Three-year outcome following neonatal encephalopathy in a high-survival cohort

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This study investigated the 3-year clinical outcomes in relation to the severity of encephalopathy in high-survival infants who underwent therapeutic hypothermia. This retrospective observational study was conducted in level II/III neonatal intensive care units in Japan. The nationwide cohort included 474 infants registered in the Baby Cooling Registry of Japan between January 2012 and December 2016. Clinical characteristics, mortality rate and severe neurological impairment at age 3 years were evaluated. Of the infants, 48 (10.4%), 291 (63.1%) and 122 (26.5%) had mild, moderate and severe encephalopathy, respectively, upon admission. By age 3, 53 (11.2%) infants died, whereas 110 (26.1%) developed major disabilities. The mild group survived up to age 3. In the moderate group, 13 (4.5%) died and 44 (15.8%) developed major disabilities. In the severe group, 39 (32.0%) died by age 3.

Adverse outcomes were observed in 100 (82.0%) infants. Mortality was relatively low in all subgroups, but the incidence of major disabilities was relatively high in the severe group. The relatively low mortality and high morbidity may be due to Japanese social and ethical norms, which rarely encourage the withdrawal of intensive life support. Cultural and ethical backgrounds may need to be considered when assessing the effect of therapeutic interventions.

Hypoxic-ischaemic encephalopathy (HIE) contributes to both infant mortality and long-term morbidity in childhood. The prevalence of moderate or severe HIE is 0.4–2.0 cases per 1000 births in high-income countries, including Japan, United States and European countries. Therapeutic hypothermia is the only neuroprotective treatment that has been proven to reduce death and neurological impairments in infants with moderate or severe HIE. However, the outcomes of HIE in infants are diverse, even after therapeutic hypothermia. In early large-scale randomised controlled trials of therapeutic hypothermia, the mortality rate and composite outcome of death or moderate to severe neurological impairments among cooled infants by 2 years of age were 23.1–33.3% and 39.2–56.0%, respectively. A more recent randomised controlled trial, which provided therapeutic hypothermia (32.0 °C or 33.5 °C for either 72 or 120 h) to encephalopathic infants, reported relatively lower mortality rates (8.7–19.4%) and adverse composite outcomes (29.3–34.5%). A lower mortality rate (7.5%) and similar composite adverse outcome rate (29.5%) were reported in a study assessing 18-month follow-up data from the Japanese national registry. Furthermore, a subgroup analysis of infants with a 10-min Apgar score of zero from the same registry indicated a relatively low mortality rate (32% versus 48–54% in previous studies), as well as a high incidence of moderate to severe neurological impairments among survivors (84% versus 42–55% in previous studies). The relatively low mortality and high morbidity rates observed in the survivors were attributed to the cultural and ethical norms in Japan, where physicians rarely propose the withdrawal of intensive life support, even for infants with the most severe degrees of HIE.

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By contrast, mild HIE has rarely been a focus of study, as its prognosis is generally considered favourable\textsuperscript{5,12–14}. However, a recent study of 43 infants found that 16% of uncooled infants with mild HIE had neurological impairments by age 18–22 months\textsuperscript{15}. Despite the lack of clinical evidence to support the benefit of therapeutic hypothermia for infants with mild HIE, a considerable proportion of these infants have received such treatment in Western countries\textsuperscript{16,17}. However, such a ‘therapeutic creep’ has not been as apparent in Japan, possibly due to a nationwide dissemination campaign encouraging physicians to adhere to evidence-based therapeutic hypothermia regimens\textsuperscript{18}.

Thus, for an appraisal of preferred neuroprotective regimens, domestic backgrounds, such as cultural and ethical backgrounds and local adherence to evidence-based guidelines, may need to be considered. To facilitate comparisons of the benefits of cooling among studies conducted in different countries, clinical outcomes need to be assessed in conjunction with the level of HIE severity.

Thus, this study aimed to review the 3-year mortality rate and incidence of severe neurodevelopmental impairments according to the initial HIE severity in a Japanese cohort of infants with a high survival rate following therapeutic hypothermia.

### Results

**Final study cohort.** Clinical data were obtained from 756 infants, who were registered at 110 intensive care units over the 5-year window period. Among these infants, 474 (62.7%, final cohort) had outcome data at 3 years of age; 282 were lost to follow-up (Fig. 1). The baseline characteristics were similar between those with and without follow-up data; an exception to this was that the encephalopathy stage was more severe among infants in the final study cohort (Table 1).

| Variables               | Outcome information | Available (n = 474) | Not available (n = 282) | P     |
|-------------------------|---------------------|--------------------|------------------------|-------|
|                         |                     |                    |                        |       |
| **Background variables**|                     |                    |                        |       |
| Gestational age (weeks) | 38.5 ± 1.7          | 38.6 ± 1.7         | 0.445                  |       |
| Birth weight (g)        | 2869 ± 485          | 2918 ± 515         | 0.197                  |       |
| Birth location          |                     |                    |                        |       |
| Inborn                  | 140 (30.0)          | 76 (27.6)          |                        |       |
| Outborn                 | 327 (70.0)          | 199 (72.4)         | 0.498                  |       |
| 10-min Apgar score      | 5 [3–7]             | 5 [4–7]            | 0.227                  |       |
| First blood gas pH      | 6.94 ± 0.21         | 6.95 ± 0.21        | 0.650                  |       |
| Base deficit (mmol/L)   | 14.4 ± 10.4         | 14.4 ± 10.4        | 0.994                  |       |
| Thompson score at admission | 11 [9–15] | 11 [8–14]      | 0.066                  |       |
| 24 h after initiating cooling | 11 [8–14] | 11 [7–14]     | 0.392                  |       |
| **Sarnat stage at admission** |             |                    |                        |       |
| Mild                    | 48 (10.4)           | 45 (16.7)          |                        |       |
| Moderate                | 291 (63.1)          | 172 (63.7)         |                        |       |
| Severe                  | 122 (26.5)          | 53 (19.6)          | 0.014                  |       |
Encephalopathy stages and clinical course during hospitalisation. Among 474 infants treated with therapeutic hypothermia, encephalopathy at admission was mild in 48 (10.4%) infants, moderate in 291 (63.1%) and severe in 122 (26.5%); data were unavailable for 13 infants. The rate of emergency delivery, gestational age and body weight at birth were similar by the severity of HIE. In contrast, there was a trend that greater HIE severities were associated with being outborn, low Apgar scores at 10 min, need for resuscitation beyond 10 min and more severe metabolic acidosis represented by lower blood pH and greater base deficit (see online Supplementary Table for details and other clinical backgrounds, including the Thompson encephalopathy scores, presence of seizures and requirement for tube feeding and mechanical ventilation).

Outcomes at 3 years of age. Among the 474 infants in the final cohort, 53 (11.2%) died by the time of the 3-year follow-up, whereas 110 (26.1%) survivors developed major disabilities; 163 (34.4%) cases of death or major disability were recorded (Table 2). Among the surviving children, 67 (15.9%) and 44 (10.5%) were dependent on tube feeding and respiratory support, respectively. Hearing loss, blindness, epilepsy, Gross Motor Function Classification System > 2 and Manual Ability Classification System > 2 were noted in 28 (6.7%), 12 (2.9%), 14 (3.3%), 89 (21.1%) and 97 (23.0%) children, respectively.

Encephalopathy stages and outcomes. All 48 infants diagnosed with mild encephalopathy upon admission survived to 3 years of age without hearing loss, blindness or requirement for chronic healthcare. Of the infants with mild encephalopathy, 4.2% (2/48) had a major disability; one infant was diagnosed with cerebral palsy (GMFCS level 3), while another infant was diagnosed with both cerebral palsy (GMFCS level 5) and epilepsy (Table 2).

Of the 291 infants diagnosed with moderate encephalopathy upon admission, 13 (4.5%) died, while 44 (15.8%) survivors developed a major disability; 57 (19.6%) cases of composite adverse outcomes were recorded. Among survivors, 21 (7.6%) were dependent on respiratory support or tube feeding. At 3 years of age, 10 (3.6%), 5 (1.8%), 30 (10.8%) and 35 (12.6%) children exhibited hearing loss, blindness, epilepsy, GMFCS > 2 and MACS > 2, respectively (Table 2).

Of the 122 infants with severe encephalopathy, 39 (32.0%) died by 3 years of age; 100 (82.0%) cases of death or major disability were noted. Among the survivors, 46 (55.4%) children required respiratory support or tube feeding. Hearing loss, blindness, epilepsy, GMFCS > 2 and MACS > 2 were noted in 17 (20.5%), 7 (8.4%), 8 (9.6%), 55 (66.3%) and 58 (69.9%) children, respectively, at 3 years of age (Table 2).

Discussion

In a cohort of infants with high-survival rate from the Japanese national registry, the relationship between the severity of encephalopathy and outcomes following therapeutic hypothermia differed from that reported in other developed countries. The 3-year outcomes of Japanese HIE infants were characterised by consistently

| Outcomes | All n = 474 | Sarnat staging at admission | | | |
|----------|------------|-----------------------------|---|---|---|
| Primary outcome | | | | | |
| Death or major disability* | 163 (34.4) | 2 (4.2) | 57 (19.6) | 100 (82.0) | |
| Secondary outcomes | | | | | |
| Death | 53 (11.2) | 0 (0.0) | 13 (4.5) | 39 (32.0) | |
| Survival | 421 (88.8) | 48 (100.0) | 278 (95.5) | 83 (68.0) | |
| Major disability* | 110 (26.1) | 2 (4.2) | 44 (15.8) | 61 (73.5) | |
| Dependence on medical support | | | | | |
| Tube feeding | 67 (15.9) | 0 (0.0) | 20 (7.2) | 45 (54.2) | |
| Respiratory support | 44 (10.5) | 0 (0.0) | 12 (4.3) | 31 (37.3) | |
| Any of the above | 69 (16.4) | 0 (0.0) | 21 (7.6) | 46 (55.4) | |
| Sensory impairment | | | | | |
| Hearing loss | 28 (6.7) | 0 (0.0) | 10 (3.6) | 17 (20.5) | |
| Blindness | 12 (2.9) | 0 (0.0) | 5 (1.8) | 7 (8.4) | |
| Epilepsy | 14 (3.3) | 1 (2.1) | 5 (1.8) | 8 (9.6) | |
| Gross Motor Function Classification System | | | | | |
| Levels 3–5 | 89 (21.1) | 2 (4.2) | 30 (10.8) | 55 (66.3) | |
| Manual Ability Classification System | | | | | |
| Levels 3–5 | 97 (23.0) | 2 (4.2) | 35 (12.6) | 58 (69.9) | |

Table 2. Outcomes of cooled infants at 3 years of age. Values are shown as the number (%). Percentages are based on the number of infants for whom data were available. *Defined as survival with at least one of the following conditions: requirement for tube feeding or respiratory support, hearing loss, blindness, epilepsy, Gross Motor Function Classification System and Manual Ability Classification System scores > 2.
and severe encephalopathy (73.5%). The association of severe encephalopathy with the combination of low mortality (32%) and high morbidity (57%, severe disabilities) was also observed in a previous study conducted among severely asphyxiated infants (10-min Apgar scores of zero) in Japan11. These findings may be attributed to the reluctance among physicians in Japan to withdraw intensive life support, even in the most severe cases of encephalopathy. Future studies of neuroprotective treatments may need to consider the influence of local social and ethical backgrounds to more accurately assess the effect of therapeutic hypothermia on long-term morbidity and mortality rates.

The follow-up rate was lower in infants with mild encephalopathy, presumably reflecting the optimistic perspective of the neurological outcome and subsequent cessation of follow-up. Therefore, our current findings may predominantly reflect outcomes associated with infants with relatively more severe disease. Second, as the assessment of neurological outcomes using individualised batteries was only performed in 40% of the study population, the use of standard outcome measures was problematic. Similarly, we were unable to incorporate potential independent variables of outcomes within the analysis, such as the type of respiratory care, use of inotropic support, incidence of pulmonary hypertension and seizures and findings of amplitude-integrated electroencephalogram (aEEG) and MRI, because the type, dose and duration of supportive treatment and assessment of ultrasound sonography, aEEG and MRI significantly differ between participating units26. The evaluation of outcomes focused on chronic healthcare needs and motor function, but not on cognitive or language function, as reported in previous studies27-29. Third, although the Baby Cooling Registry of Japan disseminated tools and domestic guidelines for the evidence-based implementation of therapeutic hypothermia, including the precise assessment of encephalopathy using the Sarnat encephalopathy staging12 and the Thompson encephalopathy scoring40, the classification of the severity of encephalopathy was not standardised for this particular registry across centres. Recently, Chalak et al. demonstrated that the long-term outcomes of encephalopathic infants can be predicted using a relatively more objective categorisation of the modified Sarnat scoring criteria25. This may improve patient selection in future prospective studies.

In conclusion, the incidence of death and major disability following mild, moderate and severe HIE was reviewed for a large-scale national cohort in Japan. Mortality was relatively low in all subgroups (patients were stratified based on HIE severity), whereas the incidence of major disabilities was relatively high in infants with severe HIE. Cultural and ethical backgrounds, as well as the quality of medical care, may need to be considered when assessing the benefits of therapeutic interventions for HIE. Although the outcomes of infants with mild HIE appeared to be optimal following therapeutic hypothermia, the benefit of such treatment for this cohort of infants needs to be validated further. The natural outcomes associated with mild HIE and the neuroprotective effect of therapeutic interventions need to be addressed in future studies.
Methods

Population and data collection. The Baby Cooling Registry of Japan is an online case registry that was established in January 2012 and includes patient data from all registered Japanese level II/III neonatal intensive care centres. The details of this registry have been reported previously. This observational study was based on 3-year outcome data from 474 infants registered between January 1, 2012, and December 31, 2016 (Fig. 1).

Assessment of outcomes. The outcomes of cooled infants were assessed at 3 years of age according to the protocol of the Baby Cooling Registry of Japan. The infants’ parents were asked to assess the outcome of their cooled infants at 18 months postconceptional age and 36 months chronological age by consulting a neonatologist, paediatrician or child neurologist. Data pertaining to the following variables were collected: hearing loss; blindness; epilepsy (requiring anticonvulsant treatment); chronic healthcare needs (e.g., requirements for tube feeding, gastrostomy, tracheotomy or prolonged ventilator management upon reaching the age of 3 years old); and neuromotor function assessed using the GMFCS and MACS. GMFCS and MACS scores range from 0 to 5, with higher scores indicating greater impairment. Major disability was defined as survival with at least one of the following conditions: requirement for tube feeding or respiratory support, hearing loss, blindness, epilepsy, GMFCS > 2 or MACS > 2.

Statistical analysis. The primary outcome was death or major disability upon the 3rd year of follow-up. To assess potential bias due to follow-up loss, baseline characteristics were compared between children with and without follow-up data at 3 years of age using Student’s t-test, Mann–Whitney U test or Chi-squared test, where appropriate. Statistical findings were not corrected for multiple comparisons. For all analyses, the level of significance was set at P < 0.05. Values are shown as a number (proportion, %) for categorical variables or mean ± standard deviation (or median and interquartile range) for quantitative variables.

Ethics approval and consent. This study was conducted in accordance with the principles of the Declaration of Helsinki. The registry protocols were approved by the Ethics Committees of the Kurume University School of Medicine and Saitama Medical University, Japan. The Ethics Committee of Kurume University School of Medicine approved that informed consent was not required because only anonymised data obtained for clinical reasons were used in the study.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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**Author contributions**

K.T., S.I., M.N. and O.I. designed the study and the survey items. All authors participated in data collection. K.T., T.I., S.I. and O.I. performed the statistical analyses. K.T., J.S., T.I., A.T., T.M., Y.S. and O.I. contributed to the interpretation of the findings. K.T. and O.I. drafted the manuscript. All authors critically reviewed and revised the manuscript and the final approval of the published version. All authors agree to be accountable for all aspects of the work.

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**Competing interests**

The authors declare no competing interests.

**Additional information**

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