sufficient to delay the onset of spontaneous respiration by more than 10 minutes or to warrant the use of alkalis at resuscitation was associated with increased mortality, stressing the need for antenatal detection and prevention of asphyxia. These factors disappear when neonatal data are added to the

model, their effect being swamped by the stronger association of adverse neonatal variables.

There is an increased predicted probability of death among handicapped survivors during the perinatal period, and the possible origin of some impairments in the antepartum period confirm this. Recent work has extended the observation of Sameroff and Chandler¹⁴ that this extends beyond conception and delivery into the socioenvironmental factors that are associated with low birth weight, and which exert influence on later development.¹⁵

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