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Characteristics of babies who unexpectedly survive long-term after withdrawal of intensive care

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Abbreviations: IC, intensive care; NICU, neonatal intensive care unit; aEEG, amplitude-integrated electroencephalography; MR, magnetic resonance; HIE, hypoxic-ischaemic encephalopathy

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SP collected the data at one of the hospital sites, analysed the data, drafted the initial manuscript and contributed to manuscript review and revision.

JJ and SJ collected the data at one of the hospital sites and contributed to manuscript review and revision.

LM reviewed the hospice database and collected data from the hospice sites and contributed to manuscript review and revision.

AC obtained parental consent, supervised data collection at one of the hospital sites, collected data, and critically reviewed manuscript drafts.

PC conceptualised and designed the study, obtained the research ethics approval, designed the data collection form, obtained parental consents, coordinated data collection from all sites, collected and analysed the data, assisted with drafting the initial manuscript, contributed to critical review and revision of manuscript drafts, and is the guarantor for this study.

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ABSTRACT

Aim: Occasional babies survive long-term after withdrawal of intensive care despite a poor prognosis. We aimed to review in detail the clinical cases, characteristics, and outcomes of neonates with unexpected protracted survival following planned withdrawal of intensive cardiorespiratory support.

Methods: We reviewed infants who unexpectedly survived for more than 1 week following planned withdrawal of intensive care in two tertiary-level NICUs over a 7-year period.

Results: We identified 8 long-term survivors (6 term, 2 preterm) between 2007-2013. All had a clinical diagnosis of grade 3 hypoxic-ischaemic encephalopathy and severely abnormal electroencephalography and neuroimaging prior to intensive care withdrawal. Intensive care was withdrawn at 5 days postnatal age (range: 2–9 days), but the possibility of protracted survival was discussed beforehand in only two cases. Three infants died before 3 months of age. Five infants remain alive, currently aged from 2.0-6.5 years, and all have significant neurodevelopmental problems.

Conclusion: Unexpected long-term survival after neonatal intensive care withdrawal occurs occasionally but unpredictably. Significant neurodevelopmental adversity was invariable in those surviving beyond infancy. Ventilator dependency along with severely abnormal electroencephalography and neuroimaging is still compatible with long-term survival. The possibility of protracted survival should be discussed routinely with parents before intensive care withdrawal.

KEYNOTES

- Long-term survival despite a poor prognosis is occasionally described after withdrawal of neonatal intensive care but little is known about the conditions, prior investigations or later outcomes of babies destined to survive.
- Severely abnormal neurology, electroencephalography and neuroimaging plus apparent ventilator dependency is still compatible with long-term survival after intensive care withdrawal.
- The possibility of unexpected long-term survival requires routine discussion with parents before intensive care withdrawal

INTRODUCTION

Withdrawal of invasive life support is an integral part of modern neonatal intensive care. Current guidelines allow withdrawal of intensive care (IC) from babies with a poor prognosis and those unlikely to survive,(1) with significant variations in end of life and withdrawal of care practices.(2) IC withdrawal has become more common since 1988.(3) Guidelines available since 1994 in the USA and since 2004 in the United Kingdom made only brief reference to the phenomenon of prolonged survival after IC withdrawal.(4-6) Parents and clinicians usually expect death to follow relatively quickly after withdrawal of intensive support.(7) Long term survival after treatment limitation discussions is reported (8, 9) but detailed information is missing regarding the clinical status and neuroinvestigations preceding IC withdrawal in infants destined to survive. Such information would potentially be helpful for clinicians dealing with families when withdrawal of IC is being considered (3, 10)

We aimed to review in detail the clinical cases, characteristics, and outcomes of a cohort of neonates with unexpected protracted survival following withdrawal of intensive cardiorespiratory support.

PATIENTS AND METHODS

We undertook a retrospective review of the medical notes and hospice records of neonates who unexpectedly survived following IC withdrawal in two tertiary-level neonatal intensive care units (NICUs) between 01/01/2007 and 12/31/2013 (a 7-year period). These centres each have associated local birth rates of approximately 6000 babies/year and approximately 25 babies/year cooled for HIE, including for inborn infants and external referrals. 'Long term' was arbitrarily defined as a duration >1 week. Cases were identified via clinician/nurse recall and cross-referencing with our hospice database, excluding babies with trisomies. The study had prior research ethics approval. Written parental consent for collection of outcome data was provided by all the parents of all surviving infants.

RESULTS

We identified eight long-term survivors, three boys and five girls; two had been born preterm. Table 1 presents their baseline data, details of their clinical characteristics, ventilatory requirements and investigations done prior to IC withdrawal, and their current neurodevelopmental status if still alive. All had a principal discharge diagnosis of grade 3 hypoxic-ischaemic encephalopathy (HIE), and all had severely abnormal amplitude-integrated electroencephalography (aEEG) and/or conventional EEG prior to IC withdrawal. Further neuroimaging (MR or computed tomography) was done prior to IC withdrawal in six cases and was also severely abnormal (Table 1).

To estimate the relative frequency of long term survival we also reviewed all infant deaths with grade 3 HIE occurring in one of our centres (Norwich) during the 7-year study period. In addition to the five long-term survivors identified in this single centre, there were an additional 25 neonates who died before the age of 7 days.

Life support and treatment prior to IC withdrawal

All neonates except for one preterm infant (case 1) received 72 hours of therapeutic cooling from NICU admission. All had received intravenous antibiotics, fluids, positive pressure ventilation (seven via an endotracheal tube), and inotropic support. No neonates were on inotropic support in the 24 hours prior to withdrawal of IC. Prior to IC withdrawal, antibiotic treatment was stopped and analgesics and/or sedatives were continued or prescribed for the first time. All had significant neurological symptoms or signs. On the day of IC withdrawal all except one infant were receiving phenobarbital as an anti-epileptic medication, and in addition most were receiving a benzodiazepine drug infusion as anticonvulsant therapy. In the 24 hours preceding IC withdrawal, all babies were nil by mouth and receiving only intravenous glucose.

Discussions with parents preceding IC withdrawal

The clinical decision for recommending IC withdrawal was made on the basis of the poor neurological states on clinical examination and the severely abnormal EEG and neuroimaging findings, and was usually made in discussion with parents. Five cases had evidence of 'shared' decision making with parents regarding IC withdrawal; two were classed as 'medical team decision with agreement of parents'; and one was mainly a medical decision with cultural support due to maternal ill health. In all cases documentation recorded that there had been sufficient understanding and agreement by parents for IC withdrawal and that they appeared to accept that it was the right decision. A 'Do not attempt resuscitation' order was in place prior to IC withdrawal in six cases (the exceptions being cases 5 and 8). The possibility of long-term survival was clearly recorded in only two of the eight cases. In Case 4, there had been full discussion with parents: *"*

> *...[We] already know that [baby] can sustain independent ventilation, she managed 20 hours off ventilator before needing re ventilation. When the ETT [endotracheal tube] is removed she could succumb early or may carry on ventilating long term and so could survive long term. Impossible to say, but [consultant's] impression is that she would likely get tired and die earlier rather than later*."

In other cases there was no specific documentation recording expectations of time to death after IC withdrawal. In all cases the notes documenting discussions that preceded IC withdrawal provided no evidence that plans for feeding after IC withdrawal were considered before the event.

IC withdrawal

IC was withdrawn with parental agreement at median 5 days postnatal age (range: 2–9 days). The duration between the day that the clinician first recommended IC withdrawal and the actual day of withdrawal ranged from 0 to 3 days (median: 1 day). Neither unit had a practice of offering the parents of these babies the option of withholding of feeds or fluids in the event of ongoing survival. Following IC withdrawal, enteral feeds were commenced in agreement with the parents in all babies and anti-epileptic medications continued in two cases. Early discussions by consultants post IC withdrawal did not mention how likely they considered prolonged survival to be, only its possibility (eg case 8: '*could breathe for few minutes or longer*').

Clinical condition was mostly stable following IC withdrawal: one baby had brief self-correcting apnoeas (case 1) and another had cyanotic spells (case 5), while the six others had stable observations and respiratory effort. Further consultant discussions within 24-48 hours after IC withdrawal raised the potential for longer-term survival: '*At present looks very likely that [baby] will survive beyond the short term. May live for weeks, months and even possibly years'* (case 1)'.

Discharge and long-term outcomes

Median age at discharge from NICU was 14 days (range: 2–31 days) and destination was home (n=2) or hospice (n=6). Hospice involvement had been offered in all cases, and was declined by one family. At discharge from the NICU, all babies had analgesia prescribed and were tolerating full enteral feeds by bottle (n=1) or nasogastric tube (n=7); five received formula, two maternal milk and one a mix of formula and maternal milk. A 'Do not attempt resuscitation' order was in place for all babies at discharge, though in one (case 4) it was

rescinded 3 days later following parental request as they considered the baby was doing so well.

Three infants died, at ages ranging between 19 and 66 days. Five infants remain alive to date with current ages ranging between 2.0-6.5 years. All five ongoing survivors have significant neurodevelopmental problems (table 1).

DISCUSSION

Our study describes long-term survival of some babies who had undergone withdrawal of invasive life support when their prognosis was considered dire or ongoing treatment deemed futile. Our study is the first to report comprehensive details of such babies destined to survive long term, namely regarding their clinical status, diagnosis, and detailed investigations immediately before IC withdrawal, and their later outcomes.

It is usually expected that death will follow relatively quickly after intensive support is withdrawn from neonates in a terminal-care phase.(7) Protracted survival was a relatively rare occurrence, averaging ~1 case per year between our two units. This incidence may be an underestimate, because case identification relied on clinician recall and hospice records, and a minority of families declined hospice involvement. Our study nevertheless implies that nationally and internationally a large number of such babies must be surviving long term.

All neonates reviewed in our cohort met the criteria for expected average time to death of 2.5-8.6 hours as previously defined by Janvier et al.(11) The time to death by underlying diagnosis is yet to be reported, as only averages have been published.(2, 11) Within our cohort only three out of eight infants died within the first 3 months whereas five have survived much longer despite requiring significant initial respiratory support. This highlights the almost-impossible challenge of accurately predicting time to death.

Most babies were receiving one or more anticonvulsant medications leading up to IC withdrawal. These medications may have affected the neurological examination and potentially caused respiratory depression in some, so demonstrating the importance of seeking additional neuroimaging for the record in all cases. A further reminder is provided by a case we excluded from our series: one baby cooled for grade 3 HIE with an initial burst-suppressed aEEG and who was on two anticonvulsant drugs for intractable seizures had a plan agreed on day 4 to withdraw IC; but after a normal brain MRI on day 5 this decision was

rescinded by parents and he had a normal BSID-3 assessment at the age of 2.4 years.

An interesting consideration is whether earlier timing of intensive care withdrawal would in the individual cases have led to earlier demise and/or prevented long-term survival. While it seems likely that earlier withdrawal would in many of these cases have hastened death or curtailed long-term survival, the premise of a missed *"window of opportunity*"(12, 13) does not necessarily take into consideration the evolving nature of HIE, the reasonable time period that clinicians must allow for demonstration of any prospect for recovery, or the time needed for proper confirmation of the suspected diagnosis and its severity through further investigations.(14) Still less does it take into consideration the gratitude that some parents do have that their children, despite some major disabilities, have survived against the odds. (Such comments were voluntarily offered by several of the parents we spoke with during this study.) Furthermore, in the acute phase the families themselves often need sufficient time to come to terms with the diagnosis and the prospect of IC withdrawal with the expectation of the imminent loss of their child; some require more time than others, as illustrated by varying period between IC recommendation and actual withdrawal seen in our series (Table 1).

In the Netherlands, neonatal euthanasia is allowed in 'exceptional circumstances' outlined by the Dutch Pediatric Association in 1992,(15) including for neonates who continue to live despite ventilator withdrawal, when palliative sedation/analgesia appears inadequate and it is felt that hastening death would treat parental suffering.(16) Neonatal euthanasia is illegal in the UK, although in 2007 a neonatologist was cleared of misconduct charges by the General Medical Council of the United Kingdom following administration of large doses of muscle relaxant to dying infants to hasten death.(17) Irrespective of the ethics of intentional life-ending actions, a protracted death with its associated symptoms or failure of anticipated death to intervene may cause anxiety and distress to unprepared families and clinicians.

Parents generally expect the process to be swift based on the level of intensive support, severity of background illness and abnormality of investigations at the time of withdrawal, and the bleak prognosis imparted by the attendant NICU staff. In one study, an asphyxiated baby survived for 36 hours after IC withdrawal, with parents repeatedly '*saying their goodbyes'* feeling '*utterly exhausted'*, and later beginning to question their decision to '*let her die'*.(7) Such anxieties may be reduced by more complete counseling and preparation of parents prior to IC withdrawal, better forward planning in terms of location of palliative care and appropriate symptom support, and by wider recognition that predictions of imminent death are sometimes very inaccurate.

Others have recently reported the phenomenon of long-term survival after withdrawal of IC.(8, 9, 18) Brecht and Wilkinson retrospectively studied outcomes following treatment limitation discussions with parents of neonates with brain injury and reported survival to discharge in 22 (28%) of 78 cases overall.(8) Of 8 cases with grade 3 HIE who survived to discharge, 3 died while 5 survived long term with 'severe disability'(8) Kutsche et al. reported the case of a preterm infant who survived IC withdrawal, and the challenges faced by the clinical team supporting the family.(9) A preliminary report by Siden described prolonged survival in five infants despite withdrawal of hydration and nutrition, with death occurring between 3 and 26 days later.(19) In all these reports of prolonged survival, the detailed characteristics, clinical details, and investigations of these infants immediately preceding IC withdrawal were not provided.

In a recent study from Canada, Hellmann et al. reported parents' retrospective views on their practice of withdrawing all forms of artificial nutrition and hydration as part of end-of-life care.(18) Most had been babies with severe HIE who had received ventilation, anticonvulsants and IV fluids before IC withdrawal. The cohort was therefore similar to that which we presently report. However we did not offer parents the option of cessation of all

nutrition and hydration following IC withdrawal -- the practice raises serious ethical and legal issues, as discussed in the recently updated framework document of the UK Royal College of Paediatrics and Child Health on decision-making regarding treatment in life-limiting and life-threatening conditions in children.(20)

The strength of our study is that ours is the first to report in detail the clinical status, neonatal investigations, plus later outcomes of infants who were destined to survive long term. We therefore believe our study will be of interest to all clinicians who deal with neonates with significant brain injury during the difficult discussions with parents that preface IC withdrawal. Yet much remains to be studied in this area. So little is known about these extraordinary children and their families who care for them on a daily basis, their needs and daily challenges. Yet they are real children within real families, and we earnestly need to learn still more about them, what support they have, and what support they feel they may still need.

One limitation of our study is that we may have slightly under-estimated numbers because identification relied mainly on clinician/nurse recall of cases. While we cross-checked with hospice records, it is possible that some babies may have been missed if their families had declined involvement of the hospice team. However our further cross-check of all fatal grade 3 HIE cases in one of our centres (Norwich) did not identify a single additional missed case in the study period. Another limitation is that this was a retrospective case note review and some relevant discussions with parents surrounding the issues of IC withdrawal may have happened but failed to be recorded.

We found wide variation in the documented assessments detailing neurological status and in the modality and timing of imaging investigations performed in the babies for whom IC withdrawal was contemplated. We suggest that future work is needed to develop a standardised approach that could enable a more rigorous and robust documentation of the

clinical examination and treatments received by these babies, with recommendations for the minimum (if not obligatory) investigations that should precede IC withdrawal. This would allow for more accurate recording and comparison of the neurological status of such infants for future prospective studies and for the medical record.

CONCLUSION

We present a cohort of 8 babies who unexpectedly survived following withdrawal of intensive care. We describe in detail their clinical conditions, neurological and ventilator status and investigations immediately preceding IC withdrawal and their outcomes. All those surviving beyond infancy have significant morbidity. We have shown that apparent ventilator dependency accompanied by severely abnormal electroencephalography and neuroimaging is still compatible with long-term survival against expectations after IC withdrawal. The possibility of protracted survival should be discussed with parents before IC withdrawal, especially in cases of grade 3 hypoxic-ischaemic encephalopathy. Even if protracted survival is considered very unlikely, the possibility should be specifically mentioned during the sensitive discussions with parents that precede IC withdrawal. Further studies are needed in the area to guide development of neonatal palliative care in these rare cases and to explore the experiences of families and professionals relating to prolonged survival. Last but not least we need a much better understanding of the specific ongoing needs of these children and their families.

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Table 1 Table showing the clinical characteristics and neurological findings of the patients

Case ref.	Gestational age (completed weeks)	Birth weight (g)	DOL clinicians first recommended IC withdrawal	DOL of IC withdrawal	Neurological examination prior to IC withdrawal	Highest Ventilatory support (and pCO2) in the 24 h prior to IC withdrawal	aEEG/cEEG classification at 48-72h	aEEG/EEG classification pre-IC withdrawal	Postnatal age at hospital discharge (days)	Neuroimaging findings [DoL]	Outcome	Current Neurodevelopmental status
1	30	1434	4	4	[d4]: Generalised hypertonia; few movements, occasional abnormal posturing; seizures. Recorded RR was = VR	CMV 24/5; FiO_2=0.21; VR 60; (pCO2 12.9)	aEEG: BS on severely abnormal background	Severely abnormal, BS (CFM discontinued d4, 1h pre IC withdrawal)	29	cUSS [d3]: Extensive severe bilateral haemorrhagic periventricular leucomalacia with evolving cystic change. In keeping with severe H-I injury	Died, aged 66 days at home	NA
2	40	3000	5	5	[d5]: Comatose, flaccid, seizures; some spontanous respirations	CMV 20/4; FiO2=0.43; VR 20. (pCO2 5.75)	Frequent seizures on severely abnormal background	BS, severely abnormal background, frequent seizuresSz. (CFM stopped as IC withdrawn)	28	MRI [d 10]: widespread abnormal SI in the cerebral hemispheres at the superficial cortical grey-white junction and in the BG particularly the globus pallidus bilaterally. Conclusion: severe global H-I injury	Alive, aged 6 years 3 months	Physically able (no CP), but GDD, with social, learning and communication difficulties, seizures, and autism
3	41	3030	6	7	[d6]: Generalised hypotonia; comatose, regular spontaneous breathing but no other spontaneous movements; seizures	CMV 14/4; FiO2=0.21; VR 15. (pCO2 5.07)	Severely abnormal; LV with frequent seizures	CFM stopped day 5: Remained severely abnormal: very LV background, BS	35	MRI [d5]: widespread abnormal SI throughout the cerebral hemispheres with restricted diffusion. particularly in the perirolandic regions and thalami. Sparing of cerebellum. Conclusion: Severe H-I injury	Alive, aged 4 years 9 months	GDD, microcephaly, visual impairment, dystonia, epilepsy, GORD (fundoplication and gastrostomy feeding)
4	41	2550	5	8	[d4]: Comatose, flaccid, decerebrate posture, absent Moro, absent gag and suck reflexes,	SIMV 14/4, VR 20 FiO2=0.21. (pCO2=7.08)	Severely abnormal: BS, low voltage and frequent Sz	CFM ceased d5. Remained severely abnormal (LV with	15	MRI [d4]: widespread abnormal SI particularly on the diffusion-weighted imaging, most marked in the perirolandic region bilaterally and thalami.	Alive, aged 4 years 7 months	GDD, Spastic quadriplegic CP, dystonia, epilepsy, sensori-neural hearing loss requiring aids, able

					regular respirations, seizures			very frequent seizures)		Conclusion: Profound H-I injury.		to eat and drink under supervision
5	42	3165	8	9	[d9]: General hypotonia with intermitted hypertonia; paucity of spontaneous movements; nystagmus, no suck/root reflex, weak gag reflex, no seizures. Recorded RR was = VR	SIMV 16/4, VR 15 FiO2=0.21 (pCO2=7.54)	Severely abnormal: mainly iso-electric, very occasional bursts.	CFM ceased d9 (1 h prior to IC withdrawal): Remained severely abnormal,BS.	11	MRI [d7]: diffuse abnormal SI involving the cortex bilaterally; widespread bilateral abnormal SI in the heads of the caudate nucleus, lentiform nuclei and the lateral thalami. Conclusion: Profound H-I brain injury	Alive, aged 3 years 6 months	Spastic quadraplegic CP, visual cortical impairment, myoclonic epilepsy
6	41	4250	5	7	[d6]: generalised hypotonia, pupils small and reactive, minimal spontaneous movements, minimal spontaneous respiratory effort, seizures	SIMV 22/6.5, VR 30 FiO2=0.50. (pCO2=8.50)	Severely abnormal, burst runs of mixed frequency activity, with complete suppression for up to 18 seconds	CFM stopped d6, remained severely abnormal with BS	6	MRI unavailable. CRUS [d0] grossly abnormal Doppler, absent diastolic flow	Died age 23 days at hospice	NA
7	41	3655	8	9	[d9]: hypotonic, poor suck and gag reflex. Some spontanous respiratory effort, seizures noted	SIMV+VG (4.5 mL/kg) VR 35. FiO2 0.55 (pCO2=8.85)	Severely abnormal, suppressed background with brief bursts, inter-burst interval 8-20 s	Severely abnormal - discontinuous activity with BS up to 26 s.	10	MRI [d7]: grossly abnormal SI in the BG, internal capsule, brainstem and corpus callosum	Alive, aged 1 year 9 months	Developmental delay and microcephaly with brisk reflexes and increased tone in lower limbs, squint with absent fixing and following
8	36	2870	1	2	[d2]: minimal spontaneous movements, tone reduced, shallow breathing (RR~30), seizures noted	nHFT, 8 l/min, FiO2= 0.21 (pCO2=7.4)	Severely abnormal, extremely LV with no measurable activity	Continuous LV/ isoelectric. No seizures or BS	2	CT head [d1]: diffuse cerebral oedema, absent grey-white matter differentiation.	Died age 19 days at hospice	NA

Legend: IC, intensive care; aEEG, amplitude-integrated electroencephalogram; cEEG, conventional electroencephalogram; MRI, magnetic resonance imaging; DoL, day of life postnatal; CMV, continuous mandatory ventilation; RR, respiratory rate; VG, volume guarantee; SIMV, synchronised intermittent mandatory ventilation; nHFT, nasal high-flow therapy; BS, burst-suppression; LV, low voltage; Sz, seizures; cUS, cranial ultrasound scan; NA, not applicable; CP, cerebral palsy; GDD, global developmental delay; H-I, hypoxic-ischaemic; GORD, gastro-oesophageal reflux disease; CT, computed tomography; FiO2, fractional inspired concentration of oxygen; pCO2, partial pressure carbon dioxide; (KPa); CFM, cerebral function monitoring; SI, signal intensity; BG, basal ganglia