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Assessment of the association between Apgar scores and seizures in infants less than 1 year old

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ABSTRACT

Purpose: The study aimed to assess the association between Apgar scores at 1 and 5 min after birth and seizures in infants less than 1 year old.
Methods: We conducted a retrospective, observational, hospital-based study by utilising medical records from the Chung-Ang University Hospital admissions from January 2006 to May 2015 in order to identify infants less than 1 year old who had a history of seizures. Using electronic medical records, infants who were diagnosed with infantile seizures at the Chung-Ang University Hospital from January 2006 to May 2015 were included in the seizure group (n = 93), and a control group consisting of 296 age-matched cases without a history of seizures was selected from a group of infants born at Chung-Ang University Hospital during the same study period.
Results: We found that Apgar scores were significant risk factors for infantile seizures. Apgar scores differed depending on gestational age and birth weight. We found strong associations between Apgar scores and infantile seizures in the full-term and the normal-birth weight groups (bodyweight $\geq$2.5 kg), regardless of delivery mode. The Apgar scores were inversely correlated with the EEG class, and only the 1-min Apgar scores were correlated with MRI findings.
Conclusion: Low Apgar scores are significant perinatal risk factors for infantile seizures, especially in full-term and normal-birth weight infants, and have a strong negative linear relationship with EEG and brain MRI results in the seizure group.

1. Introduction

The 10-point Apgar scale has been used to assess the physiologic condition and prognosis of new-born children throughout the world for over 60 years [1]. However, the use of the Apgar score has become controversial, because medical professionals have attempted to apply it as a prognostic indicator of an infant's neurodevelopment, a use for which it was not initially developed [1]. Since infantile seizures (seizures occurring at less than 1 year of age) are the most common and distinctive clinical manifestations of neurological dysfunction in an infant [2], it is therefore reasonable to assume that seizures at less than 1 year of age are related to the perinatal condition in ways that are not yet fully understood. The Apgar score is a widely used tool that reflects the overall perinatal condition of the newborn [3].

The aim of this study was to investigate the possibility of predicting the neurological prognosis of infants by analysing the correlation between the Apgar score and the incidence of infantile seizures. First, we sought to determine whether Apgar scores, among other routinely measured perinatal values, could significantly contribute to prediction of infantile seizures. Next, if the relationship with infantile seizures proved significant, our aim was to assess the strength of the association of Apgar scores with infantile seizures in terms of other perinatal values, including gestational age (GA) and birth weight. Finally, we analysed the correlation of Apgar scores with electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) findings, from which we assessed the possibility of using Apgar scores as prognostic indicators of the neurodevelopmental status of infants less than 1 year old.

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2. Materials and methods

2.1. Study population

The study population ($n = 93$) was derived from infants treated at the Chung-Ang University Hospital between January 2006 and May 2015. Control group subjects ($n = 294$) were selected from infants born at the Chung-Ang University Hospital between January 2006 and May 2015, who were younger than 1 year of age and had no history of seizures, irrespective of the presence of other diseases, including all neurological disorders except seizure or epilepsy. The control group subjects were selected from infants whose onsets of chief complaints were as close as possible to the onset of each seizure case for randomisation after excluding age, to avoid the potential for bias.

2.2. Samples and sample size

Data collection occurred over a 6-month period. A total of 130 patients and 425 control subjects were recruited for the study. Thirty-seven patients and 129 control subjects with inadequate data for various reasons (i.e., refusal to participate [$n = 10$], inability to provide hospital records of birth on telephone inquiry [$n = 128$], or unreliable data [$n = 28$]) were excluded from the study. The final study population included 93 patients in the seizure group and 296 control subjects.

2.3. Definitions

Epilepsy was defined as the presence of two or more afebrile seizures that were not associated with an acute central nervous system (CNS) insult and did not occur within a 24-h period. Diagnostic criteria for hypoxic ischaemic encephalopathy (HIE) included evidence of foetal difficulty in the final hours before birth, depression at birth and the need for resuscitation, severe metabolic acidosis, neonatal clinical and imaging signs of acute neurological abnormalities, evidence of dysfunction of other systems and exclusion of other causes of neonatal encephalopathy [4]. Intracranial haemorrhage (ICH) included primary subarachnoid-haemorrhage, germinal matrix-intraventricular haemorrhage and subdural haemorrhage. Hypocalcaemia was defined as calcium levels <7 mg/dL in a blood sample. Neurodevelopmental disruption included agenesis of the corpus callosum, brain tumour, subarachnoid cyst and Dravet syndrome. Febrile seizures were defined as seizures occurring between the ages of 3 months and 6 years in patients with no previous afebrile seizures and associated with fever but without evidence of intracranial infection or other recognised acute neurological illness. CNS infection was identified in patients with meningitis or encephalitis consequent to an inflammatory cell response on lumbar puncture. A patient was diagnosed with convulsions with gastroenteritis when presenting with seizures accompanied by symptoms of gastroenteritis, without clinical signs of dehydration or electrolyte derangement, and a body temperature below 38.0 °C before and after the seizures [5]. Different seizure types were defined according to the published International League Against Epilepsy classification of seizures and Volpe's classification [6]. We considered Apgar scores between 1 and 6 as low and those between 7 and 10 as normal, in order to determine the odds ratio (OR). Based on the EEG wave analysis, we categorised all EEG findings into 4 subgroups: normal (0 on EEG), partial seizures (1 on EEG), generalised seizures (2 on EEG), and cerebral dysfunction (3 on EEG). EEG classifications were based on EEG findings within 24 h of seizure onset. Abnormal brain MRI findings included the presence of an arachnoid cyst, hippocampal sclerosis, encephalomalacia, intracranial haemorrhage, a tumorous lesion and microcephaly. MRI was obtained during hospitalisation, and additional MRI scans were not performed for further classification under the abnormal category. Mean age at MRI scanning was 118 ± 90 days (range, 2–360).

2.4. Data collection

Patient data collected included Apgar scores, sex, mode of delivery, GA, birth weight, EEG and brain MRI findings and seizure aetiology. The medical records of all patients who experienced clinically evident infantile seizures (i.e., seizure or convulsion within the first year of life, confirmed by a paediatric neurologist) were retrospectively reviewed. We collected the infants' Apgar scores and other perinatal data using electronic medical records (EMRs). If infants were born at another hospital but transferred to the Chung-Ang University Hospital for the treatment of seizures, we obtained their Apgar scores from the referring hospital via telephone inquiry.

2.5. Statistical analysis

A multiple logistic regression model was used to determine the most significant perinatal factor among known factors including sex, Apgar scores, birth weight, GA, mode of delivery, and mother's age. Significance was determined using ORs with 95% confidence intervals (95% CIs). The 1- and 5-min Apgar scores were compared between the seizure and the control groups, between sexes, and among modes of delivery using independent t-tests. The comparison of Apgar scores among GA and birth weight groups was performed using the Kruskal–Wallis and Mann–Whitney U tests. The strength of the correlation of Apgar scores with modes of delivery, GA, and birth weight in both groups was analysed using the chi-square and Mantel–Haenszel methods. We used a bivariate correlation analysis to determine the correlation between Apgar scores and EEG findings, and the chi-square test to determine the correlation between Apgar scores and MRI findings. All P-values were derived from the two-sided test, and $P < 0.05$ was considered statistically significant. All analyses were performed using the PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA) software.

3. Results

3.1. General characteristics of seizures

Ninety-three cases of infantile seizures were included in the seizure group. The aetiology of seizures included HIE ($n = 18$, 19.4%), hypocalcaemia ($n = 12$, 12.9%), ICH ($n = 11$, 11.8%), brain anomaly ($n = 7$, 7.5%), convulsion with gastroenteritis ($n = 4$, 4.3%), febrile seizure ($n = 4$, 4.3%), CNS infection ($n = 1$, 1%) and unknown causes ($n = 35$, 37.5%). The 1- and 5-min Apgar scores (mean $\pm$ SD) varied according to aetiology (HIE: 5.17 ± 2.70, and 6.83 ± 2.46, respectively; ICH: 6.27 ± 1.85 and 8.09 ± 1.14; hypocalcaemia: 7.33 ± 1.37 and 8.58 ± 1.08; brain anomaly: 7.57 ± 1.13 and 9.14 ± 0.38; convulsion with gastroenteritis: 8 and 9; CNS infection: 8 and 9; febrile seizure: 8 and 9; and unknown causes: 7.94 ± 0.73 and 8.83 ± 0.79). The onset of seizures (days $\pm$ SD from birth) also varied according to aetiology (CNS infection: 1; HIE: 2.73 ± 3.40; ICH: 9.44 ± 15.10; metabolic causes: 13.70 ± 28.02; convulsion with gastroenteritis: 132 ± 134; brain anomaly: 175 ± 136; febrile seizures: 220 ± 131; and unknown causes 83.09 ± 96.70).

Of the 93 patients presenting with seizures, the seizure types were classified as follows: atonic, ($n = 1$:1 infant); focal clonic ($n = 7$:4 neonates, 3 infants); focal tonic ($n = 3$:1 neonate, 2 infants); generalised tonic ($n = 17$:9 neonates, 8 infants); generalised tonic clonic ($n = 33$:18 neonates, 15 infants); multifocal clonic ($n = 4$:3 neonates, 1 infant); multifocal myoclonic ($n = 2$:2 neonates); and subtle ($n = 18$:15 neonates, 3 infants).

3.2. Significance of Apgar scores in the occurrence of infantile seizures

As described above, this study included 389 infants ($n = 93$ in the seizure group and $n = 296$ in the control/non-seizure group). Of the subjects in the seizure group, 42 (45.2%) were male and 51 (54.8%) were female. In addition, 47 (50.5%) and 46 (49.5%) infants were born by vaginal delivery and caesarean delivery, respectively. Of the subjects in the non-seizure group, 150 (50.7%) were male and 146 (49.3%) were female. In addition, 145 (49%) and 151 (51%) infants were born by vaginal and caesarean deliveries, respectively. We performed a multiple logistic regression analysis to select the perinatal factor that contributed the most to infantile seizure occurrence. Factors considered included sex, Apgar scores, birth weight, mode of delivery, GA and mother's age (Table 1). These factors were first analysed as independent variables (Table 1, left column), and then as categorical variables (Table 1, right column). The results showed that although the 1- and 5-min Apgar scores, birth weight, and mode of delivery each had an OR > 1, only the 1- and 5-min Apgar scores ($P < 0.05$) were significantly associated with the occurrence of infantile seizures.

3.3. Comparisons of Apgar scores in terms of seizure aetiology, sex, mode of delivery, gestational age and birth weight

In the seizure group ($n = 93$), the mean (± SD) 1-min Apgar score was 7.11 ± 1.85 and the mean 5-min Apgar score was 8.38 ± 1.51. In the control group ($n = 296$), the mean 1-min Apgar score was 8.45 ± 1.51 and the mean 5-min Apgar score was 9.41 ± 1.10. Both 1- and 5-min Apgar scores were significantly different ($P < 0.01$) between the seizure and non-seizure groups. We found no significant differences in Apgar scores between males and females in the seizure group (1-min Apgar score, $P = 0.96$; 5-min Apgar score, $P = 0.86$). Similarly, there were no significant differences in Apgar scores between vaginal and caesarean deliveries (1-min Apgar score, $P = 0.74$; 5-min Apgar score, $P = 0.87$).

With respect to GA, we divided the entire group into the three subgroups of preterm (GA < 34 weeks), late preterm (34 weeks ≤ GA < 37 weeks) and full-term (GA ≥ 37 weeks) infants. We found a significant difference in the 1-min Apgar scores among the three subgroups ($P < 0.001$). All comparisons between the gestational subgroups differed except in comparing the late preterm and full-term groups. We found a significant difference in the 5-min Apgar scores (Table 2) among all three gestational subgroups and across all comparisons between groups.

Next, we divided the entire group into four subgroups based on birth weight: extremely low birth weight (ELBW, birth weight <1 kg), very low birth weight (VLBW, 1 kg ≤ birth weight < 1.5 kg), low birth weight (LBW, 1.5 kg ≤ birth weight < 2.5 kg), and normal birth weight (birth weight ≥ 2.5 kg). Across the four above-mentioned subgroups, the 1-min Apgar scores were significantly different ($P < 0.001$). All comparisons between birth weight subgroups differed except for comparison between LBW and NBW groups. The 5-min Apgar scores were also significantly different across all subgroups, and the comparison of the LBW and NBW groups showed a significant difference in only the 5-min Apgar scores during all dual subgroup comparisons ($P = 0.008$; Table 2).

We also compared the associations between Apgar scores and seizure occurrence in terms of aetiology. In the 1-min Apgar score analysis, HIE showed the strongest association, and gastroenteritis, febrile seizure and CNS infection had the next strongest associations. In the 5-min Apgar score analysis, HIE was also the strongest association and was followed by hypocalcaemia, ICH, febrile seizure, brain anomaly, and CNS infection. However, ICH, hypocalcaemia, brain anomaly and CNS infection in 1-min Apgar scores analysis and CNS infection and gastroenteritis in 5-min Apgar scores analysis were not statistically significant (Table 2).

3.4. Correlation analysis on the association of Apgar scores with infantile seizures

Table 3 shows the strengths of the correlation between Apgar scores and infantile seizures according to the delivery mode, GA and birth weight subcategories. Regardless of whether infants were delivered vaginally or by caesarean section, a significant correlation between Apgar score and infantile seizures was seen only in the full-term group (1-min Apgar score: $P < 0.001$, OR: 1.76 [1.10–2.80]; 5-min Apgar score: $P < 0.001$, OR: 2.44 [1.42–4.21]).

A significant correlation was only observed in the full-term group, for both vaginal deliveries (1-min Apgar score: $P < 0.001$, OR: 1.84 [1.05–3.58]; 5-min Apgar score: $P < 0.001$, OR: 2.76 [1.19–6.41]) and for caesarean section deliveries (5-min Apgar score: $P < 0.001$, OR: 2.27 [1.11–4.61]).

Table 1
Multiple logistic regression analysis to select the perinatal factor that most contributed to infantile seizure (Independent variables in the left column, categorisation of the independent variables in the right column).

	P	Odds ratio (95% CI)		Numbers (%)	*P*	Odds ratio (adjusted, 95%CI)
Sex			Sex			
	0.03	0.55 (0.32–0.94)	Male	204 (52.0)	0.14	0.63 (0.34–1.16)
Apgar score			Apgar score			
1-min Apgar score	0.005	1.57 (1.15–2.16)	1-min Apgar score: 5,6,7	178 (45.4)	<0.001	62.14 (22.30–172.90)
5-min Apgar score	0.003	2.11 (1.30–3.42)	5-min Apgar score: 1,2,3,4	5 (1.3)	0.02	34.60 (1.77–68.00)
			5-min Apgar score: 5,6,7	63 (16.1)	0.43	1.43 (0.59–3.50)
Birth weight			Birth weight			
			Birth weight < 1 kg	9 (2.3)	0.65	0.53 (0.03–8.47)
	0.99	1.00 (0.57–1.76)	1 kg ≤ birth weight < 1.5 kg	12 (3.1)	0.30	2.74 (0.4–18.70)
			1.5 kg ≤ birth weight < 2.5 kg	47 (12.0)	0.13	2.10 (0.81–5.42)
Gestational age			Gestational age			
	<0.001	0.23 (0.11–0.47)	GA < 34 weeks	37 (9.4)	0.02	0.17 (0.04–0.72)
			34 weeks ≤ GA < 37 weeks	51 (13.0)	<0.001	0.09 (0.04–0.24)
Delivery mode			Delivery mode			
	0.66	1.13 (0.64–2.00)	Normal vaginal delivery	208 (53.1)	0.75	1.11 (0.59–2.08)
Mother's age			Mother's age			
	0.84	0.99 (0.93–1.06)	Mother's age: 20–29 years old	89 (22.7)	0.09	3.80 (0.80–18.07)
			Mother's age: 30–39 years old	287 (73.2)	0.31	2.11 (0.51–8.80)

GA: gestational age; 95% CI: 95% confidence interval

Table 2
Comparison of seizure aetiologies and 1- and 5-min Apgar scores according to gestational age and birth weight using the Kruskal–Wallis and Mann–Whitney *U* tests.

	All subgroups (numbers)	Aetiology of seizure (numbers)								1-minute Apgar score (Mean ± SD)	Dual subgroup Comparisons *P*	*P*	5-minute Apgar score (Mean ± SD)	Dual subgroup Comparisons *P*	*P*
		HIE	Others												
			ICH	Hypo-calcaemia	Brain anomaly	CNS infection	Gastro-enteritis	Febrile seizure	Unknown						
Gestational age	Preterm (11)	6	4	1	0	0	0	0	0	3.91 ± 1.71	0.03	<0.001	6.09 ± 1.97	0.03	<0.001
	Late preterm (1)	1	0	2	1	0	0	0	2	6.67 ± 1.16	<0.01		8.33 ± 0.58	<0.01	
	Full-term (76)	12	7	8	6	1	5	4	33	7.57 ± 1.40	0.26		8.68 ± 1.16	0.001	
Birth weight	ELBW (7)	3	3	1	0	0	0	0	0	3.43 ± 1.99	0.03	<0.001	5.29 ± 2.06	0.07	<0.001
	VLBW (4)	3	1	0	0	0	0	0	0	4.75 ± 0.50	0.003		7.50 ± 0.58	0.23	
	LBW (13)	3	0	2	2	0	1	0	5	6.75 ± 1.91	0.84		7.38 ± 2.20	0.008	
	NBW (69)	9	8	8	5	1	4	4	30	7.62 ± 1.32			8.81 ± 0.89		
Strength of associations between A/S and seizures in terms of aetiology	1-minute Apgar score — *P*	<0.001	0.32	0.62	0.04	0.71	0.01	0.15							
	1-minute Apgar score — Odds ratio (95% CI)	2.39 (1.58-3.61)	0.28 (0.02-3.58)	0.25 (0.03-1.82)	0.21 (0.02-1.91)	1.20 (0.84-1.72)	2.25 (1.08-4.67)	1.50 (1.01-2.24)							
	5-minute Apgar score — *P*	0.02	0.04	0.83	0.02	0.72	0.01	0.08							
	5-minute Apgar score — Odds ratio (95% CI)	1.90 (1.41-2.57)	1.44 (1.01-2.08)	1.64 (1.13-2.37)	1.21 (1.05-1.40)	1.13 (0.98-1.42)	NS	1.50 (1.01-2.24)							

HIE: hypoxic ischaemic encephalopathy; ICH: intracranial haemorrhage; G/E: gastroenteritis A/S: Apgar score; SD: standard deviation; NS: nonspecific; ELBW: extremely low birth weight; VLBW: very low birth weight; LBW: low birth weight NBW: normal birth weight; Preterm: gestational age (GA) < 34 weeks; Late preterm: 34 weeks ≤ GA < 37 weeks; Full-term: GA ≥ 37 weeks; ELBW: birth weight (BW) < 1 kg, VLBW: 1 kg ≤ BW < 1.5 kg; LBW: 1.5 kg ≤ BW < 2.5 kg; NBW: BW ≥ 2.5 kg.

With regards to infant birth weight, a correlation was seen between Apgar scores and infantile seizures in the normal-birth weight group (5-min Apgar score: $P < 0.001$, 1.38 [1.02–3.64]), but not in the LBW, VLBW and ELBW groups.

When considering the mode of delivery, birth weight, and GA simultaneously, we found that the 1- and 5-min Apgar scores were both correlated with infantile seizures (1-min Apgar score: $P < 0.001$, OR: 1.55 [1.06–2.26]; 5-min Apgar score: $P < 0.001$, OR: 1.81 [1.14–2.88]).

Table 4 shows the correlation between Apgar scores and seizures with onset at less than and more than 1-month of age, respectively. Similarly to Table 3, Apgar scores correlated with seizures only in full-term and normal-birth weight (>2.5 kg) infants in both periods, and no correlation was observed in the late-preterm, preterm, LBW, VLBW or ELBW groups.

3.5. Correlation of Apgar scores with EEG and MRI findings

The correlation between Apgar scores and EEG findings in the seizure group is presented in Fig. 1. EEG was performed in 80 of the 93 cases in the seizure group. A brain MRI was performed for 52 of the 80 cases that underwent an EEG. Fig. 1 is a graph of Apgar scores vs. EEG class, obtained from the linear regression analysis after bivariate analysis. Upon bivariate analysis, the results suggested that both Apgar scores had a strong negative linear association with the EEG class. Table 5 shows the results of chi-square analysis on the correlation between Apgar score and brain MRI findings by EEG class. EEG classes were used as covariant variables in this analysis. In all EEG subclasses, P was >0.05; thus, there was no significant correlation for any particular EEG class. In contrast, the 1-min Apgar score ($P = 0.012$) showed a significant correlation with brain MRI findings, but no significant correlation was seen with the 5-min Apgar score.

4. Discussion

In this study, we found that a lower Apgar score was more strongly correlated with seizures in infants less than 1 year old when the infants were full-term (GA ≥ 37 weeks) compared to preterm or late-preterm births. A possible explanation for this finding is that the use of a low Apgar score to predict conditions that may cause damage the CNS, such as HIE, is inadequate in preterm infants [7]. In other words, the generally low values observed in some Apgar score components reflect a physiological prematurity rather than newborn distress in preterm infants [8,9], and a healthy preterm infant with no evidence of asphyxia may still receive a low score because of physiological immaturity [10]. Therefore, the strength of the association between a low Apgar score and the potential for brain damage appears to be weaker in preterm infants than in full-term infants [11]. Similarly, for example, the lower the GA, the weaker the association between low Apgar scores and acidosis; many preterm infants have low Apgar scores without any evidence of acidosis [11]. Thus, in general, the relative risk of abnormal clinical findings in conjunction with a low Apgar score just after birth decreases with decreasing GA [12]. Signs that may indicate neurodevelopmental damage in full-term infants may be relatively weakly associated with actual damage in preterm infants, since preterm infants must contend with any number of adverse outcomes just after birth regardless of the Apgar score [13]. The corollary of this finding is that the strength of the association between low Apgar scores and adverse outcome is stronger in full-term infants [14], because the Apgar score is not influenced by potentially confounding variables due to physiological immaturity [15]. The Apgar score can thus be used as a relatively strong predictor of the neurodevelopmental prognosis in full-term infants [7]. Regardless of the Apgar score, the infant's birth weight should be considered when assessing

Table 3
Comparison of associations between Apgar scores and seizures in infants less than 1 year old using the chi-square and Mantel–Haenszel methods. We considered Apgar scores of 1–6 as low, and those of 7–10 as normal, in order to determine the odds ratio.

Delivery mode	Gestational age	Birth weight	Numbers	1-min Apgar score		5-min Apgar score	
				P	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)
Normal vaginal delivery	Full-term	LBW	12	0.26	2.50 (0.39–16.05)	0.42	NS
		NBW	164	<0.001	1.75 (1.03–3.45)	<0.001	2.08 (1.51–8.53)
		Total	176	<0.001	1.84 (1.05–3.58)	<0.001	2.76 (1.19–6.41)
	Late preterm	LBW	6	0.05	NS	0.05	NS
		NBW	9	NS	NS	NS	NS
		Total	15	0.07	2.09 (0.26–16.86)	0.00	1.13 (1.00–1.26)
	Preterm	ELBW	3	0.22	NS	0.08	NS
		VLBW	3	0.39	NS	0.22	NS
		LBW	7	NS	NS	NS	NS
		NBW	3	0.39	NS	0.39	NS
		Total	16	0.09	0.71 (0.45–1.14)	0.09	3.33(0.16–70.90)
	Total	ELBW	3	0.22	NS	0.08	NS
		VLBW	3	0.39	NS	0.22	0.50 (0.125–2.00)
		LBW	25	0.08	5.25 (1.02–27.14)	0.19	NS
		NBW	176	<0.001	1.74 (1.03–3.67)	<0.001	1.44 (1.28–7.31)
		Total	207	<0.001	1.90 (1.06–3.40)	<0.001	1.70 (1.69–4.31)
Caesarean delivery	Full-term	LBW	11	0.01	6.00 (1.69–21.26)	0.01	6.00 (1.69–21.26)
		NBW	114	<0.001	1.11 (0.45–2.71)	<0.001	0.96 (0.17–5.37)
		Total	125	<0.001	1.66 (0.86–3.20)	<0.001	2.27 (1.11–4.61)
	Late preterm	VLBW	1	NS	NS	NS	NS
		LBW	10	0.66	0.50 (0.03–7.99)	0.53	1.42 (0.95–2.14)
		NBW	13	0.78	NS	0.36	NS
		Total	24	0.62	0.50 (0.04–6.44)	0.33	1.15 (0.98–1.37)
	Preterm	ELBW	9	0.83	NS	0.39	0.63 (0.37–1.07)
		VLBW	8	0.41	NS	0.47	0.33 (0.02–6.65)
		LBW	13	NS	NS	NS	NS
		NBW	3	NS	NS	NS	NS
		Total	33	0.13	0.67 (0.51–0.87)	0.06	2.22 (0.64–7.10)
	Total	ELBW	9	0.83	NS	0.39	0.63 (0.37–1.07)
		VLBW	9	0.31	NS	0.64	0.50 (0.03–8.95)
		LBW	34	0.89	1.44 (0.42–4.92)	0.02	2.74 (1.05–8.88)
		NBW	130	<0.001	1.07 (0.84–1.35)	<0.001	2.86 (1.14–5.10)
		Total	182	<0.001	1.35 (0.81–2.25)	<0.001	1.83 (1.05–3.18)
Total	Full-term	LBW	23	0.58	18 (1.56–207.4)	0.07	4.8 (2.20–10.47)
		NBW	278	<0.001	1.51 (1.01–2.42)	<0.001	1.54 (1.02–4.23)
		Total	301	<0.001	1.76 (1.10–2.80)	<0.001	2.44 (1.42–4.21)
	Late preterm	VLBW	1	NS	NS	NS	4.64 (1.26–16.77)
		LBW	16	0.41	2.25 (0.23–22.14)	0.36	1.33 (1.01–1.77)
		NBW	22	0.62	NS	0.70	NS
		Total	39	0.34	2.00 (0.25–16.16)	0.39	1.13 (1.00–1.27)
	Preterm	ELBW	12	0.79	NS	0.20	0.54 (0.31–0.94)
		VLBW	11	0.31	NS	0.73	0.37 (0.02–6.35)
		LBW	20	NS	NS	NS	NS
		NBW	6	0.49	0.67 (0.30–1.48)	0.30	1.25 (0.81–1.94)
		Total	49	0.03	0.67 (0.54–0.85)	0.02	2.45 (0.83–7.26)
	Total	ELBW	12	0.79	NS	0.20	0.55 (0.32–0.94)
		VLBW	12	0.23	NS	0.74	1.00 (0.20–4.96)
		LBW	59	0.33	2.20 (0.81–5.98)	0.02	2.71 (0.96–7.72)
		NBW	306	<0.001	1.16 (0.64–2.12)	<0.001	1.38 (1.02–3.64)
		Total	389	<0.001	1.55 (1.06–2.26)	<0.001	1.81 (1.14–2.88)

95% CI: 95% confidence interval; NS: nonspecific; ELBW: extremely low birth weight; VLBW: very low birth weight; LBW: low birth weight; NBW: normal birth weight; Preterm: gestational age (GA) < 34 weeks; Late preterm: 34 weeks ≤ GA < 37 weeks; Full-term: GA ≥ 37 weeks; ELBW: birth weight (BW) < 1 kg; VLBW: 1 kg ≤ BW < 1.5 kg; LBW: 1.5 kg ≤ BW < 2.5 kg; NBW: BW ≥ 2.5 kg.

the likelihood of neurodevelopmental damage. GA and birth weight are closely correlated and we can infer that a low birth weight may be considered a predisposing factor for neurodevelopmental damage, as has been previously established for prematurity [9]. With this in mind, we could assume that the strong association between a low Apgar score and infantile seizure in the normal-birth weight group (birth weight ≥ 2.5 kg) is more of a consequence of acquired brain damage rather than of a congenital vulnerability. This assumption is plausible since it is already firmly established that low Apgar scores in normal-weight infants are strongly associated with acquired brain damage at birth.

We also assessed the strength of the association of low Apgar scores with infantile seizures according to the age of seizure onset. Specifically, we compared an onset at less than 1 month of age (neonatal period) with an onset between 1 month and 1 year, because it is widely known that the aetiology of seizures in the neonatal period is more closely related to a perinatal insult such as birth asphyxia or intracranial haemorrhage. However, the associations between the Apgar score and seizure occurrence were both significant only in the full-term and normal birth weight groups (Table 4).

Although there have been several reports on the correlation of low Apgar scores and infantile neurodevelopmental damage with regard to GA and birth weight [16–18], there have been fewer studies evaluating the correlation between Apgar scores and EEG and brain MRI findings in infantile seizure patients. We attempted

Table 4
Comparison of associations between Apgar scores and seizures in infants with an onset of less than 1 month and more than 1 month using the chi-square and Mantel–Haenszel analysis. We considered Apgar scores of 1–6 as low and those of 7–10 as normal to determine the odds ratio.

Seizure onset		Less than 1 month					1 month—1 year				
			1-min Apgar score		5-min Apgar score			1-min Apgar score		5-min Apgar score	
		Numbers	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	Numbers	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)
Normal vaginal delivery	Full-term & NBW	134	<0.001	2.85 (1.35–16.89)	<0.001	5.00 (1.30–83.00)	116	<0.001	2.33 (1.05–13.03)	<0.001	NS
	Late preterm	26	0.33	0.83 (0.58–1.19)	0.22	1.04 (0.96–1.13)	19	0.71	1.06 (0.94–1.19)	0.61	1.06 (0.95–1.18)
	Preterm	9	0.17	0.67 (0.38–1.17)	0.32	0.60 (0.29–1.23)	6	NS	NS	NS	NS
	GA total & NBW	138	<0.001	3.06 (1.02–11.42)	<0.001	4.91 (1.29–81.43)	135	<0.001	1.87 (1.50–6.70)	<0.001	1.17 (1.09–1.25)
Caesarean delivery	Full-term & NBW	121	<0.001	1.94 (1.10–3.42)	0.04	1.30 (1.17–6.97)	82	<0.001	1.15 (1.05–1.25)	0.004	1.14 (1.05–1.24)
	Late preterm	20	0.51	6.50 (0.46–91.92)	0.59	1.19 (0.98–1.44)	25	0.76	1.05 (0.96–1.14)	0.60	1.04 (0.95–1.12)
	Preterm	17	0.15	0.36 (0.18–0.72)	0.23	6.00 (0.72–49.84)	17	NS	NS	NS	NS
	GA total & NBW	125	<0.001	3.15 (1.07–9.21)	0.001	2.71 (1.12–6.56)	116	<0.001	1.11 (1.04–1.18)	0.002	1.11 (1.04–1.18)
Delivery mode total	Full-term & LBW	2	NS	NS	NS	NS	42	<0.001	1.19 (1.05–5.94)	0.23	1.08 (0.99–1.18)
	Full-term & NBW	254	<0.001	2.93 (1.39–6.17)	<0.001	4.86 (1.17–20.20)	198	<0.001	1.34 (1.04–4.28)	<0.001	1.17 (1.1–1.24)

GA total: total gestational age; ELBW: extremely low birth weight; VLBW: very low birth weight; NBW: normal birth weight; Preterm: GA < 34 weeks; Late preterm: 34 weeks ≤ GA < 37 weeks; Full-term: GA ≥ 37 weeks; ELBW: birth weight (BW) < 1 kg, VLBW: 1 kg ≤ BW < 1.5 kg; LBW: 1.5 kg ≤ BW < 2.5 kg; NBW: BW ≥ 2.5 kg.

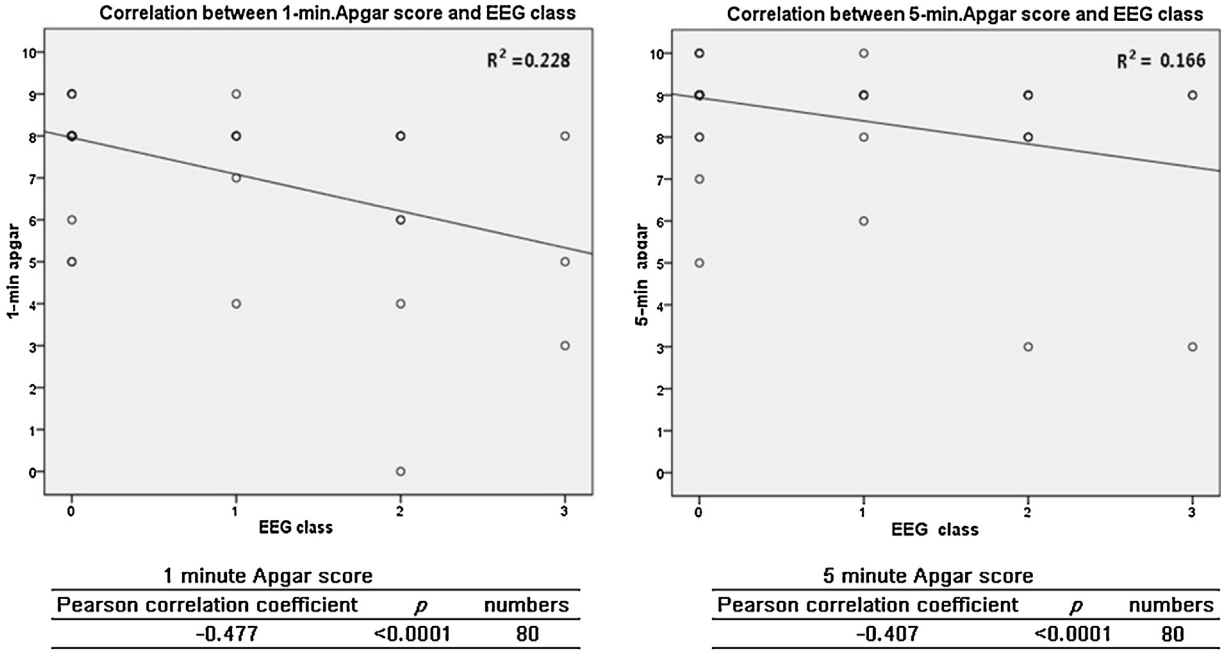

Fig. 1. The correlation between 1- and 5-min Apgar scores and EEG findings in the seizure group using a bivariate analysis.

Table 5
Comparison of the correlations between Apgar scores and brain magnetic resonance imaging findings according to electroencephalogram class, using the chi-square and Mantel–Haenszel analysis.

EEG class (severity)	Numbers (%)	1-min Apgar score vs. brain MRI findings		5-min Apgar score vs. brain MRI findings	
		χ^2	*P*	χ^2	*P*
0 (normal)	27 (51.9)	5.73	0.16	2.87	0.27
1 (partial)	11 (21.2)	2.93	1.00	3.65	0.76
2 (generalised)	9 (17.3)	4.95	0.33	3.26	0.57
3 (cerebral dysfunction)	5 (9.6)	NS	NS	NS	NS
Total	52 (100)	15.73	0.01	8.82	0.23

EEG: electroencephalogram; MRI: magnetic resonance imaging, NS: nonspecific.

to address this issue in the present study. Currently, EEG seems to be a feasible technique for identifying infants at high risk of post-asphyxia brain damage who might benefit from treatment following the episode [19]. A recent study reported that infants with normal imaging results were likely to have better outcomes when compared to those who showed diffuse, severe abnormalities [20]. In addition, children with epilepsy are more likely to have abnormal development and display concurrent abnormal findings on imaging [21]. Since MRIs can detect lesions that cannot be seen using ultrasonography, their diagnostic value is increasing rapidly in today's clinical setting [22]. In this study, we found only the 1-min Apgar score to be significantly correlated with brain MRI findings. Since the 5-min Apgar score reflects a longer period of brain damage than the 1-min Apgar score, we might assume that the 5-min score would be more strongly associated with MRI findings [23]. However, our results directly contradicted this

expectation. Therefore, we believe that the sample size should be increased with further studies to reach statistical significance before we can accept this result as fact. Regardless of this potential limitation, this study did show strong negative linear correlations between 1- and 5-min Apgar scores and EEG findings, leading us to believe that EEG findings, which reflect functional disorders of brain [24], may more accurately predict the occurrence of seizures than MRI findings, which reflect morphological and structural disorders of the brain [25].

Our study has some limitations. First, we were unable to perform a census of patient characteristics and randomise sampling of the enrolled patients to determine an appropriate control group. Second, there was probably some inconsistency in Apgar scoring within the seizure groups, because some patients were delivered directly at the Chung-Ang University Hospital, while others were delivered at outside hospitals and subsequently transferred to the Chung-Ang University Hospital following a seizure. Another limitation was the unsatisfactory feasibility of the variables examined. Perinatal factors such as GA, birth weight, mother's age, sex and delivery mode were the target variables investigated in this study. However, these are indirect measures. In future studies, more direct perinatal variables that might have a more profound impact on neurologic damage and are known to cause seizures should be considered. For example, early rupture of membranes, meconium staining, aspiration, pH and pCO2 levels on arterial blood gas analysis indicating hypoxia, and time of onset and duration of seizures [26,27]. Finally, there are numerous factors that may influence the Apgar score, including maternal sedation or anaesthesia, hypovolaemia, drugs, trauma, inter-observer variability, and significant biochemical disturbances; thus, we should consider these factors in future studies.

5. Conclusion

We believe the Apgar score will become even more useful if it is used in a more focused manner; specifically, for normal-birth weight ($\geq$2.5 kg) infants who are born at full term. We believe that Apgar scores may eventually be used as prognostic indicators of the neurodevelopmental status through our investigation of the correlation of Apgar scores with EEG and brain MRI findings. We hope this study's findings will be used as a framework for future studies.

Conflict of interest statement

The authors have no conflict of interest.

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