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**Clinical features of abruptio placentae as a prominent cause of cerebral palsy**

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**Running foot:** Abruptio placentae-induced cerebral palsy

## **Abstract**

**Background:** Although abruptio placentae causes hypoxia in the infant and thus leading to cerebral palsy (CP), its incidence and clinical features at a nation wide level have not been demonstrated.

**Aims:** To determine the proportion of abruptio placentae among antenatal and intrapartum causative factors leading to cerebral palsy (CP) and clinical features of such abruptio placentae.

**Study design:** A review was conducted in 107 infants with CP in whom CP was determined to be due to antenatal and or intrapartum hypoxic conditions by the Japan Council for Quality Health Care until April 2012.

**Results:** Abruptio placenta was responsible for 28 (26%) of the 107 CP infants, and was the single leading causative factor of CP. Of these 28 women, 22 (79%) exhibited non-reassuring fetal status on admission to obstetric facilities at  $36.2 \pm 2.6$  weeks of gestation and had neonates with umbilical cord arterial blood pH (base excess) of  $6.728 \pm 0.164$  ( $-25 \pm 5.4$  mmol/L). In these 22 women, strong abdominal pain and/or profuse vaginal bleeding occurred  $159 \pm 99$  min prior to admission to an obstetric facility, and the interval until delivery after admission was  $47 \pm 31$  min. Hypertension or isolated proteinuria preceded clinical events in one (4.5%) and five (23%) of these 22 women, respectively.

**Conclusions:** Abruptio placentae was responsible for CP in one quarter of all cases determined to be due to antenatal and/or intrapartum hypoxic conditions in Japan. New strategies to shorten the interval until admission to an obstetric facility after onset of symptoms are urgently needed.

**Key words:** abdominal pain, cerebral palsy, abruptio placentae, vaginal bleeding,

proteinuria

## **Introduction**

Although some pregnant women develop abruptio placentae during their stay in an obstetric facility [1, 2], others show non-reassuring fetal status (NRFS) caused by abruptio placentae at presentation [3]. As abruptio placentae is one of the leading causes of cerebral palsy (CP) derived from antepartum and/or intrapartum hypoxic conditions [4 – 8], prompt delivery may be important to avoid neurological handicap in the infants [3, 9, 10]. Women who develop abruptio placentae at obstetric facilities may have a shorter interval until delivery after the onset of symptoms and may be less likely to have infants with CP. Therefore, there may be large numbers of women who develop abruptio placentae outside obstetric facilities and have infants with CP. However, there is little information in the literature regarding this issue.

The Japanese government established a new medical insurance system, the Japan Obstetric Compensation System for Cerebral Palsy, to compensate for cerebral palsy (CP) derived in principle from intrapartum hypoxia and to improve perinatal care, and asked the Japan Council for Quality Health Care (JCQHC) to organize this system. This system was launched on 1 January 2009, and provides rapid monetary compensation for CP [11] certified as 1<sup>st</sup> or 2<sup>nd</sup> degree severity according to the criteria of the Japanese Social Welfare System [12] in infants with birth weight > 2000 g and/or pregnancy length > 33 weeks. Infants who do not meet the above criteria but are born at > 28 weeks are also eligible for compensation after case-by-case review [11]. This system, however, does not cover infants with disability apparently due to congenital anomalies in metabolism, chromosomal aberrations, brain malformations, transplacental infection, or postnatal factors [11]. More than 99% of pregnant women and more than 99% of obstetric facilities in Japan participate in this system. Once a patient with CP applies for

compensation, the obstetric facility that managed the applicant must disclose corresponding medical charts and relevant information at the request of the JCQHC. The decision for compensation in each case is made by the JCQHC after preliminary investigations. Then, a professional committee belonging to the JCQHC, consisting of physicians, midwives, lawyers, and citizens, investigates the causative factors in CP carefully in each case and publishes a brief summary of each case together with the cause of CP in a form with privacy protection on their website [13]. Researchers can gain access to a more detailed report made by the committee after being approved by the JCQHC in this system.

Accordingly, the present study was performed to determine the frequency of abruptio placentae among the antepartum and/or intrapartum causative factors leading to neonatal encephalopathy, and finally to cerebral palsy (CP), how many patients developed antepartum abruptio placentae at and outside obstetric facilities, and clinical features of such antepartum abruptio placentae.

## **Materials and Methods**

This study was approved by the Ethics Committee of Hokkaido University Hospital. We were provided access by the JCQHC to all 111 detailed reports made up until April 2012, in which clinical courses of 111 infants born to 111 women and results of the investigations regarding the causes of CP were recorded. In these reports, personal information regarding the date of birth, including year and month, place of birth, and maternal age, were masked for privacy protection. However, all 111 infants were born in or after January 2009, because this compensation system was instigated on

1 January 2009. These 111 reports were retrospectively reviewed focusing on clinical backgrounds and causes of CP. Women who developed hypertension (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg) alone, proteinuria ( $\geq 1+$  on dipstick test at the last two successive antenatal visits, or  $\geq 2+$  on dipstick test at the last antenatal visit) alone, or both hypertension and proteinuria at and after 20 weeks of gestation were diagnosed as having gestational hypertension, isolated proteinuria, or preeclampsia, respectively.

The JCQHC announced in May 2012 that a total of 171 infants born in 2009 were compensated for their CP until the end of March 2012.

## Results

In 4 of the 111 patients, CP was determined not to have been caused by antepartum and/or intrapartum hypoxic conditions: vertical transmission of group B streptococcus, neonatal apnea, neonatal pneumonitis, and congenital metabolic disorder were determined to be responsible for one case each. Antepartum and/or intrapartum factors leading to neonatal encephalopathy were recognized in the remaining 107 infants (Table 1). Abruptio placentae explained 28 (26%) of the 107 cases of CP derived from antepartum and/or intrapartum hypoxic conditions and was the single leading causative factor of CP. Among the 28 patients with abruptio placentae-induced CP, as many as 22 (79%) exhibited NRFS on admission to the obstetric facilities (Table 1).

Of the 22 women who had both abruptio placentae and NRFS at admission, only 4 (18%) were primiparous (Table 2). Gestational hypertension was recognized at the last antenatal visit in one patient (Case 3). Isolated proteinuria was seen in 5 patients at the last antenatal visit (Cases 15, 17, 18, 20, and 22), in whom preeclampsia was diagnosed

several hours prior to the onset of symptoms in Case 15. Gestational hypertension was seen in an additional 2 patients on admission (Cases 5 and 9).

These 22 patients gave birth to infants with birth weight of  $2473 \pm 454$  g at  $36.2 \pm 2.6$  weeks of gestation (Table 2); 9 (41%) at preterm, 14 (64%) with a low birth weight of less than 2500 g; and 17 (77%) with a 5-min Apgar score of less than 5. All except one infant (Case 18) for whom umbilical arterial blood gas data were available showed a pH of less than 7.0 with a marked base deficit and extremely low mean pH (base excess) of  $6.728 \pm 0.164$  ( $-25.0 \pm 5.4$  mmol/L). The 22 patients experienced exclusively strong abdominal pain and/or profuse vaginal bleeding, and therefore visited an obstetric facility  $159 \pm 99$  min after the onset of symptoms: only 4 (18%) visited within 90 min after the onset of symptoms. After arrival at the obstetric facility, it took  $47 \pm 31$  min for the delivery of infants, and was more than 30 min in 13 patients (59%).

## **Discussion**

The present study demonstrated that abruptio placentae is the single leading causative factor of CP derived from antenatal and/or intrapartum hypoxic conditions in Japan, accounting for approximately one quarter (28/107) of CP cases. Twenty-two of the 28 women (79%) with abruptio placentae exhibited NRFS at the time of admission to the obstetric facility.

As no data were available for comparison, it was not clear whether the figure of 79% (22/28) for the proportion of women who presented with NRFS among those with abruptio placentae was high. However, as these 22 events accounted for 21% of all 107 events leading to CP in infants, it may be helpful to focus on these 22 patients for the

development of preventive measures and to reduce the number of such cases.

The speed of response may influence the outcome of infants born to women with complications such as abruptio placentae, cord prolapse, and uterine rupture [3, 9, 10]: “examples of conditions cited by the American Academy of Pediatrics and ACOG that may require delivery within 30 minutes include hemorrhage from placenta previa, placental abruption, umbilical cord prolapse, and uterine rupture” [10]; among 126 emergent (crash) cesarean deliveries, 10, 8, and 6 were for umbilical cord prolapse, abruptio placentae, and suspected uterine rupture, respectively, in a hospital in USA. Such patients with emergent (crash) cesarean deliveries indeed showed increased risks of low 5-min Apgar score and infant intubation [9], likely attesting to the need for expedited delivery. Among 33 infants born to women presenting with abruptio placentae and fetal bradycardia at admission, 22 infants with no developmental delay had significantly shorter “decision to time of delivery” compared with 11 infants who died or survived with CP (median: 14.5 vs. 24.0 min,  $P = 0.02$ ) [3]. Thus, most researchers consider that expedited delivery may improve outcome of patients with abruptio placentae based on earlier findings [14 – 16]: duration of fetal heart rate deceleration during the end stage of labor are associated with acidotic pH of the umbilical vein blood [14]; fetal acidosis is common if the bradycardia lasts for 10 min or more, particularly if the heart rate is  $< 80$  bpm with decreased variability [15]; and the incidence of CP is approximately 1.0% in full-term surviving neonates with an Apgar score of 0 – 3 at 5 min, while the values are 9% and 57% if this score is sustained for 15 and 20 min, respectively [16].

The 22 patients were admitted to an obstetric facility  $159 \pm 99$  min after the onset of symptoms and a further  $47 \pm 31$  min were required for the delivery of infants after arrival at the obstetric facility. This resulted in an extremely low umbilical arterial blood pH of  $6.728 \pm 0.164$  with base excess ( $-25 \pm 5.4$  mmol/L) in these cases. As a large number of obstetric facilities (3333 facilities) participated in the Japan Obstetric Compensation System for Cerebral Palsy (cited 7 June 2012; available from <http://www.sanka-hp.jcqh.or.jp/search/kanyujokyo.php>), most of these 22 patients may have resided within 30 km from the obstetric facility booked for parturition, suggesting that they were able to be admitted to the obstetric facility within 60 min after symptom onset if they so wished. Although no differences were reported in time interval after the onset of symptoms until admission to hospitals between women with fetal bradycardia caused by abruptio placentae at admission having children with no developmental delay and CP (median: 60 vs. 105 min, respectively,  $P = 0.59$ ) [3], an earlier visit to the obstetric facility would have enhanced the possibility of having infants without CP in these 22 patients in this study.

Hypertension preceded events in only one of the 22 women in this study. Therefore, focusing on patients with hypertensive disorders may not contribute to the reduction of such cases presenting with NRFS caused by abruptio placentae. Rather, attention should be paid to women with isolated proteinuria; this study demonstrated that isolated proteinuria preceded events in 5 of the 22 patients (23%) suggesting that isolated proteinuria is a risk factor for not only the development of preeclampsia [17, 18] and eclampsia [19, 20], but also for the development of abruptio placentae. Abruptio placentae occurs in 0.4% - 1.0% of women in many countries [22 – 27]. Abruptio

placentae accounts for 4.0% – 6.0% of preterm delivery [22 – 24, 26], and that occurring at preterm accounts for 40% - 50% of all cases of abruptio placentae [22, 23, 26]. Fortunately, most women complain of abdominal pain and/or vaginal bleeding, leading to suspicion of abruptio placentae as in the present study, although predictive characteristics of such clinical signs for the development of abruptio placentae are unknown at present. Pregnant Japanese women were unfamiliar with abruptio placentae because most women were not informed about this life-threatening complication. Thus, it is necessary to determine the best way to inform pregnant women about this complication before 30 weeks of gestation.

The strength of our study was that the Japan Obstetric Compensation System for Cerebral Palsy established in 2009 [11] is expected to collect information on the clinical courses of all patients with both CP and a birth weight > 2000 g in and after January 2009 in Japan and in whom intrapartum factors are possible causes of CP, because compensation of approximately US\$370000 would be provided in cases in which intrapartum factors were judged to be causative of CP. In addition, there are no restrictions of the right to sue for malpractice even after compensation by this system. Therefore, the number of patients with CP associated with abruptio placentae presented here likely reflected the true number of such cases with certified 1<sup>st</sup> or 2<sup>nd</sup> degree severity according to the criteria of the Japanese Social Welfare System [12] that occurred in Japan during a certain period that we were unable to specify because the date of birth for each case was masked. This limitation also hampered the estimation of absolute risk of CP associated with abruptio placentae in Japan, which has an annual birth rate of approximately 1050000 infants with birth weight > 2000 g [tabulation

information released annually by the Japanese Ministry of Health, Labor, and Welfare]. In May 2012, the JCQHC announced that a total of 171 infants born in 2009 were compensated for CP until the end of March 2012. Thus, it was expected that these 107 study subjects were born during a period of an approximately 7.5 months in 2009 and were diagnosed with CP before the end of 2011, suggesting that the prevalence of CP derived from antenatal and/or intrapartum hypoxic conditions was 0.16 per 1000 births ( $107/656000$ ;  $1050000 \times 7.5/12$ ). The prevalence of whole CP was reported to be 1.5 – 2.5 per 1000 live births [28]. If we assume that antenatal and intrapartum hypoxic conditions account for approximately 10% - 15% of all cases of CP according to previous reports [29, 30], our estimated figure, 0.16 per 1000 births, was somewhat lower, but would be reasonable, because some infants born in 2009 will be diagnosed with CP in the near future.

In conclusion, the new Japan Obstetric Compensation System for Cerebral Palsy allowed the collection of information regarding the clinical courses of 107 infants with CP derived from antenatal and/or intrapartum hypoxic conditions. Abruption placentae presenting with NRFS at admission accounted for approximately one fifth of all cases of CP (22/107) derived from antenatal and/or intrapartum hypoxic conditions. These 22 women visited obstetric facilities approximately 160 min after the onset of abdominal pain and/or vaginal bleeding. Providing information on the nature of abruption placentae to all pregnant women before 30 weeks of gestation should be considered to reduce the time interval after the onset of symptoms until admission to an obstetric facility.

### **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. Causative factors in the 107 infants with cerebral palsy

Abruptio placentae¶	28 (22)	[26.2%]
Umbilical cord prolapse	7 (1)	[6.5%]
Uterine rupture	4 (1)	[3.7%]
Twin*	4 (2)	[3.7%]
Fetomaternal transfusion	2 (2)	[1.9%]
Breech vaginal delivery	1 (0)	[0.9%]
Shoulder dystocia	1 (0)	[0.9%]
Low-lying placenta†	1 (0)	[0.9%]
Anesthetic accident	1 (0)	[0.9%]
Birth in a motor car	1	[0.9%]
Others	57 (15)	[53.3%]

Of 111 CP infants, 4 in whom CP was determined not to have been caused by antepartum and/or intrapartum hypoxic conditions were excluded. “Others” included factors not specified in this table. Numbers of infants exhibiting non-reassuring fetal status on electronic cardiotocogram at admission to obstetric facilities are indicated in parentheses. Percentages of 107 cases are indicated in square brackets. ¶, Including one breech vaginal delivery; \*, One case was caused by twin-twin transfusion syndrome; †, Bleeding from the placenta was responsible for CP.

**Table 2. Twenty-two cases of abruptio placentae showing non-reassuring fetal status on admission**

Case	Parity	Complication	Neonate				Time interval* (min)		
			GW	Weight (g)	Apgar	pH (BE)	A	B	C
1	2	-	30	1310	1	6.817 (-20.2)	130	27	157
2	2	-	30	1743	1	6.817 (-19.0)	224	46	270
3	1	GH	33	2384	2	6.691 (-22.0)	272	48	320
4	1	-	35	2360	1	6.641 (-20.6)	435	26	461
5	1	-	35	2270	0	6.760 (-28.0)	300	61	361
6	0	-	35	2469	0	6.598 (-34.4)	110	22	132
7	2	-	35	2096	4	6.920 (-19.6)	315	26	341
8	1	-	35	2034	2	6.740 (-27.8)	145	39	184
9	1	-	36	2522	2	6.566 (-31.7)	60	96	156
10	1	-	37	3064	5	NA (NA)	170	128	298
11	2	-	37	2362	2	NA (NA)	101	44	145
12	2	-	37	2480	2	NA (NA)	160	11	171
13	2	-	37	2476	6	6.594 (-27.2)	110	58	168
14	1	-	37	2432	1	6.550 (NA)	100	27	127
15	1	IPU	38	2680	1	6.700 (-28.7)	110	9	119
16	4	-	38	2352	NA	6.543 (NA)	105	56	161
17	0	IPU	38	2418	7	6.633 (-30.5)	150	11	161
18	0	IPU	38	2914	6	7.100 (-17.7)	150	71	221
19	1	-	38	2725	4	NA (NA)	35	110	145
20	1	IPU	38	2814	0	NA (NA)	210	29	239
21	1	-	39	3170	4	6.985 (-22.5)	35	42	77
22	0	IPU	40	3340	4	NA (NA)	66	43	109
Mean	1.2		36.2	2473	2.6	6.728 (-25.0)	159	47	206
SD	0.9		2.6	454	2.1	0.164 (5.4)	99	31	97

Complications, including gestational hypertension (GH), preeclampsia (PE), and isolated proteinuria (IPU) at the last antenatal visit; GW, gestational week at delivery; Apgar, score at 5 min; †, umbilical artery blood pH (base excess, mmol/L); \*A, until admission to the facility where delivery took place after the onset of symptoms; \*B, until delivery after admission; \*C, until delivery after the onset of symptoms; NA, not available;