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Trends in Perinatal Death and Brain Damage: A Regional Population-Based Study in Southern Japan, 1998-2012

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Abstract

Assessing overall and gestational age-specific trends in perinatal mortality and cerebral palsy in Miyazaki, both neonatal death and cerebral palsy in term infants were significantly reduced for 15 years. This might be contributed by educational and referral system in perinatal medicine.

Keywords: Population-based study; Cerebral palsy; Perinatal mortality rate; Stillbirth; Neonatal death

Introduction

The prevalence of cerebral palsy (CP) has not changed over the past 50 years despite a 6-fold increase in cesarean sections [1]. The widespread use of electronic fetal heart rate (FHR) monitoring has not led to a decrease in the incidence of CP [2,3]. Clark et al. [4] concluded that CP was unpreventable considering the current status of our technology.

The prevalence of brain damage in preterm infants increased during the 1970s and 1980s as a result of their increased survival due to improvements in perinatal and neonatal management [5-8]. However, other researchers expressed different views in different periods in various countries [9-12]. In our previous study [13], preterm infants accounted for over 60% of all the infants with brain damage registered in the study region.

It is important to elucidate the causes and background of such infants with neurological damage and such information may potentially hold the key to decreasing perinatal mortality and brain damage.

Therefore, we performed a longitude study to see trends in perinatal death and brain damage by using a regional population-based study from 1998 to 2012.

Materials and Methods

In 1998, we initiated a regional population-based study focusing on perinatal death and neurological damage occurring in Miyazaki Prefecture, which has 10,000 deliveries annually and a population of 1 million. Details of our work have been reported previously [13-19].

The Miyazaki Perinatal peer-review audit conference is held twice a year, where perinatal and neonatal specialists from eight perinatal centers discuss the clinical factors associated with perinatal deaths and the neurological complications of each case. Pediatric neurologists also participate in the conference. Our criteria for registering high-risk infants with neurological damage are listed in Table 1. The definition for hypoxia to cause CP is listed in Table 2, modified from the international consensus statement on CP [20]. Congenital abnormalities include chromosomal disorders, neurological anomalies, myopathies, metabolic diseases, hydrops fetalis, known anomaly syndromes, and intrauterine exposure to teratogenic substances.

Infants were classified into five groups according to gestational age as follows: term (>37 weeks), late preterm (34-36 weeks), moderately preterm (28-33 weeks), very preterm (27-25 weeks), and extremely preterm (22-24 weeks). The infant survival rate and prevalence of neurological damage were compared among three 5-year periods, namely, 1998-2002, 2003-2007, and 2008-2012.

Using these registered cases, we investigated the prevalence of CP, clinical background, and pregnancy disorders. Perinatal deaths were defined as stillbirth occurring at >22 weeks of gestation and neonatal deaths at < 28 days of age. The study protocol was approved by the institutional ethics committee of the Faculty of Medicine, University of Miyazaki.

The chi-squared and Fisher's exact tests were used to compare proportions, and significance was taken as $p < 0.05$.

Results

Of the 156,766 deliveries in Miyazaki Prefecture from 1998 to 2012, 337 (0.21%) were stillbirths, 198 (0.13%) were neonatal deaths,

Table 1: Inclusion criteria for the neurological high-risk infants.

1	Umbilical arterial pH < 7.0 or base deficit ≥ 12 mmol/l.
2	Abnormal neurological findings during the neonatal period. a. Seizure activity b. Hypertonia or hypotonia c. Abnormal reflex d. Irritability or hyperexcitability e. Poor sucking and swallowing reflexes f. Shallow, irregular respirations g. Apnea (not caused by prematurity)
3	Abnormal neurological images during the neonatal period. a. Intraventricular hemorrhage (grades 3-4) b. Periventricular leukomalacia c. Hydrocephalus d. Congenital CNS anomalies e. Hypoxic-ischemic encephalopathy
4	Congenital infection tnat may cause neurological damage.
5	Severe IUGR (≤ 3SD)

IUGR: Intrauterine growth restriction.

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Table 2: The definition of hypoxia to cause cerebral palsy.

1 Evidence of metabolic acidosis (Umbilical arterial pH < 7.0 and base deficit > 12 mmol/l)
2 Early onset of severe or moderate neonatal encephalopathy
3 A sentinel (signal) hypoxic event occurring immediately before or during labor
4 A sudden, rapid and sustained deterioration of the fetal hypoxic sentinel event where the pattern was previously normal
5 Apgar scores of 0-6 for longer than 5 minutes
6 Early evidence of multisystem involvement
7 Imaging evidence of acute hypoxic-ischemic encephalopathy

#1 and/or #2; essential criteria, without #1, fit at least 3 of #3-7.
Modified from international consensus statement [20].

Table 3: Stillbirth, neonatal death and brain damage in each gestational age group of 5-year intervals.

		Period			p value		
		1) 1998-2002	2) 2003-2007	3) 2008-2012	1) vs 2)	2) vs 3)	1) vs 3)
Total live births		55,421	50,656	50,689			
Perinatal deaths		219	165	151	0.059	0.427	**0.007**
Stllbirth	22 to 24 wk	25	18	13	0.439	0.368	0.094
	25 to 27 wk	19	10	11	0.152	0.828	0.223
	28 to 33 wk	34	32	21	0.905	0.130	0.154
	34 to 36 wk	19	16	24	0.809	0.207	0.291
	37 wk ≤	31	27	37	0.855	0.212	0.273
	Total	128	103	106	0.355	0.839	0.449
Neonatal death	22 to 24 wk	16	18	7	0.664	**0.045**	0.095
	25 to 27 wk	12	7	6	0.354	0.999	0.322
	28 to 33 wk	18	13	9	0.517	0.521	0.190
	34 to 36 wk	8	5	4	0.694	0.990	0.476
	37 wk ≤	37	19	19	**0.038**	0.873	**0.038**
	Total	91	62	45	0.073	0.099	**0.0006**
Cerebral palsy	22 to 24 wk	20	17	8	0.826	0.109	0.065
	25 to 27 wk	11	9	14	0.982	0.405	0.410
	28 to 33 wk	30	20	31	0.272	0.124	0.633
	34 to 36 wk	11	12	17	0.829	0.354	0.17
	37 wk ≤	44	46	22	0.595	**0.004**	**0.019**
	(37 wk ≤ (excluding anomaly))	29	20	13	0.331	0.222	**0.029**
	Total	116	104	92	0.889	0.388	0.306

and 312 (0.20%) had high risk of poor neurological outcome.

Overall trends

The perinatal data for Miyazaki Prefecture are shown in Figure 1. The total number of live births was approximately 10,000 per year, with a slight decrease noted over the 15 years. The preterm birth rate increased from 5.3% in 2000 to 6.3% in 2010-2012, while the perinatal death rate significantly decreased from 6.5 to 3.0 per 1,000 births. The total prevalence of CP was 1.0-2.0 per 1,000 births with no change over the study period. The prevalence of CP in term infants appeared to be decreasing, whereas that in preterm appeared increasing.

Perinatal deaths

As shown in Table 3, perinatal deaths (including stillbirths and neonatal deaths) decreased from 219 in 1998-2002 to 151 in 2008-2012 ($p < 0.01$, chi-squared test). These findings were due to the remarkable decrease in neonatal deaths (from 91 in 1998-2002 to 45 in 2008-2012, $p=0.0006$). Neonatal mortality significantly decreased in term infants (>37 weeks) from the period 1998-2002 to the period 2003-2007 and 2008-2012 ($p=0.038$, respectively). A significant decrease was also noted for extremely preterm infants (22-24 weeks) when comparing the neonatal mortality in 2003-2007 and 2008-2012 ($p=0.045$).

Cerebral palsy

During the 15-year study period, the number of registered CP cases was 312 out of 156,766 live births (0.20%). These included extremely preterm (22-25 weeks) infants (n = 45), very preterm (25-27 weeks) infants (n = 34), moderately preterm (28-33 weeks) infants (n = 81), late preterm (34-36 weeks) infants (n = 40), and term (>37 weeks) infants (n = 112). Thus, 64% of CP cases were among the preterm infants, while 36% were among the term infants. The number of live births and prevalence of CP in each group is shown in Figure 2. In term infants, the prevalence of CP was 0.4 per 1,000 live births, while in late-preterm infants, it rose up to 3.0 per 1,000. It increased exponentially to 271 per 1,000 in extremely preterm infants.

The backgrounds of the infants with CP are shown in Figure 3. In preterm infants, the major factors were periventricular leukomalacia (26%), prematurity (23%) such as intraventricular hemorrhage, necrotizing enterocolitis, and the presence of a congenital anomaly (18%), while in term infants, the most common factor was the presence of a congenital anomaly (45%), followed by hypoxia (33%).

The trends for all CP evaluated for the 5-year intervals indicated no significant changes (Table 3). However, in term infants, the number of CP cases decreased from 44 in 1998-2002 to 22 in 2008-2012 ($p =0.019$, Fisher's exact test). Similarly, in extremely preterm infants, it decreased from 20 in 1998-2002 to 8 in 2008-2012, without significant difference ($p =0.065$). After excluding the cases of congenital anomaly, the number of CP in each time interval of 1998-2002, 2003-2007, and 2008-2012 was 29, 20, and 13, respectively.

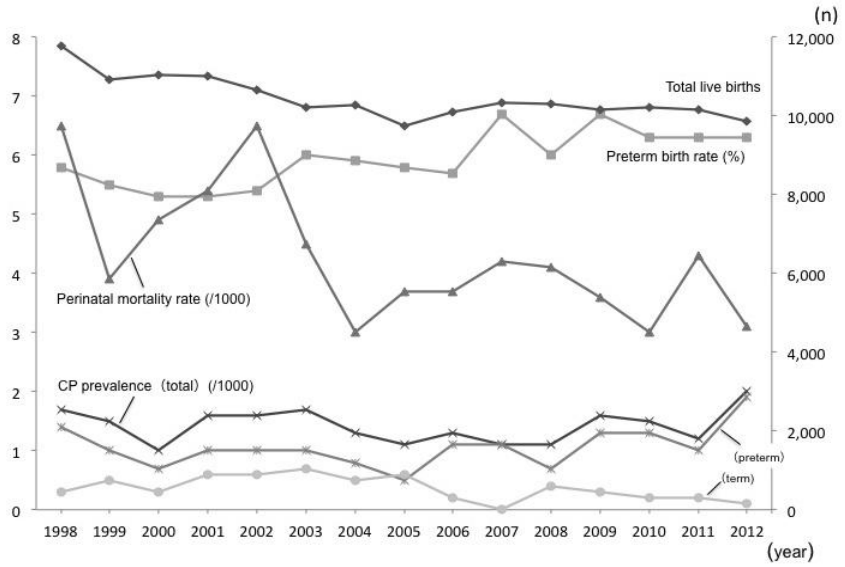

Figure 1: Trends in perinatal data in Miyazaki Prefecture (1998-2012).

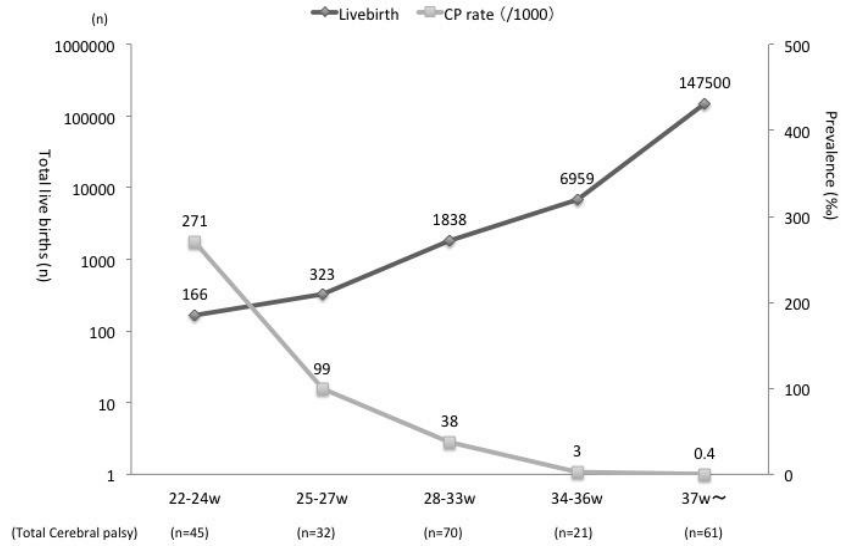

Figure 2: Prevalence of brain damage in each gestational age group, excluding congenital malformation (1998-2012).

There was a significant decrease from 1998-2002 to 2008-2012 (p =0.029). And the occurrence of hypoxia in term infants in each interval decreased significantly from 18 in 1998-2002 to 6 in 2008-2012 (p <0.05) (Figure 4).

Discussion

Some population-based studies have investigated perinatal death and CP in different regions over different time periods [9-12]. Over the past 50 years, the preterm mortality rate, especially in very low birth weight infants have shown a remarkable reduction [6-12]. Given such improved survival rates in preterm or very low birth weight infants, the prevalence of CP was noted to increase during the 1970s and 1980s [6-8]. However, in another study area, it was noted that improvements in the survival of preterm infants did not increase the prevalence of CP [9-11].

In our regional population-based study encompassing 15 years, the perinatal mortality has improved significantly with improving neonatal mortality rate. This observation is compatible with previous reports [5,8,10-12].

We observed significant reductions in the rate of death and CP in term infants. These reductions contributed to the decrease in total neonatal mortality and prevalence of CP. Hypoxia was the second major factor that accounted for one-third of all CP cases in term infants. A reduction in the occurrence of hypoxia related CP in term infants thus had a significant impact on the prevalence of CP.

A possible explanation for the improvements in mortality and prevalence of CP in term infants is the wide spread use of FHR monitoring and some outreach educations in our district. For example, we previously reported that there were 1,312 referral cases

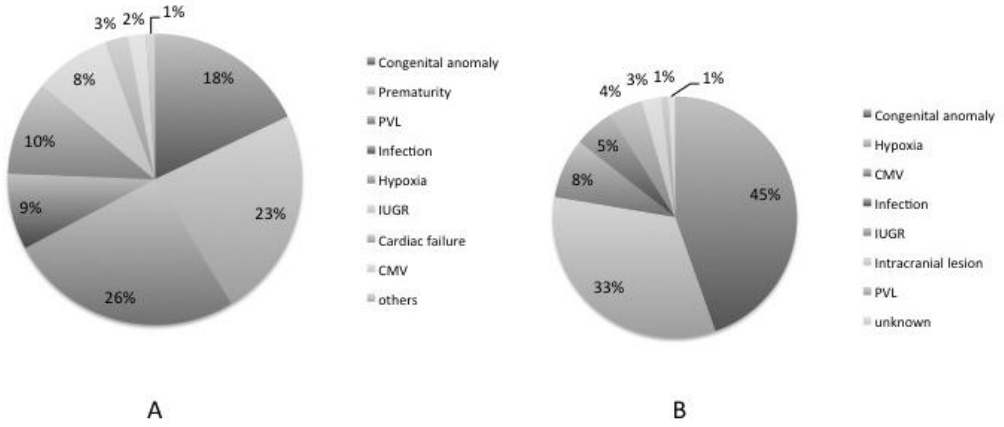

Figure 3: Background of brain damage (1998-2012) by A, preterm infant (n = 200); and B, term infant (n = 112).

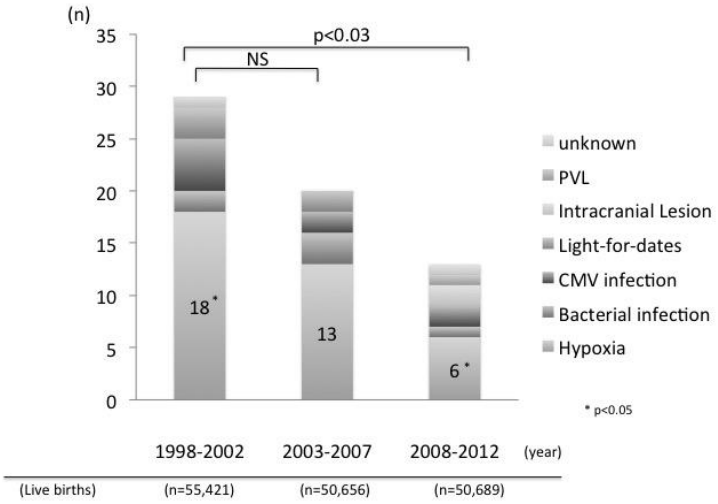

Figure 4: Brain damage in term infants in a 5-year interval, excluding congenital anomalies (1998-2012).

from primary physicians to perinatal centers for fetal indications, those were preterm labor (37%), non reassuring fetal status on FHR monitoring (35%), and preterm premature rupture of membranes (26%) [21]. Thus, referral cases due to abnormal FHR findings are relatively frequent in our district. We speculated that maternal transfer was performed during the early stages of abnormal FHR patterns and the fetuses were delivered early enough to prevent severe acidosis with adequate support for neonatal resuscitation.

Another clinical trial in our local district was the centralization of FHR monitoring with the help of specialists in the secondary centers to interpret results and determine clinical actions on a 24-h basis [22]. In that study, out of 9,139 deliveries over three-year period, FHR centralization system showed that the incidence of acidemia was significantly decreased (from 0.47% to 0.11%, p= 0.028) without a increase in cesarean birth rate due to nonreassuring FHR patterns.

The educational courses of neonatal cardiopulmonary resuscitation for obstetricians, midwives, and nurses might have also helped to achieve better outcomes for asphyxiated newborns in our district.

The US National Institute of Child Health and Human Development (NICHD) advocated the importance of late-preterm infants in 2005 [23]. Petrini JR et al. [24] reported that late-preterm infants were 3.39 times more likely to have CP than term infants. Although short-term outcomes in preterm infants appear to have improved in recent years, long-term outcomes remain unfavorable. Our data also showed that the CP prevalence of late-preterm was more than 7 times higher than that of term.

This study has several limitations. First, we mainly followed high-risk infants in the neonatal period in order to investigate neurological complications. Such an approach involves the risk of underreporting due to an incomplete dataset. In this study, we could follow the neurological development, as evaluated by pediatricians, in 90% of the high-risk infants until the age of 2 years or older. We also did not fully include neonates, who appeared normal at birth but developed neurological damage later, as reported in the Dublin study [3]. Despite these limitations, strength of our study is that our registration system was previously determined to cover 96% (136/142) of infants with neurological damage in our population [17].

The trends observed in the present study indicate that perinatal

death and the prevalence of CP in Miyazaki Prefecture from 1998 through 2012 decreased significantly in term structively normal infants. This speculated to be the establishment of the perinatal referral system, the educational system for interpretations of FHR tracings, and timely provision of necessary medical treatment.

Based on these findings, we should work out countermeasures as gestational ages in order to prevent brain damage. And still there is a room to reduce not only perinatal death but also CP. Future studies regarding the effects on the outcome should be evaluated without congenital abnormalities, which accounts for high percentage of brain damage especially in term infants.

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