Int J Clin Exp Med 2017;10(8):12322-12328
www.ijcem.com /ISSN:1940-5901/IJCEM0057432

Original Article

Effects of sialic acid in serum and breast milk on the growth and development of infants at different stages during pregnancy and lactation

Yuchun Zhu, Mei Li

The First Department of Obstetrics, Weifang People's Hospital, Weifang, Shandong Province, China

Received May 15, 2017; Accepted June 18, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: To investigate the effects of sialic acid (SA) in serum and breast milk on the growth and development of infants at different stages of pregnancy and lactation. Methods: From January 2015 to January 2016, a total of 146 local women who underwent the prenatal check-up and delivery in our hospital and their children were enrolled. Their serum SA levels at 10th, 16th and 38th weeks during the pregnancy, and the levels of SA in breast milk at Day 3, 42 and 90 post-partum were examined by ELISA kit. And the mental development index (MDI) and psychomotor development index (PDI) of infants were evaluated at day 90 after birth with a 0~3-year-infant intelligence development scale. Results: The data from 133 pairs subjects were record completely. The serum SA level played a significant role in the early mental and psychomotor development of infants in the second trimester ($P<0.01$). The MDI were higher in pregnant women with high serum SA level during the third trimester than those with low level ($P<0.05$), which was also higher in pregnant women with high SA level in breast milk than those with low level in breast milk at day 3 and 42 post-partum ($P<0.01$). While the SA levels in serum or breast milk at early pregnancy and Day 90 after delivery had no effect on the mental and psychomotor development of infants ($P>0.05$). Moreover, logistic regression analysis showed that the serum SA levels were closely associated with MDI at second and last trimester, and were closely associated with PDI at second trimester ($P<0.05$). As for breast milk, its SA level was closely associated with MDI at Day 3 and 42 after delivery ($P<0.05$). Conclusion: The levels of maternal serum SA during the second trimester can promote the early mental and psychomotor development of the infant, and the high levels of SA in both serum and breast milk during late pregnancy and 1 month post-partum have a positive effect on the early mental development of the infants.

Keywords: Sialic acid, pregnancy, lactation, breast milk, serum, infant intelligence development

Introduction

It has been proved that the material basis for human mental and motor development is the formation of neural plate during the early stage of pregnancy, which is usually formed in the Day 19 since the formation of embryo. The rapid development of human brain goes through the entire pregnancy and infancy, especially in the period from the 3rd month of pregnancy to 3 months after birth, which is characterized by the peaked growth of brain cells [1]. Therefore, it is the priority among priorities to guarantee the adequate nutrition for the fetus during this vital period, in order to promote the development and maturation of the brain cells.

Since 1937, a large number of studies on sialic acid (SA) showed that the SA content in the gray matter of human brain accounts for more than 90%, especially its amount in nerve cells was far more than other types of cells [2], indicating that SA is a very important nutrient for brain, and plays an irreplaceable role in the construction of the nervous system. Since the nutrient supply for the embryo almost completely depends on the placenta while the capacity of SA synthesis of fetus is immature, which cannot meet the huge demand for rapid development of brain and nerve system of embryo [3], it is of extraordinary significance to investigate the effect of maternal SA level during pregnancy and lactation on the growth and development of infants. However, there are only few related researches at present.

In this current study, the maternal SA levels in serum and breast milk at different stages of pregnancy and lactation were analyzed and compared, and its effects on the mental and motor development in infants were evaluated, which will provide novel insights and potential directions for clinical research.

Materials and methods

Participants

Inclusion criteria: 1) pregnant women aged from 20 to 36 years old; 2) pregnant women had the first single fetus; 3) the pregnancy was less than 8 weeks and the first pregnant check-up was at our hospital; 4) pregnant women without serious complications during pregnancy including pregnancy-induced hypertension and acute severe infection, etc.; 5) pregnant women with normal nerve system function, and without the history of exposure to toxic and hazardous substances or receiving radiation therapy during pregnancy; 6) the pregnant women and their spouses had no family history of mental disorders, cancer, immune system diseases and thyroid diseases; 7) the infants with the gestational age ≥(40±2) weeks, full-term birth, no serious asphyxia during the delivery and Apgar score >7; 8) the newborns without severe neonatal diseases, congenital defects, had full development of the nervous system and with a weight between 2500-4000 g; 9) the maternal breast milk was sufficient to newborns who were breastfed alone for the first 3 months after birth and did not suffer from severe acute diseases or severe infection.

According to the criteria, a total of 146 local women who underwent the prenatal check-up and delivery in our hospital and their newborns were enrolled in this study from January 2015 to January 2016. The information of telephone number and home address of all the participants were collected and archived.

This study was approved by the Hospital Ethics Committee, and all the enrolled pregnant women and the family members signed the written informed consent before they were recruited in.

Methods

After 12-hour fasting, the intravascular blood was collected from the pregnant women at 10th, 16th and 38th weeks of pregnancy respectively, when they took the routine pregnant check-up. The serum was prepared and stored at -70°C for further use. And the breast milk was collected from the mothers at Day 3, 42 and 90 after delivery when they received the routine physical examination, and also stored at -70°C for further use. The sialic acid levels in serum and breast milk were detected via enzyme-linked immunosorbent assay (ELISA) method.

Evaluation criteria

The levels of infant intelligence development were evaluated by using a 0~3-year-old infant intelligence development scale from *Children's Developmental Centre of China* at 90th day after birth. And the scale consists of mental scale and psychomotor scale: the mental scale is used to measure perceived accuracy, speech function, memory and simple problem-solving ability and psychological function, etc.; the psychomotor scale is used for measuring gross and fine motor ability as well as the abilities for sit, stand, walk, climb stairs, manipulation of hands and finger, etc. These two scales included 30 items and the results were expressed by the mental development index (MDI) and psychomotor developmental index (PDI) [4]. The evaluation was performed by two physicians at the same time.

Statistical analysis

All the data were analyzed via SPSS 17.0 statistical software. The measurement data were expressed as mean ± standard deviation, and the comparison was performed by using t test. Logistic regression analysis was conducted to identify the association between SA level and the development of infant intelligence. P<0.05 was considered statistically significant.

Results

General information

The data of 133 pairs (91.1%) of mothers and their infants were collected completely in the study, including 73 cases with natural childbirths, and 60 cases with cesarean sections and the average age of them was (25.5±4.2) years old. The other 13 pairs of mothers and infants were excluded from the study due to the loss to the follow-up, or not following the physicians' instruction.

Table 1. The levels of SA in serum and breast milk at different stages of pregnancy and lactation

Stages	Weeks of pregnancy			Days after delivery		
	10	16	38	3	42	90
Levels of SA (mmol/L)	2.10±0.92	2.59±0.95*	2.95±0.98*,#	5.15±0.18	1.99±0.08&	0.53±0.04&,**

Note: Compared with 10 weeks of pregnancy, *P=0.000; compared with 16 weeks of pregnancy, #P=0.003; compared with 3 d after delivery, &P=0.000; compared with 42 d after delivery, **P=0.000.

Table 2. Effects of maternal serum SA on the development of infant intelligence

Stage of pregnancy	Groups	Intelligence	
		MDI	PDI
First trimester	High level (n=66)	98.52±6.29	95.87±3.54
	Low level (n=67)	97.37±7.04	96.21±3.36
Second trimester	High level (n=66)	102.38±5.11	99.74±3.20
	Low level (n=67)	95.99±5.68*	95.86±3.43*
Last trimester	High level (n=65)	101.01±5.87	97.44±3.59
	Low level (n=68)	97.50±6.13*	96.61±3.47

Note: Compared with high-level group, *P<0.05.

The levels of SA in serum and breast milk at different stages of pregnancy and lactation

Our study showed that the levels of serum SA in pregnant women increased gradually with the increase of gestational weeks. And after delivery, the levels of SA in breast milk decreased dramatically with the elongation of lactation.

As shown in **Table 1**, during the pregnancy, the levels of serum SA at 16th and 38th weeks were significantly higher than that at 10th weeks of the pregnancy (P<0.01), which was also dramatically higher at 38th week than that at the 16th week of the pregnancy (P<0.01). And during the lactation, the levels of SA in breast milk at Day 42 and 90 after delivery were significantly reduced by comparing with that at Day 3, which was also dramatically lower at Day 90 than that at Day 42 after delivery (P<0.01).

Effects of maternal serum SA on the development of infant intelligence

All the pairs of mothers and infants were divided into two groups basing on their levels of serum SA at first trimester (with a median of 2.08 μmol/L at 10th week), second trimester (with a median of 2.64 μmol/L at 16th week) and last trimester (with a median of 2.93 μmol/L at 38th week) after pregnancy respectively: high-level group (> median) and low-level group (≤ median). Meanwhile, the MDI and PDI of the infants at Day 90 after birth were evaluated. As shown in **Table 2** and **Figure 1**, the results showed that the serum levels of SA at early stage of pregnancy had no effect on the development of infant intelligence (P>0.05). While the MDI and PDI were significantly higher in high-level group during the second trimester than those in low-level group (P<0.01). Moreover, the MDI of high-level group was significantly higher during the last trimester than that of the low-level group (P<0.05), but the PDI in high-level group was just slightly higher than that of low-level group without significant difference (P>0.05).

Effects of SA in breast milk on the development of infant intelligence

Similarly, all the pairs of mothers and their infants were divided into two groups basing on their levels of SA in breast milk at Day 3 (with a median of 5.10 mmol/L), Day 42 (with a median of 1.97 mmol/L) and Day 90 (with a median of 0.52 mmol/L) after delivery respectively: high-level group (> median) and low-level group (≤ median) and the MDI and PDI of the infants at Day 90 after birth were evaluated. As shown in **Table 3** and **Figure 2**, the results indicated that the MDI was significantly higher in high-level group at Day 3 and Day 42 after delivery than those in low-level group (P<0.01), while the PDI in high-level group was only slightly higher than that of low-level group (P>0.05). Meanwhile, the SA levels in breast milk in these two groups at Day 90 after delivery showed no evident difference, indicating that SA in breast milk at that time point had no effect on the development of infant intelligence (P>0.05).

The association between SA level and the development of infant intelligence

Furthermore, we performed the logistic regression analysis to identify the association between SA level and the development of infant

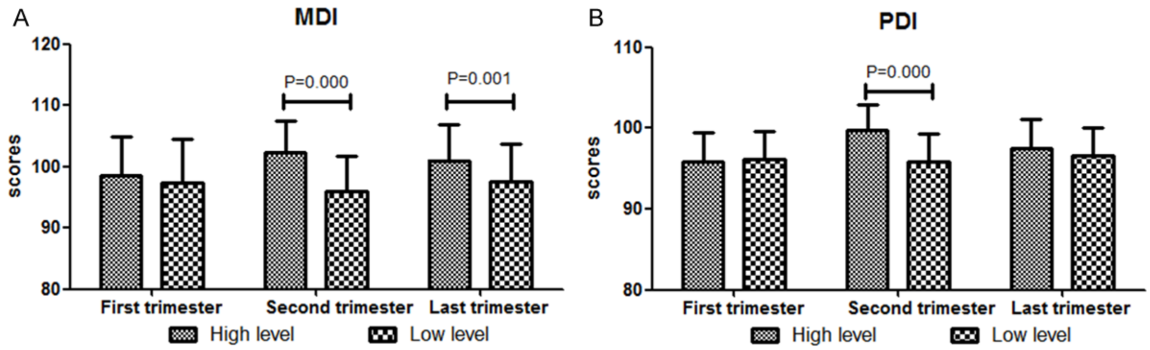

Figure 1. Effects of maternal serum SA on the development of infant intelligence. A: Effects of serum SA on MDI; B: Effects of serum SA on PDI.

Table 3. Effects of SA in breast milk on the development of infant intelligence

Stage of lactation	Group	Intelligence	
		MDI	PDI
3 d after delivery	High level (n=66)	101.93±4.22	97.85±4.00
	Low level (n=67)	93.41±3.98*	96.57±3.84
42 d after delivery	High level (n=66)	101.77±3.83	97.45±3.59
	Low level (n=67)	94.24±4.08**	97.20±3.35
90 d after delivery	High level (n=65)	98.02±5.74	97.79±3.17
	Low level (n=68)	97.31±6.07	97.64±2.93

Note: Compared with high-level group, *P=0.033, **P=0.019.

intelligence. As shown in **Tables 4** and **5**, the serum SA levels at second and last trimesters were closely associated with MDI, and serum SA level at second trimester was closely associated with PDI (P<0.05). Meanwhile, the SA levels in breast milk at Day 3 and 42 after delivery were closely associated with MDI (P<0.05), but were not associated with PDI (P>0.05).

Discussion

Fetal and infant period is not only considered as the most active and vigorous period for individual growth and development, but also known as the vital period for the growth and development of the nervous system [5]. In our study, we found that performers were better in tests of mental development in infants whose mothers had higher level of SA in serum at second to last trimesters and has higher level of SA in breast milk at early stage of lactation than those had low level of SA at the same time. What's more, logistic regression analysis showed that the serum SA levels at second and last trimesters were closely associated with MDI, and SA level at second trimester was closely associated with PDI, additionally, the SA levels in breast milk at day 3 and 42 after delivery were closely associated with MDI, indicating that SA played an important role in the construction of brain-neuron network. Therefore, it is necessary for mothers to provide enough SA to fetal and newborn otherwise it will cause the mental retardation and the delayed development of intelligence [3].

Previous studies showed that, more than 60% of SA was synthesized and stored in gangliosides in brain, which play the roles on the structure maintenance, cell recognition and material transport [6, 7]. As the diversity and amount of ganglioside varied with the development, maturity and decline of the brain [8, 9], the nervous and SA indicated a close relationship in the composition and operation. At present, SA and ganglioside containing drugs have been developed in the treatment of central nervous system injury [10]. Polysialic acid (PSA) is the main way for SA to participate in the construction and activity of the nervous system, and to regulate the gap and affinity for neural cells to communicate with neural cell adhesion molecules [11, 12], thereby it can efficiently promote the smooth construction of brain neural network and rapid development. However, this combined effect only happened in the late stage of pregnancy and early stage of infant [13].

In this study, the MDI was evaluated and compared between the high-level group and low-level group of serum SA at 10th week of pregnancy, and there was no significant difference in the MDI between the two groups, indicating

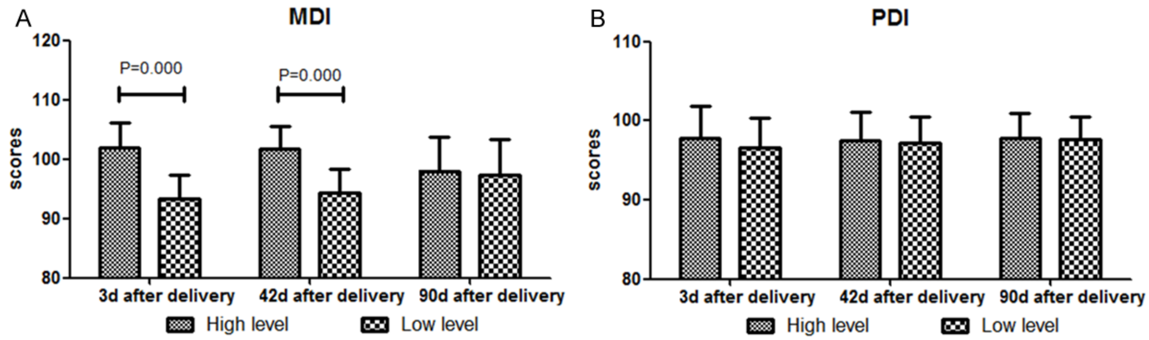

Figure 2. Effects of SA in breast milk on the development of infant intelligence. A: Effects of SA in breast milk on MDI; B: Effects of SA in breast milk on PDI.

Table 4. Association between SA level and MDI

Stages	Serum SA		Stages	SA in breast milk	
	OR (95% CI)	*P* value		OR (95% CI)	*P* value
First trimester	0.691 (0306~1.690)	0.310	3 d after delivery	0.069 (0.029~0.891)	0.017
Second trimester	0.181 (0.036~1.060)	0.031	42 d after delivery	0.081 (0.190~0.966)	0.030
Last trimester	0.160 (0.061~1.096)	0.030	90 d after delivery	0.691 (0.389~1.266)	0.311

Table 5. Association between SA level and PDI

Stages	Serum SA		Stages	SA in breast milk	
	OR (95% CI)	*P* value		OR (95% CI)	*P* value
First trimester	0.509 (0.210~1.290)	0.611	3 d after delivery	0.409 (0.269~1.377)	0.388
Second trimester	0.109 (0.030~0.910)	0.021	42 d after delivery	0.698 (0.309~1.091)	0.691
Last trimester	0.601 (0.369~1.271)	0.318	90 d after delivery	0.298 (0.091~1.219)	0.091

that maternal SA at early stage of pregnancy did not show significant influence on mental development, which might be related with the specific development period of the embryonic nervous system. Via MRI imaging technology, it can be observed that the development of brain only enters the explosive growth phase from 15th week since the formation of embryo, which is featured by the dramatic growth in number of axons and the extension of nerve fiber that covers the whole cerebral cortex, although the brain is formed at 28th day of pregnancy [14].

After birth, the infants begin to activate their ability for SA synthesis gradually, and get into the self-sufficient mode. It was shown that the SA synthase is not active in postnatal rats, while reached the highest level of at Day 15 after birth [15, 16]. In this study, our finding suggested that at Day 90 post-partum, maternal SA did not have a significant influence on the mental development. However, interestingly, the maternal serum SA levels increased steadily during pregnancy, while breast milk SA levels rapidly decreased during lactation. According to the results from previous studies, the level of SA in amniotic fluid gradually increased with the increase of estrogen throughout the pregnancy [17]. Here, we speculate that the levels of estrogen secretion during the pregnancy may cause the gradual increase of serum SA. However, the decrease of SA levels in breast milk after birth may be the evolutionary result in order to meet the needs of neonatal growth and development of the infants who begin to generate SA by themselves. Thus, there might be a very subtle link between maternal SA levels and SA requirements of offspring.

In addition, it can be seen from the results that there was an advantage on psychomotor development in infants whose mothers had a high level of serum SA during the second trimester over those whose mothers had a low level of serum SA. This may be due to the development of motor function is determined by the development of muscle, bone and nervous system, besides, the second trimester is the vital period for the development of nerve system. In addition, it was found that the PSA amount, which determines the number of synapses in the associated muscles, can determine the types of muscle: fast muscle and slow muscle [18, 19]. Therefore, SA also affects the development of motor neurons to some extent. At the same time, we noticed that the maternal SA level had more significant influence on the intellectual development than that on motor development, which might be due to that SA in the human body mainly in the service of the nervous system [20, 21].

In conclusion, the high levels of maternal SA in serum during second to last trimesters and in breast milk at early lactation have a promoting effect on the early development of infants' intelligence. Therefore, it is recommended to breastfeed, especially the colostrum. Pregnant women can increase the intake of SA from foods, and improve the self-synthesized SA via moderate exercise and a pleasant mood, which will promote the infant growth and development.

Disclosure of conflict of interest

None.

Address correspondence to: Mei Li, The First Department of Obstetrics, Weifang People's Hospital, No. 151 Guangwen Road, Weifang 261041, Shandong Province, China. Tel: +86-0536-8192192; E-mail: limeiwf@126.com

References

[1] Wang GB. Comparative study of the results of CT measurement in children with cerebral infarction in normal and brain dysplasia. Contemporary Medicine 2013; 31: 66.

[2] Li HY, Liu PF, Shi JP, Tian J. Physiological function, application and production method of sialic acid. Science and Technology of Food Industry 2014; 3: 363-368.

[3] Jin YT, Ruan LL, Hua CZ. Study on sialic acid levels in breast milk collected from early neonate's mother. Chinese Journal of Child Health Care 2014; 22: 776-778.

[4] Fang CR. CDCC scale of infantdevelopment. Unity Press; 1989; 6: 130-140.

[5] Kumar D and Rizvi SI. Erythrocyte membrane bound and plasma sialic acid during aging. Biologia 2013; 68: 762-765.

[6] Jin Y, Yan XR. Clinical efficacy of integrated Chinese traditional and western medicine in the treatment of mental retardation in 30 children. Chinese Pediatrics of Integrated Traditional and Western Medicine 2012; 1: 56-58.

[7] Zhang ZQ, Su YX. Gangliosides and brain development research. Journal of Hygiene Research 2015; 44: 147-150.

[8] Harald R. Developmental expression and possible roles of gangliosides in brain development. Guidance cues in the developing brain. Springer Berlin Heidelberg; 2003. pp. 49-73.

[9] Zhang L, Tang JL, Wu D. Effects of Monosialotetrahexosylganglioside in infants with global developmental delay: a prospective case-control study. Journal of Medical Research 2014; 6: 141-143.

[10] Gong L, Zang HC. Clinical application of monosialo hexose ganglioside. Food and Medicine 2012; 5: 207-210.

[11] Zhang XY, Zhang HX, Zou R, Zhou L, Wang Q, Liu YN. Effects of scalp acupuncture on the expression of sialic acid neural cell adhesion molecule in rats with cerebral ischemia. Journal of Integrated Traditional Chinese and Western Medicine 2011; 13: 1581-1582, 1585.

[12] Gao YY, Cai HY, Wang W. Polysialylation of neural cell adhesion molecule can be regulated by CpG methylation. Ningxia Medical Journal 2010; 3: 190, 203-205.

[13] Lu WQ, Xiao Q. Multi sialic acid neural cell adhesion molecule and cognitive function. Foreign Medical Sciences (Geriatrics) 2008; 2: 65-67.

[14] Shao ZL, Wu YJ, Xu MY. The study of the relationship between sialic acid of human milk and the early intellectual development of term infants. Journal of Nantong University (Medical Sciences) 2014; 6: 104-107.

[15] Cheng C, Gao CF. Research progress of the biological significance of sialic acid in the liver diseases. Laboratory Medicine 2013; 4: 333-336.

[16] Liu CM, Li X, Guang F. Advances in the research of sialic acid synthase Neu1 and its related signaling pathways. Biochemistry and Biophysics 2016; 43: 962-969.

[17] Hiramatsu Y, Eguchi K, Sekiba K. Alternations in polyamine levels in amniotic fluid, plasma and urine during normal pregnancy. Acta Med Okayama 1985; 39: 339-46.

[18] Liu ZD, Wang YY, Guo BH, Liu ZM, Su MY, Li YF, Gao YH. Research advances in sialic acids. Science and Technology of Food Industry 2010; 9: 368-373.

[19] Wei W, Wang SJ. Recent advance of sialic acid in human disease. Journal of Dalian Medical University 2015; 9: 610-614.

[20] Choi SS, Baldwin N, Wagner VO 3rd, Roy S, Rose J, Thorsrud BA, Phothirath P and Rohrig CH. Safety evaluation of the human-identical milk monosaccharide sialic acid (N-acetyl-d-neuraminic acid) in sprague-dawley rats. Regul Toxicol Pharmacol 2014; 70: 482-491.

[21] Choi SS, Lynch BS, Baldwin N, Dakoulas EW, Roy S, Moore C, Thorsrud BA and Rohrig CH. Safety evaluation of the human-identical milk monosaccharide, l-fucose. Regul Toxicol Pharmacol 2015; 72: 39-48.