Chapter 9

Effects of neonatal glutamine supplementation on cognitive, motor, and behavioral outcomes in very preterm children at school age

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Abstract

In very preterm (<32 weeks of gestation) and/or very low birth weight (VLBW, <1500 gram birth weight) children, serious neonatal infections are among the main causes of poor developmental outcomes later in childhood. The amino acid glutamine has been shown to reduce the incidence of serious neonatal infections in very preterm/VLBW children, while developmental effects beyond 24 months are unknown. We determined the cognitive, motor, and behavioral outcomes at school age of a cohort of 64 very preterm/VLBW children (M 7.5 years, SD 0.4 years) who participated in a randomized placebo controlled trial using enteral glutamine between day three and 30 of life. Cognitive and motor outcomes were studied using the Wechsler Intelligence Scale for Children-III (WISC-III), Movement Assessment Battery for Children (MABC), Attention Network Test (ANT), and a visual working memory task. Behavioral outcomes were evaluated using parent and teacher-rated questionnaires. IQ, processing speed, attentional functioning, working memory or parent and teacher-rated behavioral outcomes were not different between children treated with glutamine or placebo, only visuomotor abilities as measured by the Ball Skills scale of the MABC (*d*=0.67, p=.002) was poorer in the glutamine group. This effect persisted after taking into account beneficial effects of lower serious neonatal infections rates in children treated with glutamine (p=.005). In conclusion, glutamine supplementation between day three and 30 of life did neither have beneficial nor detrimental effects on long term cognitive, motor, and behavioral outcomes of very preterm/VLBW children at school age, although visuomotor abilities were poorer in children that received glutamine.

Introduction

With advances in neonatal intensive care, the survival of very preterm (gestational age <32 weeks) and very low birth weight (VLBW; birth weight <1500 grams) children has improved considerably. However, these children are at risk for poor motor, cognitive and behavioral outcomes later in childhood[1;2] due to a variety of risk factors associated with preterm birth. Risk factors include neonatal infections and inflammatory responses, both contributing to early brain injury.[3]

Over the past decade, the potential protective effects of supplementation of the amino acid glutamine in very preterm/VLBW children have been extensively studied, including the modulation of inflammatory response and stimulation of immunity.[4] Experimental studies have shown that glutamine plays an important role in maintaining the functional integrity of the gut,[5;6] which in turn leads to decreased bacterial translocation and systemic spread of bacteria,[7-9] and consequently may lead to decreased infectious morbidity. Indeed, a few studies found that glutamine-enriched enteral nutrition between day three and 30 of life decreased the number of serious neonatal infections in very preterm/VLBW children,[10;11] although other studies failed to replicate the beneficial effects of glutamine.[12] A lower number of serious neonatal infections may potentially be beneficial for long term motor, cognitive, and behavioral outcomes in very preterm/VLBW children, as evidence from several studies emphasize the negative effects of neonatal infections on long term neurodevelopment.[13-16] One study found no beneficial nor adverse effects of enteral glutamine supplementation on mental or motor outcomes at two years of age as measured by the Bayley Scales of Infant Development second edition (BSID-II),[17] while another study found that long-term enteral glutamine supplementation may lead to significant improvements in growth measures.[18] However, until now it remains unclear whether a lower incidence of neonatal infections and improved growth in very preterm/VLBW children following glutamine supplementation may be beneficial for long term motor, cognitive and behavioral development.

The aim of the current study was to determine the long term effects of enteral glutamine, supplemented in a randomized placebo controlled trial between day three and 30 of life, on the cognitive, motor, and behavioral outcomes of very preterm/VLBW children at school age.

Methods

Sample

The initial sample for this study consisted of 102 very preterm (<32 weeks) and/or VLBW (<1500 grams) infants participating in a randomized placebo controlled trial on glutamine supplementation. In this study, infants received enteral glutamine supplementation (0.3 g/kg/day) or an isonitrogenous placebo supplementation (alanine) between day three and 30 of life. All very preterm/VLBW infants admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam between September 2001 and July 2003 were eligible for inclusion. Description of baseline characteristics and techniques used to determine incidence of serious neonatal infections, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), and bronchopulmonary dysplasia (BPD) have been previously reported.[11] Of the 102 infants included in the study, 89 infants were alive at one year of age, and 74 were still participating at 6 years of age.

At 7-8 years of age, parents of all 74 children were contacted and invited to participate in the current study, of which 68 (92%) showed up, and 64 (94%) successfully completed all tasks at the mean age of 7.5 (SD=0.4) years. The remaining four children had serious motor (n=2), hearing (n=1) or vision (n=1) difficulties, crucially interfering with task execution. The final sample consisted of 30 children that had received glutamine (glutamine group) and 34 children that had received placebo (control group). From the original dataset, the presence of serious neonatal infections, and other clinical complications were extracted. Serious neonatal infections included sepsis, meningitis, pyelonephritis, pneumonia, and arthritis, accompanied by positive microbial cultures of blood, cerebrospinal fluid, urine, tracheal aspirates and synovial fluid, respectively, as previously described in more detail.[11] Socio economic status (SES) was determined by classifying the highest level of education in a household with a number ranging from one to four. A higher number indicated a higher level of education and a corresponding higher socio economic status. Characteristics of both groups are shown in Table 1.

Procedure

This study was conducted according to the guidelines laid down in the declaration of Helsinki and all procedures involving human subjects were approved by the medical ethical committee of the VU University Medical Center. Written informed consent was obtained from all subjects. Cognitive and motor assessment took place at the VU University Amsterdam by qualified and trained testers using a completely standardized instruction protocol. Both parents and teacher were asked to fill in questionnaires addressing behavioral problems at home and at school, respectively. Parents filled in the questionnaires in the presence of an interviewer.

Cognitive and Motor Measures

Main aspects of cognitive and motor functioning were assessed, including intellectual development, working memory, motor development, aspects of attentional functioning and processing speed. Intellectual development was measured by a short-form of the Wechsler Intelligence Scale for Children-III (WISC-III[19]), including the subtests Vocabulary and Block Design. Both subtests correlate strongly (r>.90) with Full Scale IQ.[20] Scores on this test were normalized with a mean (SD) of 100 (15). Two aspects of working memory abilities were assessed: verbal working memory and visual working memory. Verbal working memory abilities were measured using the Digit Span subtest of the WISC-III. In this subtest, children had to verbally reproduce dictated series of digits increasing in length, both in a forward and a backward condition. Maximal span of reproduced digits for both the forward as well as backward condition were included as dependent variables in analysis. Visual working memory abilities were measured using an adapted version of a task developed by Nutley et al.[21] In this task, children had to reproduce sequences of circles appearing in a 4x4 grid on a touch screen. Difficulty level was increased during the course of the task by increasing span and by manipulating the position of the stimuli. Two trials were administrated for each difficulty level, and the task was terminated when the child failed to accomplish both trials at a certain difficulty. Maximal difficulty level with forward reproduction and backward reproduction were included as dependent variables in analysis.

Motor development was assessed using the Movement Assessment Battery for Children (MABC),[22] and outcomes on the scales Manual Dexterity, Balance Skills and Ball

Skills were included in analysis. Scores on the scales of the MABC were normalized using T-scores with a mean (SD) of 50 (10).

Orienting, executive, and alerting attention were assessed using an adapted version of the Attention Network Test (ANT[23]) suitable for the use with young children. In this task, children had to respond as accurate and fast as possible to the appearance of a target on the left side or the right side of the screen by pressing a button corresponding to the location at which the target appeared. There were four types of trials. Neutral trials contained a neutral cue in the middle of the screen which preceded the target. Orienting trials contained a directional cue in the middle of the screen pointing to the position of the target which subsequently followed. Executive trials contained directional cues incongruent with the position of the target. Alerting trials contained no cue at all and the target was presented instantaneously. The four trial types were randomly presented in four blocks of 48 trials. Measures of orienting, executive, and alerting attention were obtained by subtracting the mean response time on the orienting, executive, and alerting trials from the mean response time on neutral trials, respectively. In this way, measures of orienting, alerting and executive attention are controlled for differences in information processing capacities between children. The gain in response time in an orienting trial as compared to a neutral trial was used as measure of the ability to aim attention (orienting attention). More gain in response time corresponds to better orienting attention. The loss in response time in an executive trial as compared to a neutral trial was used as measure of the ability to actively ignore irrelevant information (executive attention). Less loss in response time corresponds to better executive attention. The loss in response time in an alerting trial as compared to a neutral trial was used as measure of alertness (alerting attention). Less loss in response time corresponds to better alerting attention. Finally, the combined effects of cognitive and motor speed were assessed by mean response time in neutral trials and included as measure of overall processing speed in analysis.

Behavioral Measures

Parents rated their children's behavioral difficulties using the Child Behavior Checklist (CBCL),[24] and the parent-rated Disruptive Behavior Disorders questionnaire (PDBD).[25] Teachers rated their pupil's behavioral difficulties using the Teacher Report Form (TRF)[26] and teacher version of the Disruptive Behavior Disorders questionnaire (TDBD).[25] The CBCL and

TRF encompass three broad-band scales assessing total, externalizing, and internalizing behavior problems, and the PDBD and TDBD comprise two scales addressing inattention and hyperactivity problems. Scores on all scales were depicted as normalized T-scores with a mean (SD) of 50 (10), and higher scores indicated greater severity of problems. All questionnaires are widely used and have excellent psychometric properties.

Statistical Analyses

All analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA), and raw continuous data were successfully standardized and normalized by applying a Van der Waerden transformation. Pearson and point bi-serial correlations were used to explore the effects of serious neonatal infections, SES, and GA on cognitive, motor, and behavioral outcomes at school age. To study the effects of glutamine supplementation, univariate analyses of variance with intervention as between subject factor and SES and GA as covariates were conducted on the dependent measures of the cognitive and motor tasks and parent and teacher rated questionnaires. To adjust for possible beneficial indirect effects of glutamine on the outcome measures by decreasing the number of serious neonatal infections, the analysis was repeated with serious neonatal infections as a second between subjects factor. Standardized group differences were quantified in terms of effect-sizes (Cohen's *d*),[27] which is an effect-size defined by the difference between two group means divided by the pooled SD, enabling the opportunity to indicate the size of an effect independent of group size. Cohen's *d* guidelines were followed to indicate the strength of the group differences, with values of 0.20, 0.50 and 0.80 referring to small, medium and large effects, respectively.[27] To minimize the possibility for a type 2 error, which may erroneously lead to the conclusion that no detrimental or beneficial effects of glutamine enriched feeding exists on long term outcomes, α was not corrected for multiple comparisons and set at .05.

Results

Sample Characteristics

Clinical characteristics of the glutamine group and the placebo group are shown in Table 1. The two groups did not differ on the majority of clinical characteristics, indicating

that there were no differences in illness severity between groups. However, socio economic status (SES) and gestational age (GA) were higher for the glutamine group as compared to the placebo group. In addition, as was found in a previous study,[11] the rate of serious neonatal infections was lower in the glutamine group than in the placebo group (p=.006).

Table 1. Sample characteristics

	Placebo (N = 34)		Glutamine (N = 30)		
	M	SD	M	SD	p[1]
Age at assessment, in years	7.5	0.4	7.5	0.4	.45
Birth weight, in grams	1204	334	1301	380	.28
Gestational age, in weeks	29.0	1.6	29.7	1.6	**.04**
Head circumference, in cm	26.7	2.5	27.6	2.0	.12
Socio economic status	3.0	0.7	3.2	0.7	**.04**
Male gender, n (%)	17 (50)		15 (50)		
Birth weight in grams, median (range)	1175 (690 - 1795)		1268 (560 - 2325)		
Gestational age in weeks, median (range)	29.0 (25.7 - 31.7)		30.1 (25.4 - 31.7)		
Birth weight < 10th percentile, n (%)	8 (24)		8 (27)		.77
Maternal HELLP syndrome, n (%)	6 (18)		4 (13)		.64
Prenatal corticosteroids, n (%)	31 (91)		22 (73)		.06
BPD, n (%)	11 (32)		7 (23)		.42
IVH grade I/II, n (%)	6 (18)		6 (20)		.81
IVH grade III/IV, n (%)	0 (0)		1 (3)		.28
PVL, n (%)	2 (6)		1 (3)		.63
Apgar score after 5 minutes < 6, n (%)	2 (6)		3 (10)		.54
Caesarean delivery, n (%)	19 (56)		17 (57)		.95
1 or more serious infections, n (%)	27 (79)		14 (47)		**<.01**

Note. BPD = Bronchopulmonary Dysplasia; Maternal HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; IVH = Intraventricular Haemorrhage; PVL = Periventricular Leukomalacia; ROP = Retinopathy of Prematurity. [1] Chi-square and t-tests. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05).

Correlational analyses

Higher SES was associated with higher full scale IQ scores (*r*=.26, p=.002), and a shorter GA was associated with higher ratings on the TDBD Hyperactivity scale (*r*=-.34, p=.006). Furthermore, the presence of serious neonatal infections was positively associated with multiple scales of parent and teacher-rated questionnaires, including TRF Total Problems (*r*=.25, p=.04); TRF Externalizing (*r*=.25, p=.04); PDBD Inattention (*r*=.25, p=.04); TDBD Inattention (*r*=.27, p=.03) and TDBD Hyperactivity (*r*=.27, p=.03), indicating that presence of infections is associated with higher ratings of behavioral problems and symptoms of ADHD in particular.

Table 2. Cognitive, motor, and behavioral functioning for the placebo and glutamine group

	Placebo (N=34)		Glutamine (N=30)			Adjusted: GA, SES, infections	Adjusted: GA, SES
	M	SD	M	SD	Effect size	p	p
Cognitive functioning							
WISC-III estimated FSIQ[2]	93.6	17.2	102.0	17.7	0.48	.23	.12
Motor development							
MABC Balance Skills[2]	53.1	14.9	54.4	19.8	0.03	.22	.40
MABC Ball Skills[2]	57.4	13.0	66.0	13.9	0.67	**.002**	**.005**
MABC Manual Dexterity[2]	53.5	12.3	57.8	14.7	0.36	.14	.11
Attentional functioning							
Orienting attention[1]	139	73	149	99	0.14	.64	.54
Alerting attention[1]	-86	75	-78	71	0.12	.88	.83
Executive attention[1]	-174	210	-253	215	0.49	.06	.07
Working memory							
Visual forward[1]	4.9	0.8	4.7	0.7	0.42	.14	.07
Visual backward[1]	4.4	0.9	4.1	0.8	0.36	.10	.16
WISC-III Digit Span forward[1]	6.4	1.6	6.6	1.7	0.18	.37	.82
WISC-III Digit Span backward[1]	3.5	1.4	3.9	1.3	0.27	.96	.59
Information processing							
Overall processing speed[1]	706	138	764	161	0.35	.32	.28
Parent report of behavior							
CBCL Total[2]	50.0	8.6	49.7	9.3	0.10	.94	.88
CBCL Internalising[2]	49.1	7.0	50.5	9.0	0.10	.57	.79
CBCL Externalising[2]	49.1	9.8	48.4	8.3	0.04	.92	.93
PDBD Inattention[2]	55.0	10.3	49.8	8.7	0.52	.39	.17
PDBD Hyperactivity[2]	53.1	10.2	50.0	6.7	0.39	.52	.31
Teacher report of behavior							
TRF Total[2]	51.6	14.7	46.6	7.3	0.32	.32	.27
TRF Internalising[2]	48.9	11.1	46.3	6.1	0.23	.29	.48
TRF Externalising[2]	50.6	13.1	46.0	5.7	0.38	.53	.25
TDBD Inattention[2]	58.0	16.9	52.1	9.0	0.32	.65	.30
TDBD Hyperactivity[2]	54.5	13.8	48.9	7.3	0.43	.32	.29

Note. CBCL = Child Behavior Checklist; FSIQ = Full scale intelligence quotient; GA = Gestational Age; MABC = Movement Assessment Battery for Children; PDBD = Parent Disruptive Behavior Disorders questionnaire; SES = Socio Economic Status; TDBD = Teacher Disruptive Behavior Disorders questionnaire; TRF = Teacher Report Form; WISC-III = Wechsler Intelligence Scales for Children 3rd edition. [1]Raw scores; [2]Normalized T scores, higher scores indicate poorer performance. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05). Effect sizes are depicted as Cohen's *d*.

Cognitive, motor, and behavioral outcomes

Cognitive, motor, and behavioral outcomes are shown in Table 2. After adjusting for SES, GA, and including the presence of serious neonatal infections as a second between subjects factor, the glutamine group showed poorer ball skills (Cohen's *d*=0.67, p=.002), indicating that ball skills were more impaired in the glutamine group as compared to the placebo group. Furthermore, the glutamine group showed poorer executive attention as

compared to the placebo group, although this effect was of marginal significance (*d*=0.49, p=.06). When only adjusting for SES and GA, poorer ball skills for the glutamine group remained significant (p=.005), indicating that a reduced presence of serious neonatal infections following glutamine supplementation could not compensate the differences in ball skills between the glutamine and the placebo group. For none of the remaining cognitive and motor measures a significant difference was found between the glutamine and placebo group.

Behavioral outcomes

Behavioral outcomes as measured by parent and teacher-rated questionnaires did not differ significantly between the glutamine and placebo group. Including serious neonatal infections as a second between subjects factor did not change the results of the primary analysis.

Discussion

The majority of long term cognitive, motor and behavioral outcome measures were not different in the glutamine group and the placebo group. These findings demonstrated that glutamine supplementation between day three and 30 of life did not have beneficial or detrimental effects on a wide range of cognitive and motor functions or on parent and teacher reported behavioral outcomes at school age. However, ball skills as measured by the MABC were found to be significantly poorer in the glutamine group as compared to the placebo group, suggesting the possibility that glutamine treatment in the first month after birth may have adverse effects on visuomotor development.

Many factors may influence developmental outcomes between birth and eight years of age, thereby diluting the effects of enteral glutamine supplementation between day three and 30 of life. The current cognitive, motor, and behavioral measures were selected to maximize the ability to chart any long term effects on outcomes at school age. Furthermore, long term effects on cognitive, motor and behavioral development of enteral glutamine supplementation could be expected, as glutamine treatment reduced the incidence of serious neonatal infections known to affect brain development.[3;15] Indeed, significant associations were present between the presence of serious neonatal infections and the

selected behavioral outcomes, including inattention and hyperactivity, indicating that an increase in the presence of serious neonatal infections may be associated with poorer outcomes. Nonetheless, no major effects of enteral glutamine supplementation on long term cognitive, motor, and behavioral outcomes were present.

The unfavorable effects of glutamine supplementation on visuomotor development as measured with the Ball Skills scale of the MABC was an unexpected finding, as our previous work has shown no unfavorable short term effects of enteral glutamine supplementation,[17] and no direct detrimental effects of glutamine on the brain have been reported.[28] However, derivates of glutamine, including glutamate and ammonia, have been associated with neurotoxicity,[28;29] and could underlie detrimental outcomes following glutamine treatment. In patients with hepatic encephalopathy (HE), ammonia was shown to affect the metabolism and function of astrocytes, leading to astrocytic swelling which in turn leads to cerebral edema. Glutamine is synthesized in excess from ammonia and glutamate by glutamine synthetase, an astrocyte enzyme. Recent data suggest that many aspects of ammonia toxicity in HE are mediated by glutamine.[30] Nevertheless, plasma concentrations of glutamine, glutamate and other amino acids were not different between the glutamine and the placebo group in the neonatal period in our study sample,[31] and highest median glutamate (68 µmol/l glutamine group; 70 µmol/l placebo group) or glutamine concentrations (555 µmol/l glutamine group; 515 µmol/l placebo group) were within normal reference ranges.[32] Furthermore, if adverse neurological effects as a consequence of neurotoxicity occurred, more widespread consequences on cognitive, motor, and behavioral outcomes would have been expected, given that visuomotor skills concern interplay between perception, motor skills and timing, involving multiple brain systems. Hence, direct effects on the brain seem unlikely, and we speculate that the presence of differences in visuomotor skills between the glutamine and placebo group is related to baseline differences in visuomotor abilities at the moment of randomization.

Several studies in very low birth weight (VLBW) infants have investigated the effects of parenteral or enteral glutamine supplementation on morbidity, mortality and (growth) outcome in the neonatal period.[10;18;33-36] No evidence of toxicity of glutamine supplementation was found in these clinical trials, but the results of efficacy on a limited number of outcomes have been mixed,[12] possibly due to differences in supplementation methods, dose and definition of infections. As a consequence, the use of glutamine

supplementation has not become routine. However, the effects of glutamine supplementation on the incidence of serious neonatal infections warrants further investigation, given that our findings indicate no clear evidence of long term detrimental effects on motor, cognitive, and behavioral development, underlining the relative safe use of glutamine supplementation in very preterm/VLBW children in future research or clinical practice.

This study has some limitations that need to be taken into account when interpreting the current findings. First, power of analyses was somewhat limited due to the fact that not all children were still participating nearly eight years after original enrollment in this study. However, drop-out rates were low for this type of long term follow up, and drop out was equally present in the glutamine and the placebo group. Furthermore, power was sufficient to detect any medium to large sized beneficial or detrimental effects of glutamine treatment, as calculated using G-power software.[37] Second, to reduce the chance of a type 2 error that erroneously may lead to the conclusion that no detrimental or beneficial effects of glutamine enriched feeding on long term outcomes exists, no alpha correction for multiple comparisons was conducted. The flip side of the coin is that our finding of unfavorable effects on visuomotor abilities of glutamine intervention might result from an unadjusted alpha level in our statistical tests.

In summary, with one single exception (visuomotor abilities), no medium or large-sized beneficial nor detrimental effects of short term enteral glutamine supplementation in the neonatal period were found on long term cognitive, motor, and behavioral outcomes of very preterm/VLBW children at school age.

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