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Risk of cerebral palsy associated with neonatal encephalopathy in macrosomic neonates

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Running foot: Overgrowth and cerebral palsy

ABSTRACT

Aims: To determine whether macrosomic infants with birth weight ≥ 4.0 kg have increased risk of cerebral palsy associated with neonatal encephalopathy (Enc-CP).

Study design: A retrospective review of 132 singleton infants with Enc-CP fulfilling all of the following criteria: born at gestational week (GW) ≥ 37 (*n* = 126) or weighing ≥ 2.5 kg at birth (*n* = 116) in or after January 2009 in Japan, no identifiable causes of cerebral palsy other than antenatal or intrapartum hypoxia, and exhibition of neonatal encephalopathy. National statistics of Japan were used to determine the numbers of infants according to birth weight categories.

Results: Of the 116 infants with birth weight ≥ 2.5 kg, 46 (39.7%), 49 (42.2%), 17 (14.7%), and 4 (3.4%) infants had birth weight of 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg, respectively. Corresponding figures among Japanese infants born in 2009 – 2011 were 42.8%, 45.4%, 10.9%, and 0.90%, respectively. Infants with birth weight ≥ 4.0 kg had a relative risk (95% confidence interval) of Enc-CP of 3.89 (1.52 – 9.95) compared to those with birth weight of 2.5 – 2.99 kg.

Conclusions: Japanese infants with birth weight ≥ 4.0 kg have increased risk of Enc-CP.

Keywords: cerebral palsy, diabetes mellitus, gestational hypoxic encephalopathy, macrosomia

INTRODUCTION

Macrosomia in neonates is associated with adverse maternal and neonatal outcomes, including dystocia, cesarean delivery, severe perineal laceration, postpartum hemorrhage, and puerperal infection in the mother and persistent injury and Erb's palsy in the neonate.[1 – 4] A high birth weight is associated with shoulder dystocia, which is a potentially devastating obstetric complication that can lead to permanent neurological injury. Rates of operative delivery and infants with low Apgar score increase with advancing gestational week (GW) at delivery among primiparous women with spontaneous onset of labor at term.[5] Post-term pregnancy with gestational week (GW) 42 or more is associated with increased risk of fetal macrosomia and cerebral palsy (CP) .[6] These results suggest that intrapartum hypoxia is likely to occur in infants with a high birth weight or born at post-term (GW ≥ 42) compared to those with an appropriate birth weight or those born at GW 37 – 39.

The prevalence of overall CP is estimated to be 0.5 – 1.4 per 1000 live births for infants weighing ≥ 2.5 kg.[7, 8] Neonates with intrapartum hypoxia exhibit newborn encephalopathy,[9] but intrapartum hypoxia accounts for less than 30% of all cases of newborn encephalopathy[10, 11] and newborn encephalopathy accounts for approximately one quarter of all cases of CP.[12] Thus, as CP associated with neonatal encephalopathy (Enc-CP) is rare, accounting for approximately 10% of all CP,[13] it requires a large cohort to substantiate whether infants with a high birth weight actually have a higher risk of developing Enc-CP. This issue has not been extensively studied mainly due to the rare occurrence of Enc-CP.

This retrospective study was performed to determine whether infants with higher birth weight have increased risk of developing Enc-CP using a unique cohort consisting of women who gave birth to infants with Enc-CP and received monetary compensation for their children's CP from the Japan Council for Quality Health Care (JCQHC)[14] and National Statistics of Japan.

MATERIALS AND METHODS

This study was conducted after being approved by the Ethics Committee of Hokkaido University Hospital.

The Japan Obstetric Compensation System for CP, to compensate for CP derived in principle from peripartum hypoxia and to improve perinatal care, was launched by the JCQHC on 1 January 2009, and provides rapid monetary compensation for CP in infants with birth weight > 2000 g and/or pregnancy length > 33 weeks.[14] Infants who do not fulfill the above criteria but are born at > 28 weeks are also eligible for compensation after case-by-case review. This system was described in detail previously.[15] Until the end of December 2012, a total of 425 women received monetary compensation for their children's CP because peripartum hypoxic conditions were not excluded as causative factors of CP by preliminary investigation according to an announcement by the JCQHC [cited on 5 Jun 2013, available from URL: http://www.sanka-hp.jcqhc.or.jp/pdf/Saihatsu_Report_03_All.pdf]. A professional committee belonging to the JCQHC then investigated causative factors for CP in 182 of the 425 patients and published 182 brief reports regarding 182 patients before the end of December 2012.

We were given access to information on the detailed clinical courses of all 182 women whose causative factors were investigated by a professional committee belonging to the JCQHC until the end of December 2012. Information leading to identification of an individual, such as age, body composition characteristics, time, and city when and where delivery occurred, was masked in these reports describing the detailed clinical courses of 182 women. Thus, we were unable to specify the time when delivery occurred from these reports. However, all women gave birth on or after 1 January 2009, and information on clinical courses, such as GW at delivery, birth weight, singleton or multifetal pregnancy, and causative factors for CP in the infant, were available. We reviewed these 182 cases.

Finally, we analyzed 132 infants with Enc-CP born to 132 women after excluding 50 infants who did not meet the inclusion criteria. All 132 infants fulfilled the following criteria: singleton infant, born at GW ≥ 37 or weighing ≥ 2.5 kg at birth, no identifiable apparent cause of CP other than antenatal or intrapartum hypoxia, and exhibition of neonatal encephalopathy defined as seizures alone or any two of the following lasting for longer than 24 h: difficulty maintaining respiration (of presumed central origin),

difficulty feeding (of presumed central origin), and disturbed consciousness. Of the 132 infants, 16 had birth weight < 2.5 kg and six were born preterm at GW < 37. Demographic characteristics of the 132 study subjects are shown in Table 1. Operative delivery was conducted in 28 women, but was unsuccessful in 11 women. There was only one woman in whom shoulder dystocia was determined as a causative factor for CP by the JCQHC.

We determined the relative risk of Enc-CP among infants with higher birth weight or born to women at GW ≥ 40 compared to those with lower birth weight or born at GW 37 – 39 on the assumption that these 132 infants originated from 1000000 to 1600000 singleton infants who were born with birth weight ≥ 2500 g or born at and after GW 37. Vital statistics of Japan were obtained from the website of the Japan Ministry of Health, Labour, and Welfare (JMHLW) [cited June 23, 2013, available from URL: http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001101883].

All of the data are presented as the median (range). The unpaired *t* test, Kruskal–Wallis test, and Mann–Whitney U test were used to analyze the results. Fisher's exact test was used for comparison of frequencies. The software package Stat View 5.0 for Macintosh (SAS Institute Inc. Cary, NC) and VassarStats: Website for Statistical Computation (http://vassarstats.net/index.html) were used for all statistical analyses, and $P < 0.05$ was taken to indicate significance.

RESULTS

Of the 126 infants with Enc-CP born at term (GW ≥ 37), 75 (59.5%), 50 (39.7%), and 1 (0.8%) infant were born at GW 37 – 39, 40 – 41, and ≥ 42, respectively (Table 1). Of the 116 infants with birth weight ≥ 2.5 kg, 46 (39.7%), 49 (42.2%), 17 (14.7%), and 4 (3.4%) infants had birth weights of 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg, respectively (Table 1).

The data indicated that 1008622, 1009615, and 990146 neonates were born at term (GW ≥ 37) in 2009, 2010, and 2011, respectively, in Japan (Table 2). Among them, infants born at GW 37 – 39, 40 – 41, and ≥ 42 accounted for approximately 62%, 37%, and 0.35%, respectively, each year (Table 2). There were 967141, 968015, and 950198

neonates with birth weight ≥ 2.5 kg in 2009, 2010, and 2011, respectively. Among them, infants with birth weight of 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg accounted for approximately 42.8%, 45.4%, 10.9%, and 0.9%, respectively, each year (Table 2). These percentages were used in further analyses as shown in Tables 3 and 4.

Risk of cerebral palsy associated with neonatal encephalopathy according to gestational week at delivery

We assumed that 126 infants with Enc-CP born at term (GW ≥ 37) originated from 1000000 to 1600000 infants born at term. For example, if we assumed that the 126 infants with Enc-CP were from 1000000 infants born at term, the 75, 50, and 1 infants with Enc-CP born at GW 37 – 39, 40 – 41, and ≥ 42 would be from 620000 (62% of 1000000 infants), 376300 (37.6% of 1000000 infants), and 3700 (0.37% of 1000000 infants) infants born at GW 37 – 39, 40 – 41, and ≥ 42, respectively (Table 3). Based on this assumption, the occurrence rates of Enc-CP would be 1.21, 1.33, and 2.70 per 10000 infants born at GW 37 – 39, 40 – 41, and ≥ 42, respectively, and the differences between groups would not reach statistical significance. In any assumption of the background population ranging from 1000000 to 1600000, no significantly increased risk of Enc-CP occurred with advancing GW at delivery.

Risk of cerebral palsy associated with neonatal encephalopathy according to birth weight

The number of newborns with birth weight ≥ 2.5 kg corresponded to approximately 96% of the number of infants born at term (Table 2) (95.8% [967141/1008622] in 2009, 95.9% [968015/1009615] in 2010, and 96.0% [950198/990146] in 2011). Thus, the numbers of infants with birth weight ≥ 2.5 kg would be 960000, 1152000, 1344000, and 1536000 assuming the numbers of infants born at term were 1000000, 1200000, 1400000, and 1600000, respectively (Table 4). As infants with birth weight 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg accounted for approximately 42.8%, 45.4%, 10.9%, and 0.9% of all infants with birth weight ≥ 2.5 kg, respectively (Table 2), the numbers of infants with birth weight 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg, for example, would be 410880, 435840, 104640, and 8640, respectively, assuming that the 116 infants with Enc-CP and birth weight ≥ 2.5 kg were from 960000 infants (Table 4). Under this assumption, 46, 49, 17, and 4 infants with Enc-CP were

from 410880, 435840, 104640, and 8640 infants, respectively, with Enc-CP occurrence rates of 1.12, 1.12, 1,62, and 4.63 per 10000 infants with birth weight 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg, respectively (Table 4). The relative risk (RR) (95% confidence interval [CI]) of Enc-CP was 3.89 (1.52 – 9.95) for infants with birth weight ≥ 4.0 kg compared with those with birth weight 2.5 – 2.99 kg. This RR (95%CI) did not change according to the assumed size of the background population. Thus, infants with birth weight ≥ 4.0 kg had a significantly higher risk of developing Enc-CP than those with birth weight 2.5 – 2.99 kg.

Clinical features in the 4 patients with Enc-CP and birth weight ≥ 4.0 kg

All four women gave birth at and after GW 39 and all except one (Case 4, in Table 5) were expected to have relatively large infants. One woman was diagnosed with gestational diabetes mellitus (Case 1). Case 1 may have needed an earlier delivery with emergency cesarean section. Non-reassuring fetal status occurred after a failed vacuum delivery in Case 2. Cord prolapse occurred soon after an amniotomy in Case 3. No screening for gestational diabetes mellitus was performed in Case 4 and there was a large dissociation between an estimated fetal body weight (3100g) and an actual birth weight (4030g) in this patient. Placental abruption occurred 1.5 hour after an administration of prostaglandin E_2 in Case 4.

DISCUSSION

This study demonstrated that birth weight ≥ 4.0 kg is a risk factor for Enc-CP. In a study using 1359878 children born at term during 1984 –1990 in the Swedish Medical Birth Registry,[16] infants with birth weight > mean + 3 standard deviation had an odds ratio of CP (95% confidence interval), 1.7 (0.98 – 2.8). Thus, the odds ratio did not reach a significant level even in a large cohort of 1359878 children. Although the Swedish study has suggested an increased risk of Enc-CP among macrosomic infants, it has not been shown that infants with birth weight ≥ 4.0 kg are at an increased risk of CP.

The risk of macrosomia is high in pregnancies at GW ≥ 41.[11] The risk of neurologic complications including hypoxic ischemic encephalopathy and cerebral palsy is increased in pregnancy at GW ≥ 42 in a recent study based on PubMed search and Cochrane library.[11] These results together with our patients shown in Table 5 strongly

suggested that difficult labor associated with macrosomia was a contributing factor to Enc-CP.

Although macrosomic neonates with birth weight ≥ 4.0 kg occur frequently in the USA, with incidence rates ranging from 7.6% to 13% among full-term USA infants,[1,3,17] its prevalence is very low accounting for only 0.9% of all full-term neonates in Japan,[18] as was also confirmed in the present study. However, neonates with birth weight ≥ 4.0 kg accounted for 3.4% (4/116) of all cases of Enc-CP in this study, suggesting that macrosomic neonates with birth weight ≥ 4.0 kg are at an increased risk of neonatal encephalopathy leading to CP.

This study included four infants with birth weight ≥ 4.0 kg who developed Enc-CP. As all data regarding patients with Enc-CP were dependent on information released by the JCQHC in which birth date of study subjects was masked, the main weakness of this study was that the background population from which the 132 study subjects with Enc-CP originated was unclear. Therefore, we assumed in this study that the 116 study subjects with Enc-CP and birth weight ≥ 2.5 kg originated from 960000 to 1536000 newborn infants with birth weight ≥ 2.5 kg. As shown in Table 4, the RR (95%CI) of Enc-CP, 3.89 (1.52-9.95) for infants with birth weight ≥ 4.0 kg (reference, infants with birth weight 2.5 – 2.99 kg) did not change according to the assumed size of the background population from 960000 to 1536000, thus demonstrating a significantly higher risk of Enc-CP among macrosomic infants compared to those with birth weight 2.5 – 2.99 kg. However, as expected, the absolute risk of Enc-CP changed according to the size of the assumed background population.

Neonates suffering from intrapartum hypoxia inevitably exhibit neonatal encephalopathy,[9] and intrapartum hypoxia accounts for less than 30% of all cases of neonatal encephalopathy. [10,11] Furthermore, neonatal encephalopathy accounts for one quarter of all cases of CP.[12] The overall prevalence of CP does not differ markedly between countries,[8] and was estimated to be 0.5 – 1.4 per 1000 live births for infants weighing ≥ 2.5 kg. [7,8] Assuming that 10% of all cases of CP were Enc-CP, [13] the prevalence of Enc-CP would be 0.5 – 1.4 per 10000 live births for infants weighing ≥ 2.5 kg. The absolute risk of Enc-CP for macrosomic infants with birth weight ≥ 4.0 kg

increased from 2.89 to 4.63 per 10000 infants with decreasing size of the assumed background population from 13824 to 8640 infants with birth weight ≥ 4.0 kg (Table 4). However, there were approximately 8700 macrosomic newborns with birth weight ≥ 4.0 kg yearly totaling 34800 infants during the 4-year period after establishment of the compensation system for CP in January 2009. However, as applicants for our compensation system must be certified with CP, and diagnosis of CP is usually feasible in children 1 year of age or more, four macrosomic infants with Enc-CP in this study may have been born by the end of 2011. Therefore, the background population of four macrosomic infants with Enc-CP must be at most 26100. Under this assumption, the absolute risk of Enc-CP for macrosomic infants with birth weight ≥ 4.0 kg would be 1.53 per 10000 (4/26100), total number of background of population of infants with birth weight ≥ 2.5 kg would be 2880000, and the risk of Enc-CP among infants with birth weight ≥ 2.5 kg would be 0.4 per 10000 live births (116/2880000), somewhat lower than that of 0.5 per 10000 live births, a lower range figure derived from the assumption that Enc-CP accounted for 10% of all CP. In the assumed ranges of background population in this study, the absolute risk of Enc-CP for infants with birth weight ≥ 2.5 kg was between 0.76 (116/1536000) and 1.21 (116/960000) per 10000. Thus, our assumption regarding the background population may have been reasonable to estimate the absolute risk of Enc-CP according to birth weight.

In conclusion, the present study demonstrated that macrosomic infants with birth weight ≥ 4.0 kg were at a 3.9-fold higher risk of developing cerebral palsy associated with neonatal encephalopathy compared to those with birth weight 2.5 – 2.99 kg. The absolute risk of cerebral palsy associated with neonatal encephalopathy for macrosomic infants with birth weight ≥ 4.0 kg ranged from 2.9 to 4.6 per 10000 under our assumptions. In this study, three of the 4 macrosomic infants with Enc-CP were expected to have a greater birth weight more than 3500g. Although Enc-CP is rare occurrence even in macrosomic infants as shown in this study, clients and physicians may need to be careful in choosing delivery mode in such pregnancies with a possible macrosomic infants[19] for the avoidance of neonatal encephalopathy leading to cerebral palsy.

Conflict of Interest

All authors declare that they have no financial relationships with biotechnology manufacturers, pharmaceutical companies, or other commercial entities with an interest in the subject matter or materials discussed in this manuscript.

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Table 1. Demographic characteristics of 132 study subjects

Primipara	73 (55.3%)
Placental abruption	36 (27.3%)
Umbilical cord prolapse	11 (8.3%)
Uterine rupture	6 (4.5%)
Fetomaternal transfusion	2 (1.5%)
Shoulder dystocia	1 (0.8%)
Breech vaginal delivery	1 (0.8%)
Operative delivery†	28 (21.2%)
Emergency cesarean delivery	76 (57.6%)
Apgar score at 5 min < 4	69 (52.3%)
UAB pH < 7.0	50 (50/132:37.0%, 50/87:57.5%)‡
GW at delivery*	38.9±1.4
37 – 39	75 (59.5%)
40 – 41	50 (39.7%)
42 –	1 (0.8%)
Birth-weight (kg)*	3021±456
2.5 – 2.99	46 (39.7%)
3.0 – 3.49	49 (42.2%)
3.5 – 3.99	17 (14.7%)
4.0 –	4 (3.4%)

UAB, umbilical arterial blood; †, 11 of 28 women underwent emergency cesarean section after an unsuccessful operative delivery; ‡, Data were available for 87 infants; *, Of the 132 infants with cerebral palsy associated with neonatal encephalopathy, 6 were born at preterm (GW < 37) and 16 had birth weight < 2.5 kg.

Table 2. Number of newborns according to gestational week at delivery and birth weight in Japan 2009 – 2011

	GW at delivery			Birth-weight (kg)			
Year	37 – 39	40 – 41	≥ 42	2.5 – 2.99	3.0 – 3.4	3.5 – 3.99	≥ 4.0
2009	623682	380998	3942	413013	439503	105670	8955
	(61.8%)	(37.8%)	(0.39%)	(42.7%)	(45.4%)	(10.9%)	(0.93%)
2010	631659	374374	3582	415293	439329	104680	8713
	(62.6%)	(37.1%)	(0.35%)	(42.9%)	(45.4%)	(10.8%)	(0.90%)
2011	621934	364994	3218	405714	431711	104195	8578
	(62.8%)	(36.9%)	(0.33%)	(42.7%)	(45.4%)	(11.0%)	(0.90%)

This table was based on the data released by the Japanese Ministry of Health Labour, and Welfare (cited June 23, 2013, available from URL: http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001101883). Percentage of infants with varied gestational week (GW) at delivery or varied birth-weight is indicated in parenthesis.

Table 3. Risk of cerebral palsy associated with neonatal encephalopathy according to gestational week at delivery

	Gestational week at delivery		
	37 – 39 (62.0%*)	40 – 41 (37.6%*)	≥ 42(0.37%*)
Background population†			
1000000	75/620000	50/376300	1/3700
	(1.21/10000)	(1.33/10000)	(2.70/10000)
	1.0 (Ref.)	1.06 (0.85–1.31)	2.22 (0.32-15.55)
1200000	75/744000	50/451560	1/4440
	(1.01/10000)	(1.11/10000)	(2.25/10000)
	1.0 (Ref.)	1.06 (0.85–1.31)	2.22 (0.32-15.55)
1400000	75/868000	50/526820	1/5180
	(0.86/10000)	(0.95/10000)	(1.93/10000)
	1.0 (Ref.)	1.06 (0.85–1.31)	2.22 (0.32-15.55)
1600000	75/992000	50/602080	1/5920
	(0.76/10000)	(0.83/10000)	(1.69/10000)
	1.0 (Ref.)	1.06 (0.85–1.31)	2.22 (0.32-15.55)

*, Assumed percentage based on figures in Table 2; †, 126 Enc-CP infants consisting of 75, 50, and 1 with a GW at delivery 37 – 39, 40 – 41, and ≥ 42, respectively, were assumed to originate from varied populations ranging from 1000000 to 1600000 infants born at GW ≥ 37.

Table 4. Risk of cerebral palsy associated with neonatal encephalopathy according to birth weight

	Birth weight (kg)			
	2.5 – 2.99 (42.8%*)	3.0 – 3.49 (45.4%*)	3.5 – 3.99 (10.9%*)	≥ 4.0 (0.90%*)
Background population†				
960000	46/410880	49/435840	17/104640	4/8640
	(1.12/10000)	(1.12/10000)	(1.62/10000)	(4.63/10000)
	1.0 (Ref.)	1.00 (0.82-1.22)	1.33 (0.89-2.00)	3.89 (1.52-9.95)
1152000	46/493056	49/523008	17/125568	4/10368
	(0.93/10000)	(0.94/10000)	(1.35/10000)	(3.86/10000)
	1.0 (Ref.)	1.00 (0.82-1.22)	1.33 (0.89-2.00)	3.89 (1.52-9.95)
1344000	46/575232	49/610176	17/146496	4/12096
	(0.80/10000)	(0.80/10000)	(1.16/10000)	(3.31/10000)
	1.0 (Ref.)	1.00 (0.82-1.22)	1.33 (0.89-2.00)	3.89 (1.52-9.95)
1536000	46/657408	49/697344	17/167424	4/13824
	(0.70/10000)	(0.70/10000)	(1.02/10000)	(2.89/10000)
	1.0 (Ref.)	1.00 (0.82-1.22)	1.33 (0.89-2.00)	3.89 (1.52-9.95)

*, Assumed percentage based on figures in Table 2; †, 116 Enc-CP infants consisting of 46, 49, 17, and 4 with birth weight 2.5 – 2.99 kg, 3.0 – 3.49 kg, 3.5 – 3.99 kg, and ≥ 4.0 kg, respectively, were assumed to originate from varied populations ranging from 960000 to 1536000 infants born with birth weight ≥ 2.5 kg.

Table 5. Details in the four patients with Enc-CP and birth weight ≥ 4.0 kg

	Parity	GDM	EFBW/ GW	Birth weight/ GW at delivery	Time interval†	Use of uterotonics	Episodes/ delivery mode
Case 1	0	Yes	3900/40	4032/40	18 h	No	PNRFS, VD
Case 2	1	No	3800/40	4110/41	14 h	Yes	DL, FVD, ECS
Case 3	2	No	3700/38	4268/39	22 h	Yes	DL, Amniotomy, CP, ECS
Case 4	0	NA	3100/39	4030/39	1.5 h	Yes	Placental abruption, ECS

CP, cord prolapse; DL, difficult labor; ECS, emergency cesarean section; EFBW, estimated fetal body weight with ultrasound study; FVD, failed vacuum delivery followed by non-reassuring fetal status; GDM, gestational diabetes mellitus; GW, gestational week; NA, not assessed; PNRS, prolonged non-reassuring fetal status with cardiotocography; VD, vaginal delivery; †, time interval (hours) after onset of labor pains or initiation of uterotonics until delivery. Uterotonics included oxytocin, prostaglandin $F_{2\alpha}$ and prostaglandin E^2.