Impact of maternal hypertensive disorders of pregnancy on brain volumes at term-equivalent age in preterm infants: a voxel-based morphometry study

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Abstract

Objectives

Infants born to mothers with hypertensive disorders of pregnancy (HDP) reportedly have negative behavioral and neurodevelopmental outcomes. However, the effects of maternal HDP on infant brain growth have not been fully evaluated. We aimed to evaluate brain volumes and brain injury in preterm infants born to mothers with HDP, using magnetic resonance (MR) imaging at term-equivalent age.

Study design

In this cohort study, MR imaging was performed for 94 preterm infants born before 34 weeks of gestation at Nagoya University Hospital between 2010 and 2018. Twenty infants were born to mothers with HDP and 74, to mothers without HDP.

Main outcome measures

Total brain volumes and regional volumetric alterations were assessed by voxel-based morphometry, and brain injury was evaluated using the Kidokoro global brain abnormality score. Developmental quotient was assessed at a corrected age of 1.5 years in 59 infants (HDP, n=11; non-HDP, n=48).

Results

No significant differences were observed in the gray and white matter volumes of the two groups (HDP: 175 ± 24 mL, 137 ± 13 mL, respectively; non-HDP: 172 ± 24 mL, 142 ± 13

mL, respectively). Additionally, no regional volumetric alterations were observed between the two groups after covariate adjustment (gestational age and infant sex). The total Kidokoro score and developmental quotient were similar in both groups.

Conclusions

No significant differences in the global and regional brain volumes were observed. Further research is needed to confirm our findings at different time points of MR imaging and in different populations.

Keywords

Brain injury, brain volume, hypertensive disorders of pregnancy, neurodevelopment, voxel-based morphometry

Abbreviations

DQ, developmental quotient; HDP, hypertensive disorders of pregnancy; KSPD, Kyoto Scale of Psychological Development; MR imaging, magnetic resonance imaging; NICU, neonatal intensive care unit; VBM, voxel-based morphometry.

Introduction

Hypertensive disorders of pregnancy (HDP) are common pregnancy complications, affecting up to 10% of all pregnant women worldwide (1). Approximately 20% of very preterm births are attributed to HDP (2). Preterm infants born to mothers with HDP often have major morbidities, resulting in adverse health outcomes from the neonatal period right up to adulthood (3). Recent evidence suggests that intrauterine exposure to maternal HDP, especially preeclampsia, exerts an overall negative impact on the behavioral and neurological development of infants, such as motor competence, verbal ability, intelligence quotient, cognitive function, and mental wellbeing (4-9). Moreover, recent meta-analyses have highlighted a significant association between HDP and neurodevelopmental disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder (10-12).

Although the pathophysiology of neurodevelopmental disorders in infants born to mothers with HDP has not been fully elucidated, evidence supports the idea that these adverse neurodevelopmental consequences occurring later in life may originate from early programming because of the hostile intrauterine environment during fetal development (13, 14). Various complications during the perinatal period, such as maternal nutritional problems, psychological stress, infection, pregnancy complications, and postnatal treatment in neonatal intensive care units (NICUs), cause epigenetic alterations in infants. These alterations affect

the functional and structural aspects of various organs in an infant, resulting in altered lifelong susceptibility to a wide range of diseases (15). In cases of HDP, especially early-onset preeclampsia, fetuses are exposed to hypoxia, under-nutrition, oxidative stress, and inflammation due to placental insufficiency (16). However, whether intrauterine exposure to maternal HDP affects brain growth in neonates has not been fully evaluated.

Recent evidence suggests that cerebral 3D volumetric approaches using magnetic resonance (MR) imaging (e.g., voxel-based morphometry [VBM]) may be used to detect global and regional brain structural alterations in patients with various conditions such as Alzheimer's disease, autism spectrum disorder, and schizophrenia (17-19). In neonatology, VBM can provide detailed insight into the relationship between brain growth at term-equivalent age and subsequent adverse neurodevelopmental outcomes in very preterm infants (20-22). In addition, scoring systems using cerebral MR imaging in preterm infants at term-equivalent age are valid and reliable tools for identifying infants at high risk of subsequent neurodevelopmental impairment (23-25). Previously, we developed an assessment tool, the Kidokoro score, that could provide a more comprehensive and objective classification of regional and global brain abnormalities and aid in identifying high-risk preterm infants, using conventional MR imaging at term-equivalent age (24).

To date, limited evidence exists regarding the effects of maternal HDP on the neonatal brain, especially in preterm infants. Thus, the aim of this study was to test the hypothesis that preterm infants born to mothers with HDP show altered brain volumes at both global and regional levels by using VBM. We evaluated global brain volumes and regional volumetric alterations in infants born before a gestational age of 34 weeks, using MR imaging, at term-equivalent age. Further, we evaluated the presence of any brain injury or altered brain growth using the Kidokoro score.

Methods

1. Study population

We conducted a cohort study of preterm infants born at Nagoya University Hospital between January 2010 and December 2018. Three hundred four infants born between 22 $^{0/7}$ and 33 $^{6/7}$ weeks of gestation were admitted to the NICU (Figure 1). Exclusion criteria were: multiple pregnancies, major congenital and/or chromosomal abnormalities, missing MR imaging results (e.g., in-hospital death, transferred before MR imaging, respiratory and/or circulatory problems rendering MR imaging unfeasible, and refusal to participate), low-quality MR imaging results (1.5 Tesla MR imaging, motion artifacts, or ghost artifacts), and severe brain injury (intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, encephalitis, or persistent ventricular dilatation) (Figure 1). Neurodevelopmental assessment

at a corrected age of 1.5 years was not performed in patients transferred to another hospital, lost to follow-up, or below a corrected age of 1.5 years at the time of outcome measurement. Finally, 20 infants born to mothers with HDP (HDP group) and 74 infants born to mothers without HDP (non-HDP group) were included in this study.

Data on maternal and neonatal characteristics were obtained from electronic medical records. Maternal characteristics included age, parity, gestational age at delivery, body mass index before pregnancy, mode of delivery, type of HDP, diabetes mellitus, gestational diabetes mellitus, antenatal corticosteroid treatment, antenatal magnesium treatment, and histological chorioamnionitis. Neonatal characteristics included sex, birth weight, height, head circumference, small for gestational age, along with short-term neonatal outcomes such as respiratory distress syndrome, duration of intubation, chronic lung disease, intraventricular hemorrhage (grade I or II), patent ductus arteriosus banding, inotrope use, postnatal steroid use, necrotizing enterocolitis, infection, treated retinopathy of prematurity, and duration of hospitalization. This study was approved by the Institutional Ethics Board of Nagoya University (approval number: 2018–0026), and written informed consent was obtained from all parents.

2. Definition

HDP was defined as hypertension with systolic blood pressure ≥140 mmHg and/or diastolic

152 blood pressure ≥90 mmHg during pregnancy according to the Japanese guidelines, which
153 conforms to international standards (1, 26). Preeclampsia was defined as hypertension and
154 either proteinuria, end-organ dysfunction, or placental insufficiency such as fetal growth
155 restrictions and umbilical artery flow abnormality occurring after 20 weeks of pregnancy.
156 Antenatal corticosteroid treatment was defined as two 12 mg doses of betamethasone
157 administered before delivery. Histological chorioamnionitis was defined as presence of
158 placental inflammatory infiltration, based on pathological examination. Small for gestational
159 age was defined as birth weight and height less than the 10^{th} percentile for gestational age,
160 based on a Japanese gender-specific neonatal anthropometric chart established in 2000 (27).
161 Respiratory distress syndrome was diagnosed based on clinical manifestations and chest
162 radiography findings. Chronic lung disease was defined as requirement for oxygen therapy at
163 36 weeks of postmenstrual age. Intraventricular hemorrhage was diagnosed using ultrasound
164 or MR imaging according to the classification given by Papile *et al.* (28). Necrotizing
165 enterocolitis was defined as stage 3 of Bell's criteria, which requires surgery (29). Neonatal
166 infection was defined as clinical symptoms of infection or an increase in C-reactive protein
167 levels. Treated retinopathy of prematurity included treatment with laser photocoagulation.
168
169 *3. MR imaging acquisition*
170 MR imaging was performed using a 3.0 Tesla scanner system (MAGNETOM Verio; Siemens,

171 Erlangen, Germany) with a 32-channel head coil at Nagoya University Hospital (30). For
172 safety reasons, MR imaging was performed at term-equivalent age in infants weighing
173 approximately 2,000 g, and with stable respiratory and circulatory systems. Data on physical
174 assessment at term-equivalent age were obtained at the nearest possible time-point of MR
175 imaging acquisition (Table 2). Anatomical images were obtained with a high-resolution
176 three-dimensional magnetization-prepared rapid acquisition of gradient echo (3D MPRAGE)
177 T1-weighted sequence (TR, 1570 ms; TE, 2.2 ms; voxel size, $1 \times 1 \times 1$ mm^3), and a turbo
178 spin-echo T2-weighted sequence (TR 3200 ms; TE, 499 ms; voxel size, $1 \times 1 \times 1$ mm^3; echo
179 train length, 123.0). MR imaging was performed under sedation with triclofos sodium (60–80
180 mg/kg) between January 2010 and March 2017 after informed consent was obtained, whereas
181 most infants required no sedation by using a vacuum mattress (CFI Medical Solutions, MI,
182 USA) between April 2017 and 2018.
183
184 *4. Voxel-based morphometry analysis*
185 Anatomical T1-3D images were used for VBM analysis after visually inspecting the images
186 to exclude low-quality data. Image processing of the VBM analysis was conducted using the
187 Statistical Parametric Mapping software version 12 (SPM12) implemented in MATLAB
188 (version 22, MathWorks, Inc., MA, USA). The images were automatically segmented into
189 gray matter, white matter, and cerebrospinal fluid using a segmentation tool. The quality of

190 the automatic segmentations was visually evaluated. Images having low quality of
191 segmentation were excluded. Subsequently, normalization was performed using the
192 diffeomorphic anatomical registration through the exponentiated Lie Algebra algorithm
193 (DARTEL) in SPM12 to provide more precise spatial normalization to the template. The
194 images were warped to this average template, and normalized to the Montreal Neurological
195 Institute space. The images were modulated in a non-linear manner to correct individual brain
196 sizes. Finally, the warped modulated images of gray and white matter were smoothened with
197 a 4-mm full width at half-maximum isotropic Gaussian kernel.

198 Brain volumes were obtained from the segmented images of each subject using a
199 script provided by Ridgway (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).
200 Global brain volumes (total volume, gray matter volume, and white matter volume) were
201 compared between the two groups with and without adjustment for two covariates
202 (gestational age and infant sex). To evaluate regional volumetric alterations in the
203 cluster-level analysis between the two groups, unpaired *t*-test comparisons were performed.
204 For visualization, significant clusters with a minimum cluster size of >52 voxels (uncorrected
205 p <0.001) were reported to identify the affected structures and networks. The results were
206 visualized using the MRIcron software package
207 (https://people.cas.sc.edu/rorden/mricron/index.html). All results were subjected to
208 family-wise error (FWE) correction for multiple comparisons and were adjusted for two

covariates (gestational age and infant sex). For VBM analysis, the statistical significance level was set at 0.05 after FWE correction for multiple comparisons.

5. Assessment of brain injury

The Kidokoro score is a validated MR imaging assessment tool for brain injury and altered growth, consisting of four separate categories: 1) cerebral white matter abnormality, 2) cortical gray matter abnormality, 3) deep gray matter abnormality, and 4) cerebellum abnormality (24). The Kidokoro score was calculated as the sum of these regional scores and classified as normal (score 0–3), mild (score 4–7), moderate (score 8–11), and severe (score ≥12) (24). All qualitative and quantitative assessments of the MR imaging results were performed by a single neonatal neurologist (H.K.) blinded to the clinical variables.

6. Developmental follow-up

Experienced clinical psychologists performed neurodevelopmental assessments at a corrected age of 1.5 years using the Kyoto Scale of Psychological Development (KSPD). The KSPD is widely used in Japan and has been reported to be comparable to the third edition (Bayley III) of the Bayley Scales of Infant and Toddler Development (31, 32). The KSPD consists of three separate categories (mean = 100): 1) postural and motor area, 2) cognitive and adaptive area, and 3) language and social area.

7. Statistical analysis

Statistical analyses were performed using SPSS 26 software (SPSS Inc., Chicago, IL, USA). Differences between the two groups were assessed using the Mann-Whitney U test or unpaired *t*-test for continuous variables. Chi-square, or Fisher's exact test was used for categorical variables. Statistical significance for all analyses was set at $p < 0.05$.

Results

During the study period, 304 infants were born between 22 $^{0/7}$ and 33 $^{6/7}$ weeks' gestation. Ninety-four infants were included and 210 were excluded from this study (Figure 1). Of these ineligible infants; 81 were multiple pregnancies, 62 had major congenital and/or chromosomal abnormalities, 62 did not have suitable MR imaging results for analysis because either no MR imaging was performed (n = 32) or the quality of the MR imaging was low (n = 30), and 5 had severe brain injury [intraventricular hemorrhage grade III or IV (n = 2), cystic periventricular leukomalacia (n = 2), encephalitis during NICU stay (n = 1), and persistent ventricular dilatation (n = 1)]. One infant had both intraventricular hemorrhage and persistent ventricular dilatation. All five infants with severe brain injury were born to mothers without HDP. Ninety-four infants (HDP, n = 20; non-HDP, n = 74) were assessed for brain volumes and brain injury scores.

Baseline maternal and infant characteristics are shown in Table 1. In the HDP group, 13 women were diagnosed with preeclampsia. Mothers of infants in the HDP group were older and more likely to receive antenatal magnesium treatment than were those in the non-HDP group. No significant differences were observed in terms of gestational age or infant sex. Compared to infants in the non-HDP group, those in the HDP group showed significantly lower birth weight and height, with an increased incidence of small for gestational age infants. Neonatal complications and treatments during the NICU stay were not significantly different between the two groups. Supplementary Table 1 shows the detailed maternal clinical characteristics of the HDP group. Supplementary Table 2 shows the difference in baseline characteristics between infants with suitable MR imaging (n = 94) and infants without MR imaging, except for specific reasons such as in-hospital death and respiratory and/or circulatory problems making MR imaging unfeasible (n = 52). Almost all maternal and neonatal characteristics were similar between infants with and without MR imaging. Supplementary Figure 1A shows the relationship between gestational age and postmenstrual age at the time of MR imaging. Compared with the non-HDP group, infants in the HDP group underwent MR imaging later, even at the same gestational age. Supplementary Figure 1B shows the relationship between birth weight and gestational age on MR imaging. Infants in the HDP group had a lower birth weight than did those in the

non-HDP group.

Data regarding physical and MR imaging assessments at term-equivalent age and neurodevelopmental assessment at a corrected age of 1.5 years are presented in Table 2. Infants in the HDP group did not have catch-up growth of body weight and height at term-equivalent age; however, they had catch-up growth of head circumference. No statistically significant differences in global brain volumes (total volume, gray matter volume, and white matter volume) were observed between the two groups without adjustment for covariates (Table 2). Additionally, no significant differences were observed after adjustment for covariates including gestational age and infant sex (data not shown). The Kidokoro scores in each category and severity in the HDP group were comparable to those observed in the non-HDP group. Of the 94 infants, 59 (HDP, n = 11; non-HDP, n = 48) had DQ assessment at a corrected age of 1.5 years. The DQ was also similar between the two groups.

We performed an additional analysis to detect regional volumetric alterations in gray and white matter, considering the possibility that regional alterations may exist even though the total brain volumes were not significantly different. Compared with those in the non-HDP group, infants in the HDP group showed reduced volumes of gray matter in certain regions and increased volumes of gray matter in other regions (uncorrected $p < 0.001$; Figure 2A-B).

However, no significant regions were observed after FWE correction for multiple comparisons in the cluster-level analysis (p <0.05), and after adjustment for covariates including gestational age and infant sex. Furthermore, in comparison to those in the non-HDP group, infants in the HDP group showed reduced volumes of white matter in some regions and increased volumes of white matter in other regions (uncorrected p <0.001; Figure 3A-B). However, no significant differences were observed after FWE correction for multiple comparisons and after adjustment for covariates.

Discussion

In this cohort study, we sought to investigate the impact of maternal HDP on brain volumes and brain injury at term-equivalent age in preterm infants born before 34 weeks of gestation. The main finding of this study was that global and regional volumetric alterations were not observed in preterm infants born to mothers with HDP compared with those born to mothers without HDP. Moreover, brain injury scores at term-equivalent age and DQ at a corrected age of 1.5 years were not significantly different between the two groups. These findings indicate that the impact of maternal HDP on infant brains may cause limited harm to subsequent neurodevelopment than other factors associated with preterm birth and that brain volumes might catch up by term-equivalent age with appropriate postnatal treatment or environment in NICUs despite exposure to maternal HDP in the uterus.

To date, insufficient evidence exists regarding the effects of maternal HDP on infant brain volumes, except for a previous pilot study that demonstrated brain structural alterations in 7-to-10-year-old children born to mothers with preeclampsia at term (33). Our results were consistent with those of this pilot study, which reported no significant difference in total intracranial brain volumes between children born to mothers with preeclampsia and to controls. However, contrary to our results, infants in this pilot study exhibited significantly enlarged brain volumes in the bilateral amygdala, cerebellum, temporal lobe, and brainstem after adjustment for age, height, and weight. Interestingly, some reports have shown that an enlarged amygdala, a part of the limbic system, is associated with autism spectrum disorder (34, 35). However, our volumetric analysis showed no changes in the amygdala or other areas of the limbic system. Possible explanations for this discrepancy in volumetric alteration between our study and the pilot study (33) are as follows: 1) study target (born very preterm vs. born at term), 2) timing of MR imaging assessment (term-equivalent age vs. early adolescence), 3) postnatal environment (NICU vs. home), 4) total sample size (94 vs. 20), and 5) the definition of control (very preterm infants vs. healthy controls). Particular attention needs to be paid to the fact that the non-HDP group in our study included very preterm infants with several comorbidities attributed to preterm birth, chorioamnionitis, or fetal growth restrictions. These differences in study settings might have affected our results; thus,

323 further studies are required to investigate the effects of HDP on infant brain structure and
324 brain injury at different times of MR imaging (e.g., early childhood) and across different
325 populations (e.g., term neonates). In this study, we focused on brain volumetric alteration or
326 brain injury attributed to maternal HDP in preterm infants; however, other neuroimaging
327 techniques such as functional MR imaging and diffusion tensor imaging may also provide
328 valuable insight into brain functional alterations associated with subsequent
329 neurodevelopmental impairment in infants born to mothers with HDP.
330
331 A recent animal study demonstrated that offspring of mice with placental growth
332 factor deficiency (*Pgf*$^{-/-}$), which exhibit characteristics of preeclampsia, showed poorer spatial
333 memory and less exploratory behavior (36). MR imaging of neuroanatomy revealed that
334 smaller brain volumes were detected in 10 structures (e.g., entorhinal cortex, occipital cortex,
335 and cerebellar cortex) in *Pgf*$^{-/-}$ mice as compared to *Pgf*$^{+/+}$ mice (36). Additionally,
336 depression-like behavior and neuroanatomical alterations showed improvement by postnatal
337 replacement of recombinant placental growth factor (37). These findings suggest that
338 neurodevelopmental disorders in the offspring of preeclampsia pregnancies result in impaired
339 angiogenesis during pregnancy. Alterations in circulating angiogenic factors such as vascular
340 endothelial growth factor, placental growth factor, and soluble fms-like tyrosine kinase-1
341 during pregnancy may affect fetal cerebrovascular function and cause neuroanatomical

342 alterations, negatively impacting the neurodevelopmental processes in later life (38).

343

344 Another study using a rat model, in which preeclampsia was induced by nitric oxide
345 synthase inhibitor (L-NAME), demonstrated that the brain-body weight ratio of offspring was
346 similar but their cerebral cortex was thicker and spatial learning and memory were severely
347 impaired (39). Conversely, another rat model, in which preeclampsia was induced by
348 maternal inflammation using lipopolysaccharide (LPS), did not show morphological
349 alterations in the brain of offspring, but showed impaired learning and memory functions (40).
350 Until now, we could not conclude on whether HDP alters the brain volumes in infants on the
351 basis of available animal studies.

352

353 The main strength of this study is that, to the best of our knowledge, this is the first
354 report analyzing brain volumetric and brain injury assessments in preterm infants to evaluate
355 the impact of maternal HDP exposure during pregnancy on infants' neuroanatomy. Moreover,
356 we assessed MR imaging at term-equivalent age, which is a very early stage of life in contrast
357 to a previous report (33). Finally, we also evaluated brain injury at term-equivalent age using
358 an MR imaging assessment tool, which is valid for identifying infants with subsequent
359 neurodevelopmental impairment.

360

Several limitations of this study should be acknowledged. First, the timing of MR imaging varied depending on the infants' condition (e.g., respiratory and/or circulatory systems) and body weight for safety reasons. Infants in the HDP group were more likely to develop complications with growth restrictions. Consequently, MR imaging was performed later in the HDP group compared to the non-HDP group (Supplementary Figure 1A). In other words, the timing of MR imaging was largely dependent on the presence of fetal growth restrictions, which have common etiologies with HDP. Therefore, we did not incorporate postmenstrual age at MR imaging into the covariates for adjustment of volumetric alterations because of multicollinearity among the explanatory variables. Second, we could not rule out the possibility that neonatal complications and various treatments during the NICU stay due to preterm birth could have influenced our results, even though these factors were not significantly different between the two groups. If we could assess brain volumes shortly after birth, different results may have been obtained. However, safely performing MR imaging in extremely and very preterm infants is technically difficult. Finally, the target of this study was infants born before 34 weeks of gestation. Preterm birth itself may influence subsequent neurodevelopment; thus, it may be difficult to address the differential effect of HDP and prematurity because these two independent conditions occur simultaneously, and both can contribute to impaired neurodevelopment. Further studies analyzing infants born at term shortly after birth would eliminate the effect of prematurity, neonatal complications, and

postpartum treatment on infant brain volumes.

In conclusion, significant alterations in brain volumes and injury at term-equivalent age were not observed in preterm infants born to mothers with HDP. The effect of maternal HDP on brain growth in preterm infants might be less than that of other factors associated with preterm birth. Additionally, brain volumes may catch up by term-equivalent age following appropriate postnatal treatment or environments in NICUs. Further research is needed to confirm the consistent validity of our results at different time points and among different populations.

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Declarations of interest

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Figure legends

Figure 1. Flow diagram of the study population.

Data on 304 infants born at Nagoya University Hospital between January 2010 and December 2018 were available. Assessments of the brain volumes and brain injury were performed in 94 infants (HDP, n = 20; non-HDP, n = 74). MR imaging, magnetic resonance imaging; HDP, hypertensive disorders of pregnancy.

Figure 2. Regional volumetric alterations in the gray matter between the HDP and non-HDP groups.

A: Red-colored areas represent regions showing smaller volumes in the gray matter in the HDP group compared with the non-HDP group (uncorrected p <0.001 for visualization purposes only); **B:** Green-colored areas represent regions showing larger volumes in the gray matter in the HDP group than in the non-HDP group (uncorrected p <0.001 for visualization purposes only). L, left; R, right; P, posterior; A, anterior; the threshold of a minimum cluster size of >52 voxels.

Figure 3. Regional volumetric alterations in the white matter between the HDP and non-HDP groups.

A: Red-colored areas represent regions showing smaller volumes in the white matter in the HDP group compared with the non-HDP group (uncorrected p <0.001 for visualization purposes only); **B**: Green-colored areas represent regions showing larger volumes in the white matter in the HDP group than in the non-HDP group (uncorrected p <0.001 for visualization purposes only). L, left; R, right; P, posterior; A, anterior; the threshold of a minimum cluster size of >52 voxels.

Supplementary Figure 1. Relationships between gestational age and postmenstrual age at MR imaging and between birth weight and postmenstrual age at MR imaging.

Figure 1A shows a graph of the gestational age plotted against the postmenstrual age at MR imaging for the entire population, depicting the distribution. Figure 1B shows a graph of the birth weight plotted against the postmenstrual age at MR imaging for the entire population, depicting the distribution. Black dots indicate infants in the HDP group and white dots indicate infants in the non-HDP group. MR imaging, magnetic resonance imaging; HDP, hypertensive disorders of pregnancy.

553 Table 1. Maternal and neonatal characteristics in the HDP and non-HDP groups.

	HDP (n = 20)	non-HDP (n = 74)	*p*-value
Maternal characteristics			
Maternal age (year)	36.4 ± 4.5	33.8 ± 5.4	0.04
Primiparous (%)	14 (70.0)	33 (44.6)	0.07
Gestational age at delivery (weeks)	29.7 ± 2.5	30.5 ± 2.6	0.20
Pre-pregnancy BMI (kg/m^2)	24.2 ± 5.7	21.6 ± 4.1	0.07
Cesarean section (%)	20 (100)	64 (86.5)	0.08
Preeclampsia (%)	13 (65.0)	NA	NA
GDM/DM (%)	0 (0.0)	4 (5.4)	0.38
Antenatal corticosteroid treatment (%)	12 (60.0)	48 (64.9)	0.69
Antenatal magnesium treatment (%)	13 (65.0)	20 (27.0)	<0.01
Histological chorioamnionitis (%)	2 (10.0)	21 (28.4)	0.07
Neonatal characteristics			
Male (%)	10 (50.0)	41 (55.4)	0.66
Birth weight (g)	991 ± 470	1,424 ± 475	<0.01
Height (cm)	33.7 ± 5.3	39.3 ± 4.6	<0.01
Head circumference (cm)	25.4 ± 3.1	27.9 ± 2.6	<0.01
Small for gestational age (%)	13 (65.0)	9 (12.2)	<0.01
Respiratory distress syndrome (%)	9 (45.0)	37 (50.0)	0.69
Days of intubation (day)	22 ± 31	9 ± 19	0.12
Chronic lung disease (%)	5 (25.0)	13 (17.6)	0.32
Intraventricular hemorrhage grade I or II (%)	1 (5.0)	3 (4.1)	0.62
Patent ductus arteriosus banding (%)	1 (5.0)	1 (1.4)	0.38
Inotrope use (%)	3 (15.0)	6 (8.1)	0.29
Postnatal steroid use (%)	4 (20.0)	4 (5.4)	0.06
Necrotizing enterocolitis (%)	0 (0)	0 (0)	1
Infection (%)	2 (10.0)	7 (9.5)	0.62
Treated retinopathy of prematurity (%)	4 (20.0)	9 (12.2)	0.28
Days of hospitalization (day)	87 ± 35	69 ± 33	0.05

554 HDP, hypertensive disorders of pregnancy; BMI, body mass index; GDM, gestational
555 diabetes mellitus; DM, diabetes mellitus; NA, not applicable. Data are presented as mean ±
556 standard deviation or n (%).
557

Table 2. Physical, MR imaging, and neurodevelopmental assessments in the HDP and non-HDP groups.

	HDP (n = 20)	non-HDP (n = 74)	*p*–value
PMA at assessments (weeks)	40.2 ± 2.2	38.8 ± 1.7	<0.01
Body weight (g)	2,017 ± 394	2,394 ± 427	<0.01
Height (cm)	40.8 ± 5.2	44.2 ± 3.7	0.01
Head circumference (cm)	31.8 ± 1.8	32.6 ± 1.9	0.10
Brain volumes			
Gray matter volume (ml)	174.7 ± 24.3	172.0 ± 24.0	0.66
White matter volume (ml)	136.8 ± 13.3	141.9 ± 12.5	0.14
Total volume (ml)	311.6 ± 26.3	313.9 ± 27.4	0.73
Kidokoro score			
Cerebral white matter score (0–17)	2 (0–5)	3 (1–5)	0.18
Cortical gray matter score (0–9)	0 (0–1)	0 (0–3)	0.70
Deep gray matter score (0–7)	0 (0–2)	0 (0–3)	0.99
Cerebellum score (0–7)	1 (0–2)	1 (0–2)	0.82
Total score (0–40)	3 (0–8)	4 (1–9)	0.36
Kidokoro score severity			
Normal (0–3)	11 (55.0)	30 (40.5)	0.40
Mild (4–7)	8 (40.0)	41 (55.4)	
Moderate (8–11)	1 (5.0)	3 (4.1)	
Severe (12–40)	0 (0)	0 (0)	
DQ at a corrected age of 1.5 years	(n = 11)	(n = 48)	
Postural and Motor area	91.4 ± 20.6	86.9 ± 17.7	0.52
Cognitive and Adaptive area	82.8 ± 16.5	90.9 ± 15.2	0.18
Language and Social area	83.1 ± 25.6	86.2 ± 18.3	0.71
Total	84.9 ± 15.0	89.2 ± 14.1	0.40

HDP, hypertensive disorders of pregnancy; MR imaging, magnetic resonance imaging; PMA, postmenstrual age; DQ, developmental quotient. Data are presented as mean ± standard deviation, median (range), or n (%).