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[ORIGINAL ARTICLE] for JOGR

Title: Intrapartum risk factors for neonatal encephalopathy leading to cerebral palsy among women without apparent sentinel events

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Running foot: Intrapartum risk factors for CP

20 **Abstract**

21 **Aims:** To determine intrapartum factors associated with neonatal encephalopathy
22 leading to cerebral palsy (NE-CP).

23 **Methods:** Analyses of 70 NE-CP cases fulfilling all of the following criteria: cephalic
24 singleton pregnancy attempting vaginal delivery (AVD) at gestational week (GW) ≥ 36 ,
25 intrapartum occurrence of non-reassuring fetal status without apparent causes following
26 reassuring fetal status on admission, and development of NE-CP, in comparison with
27 210 AVD controls with infants with 1- and 5-min Apgar scores ≥ 8 matched for GW,
28 maternal parity, and use of uterotonics. Suboptimal care was defined as delayed reaction
29 resulted from misinterpretation of fetal heart rate (FHR) tracing or inappropriate trial of
30 instrumental delivery (TOID). Successful and failed TOID were defined as vaginal and
31 cesarean deliveries after TOID, respectively. The 210 controls were assumed not to have
32 had suboptimal care.

33 **Results:** The rates of successful (34% vs. 12%) and failed TOID (11% vs. 0.0%),
34 cesarean section (34% vs. 14%), suboptimal care (57% vs. 0.0%), pregnancy-induced
35 hypertension (11% vs. 2.4%), birth weight ≥ 3800 g (8.6% vs. 1.9%), subgaleal
36 hemorrhage (16% vs. 0.0%) were significantly higher in cases than controls. Selection
37 with the stepwise method and logistic regression analysis identified four independent
38 risk factors for NE-CP: suboptimal intrapartum care (odds ratio [95% confidence
39 interval], 2.21 [1.99 – 2.47]), cesarean section (1.19 [1.08 – 1.31]), successful TOID
40 (1.14 [1.03 – 1.25]), and hypertension (1.20 [1.01 – 1.42]).

41 **Conclusions:** Training programs for improved interpretation of FHR tracing and
42 appropriate TOID are required to prevent NE-CP among healthy and mature fetuses in
43 Japan.

44 (Word count <250)

45 **Key words:** fetal heart rate tracing, instrumental delivery, macrosomia, non-reassuring
46 fetal status, shoulder dystocia, vacuum delivery

47

Introduction

Healthy fetuses based on fetal heart rate (FHR) tracing at the onset of labor pains can develop neonatal encephalopathy (NE) and subsequently develop cerebral palsy (CP). Well-known causative factors for CP derived from hypoxic conditions include placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, or placenta previa [1 - 5]. However, some infants develop NE leading to CP (NE-CP) in the absence of such risk factors.

As suboptimal intrapartum care is commonly seen with NE, especially in neonates with metabolic acidemia in Sweden [6], and as NE proceeds to CP in some cases [7], suboptimal intrapartum care may be a risk factor for NE-CP. Instrumental deliveries, including vacuum and forceps deliveries, are widely used in patients requiring facilitated delivery. However, as some trials of instrumental deliveries (TOID) fail to provide successful vaginal delivery, some cases of failed TOID require cesarean section during labor. In such cases with failed TOID for non-reassuring fetal status (NRFS), delay in delivery increases the theoretical risk of NE-CP. Vacuum delivery is associated with serious complications, such as subgaleal hemorrhage (SGH), and some of neonates with SGH die or develop CP later [8, 9]. Thus, TOID may be associated with increased risk of NE-CP. However, as the prevalence of CP is low, approximately 1 per 1000 live births for infants weighing ≥ 2.5 kg [10, 11], and as intrapartum hypoxia accounts for less than 30% of all cases of NE [12, 13], it is unclear whether suboptimal intrapartum care and TOID increase the risk of NE-CP.

The present study was conducted to determine the intrapartum factors associated with increased risk of NE-CP.

71

72 **Materials and Methods**

73 This study was conducted after approval by the Ethics Committee of Hokkaido
74 University Hospital.

75 *Selection of 70 cases with NE-CP*

76 The Japan Council for Quality Health Care (JCQHC) launched a new medical insurance
77 system, the Japan Obstetric Compensation System for Cerebral Palsy, on January 1,
78 2009, to compensate for cerebral palsy (CP) derived in principle from intrapartum
79 hypoxia and to improve perinatal care. The details of this system were described
80 previously [4]. In this system, maternal and neonatal records were audited by members
81 of the investigation committee belonging to the JCQHC. One of the authors (HM) was a
82 member of this committee. Each case was clinically assessed for the presence or
83 absence of suboptimal ante- and intrapartum care, which was assigned by consensus.
84 Researchers can gain access to a detailed report made by the committee after approval
85 by the JCQHC. We were provided access by the JCQHC to 244 detailed reports made
86 up to March 31, 2013, in which detailed clinical courses of 244 infants born to 244
87 women, causative factors for NE-CP determined by the investigation committee, and
88 the presence or absence of suboptimal care were recorded. However, personal
89 information regarding the date of birth, including year and month, place of birth,
90 maternal age, and maternal body height and weight, were masked for privacy protection.
91 All of the 244 infants were born in or after January 2009.

92 We reviewed all 244 reports for the 244 cases, focusing on clinical courses, FHR tracing,
93 causative factors for CP, and the presence or absence of misinterpretation of FHR

tracing, inappropriate TOID, and neonatal SGH. We identified 70 and 174 cases that did and did not fulfill all of the following four conditions: (1) cephalic singleton pregnancy attempting vaginal delivery (AVD) on or after gestational week (GW) 36, (2) reassuring fetal status at the onset of labor pains based on FHR tracing, (3) intrapartum occurrence of NRFS on FHR tracing in the absence of placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, or placenta previa/low lying placenta, and (4) diagnoses of NE at birth and subsequently CP by neuropsychiatrists. Thus, all 70 cases were judged to be NE-CP associated with intrapartum factors other than placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, or placenta previa/low lying placenta. The 70 neonates exhibited a pH of 6.86 ± 0.78 with base deficit of 20.1 ± 6.9 mmol/L in the umbilical cord blood or neonatal blood at birth or on admission to neonatal intensive care unit. In these 70 neonates, Apgar score at 1-min was < 3 in 50 (71%), < 5 in 64 (91%), and < 7 in 68 (97%) neonates, and that at 5-min was < 3 in 24 (34%), < 5 in 47 (67%), and < 7 in 64 (91%) neonates. Neither congenital malformation, inborn error of metabolism, nor infection was detected in the 70 infants.

Selection of 210 controls

We used a database provided by the Japan Society of Obstetrics and Gynecology (JSOG) [14] that included information on 11724 mothers who were registered at the JSOG Successive Pregnancy Birth Registry System and gave birth during the period from November 1, 2009, to December 31, 2009. From this database, we abstracted 2809 mothers who fulfilled all three of the following conditions: (1) AVD with cephalic presentation on and after $GW \geq 36$, (2) no occurrence of placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, or placenta previa/low lying placenta, and (3) neonate with both 1- and 5-min Apgar scores of ≥ 8 . Three controls for each case (3:1) were chosen after matching for GW at delivery, maternal parity (nulliparous

or not), and use of uterotonics. Thus, a total of 210 mother–child pairs were chosen from the database of the JSOG Successive Pregnancy Birth Registry System for controls. In these 210 neonates, neither congenital malformation, inborn error of metabolism, SGH, nor infection was detected during a several-day stay at the obstetrical facilities. Data on the umbilical cord blood pH were not available for these control infants.

Definitions and predefined assumption in this study

Suboptimal intrapartum care was defined as delayed reaction to NRFS due to misinterpretation of FHR tracing and or inappropriate TOID not fulfilling two prerequisite conditions, i.e., “fetal head engagement” and “full dilatation of the uterine cervix.” The delayed reaction to NRFS due to misinterpretation of FHR tracing was defined as follows: the investigation committee belonging to the JCQHC pointed out that an early delivery had not been attempted in the presence of NRFS based on FHR pattern of level ≥ 4 (according to the Japanese guidelines [14]) lasting for a considerable time and/or FHR pattern of level 5 lasting more than 120 min until delivery. The inappropriate TOID was defined as a follow: the investigation committee concluded that TOID performed before full dilatation of the uterine cervix and/or fetal head engagement worsened fetal condition. As the 210 control infants left obstetric facilities several days after birth according to the clinical path of each facility, all of the 210 controls were assumed not to have developed NE and not to have received suboptimal care. Successful and failed TOID were defined as vaginal and cesarean deliveries after TOID, respectively, irrespective of the condition of the neonate at birth. Emergent cesarean section (ECS) was defined as that performed in women during labor. Hypertensive disorders included preeclampsia and gestational hypertension. Hypertensive disorders included preeclampsia and gestational hypertension.

Statistical analyses

All of the data are presented as the means $\pm$ SD or frequency. Fisher's exact test was used for comparison of categorical data. Factors that were significantly correlated with NE-CP were determined by univariate and multivariate logistic regression analyses performed using IBM SPSS Statistics 18.0 software (SPSS Inc., Chicago, IL). We used a stepwise method (Wald) to choose independent risk factors for NE-CP and used logistic regression analysis to determine the odds ratio (OR) with 95% confidence interval (95%CI) of independent risk factors. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

The suboptimal intrapartum cares were identified in as many as 40 (57%) of the 70 cases (Table 1). The delayed reaction to NRFS due to misinterpretation of FHR tracing and the inappropriate TOID occurred in 38 and 4 women, respectively. Thus, both the delayed reaction to NRFS and inappropriate TOID occurred in two women. In three of four women with inappropriate TOID, TOID was performed before full dilatation of the uterine cervix and fetal head engagement. Frequency of low Apgar scores of < 3 , < 5 , and < 7 did not differ significantly between women with and without suboptimal cares (Table 2).

The mean GW at delivery, distribution of GW at delivery, frequencies of nulliparous women, and the rate of uterotonics use did not differ between the 70 cases and 210 controls (Table 3). As control subjects were matched for cases with regard to the use of uterotonics, the rate of uterotonics use in controls in the present study (54%) was higher

than that of approximately 23% in general pregnant Japanese women [15]. Frequencies of TOID, successful and failed TOID, ECS, suboptimal intrapartum care, hypertensive disorders, birth weight ≥ 3800 g, and SGH were significantly higher in the cases than controls. Of the 11 cases with SGH, 10 (91%) experienced TOID, and four of the 10 with TOID and SGH experienced failed TOID. Thus, within the NE-CP cohort, SGH occurred significantly more often in cases with than without TOID (31% [10/32] vs. 2.6% [1/38], respectively, $P = 0.0017$).

In univariate analysis, the OR (95% CI) for 70 cases compared to 210 controls was 5.96 (3.19 – 11.13) for TOID, 3.69 (1.94 – 7.02) for successful TOID, 27.0 (3.31 – 220) for failed TOID, 3.13 (1.67 – 5.86) for ECS, 279 (36.9 – 2103) for suboptimal intrapartum care, 5.29 (1.67 – 16.8) for hypertensive disorders, 2.08 (0.95 – 4.54) for birth weight ≥ 3500 g, 4.83 (1.32 – 17.6) for birth weight ≥ 3800 g, and 39.0 (4.93 – 308) for SGH. All nine of the above factors were candidates as independent risk factors for NE-CP. After selection with the stepwise method, the following four factors were chosen as independent risk factors for NE-CP (Table 4): suboptimal intrapartum care (OR, 2.21; 95%CI, 1.99 – 2.47), hypertensive disorders (1.20; 1.01 – 1.42), ECS (1.19; 1.08 – 1.31), and successful TOID (1.14; 1.03 – 1.25). Thus, among the causative factors other than placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, and placenta previa/low lying placenta, suboptimal intrapartum care was the greatest risk factor for NE-CP in fetuses assumed to be healthy at the commencement of labor.

Discussion

The present study demonstrated that suboptimal intrapartum care was the greatest risk factor for NE-CP among pregnant Japanese women who attempted vaginal delivery

with cephalic presentation of healthy fetuses at GW 36 or later and did not develop placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, or placenta previa/low lying placenta. Other independent risk factors for NE-CP determined in this study included hypertensive disorders, ECS, and successful TOID.

Suboptimal intrapartum care, defined as a delayed reaction to NRFS and/or inappropriate TOID not fulfilling prerequisite conditions, was noted in 40 (57%) of the 70 cases with NE-CP and increased the risk of NE-CP independently by 2.2-fold compared to women who were not given suboptimal intrapartum care in this study. This was suggested by previous studies in infants without congenital malformation, inborn error of metabolism, or infection [6, 16 - 18]: in a study of 141 term infants with CP born in 1984 – 1987 in the UK, care giver's failure to respond to NRFS occurred more often for CP compared to controls (OR, 4.5; 95%CI, 2.4 – 8.4) [16]; in regional audits of 49 cases with NE born in 1997 in the UK, significant or major episodes of suboptimal care were identified in 64% of NE cases [18]; in regional audits of 52 term infants born with NE in 1997 – 2000 in New Zealand, suboptimal fetal monitoring practice was identified in at least 42% of cases [17]; and in audits of 47 and 22 NE infants with and without metabolic acidemia at birth defined as by umbilical artery pH < 7.00 and base deficit $\geq$ 12 mmol/L born in 2003 – 2010 in Sweden, suboptimal care was identified in 47% (22/47) and 20% (6/30) of cases, respectively [6]. Thus, suboptimal intrapartum care is prevalent worldwide among neonates with NE and is a major intrapartum risk factor for NE and/or NE-CP after excluding well-known risk factors, such as placental abruption, uterine rupture, and cord prolapse.

TOID was not an independent risk factor for NE-CP in this study. However, both ECS and successful TOID increased the risk of NE-CP independently by 19% and 14%, respectively. As failed TOID inevitably requires ECS and even successful TOID was an

independent risk factor for NE-CP, the present study suggested that TOID should be considered as an independent risk factor for NE-CP.

Both TOID and ECS are known to be associated with CP in term infants having OR of 1.9 (95% CI, 1.6 - 2.3) and 1.8 (1.6 - 2.0), respectively compared to population with counterpart characteristics [1]. However, it is uncertain whether TOID is a causative factor for NE-CP. ECS is used in women with difficult labor irrespective of the use of TOID, and ECS without TOID accounted for 67% (16/24) of cases and for 100% (30/30) of controls in this study. In a population-based study on the frequencies of subdural and cerebral hemorrhage according to delivery mode by Towner et al. [19] examining 583340 live-born singleton infants born to nulliparous women between 1992 and 1994 and weighing between 2500 and 4000 g in California, OR of subdural or cerebral hemorrhage compared with spontaneous vaginal delivery was 1.4 (0.8 – 2.6) for cesarean section without labor, 2.3 (1.7 – 3.2) for ECS without TOID, 2.7 (1.9 – 3.9) for vaginal delivery with vacuum extraction, 3.4 (1.9 – 5.9) for vaginal delivery with forceps delivery, 7.3 (2.9 – 17.2) for vaginal delivery with combined use of vacuum and forceps, and 8.8 (3.9–19.9) for ECS after TOID [19]. The risk of subdural or cerebral hemorrhage associated with ECS (OR of 0.9 [0.6 – 1.4] compared to vacuum extraction) did not differ from that associated with vaginal delivery after vacuum extraction, suggesting that difficult labor requiring cesarean section or vacuum extraction was causative for subdural or cerebral hemorrhage, although an increased number of operative interventions, including vacuum extraction, use of forceps, and ECS, additively increased the risk of subdural or cerebral hemorrhage [19]. Thus, it was not surprising that both ECS and successful TOID were independent risk factors for NE-CP in this study.

SGH is a rare but potentially lethal medical emergency, and is associated with an

increased risk of NE [8, 9, 20, 21] as was confirmed in this study, although not an independent risk factor for NE-CP in this study. Its frequency is estimated to be 4 to 5 per 10000 spontaneous deliveries and 40 to 60 per 10000 vacuum-assisted deliveries [8, 9]. Ten (91%) of the 11 neonates with both SGH and NE-CP were after TOID in this study. In other studies, the frequency of TOID among neonates with SGH varied from 64% (79/123) [8], 77% (32/42) [9], 85% (27/33) [22], and to 97% (36/37) [20]. As the general frequency of TOID was estimated to be less than 20% based on previous studies (instrumental delivery of 7% $\pm$ 4% in 2004 in 124 facilities in the USA [23], the vacuum delivery of 10% in 1982-92 in Western Australia [20], the vacuum delivery rate of 14% in 2012 in Sweden [24] as well as 12% in the 210 control women in this study), it was apparent that TOID increased the risk of SGH. Poor outcome is likely to occur in neonates with SGH; of 42 neonates with SGH in Taiwan, 13 (31%) had poor outcomes, including death in five, epilepsy in four, severe auditory dysfunction in three, CP in two, and renal vein thrombosis in one [9]. In another study in Western Australia [20], of 37 neonates with SGH, one died and four of 25 with follow-up developed minor neurological disabilities.

Hypertensive disorder in pregnancy was also an independent risk factor for NE-CP in this study. There has been controversy regarding whether preeclampsia is associated with increased risk of CP. Mann et al. [25] conducted a population-based study to address this issue, examining 122476 mother–child pairs, including 337 children (0.28%) with CP and 4226 (3.5%) women with preeclampsia. Children born to mothers with preeclampsia were more likely to have CP compared to those of mothers without preeclampsia (OR of 1.94 [1.25 – 2.97]) [25]. These observations suggested that more intensive monitoring is required at term in women with hypertensive disorders, and this is emphasized in the current Japanese guidelines [26].

A major limitation of this study was that control mother–child pairs were assumed not to have had suboptimal intrapartum care. It is possible that suboptimal intrapartum care was given in a very small number of control women, but not leading to NE in the neonate. Therefore, there is the possibility of overestimation in the risk of NE-CP associated with suboptimal intrapartum care in this study.

In conclusion, the present study suggested that, among factors other than well-known factors, including placental abruption, uterine rupture, cord prolapse, fetomaternal hemorrhage, and placenta previa/low lying placenta, suboptimal intrapartum care was the greatest risk factor for NE leading to CP among mature and healthy fetuses on admission to facilities for delivery and confirmed that ECS as well as successful TOID, defined as vaginal delivery after TOID, were significant risk factors for NE leading to CP. Training programs for improved interpretation of FHR tracing and appropriate TOID are required to prevent NE-CP.

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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. Suboptimal intrapartum cares seen in 40 cases

1. Delayed reaction to NRFS due to misinterpretation of FHR tracing	n=38
1) FHR pattern of level ≥ 4 lasting for a considerable time	n=35
2) FHR pattern of level 5 lasting for ≥ 120 min	n=5
Sentinel events (FHR patterns) seen in the 38 women	
Decreased FHR baseline variability	n=23
with recurrent late deceleration	n=17
with recurrent variable deceleration	n=15
with prolonged deceleration	n=20
Normal FHR baseline variability	n=15
with recurrent late deceleration	n=9
with recurrent variable deceleration	n=11
with prolonged deceleration	n=15
2. Inappropriate TOID	n=4
1) Before full dilatation of the uterine cervix	n=4
2) Before fetal head engagement	n=3

Table 2. Apgar scores in 40 and 30 cases with and without suboptimal cares

	1 min Apgar score			5 min Apgar score		
	< 3	< 5	< 7	< 3	< 5	< 7
Suboptimal care (n=40)	29 (73%)	37 (93%)	39 (98%)	14 (35%)	27 (68%)	38 (95%)
No suboptimal care (n=30)	21 (70%)	27 (90%)	29 (97%)	10 (33%)	20 (67%)	26 (87%)
Overall (n=70)	50 (71%)	64 (91%)	68 (97%)	24 (34%)	47 (67%)	64 (91%)

No significant differences in frequency of low Apgar scores between two groups with and without suboptimal care

Table 3. Demographic characteristics of study subjects

	Case (n=70)	Control (n=210)	P-value
Gestational week at delivery	39.4±1.2	39.4±1.2	>0.9999
36	2 (2.9%)	6 (2.9%)	>0.9999
37 - 38	10 (14.3%)	30 (14.3%)	>0.9999
39 - 40	45 (64.3%)	137 (65.25)	0.8852
41	13 (18.6%)	37 (17.6%)	0.8570
≥42	0 (0.0%)	0 (0.0%)	>0.9999
Nulliparous women	53 (75.7%)	160 (76.2%)	>0.9999
Use of uterotonics	38 (54.3%)	114 (54.3%)	>0.9999
Oxytocin alone	25 (35.7%)	82 (39.0%)	0.6714
Prostaglandins alone	6 (8.6%)	9 (4.3%)	0.2168
Both	7 (10%)	23 (11.0%)	0.8238
Rupture of fetal membranes*	24 (34.3%)	54 (25.7%)	0.1659
Trial of instrumental delivery (TOID)	32 (45.7%)	26 (12.4%)	<0.0001
Successful TOID	24 (34.3%)	26 (12.4%)	<0.0001
Failed TOID	8 (11.4%)	0 (0.0%)	<0.0001
Emergent caesarean section	24 (34.3%)	30 (14.3%)	0.0002
Suboptimal intrapartum cares	40 (57%)	0 (0.0%)	<0.0001
Hyperglycemia†	3 (4.3%)	5 (2.4%)	0.4076
Hypertensive disorders¶	8 (11%)	5 (2.4%)	0.0018
Birth-weight (g)	3099 ± 404	3031 ± 355	0.1809
≥ 3200	25 (35.7%)	66 (31.4%)	0.5073
≥ 3500	12 (17.1%)	19 (9.0%)	0.0616
≥ 3800	6 (8.6%)	4 (1.9%)	0.0092
≥ 4000g	1 (1.4%)	1 (0.5%)	0.4382
Subgaleal hemorrhage (SGH)	11 (15.7%)	0 (0.0%)	<0.0001

*, Rupture of fetal membranes was found on admission to hospital for delivery.

†, Including gestational diabetes mellitus and diabetes mellitus.

¶, Including gestational hypertension and preeclampsia.

Table 4. Independent risk factors for cerebral palsy following neonatal encephalopathy

	B	SE	OR (95%CI)	<i>P</i> -value
Suboptimal intrapartum care	0.795	0.055	2.21 (1.99 – 2.47)	<0.001
Hypertensive disorders	0.182	0.086	1.20 (1.01 – 1.42)	0.035
Emergent cesarean section	0.175	0.048	1.19 (1.08 – 1.31)	<0.001
Successful TOID	0.127	0.050	1.14 (1.03 – 1.25)	0.012

B₀ (SE) was 0.072 (0.023) in this analysis.