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Original Research Article

Effect of Maternal Folate Use on Offsprings' Cerebellar Morphometric Parameters: An Experimental Study in A Rat Model

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ABSTRACT

Background: Folate is an important nutrient in fetal and early postnatal brain development, and its supplementation during pregnancy has been widely recommended. Folate supplementation has been linked to improved cerebellar function, specifically motor and neuropsychological abilities. It is still unclear exactly how folate affects the cerebellum's structural growth. This study aimed to describe the effects of maternal folate use on cerebellum postnatal development.

Methods: Twelve adults (6–8 week old) female rats (Rattus norwegicus) were randomly divided into four groups and fed one of four premixed diets: a standard diet (folate 2 mg/kg), a folate-supplemented diet (folate 8 mg/kg), or a folate supra-supplemented diet (folate 40 mg/kg). The rats were introduced to their respective diets 14 days before mating, and remained on the same diet throughout gestation and lactation. On postnatal days 1, 7, 21, and 35, five pups from each group were sacrificed and their brains harvested for analysis. The data gathered included the brain's weight, brain length and width, cerebellar length and width, and vermis length and width.

Results: The folate-deficient offspring's brains weighed significantly less at birth than the other groups' brains ($p<0.05$). As they aged, the folate-deficient group gained weight more slowly than the others. The folate-deficient group had significantly smaller cerebellar length, cerebellar width, vermis length, and vermis width than the other study groups. The folate-supplemented group had larger cerebellar dimensions than the folate supra-supplemented group, but these differences were not statistically significant.

Conclusion: Folate deficiency during pregnancy and breastfeeding is linked to a smaller cerebellum in the offspring. These results could affect the health of the children. Furthermore, there is no additional benefit to folate supra-supplementation over recommended folate supplementation in cerebellum development.

KEYWORDS: Folate deficiency, folate supplementation, cerebellum.

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INTRODUCTION

Nutrition is an important factor that affects the developing brain [1,2]. Nutrients such as folate, protein, vitamin B12, iron, and zinc have been shown to greatly affect fetal and early postnatal brain development [2–5]. Maternal folate deficiency has been associated with neural tube defects as well as significant infant motor and cognitive deficits [3,6].

Consequently, folate supplementation has been widely recommended to all pregnant women [7,8]. This supplementation has been associated with improved neuropsychological and motor development in children [9–11]. Although the general effects of folate on the nervous system are known, the specific effects on the structural organization of the cerebellum remain unexplored.

The cerebellum has important motor and neuropsychological functions [12,13]. The role of the cerebellum in the control of balance, posture, and movement has been widely discussed in the literature [13].

However, until recently, non-motor functions of the cerebellum, namely perception, cognition, emotions, and memory, were largely undescribed [12,14,15]. Although the motor and neuropsychological manifestations of folate deficiency have previously been associated with cerebral abnormalities, a recent study has revealed cerebellar involvement [16]. In this study, folate supplementation during pregnancy was associated with increased fetal cerebellar size. There is, however, a scarcity of data on the effects of folate on the structure of the cerebellum. This study, therefore, aimed at describing the effect of maternal use of folate during pregnancy and lactation on the structure of the cerebellar cortex of their offspring.

MATERIALS AND METHODS

Experimental animals: Twelve adult (6–8 week old) female albino rats (Rattus norwegicus) were randomly assigned into four groups, which were fed on folate deficient (folate 0 mg/kg), standard diet (folate 2 mg/kg), folate supplemented (folate 8 mg/kg), and folate supra-supplemented (folate 40 mg/kg) premixed diets. These rats were obtained from the Department of Biochemistry, University of Nairobi. These rats were started on their respective diets 14 days prior to mating, and the same diet continued throughout gestation and lactation. On postnatal days 1, 7, 21, and 35, five pups from each group were sacrificed and their brains harvested for analysis.

Study diets: In this study, amino-acid-based diets based on the American Institute of Nutrition (AIN-93G) diet for rodents were used [17–19]. Previous studies have shown that amino acid-defined diets with different folic acid levels are the most reliable method for studying the exclusive effect of dietary folic acid without confounding factors [20–22]. These diets were purchased from Dyets Inc. (Bethlehem, PA, USA), a company with experience producing diets used in a number of folic acid studies [21,23–27].

The control diet containing folate at 2 mg/kg is accepted as the basal dietary requirement (BDR) for rats and approximates the recommended daily allowance (RDA) of 0.4 mg dietary folate equivalent in humans [26]. The diet with 8 mg folic acid/kg (x4 BDR) appr oximates the likely total folate intake (1.6 mg/day or four times RDA) in humans, which is recommended for all pregnant or planning to be pregnant women [26,27]. A diet containing 40 mg/kg folic acid (x20 BDR) is based on recommendations for women who have had a baby with neural tube defects to increase their folic acid dose to 4 mg/d, which equates to 20 times the RDA [28].

Ethical considerations: The Biosafety, Animal Care, and Use Committee of the University of Nairobi's Faculty of Veterinary Medicine granted approval to conduct the study. This study was conducted in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals in biomedical research [29].

Tissue preparation and harvesting: On postnatal days 1, 7, 21, and 35, five pups were randomly selected from each of the four study arms for tissue harvesting. Following weight determination, the rats were euthanized with intraperitoneal ketamine (100 mg/kg) and xylazine (10 mg/kg). Once death was confirmed by the loss of pupillary light reflex and corneal reflex, the thoracic cavity was opened and intracardiac perfusion with normal saline began, followed by 200-300ml of 4% paraformaldehyde in 0.1M phosphate buffer, pH 7.4. The brains were quickly removed from the skulls, placed in buffered formaldehyde, and refrigerated for 24 hours. Prior to fixation, the weight of the entire brain was recorded.

Data collection and analysis: The offspring's weight, brain weight, brain length, cerebellar length, and vermis length were measured (Figure 1). The measurements were taken with a digital micrometer screw gauge. The collected data were inputted into the software Statistical Package for the Social Sciences (Version 21.0, Chicago, Illinois) for coding, tabulation,

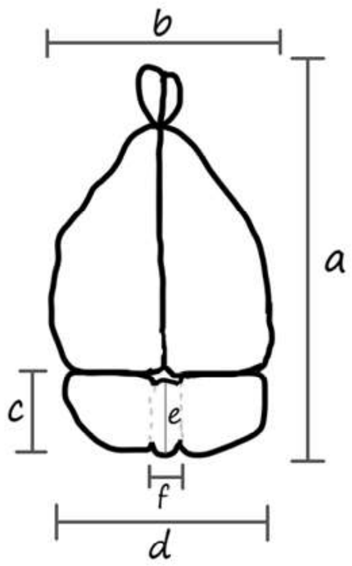

Fig. 1: Variables measured on the brain. a - brain length, b - brain width, c - cerebellar length; d - cerebellar width, e - vermis length, f - vermis width.

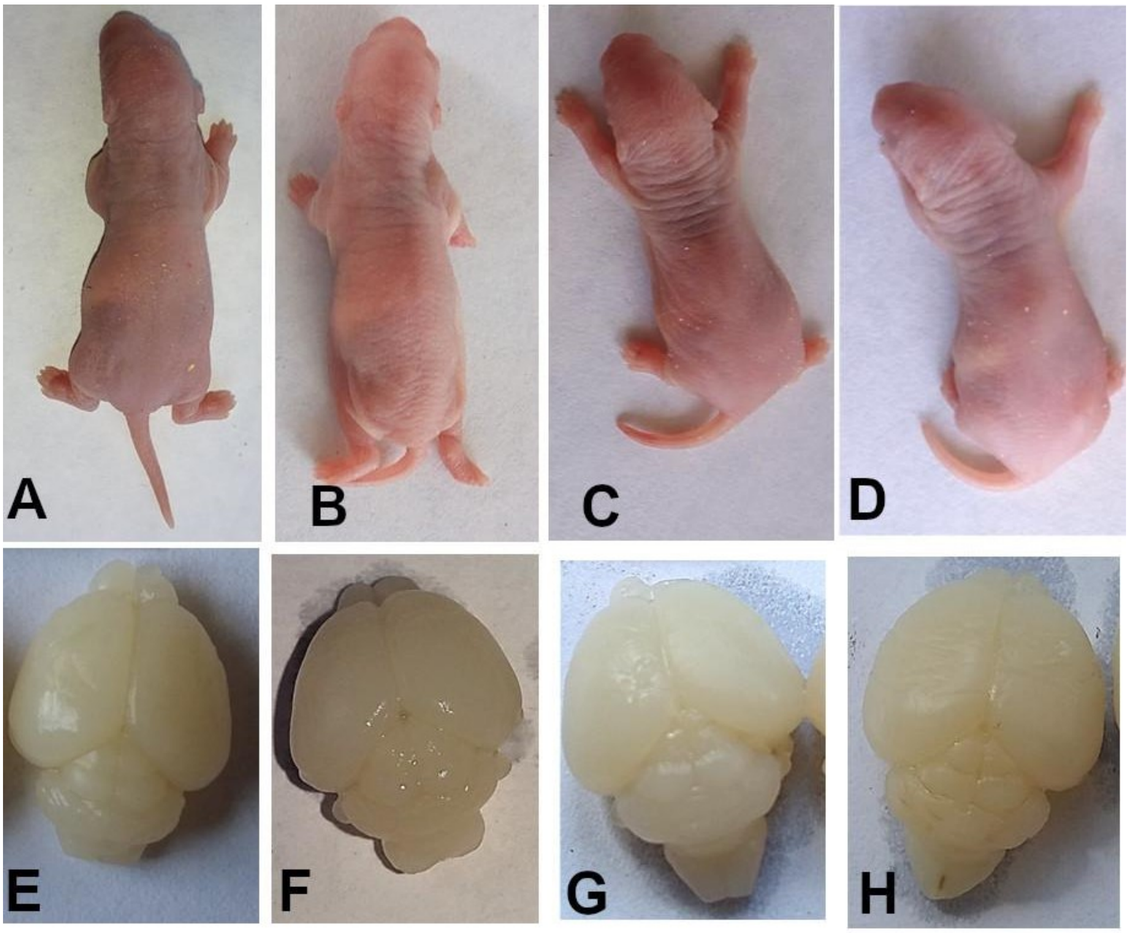

Fig. 2: Gross features of the rats and the brains. **A-D: Postnatal Day 1 rats.** A, Folate deficient group; B, Standard folate group; C, Folate supplemented group; A, Folate supra-supplemented group. **E-H: Post natal day 7 brains.** E, Folate deficient group; F, Standard folate group; G, Folate supplemented group; H, Folate supra-supplemented group.

and statistical analysis. Parametric tests were used to compare variable means after histograms and box plots confirmed the data was normally distributed. The Analysis of Variance (ANOVA) test was used to compare the means of each variable. A p value ≤ 0.05 was considered significant at 95% confidence interval.

RESULTS

Rat weight: The offspring of the folate deficient diet group were smaller than those of the other groups. There were no obvious, grossly distinguishing features between the four study groups (Figure 2). Rats fed a folate deficient diet weighed significantly less than the other groups (Table 1). The folate-supplemented and folate-suprasupplemented rats weighed more than the control rats (standard folate diet). These differences were most pronounced on postnatal days 21 and 35.

Brain weight: At birth, the brains of folate-deficient offspring weighed significantly less than those of the other research groups (Table 1). As they aged, the folate deficient group gained weight at a much slower rate than the other groups (Table 1). Although the folate-supplemented group's brains weighed more than those of the folate supra-supplemented group, the weight differences were not statistically significant.

Brain length and width: The length and width of the brain were significantly lower in folate-deficient groups compared to control groups across all study periods. There were no statistically significant differences between the folate supplemented and folate supra-supplemented diet groups (Table 1).

Cerebellar Dimensions: In comparison to the other study groups, the folate-deficient group had significantly smaller cerebellar length, cerebellar width, vermis length, and vermis width (Table 2). The folate supplemented group appeared to have larger cerebellar dimensions than the folate supra-supplemented group, but these differences were not statistically significant (Table 2).

Table 1: Rat offspring brain morphometric parameters.

	Group	P1		P7		P21		P35	
		Mean±SD	p-value	Mean± SD	p-value	Mean± SD	p-value	Mean± SD	p-value
Rat weight (g)	A	5.75±0.08	0.015	12.15±2.45	0.067	16.66±2.02	0.001	24.53±1.45	<0.001
	B	6.31±0.70		12.15±1.78		28.34±2.85		36.42±2.35	
	C	6.19±0.56		14.53±0.99		31.02±3.29		58.36±1.32	
	D	6.80±0.45		15.02±2.39		44.06±4.32		85.14±2.81	
Brain weight (g)	A	0.28±0.01	<0.001	0.69±0.08	0.012	1.16±0.07	<0.001	1.28±0.03	<0.001
	B	0.35±0.01		0.75±0.04		1.60±0.07		1.63±0.13	
	C	0.34±0.01		0.82±0.07		1.68±0.09		1.64±0.09	
	D	0.31±0.01		0.76±0.04		1.61±0.15		1.64±0.09	
Brain length (mm)	A	9.51±0.01	<0.001	12.77±0.72	0.012	15.00±0.75	<0.001	13.98±0.46	<0.001
	B	10.21±0.11		13.32±0.84		17.00±0.22		16.95±0.54	
	C	10.68±0.27		14.02±0.55		17.48±0.33		17.78±0.59	
	D	10.46±0.29		13.69±0.28		17.10±0.43		17.71±0.45	
Cerebral width (mm)	A	8.35±0.53	<0.001	11.39±1.17	0.006	12.4±0.52	<0.001	12.38±0.16	<0.001
	B	9.16±0.28		12.25±0.58		14.56±0.35		14.09±0.21	
	C	9.48±0.38		12.88±0.35		14.8±0.51		14.43±0.71	
	D	9.57±0.39		12.68±0.37		14.5±0.58		14.56±0.56	

A: Folate deficient diet; B: standard folate diet (2 mg/kg); C: folate supplemented diet (8 mg/kg); D: folate supra-supplemented diet (40 mg/kg).

Table 2: Rat offspring cerebellar morphometric parameters.

	Group	P1		P7		P21		P35	
		Mean±SD	p-value	Mean± SD	p-value	Mean± SD	p-value	Mean± SD	p-value
Cerebellar length (mm)	A	4.18±0.26	<0.001	4.05±0.55	<0.001	4.04±0.17	<0.001	4.26±0.18	<0.001
	B	4.87±0.19		5.32±0.34		5.15±0.26		4.73±0.54	
	C	5.02±0.3		5.46±0.65		6.06±0.15		5.62±0.32	
	D	4.96±0.27		5.38±0.09		5.14±0.39		5.46±0.40	
Cerebellar width (mm)	A	6.04±0.22	<0.001	7.76±0.85	0.008	9.49±0.3	<0.001	8.45±0.26	<0.001
	B	6.34±0.1		8.63±0.58		11.6±0.24		11.25±0.19	
	C	6.52±0.15		9.05±0.41		11.69±0.3		11.51±0.58	
	D	6.57±0.17		8.60±0.42		11.6±0.36		11.05±0.41	
Vermis Length (mm)	A	1.34±0.05	0.013	2.66±0.65	0.614	3.45±0.62	<0.001	3.88±0.39	0.007
	B	1.78±0.19		2.67±0.56		4.86±0.36		4.37±0.47	
	C	1.68±0.35		2.91±0.35		5.56±0.5		4.84±0.48	
	D	1.54±0.19		2.99±0.52		4.75±0.45		4.77±0.25	
Vermis width (mm)	A	1.33±0.15	<0.001	1.65±0.32	<0.001	2.11±0.3	<0.001	2.16±0.19	<0.001
	B	1.4±0.22		2.5±0.29		3.35±0.17		3.13±0.17	
	C	1.92±0.21		2.97±0.39		3.62±0.17		3.27±0.06	
	D	1.76±0.23		2.65±0.31		3.51±0.18		3.24±0.08	

Group A: Folate deficient diet; B: standard folate diet (2mg/kg); C: Folate supplemented diet (8mg/kg); D: folate supra-supplemented diet (40mg/kg).

DISCUSSION

Nutrition is important in the development of the brain. Nutrients such as folate, protein, vitamin B12, iron, and zinc have been shown to greatly affect fetal and early postnatal brain development [1,2,5,30]. There are few studies on the effects of nutrition on the structure of the developing cerebellum. This has largely been because the effects of malnutrition were previously thought to arise from the cerebral cortex. Recent studies have however, revealed that indeed the cerebellum is involved in 'higher functions' such as cognition, emotions, memory and perceptions [12,14,15].

In the current study, rats fed folate-enriched diets were significantly heavier than rats fed a folate-deficient diet. Similar findings have been reported by other studies [31,32].

According to these studies, diets rich in folate result in an increase in food intake by altering hypothalamic feeding pathways. High folate diet lowers the expression of appetite suppressing factors namelypro-opiomel-anocortin and Serotonin 5-HT2A receptors through DNA methylation [31].

The current study has also shown that a folate deficiency causes a decrease in the weight and size of both the cerebellum and the brain. Koning et al. (2015) investigated the impact of folate supplementation during pregnancy on the development of the human fetal cerebellum using ultrasound. They reported a significant increase in cerebellar size in the fetuses of mothers who took folate during pregnancy [16]. Other studies have revealed that folate supplementation in pregnancy is associated with better cognitive function scores in children and improved motor development [6,11,33]. The findings of these studies have been associated with the development of the cerebellum.

The development of the brain is a complex process that begins in utero and continues into the postnatal period [34]. The brain grows quickly, which is heavily reliant on the expression of specific combinations of Hox genes and other transcription factors [34]. This process is susceptible to changes in DNA methylation patterns (epigenetics), which can lead to long-lasting modifications in gene expression and postnatal phenotypes. One-carbon metabolism, required for cellular growth and differentiation throughout the course of human life, is crucial for DNA methylation and the synthesis of RNA, lipids, and proteins [35]. Folate and folic acid provide the necessary one-carbon molecules for cell division and epigenetic programming [34].

Concerning the development of the cerebellum and brain in general, the current study shows that folate supra-supplementation (folate 40 mg/kg) provides no additional benefit over the recommended folate supplementation. The offspring of the folate supra-supplemented rats weighed more than the other groups. However, all other brain parameters were lower in this group compared to the folate-supplemented group, though these differences were not statistically significant.

CONCLUSION

Folate deficiency during pregnancy and lactation is associated with the development of a smaller cerebellum. These findings may impact the health of the offspring. Furthermore, we discovered that folate supra-supplementation provides no additional benefit over recommended folate supplementation in terms of cerebellum and brain development in general.

Conflicts of Interests: None

There was no competing interest among the authors in this article.

Author Contributions

Philip Maseghe Mwachaka: Concept, drafting and communication with journal

Peter Gichangi: Concept, drafting and communication with journal

Adel Abdelmalek: Concept, drafting and communication with journal

Paul Odula, Julius Ogeng'o: Concept, drafting and communication with journal

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