The Impact of Caffeine Citrate Therapy on Brain Growth on Head Ultrasound in Preterm Neonates

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INTRODUCTION

●Preterm newborns are vulnerable to impaired neurodevelopment.

●Caffeine citrate (CC) is the standard treatment for apnea of prematurity, with evidence suggesting neuroprotective effects.[1]

●This study investigates the association between cumulative CC exposure in extremely premature infants and brain growth using cranial ultrasound (CUS).

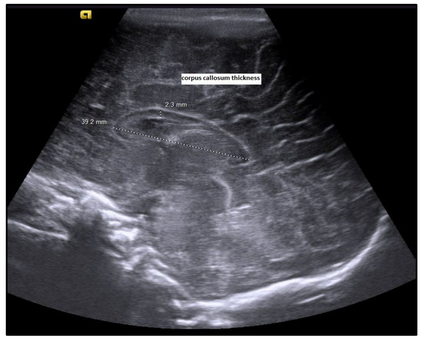

Fig 1. Cranial Ultrasound - Sagittal Section showing corpus callosum.

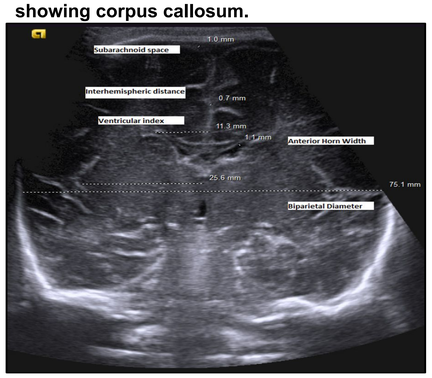

Fig 2. Cranial Ultrasound - Coronal Section

METHODS

●A retrospective study of preterm infants (<32 weeks gestation) born between January 2020 - December 2024 at Corewell Health Children's Hospital and followed at the neurodevelopmental clinic

● We excluded infants with intrauterine growth restriction, genetic syndromes, intraventricular hemorrhages grades 3-4, out-born, or if no CUS available for review.

●We analyzed the correlation between total CC dosage received in the NICU and cerebral growth on CUS at term-equivalent age.

● Brain growth was evaluated using multiple linear measurements: Anterior horn widths, ventricular indices, biparietal diameter, interhemispheric space, subarachnoid space, and the length and thickness of the corpus callosum (Figures 1 and 2).

● We performed an unequal variance two-sample t-test, Pearson correlation, univariable and multivariable regression models, and a matched analysis using univariable regression.

RESULTS

●190 included preterm infants born <32 weeks gestation were included, 184 (96.8%) received CC after birth per our hospital protocol.

●The median total CC dose was 342mg/kg (range 20-831mg/kg).

● A univariate correlation analysis between the total CC and CUS measurements in shown in table 1

Dependent	Estimate	p value
Left Anterior Horn Width	0.0031	0.00076
Right Anterior Horn Width	0.0022	0.0082
Basal Ganglia Insula diameter	0.00065	0.61
Biparietal diameter	0.0025	0.56
Bitemporal diameter	0.002	0.37
Biventricular diameter	0.0026	0.23
Corpus Callosum Length	-0.0047	0.021
Corpus Callosum Thickness	-0.00027	0.21
Interhemispheric Space	0.0029	<0.0001
Size of Subarachnoid space	0.0028	<0.0001
Left Ventricular Index	0.0016	0.15
Right Ventricular Index	0.0008	0.46
Mid-size Lateral Ventricle	0.0000086	1

Table 1. Correlation analysis between CC cumulative dose and the different measurements on CUS

● In a multivariable model adjusting for significant confounding variables (gestational age, length of stay in the neonatal unit, the diagnosis of bronchopulmonary dysplasia, the use of cortical steroids postnatally) a significant positive correlation remained between total CC dose and left anterior horn width (p=0.036) and corpus callosum length (p=0.02),

CUS Corpus Length	Estimate	p value
Univariable Model	-0.0047	0.021
Multivariable Model	-0.0074	0.022
Matched Data	-0.015	0.00054

Table 2. Comparison of Corpus Callosum Length Across Univariable, Multivariable, and Matched Analyses

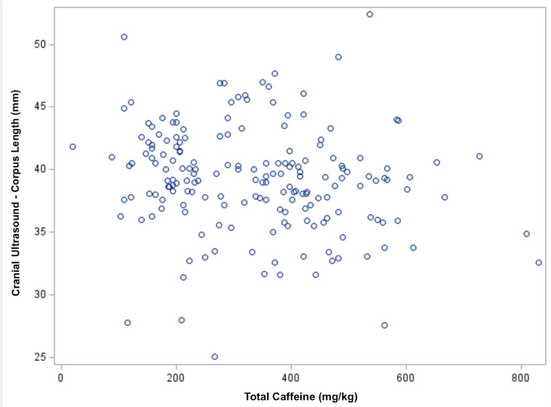

Fig 3. Scatter plot demonstrating the correlation between total caffeine citrate dose and corpus callosum length

DISCUSSION

● Our findings suggest no positive effect of caffeine citrate on early brain development in extremely premature infants, as seen on early CUS

●Confounding variables were addressed in our analysis; however, residual confounding from unmeasured factors may still be present

●Given these findings, long-term neurodevelopmental follow-up may be beneficial for preterm infants receiving high caffeine doses.

REFERENCES

1.Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. *World J Clin Pediatr*. 2015;4(4):81-93. Published 2015 Nov 8. doi:10.5409/wjcp.v4.i4.81