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Research report

Sialic acid and anti-ganglioside antibody levels in children with autism spectrum disorders

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ABSTRACT

Background: Autism spectrum disorders (ASD) may result from a combination of genetic and environmental factors, and impact neurological functions and behaviors. Sialic acid (SA) is an indispensable nutrient for early brain development, and its polymer polySia (PSA) can modify neural cell adhesion molecules (NCAM), thereby indirectly mediating neuronal outgrowth, synaptic connectivity and memory formation. To investigate the association between SA and ASD, we conducted a case-control study.
Methods: The study sample included 82 autistic children and 60 healthy children. We measured the levels of plasma SA and serum anti-gangliosides M1 antibodies (anti-GM1 antibodies) in the ASD and control groups. We also examined the severity of autistic children.
Results: The level of plasma SA in the control group was significantly higher than that in the ASD group ($p < .01$). Autistic children had higher positive rates of anti-GM1 antibodies (37.8%) than controls (21.67%, $P = .04$). However, there was no correlation between autistic severity and the levels of SA. SA may be as a biomarker for diagnosis of ASD with a positive predictive value of 84.42%, a negative predictive value of 73.85% and an area under the ROC curve value of 0.858.
Conclusions: These results indicate that SA and anti-GM1 antibodies are associated with ASD. Our data suggested that future studies to explore the function of SA in the etiology of ASD may be needed.

1. Introduction

Autism spectrum disorders are a complex group of developmental disorders that are characterized by social deficits, impaired communication, and repetitive stereotypic behaviors (Pace et al., 2016; Stoner et al., 2014; Young and Barrett, 2015). The prevalence of ASD has surged in recent years. According to the 2014 National Health Interview Survey, the prevalence of ASD has increased to 2.24% in the United States (Zablotsky et al., 2015). Despite intense research efforts over the past decade, the pathogeny of ASD is still unknown, and there are no definite biological or clinical markers for diagnosing ASD. If ASD children can be diagnosed early and given a reasonable intervention, this may markedly improve their prognosis.

Sialic acid, a family of 9-carbon sugar acids, is an essential nutrient for brain development and cognition (Wang, 2009). Moreover, sialic acid is an elementary constituent part of gangliosides. As a result of the synergistic effect of polysialyltransferases (ST8Sia2 and ST8Sia4), SA can be synthesized into polysialic acid glycan, which associates with neural cell adhesion molecules (NCAM) to form PolySia-NCAM (PSA-NCAM) (Wang, 2012), which in turn impacts molecular interactions during synaptic plasticity and neural development. Sato et al. (2016) suggested that polySia is involved in learning, memory and social behaviors and is associated with ASD. Recently, a study showing a connection between polySia and ASD-like behaviors reported that mice deficient in ST8SIAII exhibited reduced social motivation, increased aggression and hyperactivity (Calandreau et al., 2010). Several studies have reported that NCAM gene variants are associated with ASD (Marui et al., 2009; Zhang et al., 2014). However, limited information is available about the relationship between SA and ASD.

Gangliosides, which are sialylated glycosphingolipids, are the most abundant sialoglycans expressed in nerve cells and may play an important role in axon-myelin interactions, axon stability, axon regeneration, and modulating nerve cell excitability (Schnaar et al., 2014). Under normal circumstances, gangliosides in the nervous

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system are not attacked by the immune system. When stimulated by internal or external factors, B lymphocytes produce anti-ganglioside antibodies and then facilitate the ganglioside involvement of injured neurons. The changes of ganglioside expression may contribute to abnormal behaviors associated with ASD (Schengrund et al., 2012). Moreover, one study reported that the level of GM1 increased in the cerebral spinal fluid of ASD children (Nordin et al., 1998). Anti-GM1 antibody, especially those directed at GM1, was reported to be associated with some immune-mediated neuropathies (Uncini, 2012). The presence of brain-specific auto-antibodies could play the role in the cause of ASD (Mostafa et al., 2008). A previous study also showed that increased serum levels of anti-GM1 auto-antibodies were correlated with the autistic severity of ASD children (Mostafa and Al-Ayadhi, 2011). However, Moeller et al. (2013) found that ASD and anti-GM1 antibodies were not directly associated. Altogether, more evidence is needed to understand the relationship between anti-GM1 antibodies and autistic children.

No studies have reported an association between plasma SA levels and ASD to date. Therefore, we examine the levels of sialic acid and anti-GM1 antibodies in autistic children and explore the relationship between these factors and autistic behavioral symptoms.

2. Results

2.1. Demographic characteristics

The ASD group had 82 children (71 males, 11 females, and a male to female ratio 6.45:1); the mean age was 4.22 ± 1.01 years old. The control group included 60 healthy children (47 males, 13 females, and a male to female ratio 3.62:1); the mean age was 4.52 ± 0.84 years old. There were no significant difference in age ($p = .062$) and sex ($p = .257$) between the ASD and control groups.

2.2. Plasma levels of sialic acid in autistic and control children

By colorimetric analysis, the level of SA in the control group was higher than that in the ASD group ($p < .01$). However, there were no significant differences in the SA levels of different sexes when comparing the two groups (Table 1).

2.3. The relationship between the levels of sialic acid and the severity of ASD

After assessing the severity of ASD children, we did not find that the level of SA was significantly different in children with ASD at different levels of severity ($p > .05$). Moreover, the level of SA was not significantly different in children with different intelligence quotients ($p > .05$) (Table 2).

Table 1
The levels of sialic acid in autistic and healthy children.

Items	SA (m mol/L) Mean ± SD	*t*	*P*
Control	5.32 ± 1.85	−8.73	<.01
ASD group	3.27 ± 0.90		
Male autistic children	3.28 ± 0.94	0.23	.82
Female autistic children	3.21 ± 0.57		
Male healthy children	5.45 ± 1.94	1.06	.29
Female healthy children	4.84 ± 1.36		

2.4. Receiver operating characteristic analysis

Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive power of SA levels to distinguish between ASD children and controls. Area under the ROC curve (AUC) was demonstrated the diagnosis value of SA, with a higher AUC being correlated with high sensitivity, specificity, and accuracy. The analysis showed the diagnostic values of the SA levels for ASD, including high values for sensitivity (79.27%) and specificity (80%), positive predictive value (84.42%), negative predictive value (73.85%) and AUC (0.858, $p < .01$) (Fig. 1).

2.5. The positivity rates of anti-GM1 antibodies in autistic and control children

Autistic children had a significantly higher positivity rate of anti-GM1 antibodies (37.8%) in comparison to healthy controls (21.67%), $P = .04$. However, neither autistic nor healthy children showed differences in the positive rate of anti-GM1 antibodies between different sexes (Table 3).

2.6. The relationship between the positivity rates of anti-GM1 antibodies and the severity of ASD

The result of the ABC scale demonstrated that the severity of ASD was not different between the positive and negative anti-GM1 antibody groups ($p > .05$). However, CARS scores were different between positive and negative anti-GM1 antibody groups ($p < .05$). We also found that the intellectual development of ASD children was significantly different when comparing the positive and negative anti-GM1 antibody groups ($p < .05$) (Table 4).

3. Discussion

Although a small number of studies have focused on the association between PolySia or PSA-NCAM and ASD, most studies have used either autistic model mice or cell lines for their experiments. The current study sought to investigate the association between sialic acid and the autistic phenotype in children. By colorimetric analysis, we found that the level of plasma SA in ASD children was significantly lower compared with that in control children ($p < .01$). However, there was no correlation between the SA level and the severity of ASD or the intellectual development of autistic children. It is noteworthy that the diagnostic values of SA levels can be used to distinguish between ASD individuals and controls. There were high values for sensitivity (79.27%), specificity (80%) and the area under the curve (AUC = 0.858). Therefore, sialic acid may be used as a biomarker for the diagnosis of ASD. In the current study, we also found that the positive rates of anti–GM1 antibodies in ASD children were significantly different than those in control children ($p = .04$). Moreover, it was discovered that anti-GM1 antibody levels were associated with the intelligence quotient of ASD children according to PPVT results ($p = .023$).

Sialic acid is an important nutrient and plays a role in neurodevelopment of infants (Wang, 2009, 2012). Wang et al. (2007) found that dietary sialic acid supplementation improves learning and memory in piglets. Polysialic acid and PSA-NCAM are most abundantly expressed in brain tissue, but it is difficult to obtain patient brain tissue samples for studies. Thus, autistic rodent models are typically used for functional studies. At present, two common ASD rodent models are used: the inbred mouse strain BTBR T + tf/J (BTBR mice) and rats exposed to the valproic acid (VPA rats). Stephenson et al. (2011) showed that there were marked reductions of PSA-NCAM in the hippocampus of the BTBR mouse strain compared with B6 mice. Codagnone et al. (2015) found that the