Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Correlation between 5-HT, Hcy and the incidence and severity of autism in children

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ARTICLE INFO

Original paper

Article history:
Received: November 29, 2022
Accepted: January 10, 2023
Published: January 31, 2023

Keywords:

Children, autism, 5-hydroxytryptamine, psychological intervention, homocysteine level, correlation

ABSTRACT

This experiment was conducted to investigate the effects of serotonin or 5-hydroxytryptamine (5-HT) and homocysteine (Hcy) levels on the incidence and severity of autism in children. For this aim,120 autistic children were selected as the study group, and 120 children who took early psychological intervention were included in the study group I, and 120 children who took late psychological intervention were included in study group II. 120 non-autistic children hospitalized in the same period were selected as the control group. The levels of serotonin and Hcy were compared between the two groups. At the same time, the effects of different levels of serotonin and Hcy on the severity of autism in children were compared. Results showed that there were significant differences in 5-HT level, Hcy level, cesarean section, breast milk mode, premature delivery, vitamin B12 level, birth weight and early illness between study group I and control group, and between study group II and control group (all $P < 0.01$). The ASD score growth rate, ASD score change rate, 5-HT change rate and complications of study group I were lower than those of study group II, but the cure rate was significantly higher than that of study group II ($P < 0.01$). 5-HT, breast feeding, Hcy, vitamin B12 level, febrile convulsion and traumatic brain injury were the main risk factors for children with autism, while the psychological intervention was the main protective factor, which had a significant positive impact on the severity of children with autism ($p < 0.05$). 5-HT and Hcy levels have significant predictive effects on the development of children with autism and can be used as predictive indicators for the development of autism. In conclusion, 5-HT, feeding mode, Hcy, vitamin B12 level and febrile convulsion are the main risk factors for autism in children, and there are significant correlations.

Doi: http://dx.doi.org/10.14715/cmb/2022.69.1.10

Introduction

Children's autism is a serious psychological developmental disorder, which mostly occurs before the age of 3. Its clinical manifestations are decreased social skills, speech expression obstacles, repetitive and rigid behaviors, narrow interests and abnormal perception. WHO survey shows that the number of five children with autism is 21,120/100,000, and this number is on the rise, reaching 28,51/100,000 in 2030 (1). Children's autism seriously affects children's mental health, and also brings a serious burden to families and society. Some scholars have proposed that abnormal serotonin or 5-hydroxytryptamine (5-HT) is a neurobiochemical hypothesis for the development of autism in children. This scholar believes that serotonin is an important neurotransmitter in the human body. After being released by synapses, serotonin and its receptor exert biological effects (2) and complete the conduction of neuroelectric. Among them, 5-hydroxytryptamine has the function of regulating synaptic space (3) and achieves the purpose of controlling nerve electrical release. Some scholars have put forward the hypothesis that homocysteine (Hcy) level and autism in children (4), and think that homocysteine is an important intermediate product of methionine and cysteine metabolism, which inhibits the activity of cystathionine-β-synthase, and participates in the development of the human nervous system with vitamin B12 and folic acid, and ensures the normal function of the nervous system (5). Clinical research shows that children's autism is characterized by aggregation and familial, suggesting that the disease has a certain genetic tendency (6). With the development of biological technology and genetic technology, the incidence of children's autism is related to susceptible genes, so children's autism may be related to 5-hydroxytryptamine and homocysteine. At present, the etiology and pathogenesis of children's autism are unknown (7), but it is related to the lack of neuro-nutrients. Therefore, an in-depth study of the pathogenesis and causes of children's autism can effectively promote the cure of children's autism. Some scholars believe that early psychological intervention, homocysteine supplementation and 5-hydroxytryptamine can control the development of children's autism, while others believe that early psychological intervention, homocysteine supplementation and 5-hydroxytryptamine supplementation can achieve a better therapeutic effect (8,9). Therefore, there are controversies about the correlation between homocysteine, 5-hydroxytryptamine and autism in children and the choice of treatment methods for autistic children. In order to further find the influencing factors of children's autism and choose the best treatment for children's autism, this paper analyzes the influencing factors of children's autism and different treatment schemes. Specific reports are as follows.

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Materials and Methods

Research data

120 autistic children admitted to the Children's Mental Health Clinic of our hospital from March 2020 to November 2021 were taken as the research group. The selected children met the diagnostic criteria in the Manual of Diagnosis and Statistics of Mental Diseases: 5th Edition (10), and 120 non-children with autism were selected as the control group in the same period. In the study group, 120 children with the early psychological intervention were included in study group I, and 120 children with the late psychological intervention were included in study group II. Male/female in the study group I = 70/50; The degree of autism in children: 62 cases were mild and 58 cases were moderate. The age ranged from 6 ~10 years old, with an average of 4.14±1.15 years old. The onset time ranged from 1~ 4 years, with an average of 1.12±0.13 years. Male/female in study group II = 69/51; The degree of autism in children: 59 cases were mild and 61 cases were moderate. The age ranged from 6 ~ 9 years old, with an average of 4.24±1.24 years old. The onset time ranged from 1~ 3 years, with an average of 1.24±0.36 years. Male/female in control group = 60/60; The degree of autism in children: 58 cases were mild and 62 cases were moderate. The age ranged from 5 ~11 years old, with an average of 4.13±1.12 years old. The onset time ranged from 1 ~ 4 years, with an average of 1.12±0.25 years. There is no significant difference in clinical data such as age, onset time and autism degree among the above three groups of children, so the experiment can be carried out with the consent of the Ethics Association of our hospital. Inclusion criteria: 1) No major diseases in important organs such as the heart and liver (2); 2) No circulatory system diseases; 3) No sedatives and antidepressants such as methotrexate and sulfanilamide were taken. Exclusion criteria: 1) Those who quit halfway or those who falsified clinical data (11); 2) Those who take antidepressants by themselves halfway; 3) Those with a family history of genetic diseases, history of head trauma and patients with malignant tumors.

Research methodology

Children in the study group were tested for 5-HT and Hcy daily after admission, and the degree of childhood autism was evaluated.

1) Take 3ml blood, wait for 20 min at 20 ℃, centrifuge at 3000r/min for 15min, and wait at-80 ℃. Hcy was detected by an automatic immunoluminescence instrument (Shandong, Biomedical Devices Co., Ltd., BKI4200) and a matching kit. 5-HT concentration was detected by enzyme-linked immunosorbent assay, and the kit was (Wuhan, Aidi Anti-Biological Co., Ltd.), which was detected in strict accordance with the operating instructions (12).

2) The score of the autism assessment scale is 15 items, which are general impression, activity level, verbal communication, visual response, intellectual activity level and consistency, auditory response, emotional response, imitation ability, nonverbal communication, tension and fear, relationship with others, taste and touch response, body movements, adaptability to changes, and use of objects (13). The score of each item is 1 ~ 4 points, and the total score is 60 points. The higher the score, the higher the degree of loneliness. Scores > 36 are classified as severe, 30 ~ 36 as moderate and 20 ~ 30 as mild.

The Study Group I. within 14 days after admission, music therapy, total nutrition guidance, correction of water and electrolyte disturbance, outdoor games, hyperbaric oxygen and other interventions were adopted.

1) Music therapy, listen to light music every day, and encourage children to participate in singing, so that they can play their singing and melody, 15min each time, 6 times a week. 2) Total nutrition guidance, allocate the content ratio of grain, animal and plant protein, cellulose, etc., and formulate daily recipes to ensure the balance of various nutrients. 3) Correction of water and electrolyte disorder, once every 14 days according to the electrolyte situation of children. 4) Outdoor games, outdoor games are played four times a week, including scene-setting, competitive games, thinking games, etc., and the game content and time are adjusted according to the scores of the autism evaluation table of children. 5) Hyperbaric oxygen, children are treated in a hyperbaric oxygen chamber three times a week for 10 ~ 15min each time, and attention should be paid to prevent children from middle ear barotrauma and oxygen poisoning.

The Study Group II. After 14 days after admission, the auxiliary intervention was carried out, and the intervention method was consistent with the study I.

The observation indicators

The ASD scores, 5-HT and Hcy levels, vitamin B12 levels, premature delivery, mode of production, feeding patterns, and early illness were recorded. Among them, the early diseases include respiratory distress, craniocerebral trauma and febrile convulsion. Improvement rate = (the number of people whose ASD scores decreased by 10% during 0 ~ 3 months + the number of people whose ASD scores did not increase) ÷ the total number of children in each group * 100%

Statistical analysis

The related data were statistically analyzed by SPSS20.0 software. Numerical variables are expressed by $x \pm s$, and *T*-test is used between groups. Classification variables are expressed by%, and the χ^2 test is adopted. The logistic analysis was carried out on the indicators with significant differences. Among them, $P < 0.05$ means there is a significant difference.

Results

5-HT level, Hcy level, cesarean section and breast milk mode comparison

There were significant differences in 5-HT level, Hcy level, cesarean section and breast milk mode between study group I and control group, study group II and control group (all $P < 0.01$), but there was no significant difference in milk powder and mixed mode (all $P > 0.05$). There is no significant difference between study group I and study group II, and there is no statistical significance between study group I and study group II ($P > 0.05$). The results are shown in Table 1.

Comparison of premature birth, vitamin B12 level, birth weight and early illness

There were significant differences among study group I, the control group and study group II in terms of premature delivery, vitamin B12 level, birth weight and early

Table 1. Comparison of HT, Hcy, Cesarean Section and Feeding Methods [$\bar{x} \pm s$].

Group	5-HT (μmol/l)	Hcy (μmol/l)	Cesarean section (%)	Feeding mode (%)		
				Breast milk	Milk powder	Mixing
Study Group I (n=120)	11.28±1.24	9.13±1.12[a]	51.41±1.17[ab]	60.17±1.09[abc]	511.17±1.51[abcd]	8.17±1.49[abcde]
Control (n=120)	1.41±1.41	2.17±1.37[a]	111.17±1.49[ab]	31.41±1.41[abc]	511.39±1.51[abcd]	8.17±1.08[abcde]
T	31.127	13.177	19.241	19.316	1.491	1.032
P	<0.001	<0.001	<0.001	<0.001	0.265	0.328
Study Group II (n=120)	11.17±1.35	12.17±1.12[a]	52.09±1.13[a]	60.73±1.25[abc]	511.25±1.08[abcd]	8.94±1.08[abcde]
Control (n=120)	1.41±1.41	2.17±1.37[a]	111.17±1.49[a]	31.41±1.41[abc]	511.39±1.51[abcd]	8.17±1.08[abcde]
T	19.395	34.6120	1011.907	911.1209	0.348	1.749
P	<0.001	<0.001	<0.001	<0.001	0.419	0.092
Study Group I (n=120)	11.28±1.24	9.13±1.12[a]	51.41±1.17[a]	60.17±1.09[abc]	511.17±1.51[abcd]	8.17±1.49[abcde]
Study Group II (n=120)	11.17±1.35	12.17±1.12[a]	52.09±1.13[a]	60.73±1.25[abc]	511.25±1.08[abcd]	8.94±1.08[abcde]
T	0.326	0.296	0.782	0.326	0.948	0.412
P	0.425	0.742	0.257	0.448	0.326	0.815

Compared with 5-HT in this group, [a]*P*>0.05; Compared with Hcy in this group, [b]*P*>0.05; Compared with cesarean section in this group, [c]*P*>0.05; Compared with breastfeeding in this group, [d]*P*>0.05; Compared with milk powder feeding in this group, [e]*P*>0.05.

Table 2. Comparison of HT, Hcy, cesarean section and feeding methods [$\bar{x} \pm s$].

Group All: (n=120)	Premature birth (%)	Vitamin B12 level (pmol/l)	Birth weight (kg)	Early illness (%)		
				Respiratory distress	Craniocerebral trauma	Hyperfebrile convulsion
Study Group I	60.12±1.17	419.17±0.17[a]	12.25±20.09[ab]	21.17±1.09[abc]	9.12±0.17[abcd]	15.81±1.28[abcde]
Control Group	3.17±1.49	498.12±0.17[a]	15.17±19.12[ab]	1.25±0.17[abc]	0.61±0.08[abcd]	4.13±1.26[abcde]
T	30.418	95.099	45.405	8.739	29.810	411.473
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Study Group II	60.17±1.05	419.27±0.93[a]	12.36±20.96[a]	21.15±1.28[abc]	9.25±0.17[abcd]	15.09±1.17[abcde]
Control Group	3.17±1.49	498.12±0.17[a]	15.17±19.12[ab]	1.25±0.17[abc]	0.61±0.08[abcd]	4.13±1.26[abcde]
T	14.743	34.579	211.2120	14.127	111.614	41.403
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Study Group I	60.12±1.17	419.17±0.17[a]	12.25±20.09[ab]	21.17±1.09[abc]	9.12±0.17[abcd]	15.81±1.28[abcde]
Study Group II	60.17±1.05	419.27±0.93[a]	12.36±20.96[a]	21.15±1.28[abc]	9.25±0.17[abcd]	15.09±1.17[abcde]
T	0.140	0.170	0.818	0.127	1.132	0.292
P	0.847	0.154	0.426	0.931	0.229	0.741

Compared with vitamin B12 level in this group, [a]*P*>0.05; Compared with the birth weight of this group, [b]*P*>0.05; Compared with respiratory distress in this group, [c]*P*>0.05; Compared with neonatal pneumonia in this group, [d]*P*>0.05; Compared with febrile convulsion in this group, [e]*P*>0.05.

Table 3. Therapeutic effects of different psychological intervention opportunities.

Group	ASD score growth rate	Vitamin B12 change rate	5-HT rate of change	Hcy level	Overall improvement rate of ASD score
Study Group I (n=120)	11.13±1.13	11.13±0.17	26.36±1.14	2.17±0.32	45.34±2.11
Study Group II (n=120)	4.12±1.41	8.09±0.13	23.42±1.27	2.37±0.69	10.37±0.14
T	12.602	21.85	13.84	121.82	21.12
P	0.031	<0.001	<0.001	<0.001	<0.001

illness (P < 0.01). However, there was no significant difference between study group I and study group II, and within the group (P > 0.05). The results are shown in Table 2.

Timing of psychological intervention

The ASD score growth rate, ASD score change rate, 5-HT change rate and complications in the study group I were lower than those in study group II, while the cure rate was significantly higher than that in study group II, with significant differences and statistical significance (*P* < 0.01). The results are shown in Table 3.

Main risk factors affecting autism in children

The factors with significant differences in Tables 1, 2 and 3 are taken as independent variables, and the degree of autism in children is taken as dependent variables, and multi-factor logistic analysis is carried out. The assignment of each variable factor is shown in Table 4.

Table 4. Assignment of main influencing factors.

Indicators	Assignment
5-HT level	>8μmol/l =1, <8μmol/l =0
Hcy level	>7μmol/l =1, <7μmol/l =0
Cesarean section	Cesarean section = 1, natural birth = 0
Breast milk	Milk powder or mixed feeding = 1, breastfeeding = 0
Premature birth	28 ~ 37 weeks = 1, > 37 weeks = 0
Vitamin B12 level	>420pmol/l =1, <420pmol/l =0
Birth weight	Weight < 1.5 g=1, > 1.5 g=0
Respiratory distress	Has been embarrassed = 1, has not been embarrassed = 0
Craniocerebral trauma	Have had craniocerebral trauma = 1, have not had craniocerebral trauma = 0
Hyperfebrile convulsion	Excessive febrile convulsion = 1, no febrile convulsion = 0
Opportunity of psychological intervention	Late psychological intervention = 1, early psychological intervention = 0

Table 5. Results of logistic analysis of main risk factors.

Related factors	*b* value	Standard error	*Wald* value	*RR* value	OR (95%*CI*)	*p*
5-HT level	1.331	0.012	4.517	1.242	2.943 (2.812-3.891)	0.003
Hcy level	1.212	0.088	5.171	1.1320	2.121 (1.982-3.173)	0.002
Cesarean section	1.095	0.023	2.585	1.012	0.312 (0.133-1.094)	0.475
Breast milk	1.325	0.019	3.232	1.124	0.312 (0.2120-1.722)	0.082
Premature birth	1.212	0.042	2.142	1.495	0.171 (0.131-1.813)	0.171
Vitamin B12 level	2.371	0.031	1.212	1.131	1.312 (0.472-1.821)	0.001
Birth weight	1.171	0.019	1.518	1.254	0.492 (0.211-1.173)	0.092
Respiratory distress	1.3120	0.023	2.024	1.341	0.312 (0.102-1.413)	0.616
Craniocerebral trauma	1.125	0.031	4.975	1.965	0.314 (0.272-1.413)	0.021
Hyperfebrile convulsion	1.123	0.042	4.131	1.192	1.172 (0.541-1.571)	0.000
Opportunity of psychological intervention	-1.476	0.032	5.172	1.243	3.172 (2.822-3.412)	0.007

By logistic analysis of the above variables, the results showed that 5-HT, breast feeding, Hcy, vitamin B12 level, febrile convulsion and traumatic brain injury were the main risk factors for the development of children's autism, while the timing of the psychological intervention was the main protective factor, which had a significant positive impact on the severity of children's autism ($p < 0.05$), as shown in Table 5.

According to the contents in Table 5, the ROC curve analysis of 5-HT level and Hcy level is carried out, and the results are shown in Figure 1.

According to Fig. 1, 5-HT level and Hcy level have significant predictive effects on the development of autism in children and can be used as predictive indicators for the development of autism. At the same time, breastfeeding, vitamin B12 level, febrile convulsion and traumatic brain injury can be used as reference indicators, while the timing of psychological intervention is an inhibitory indicator for the development of autism in children.

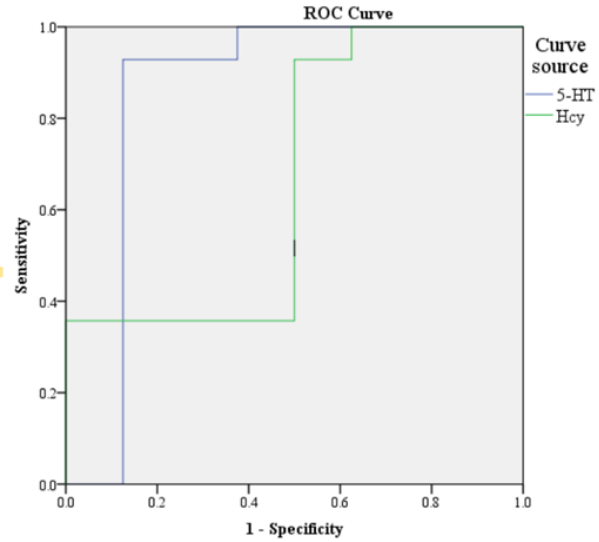

Figure 1. Figure 1. ROC curves of Hcy, 5-HT levels and the occurrence of autism.

Discussion

Correlation between premature birth, respiratory distress and mode of production and autism

Autism in children is caused by neuronal ischemia and hypoxia caused by various reasons in the neonatal period, which leads to children's social ability decline, speech expression disorder, repetitive and rigid behavior, narrow interest and abnormal perception, and is a serious nervous system disease. Because the ASD score of children with autism rises between 18% and 25% within 15 years, and there will be mental problems such as anorexia and abnormal perception (14,15), 50% of children will choose psychological intervention treatment, and with the influence of individual differences, some children's autism develops more rapidly. Therefore, it is particularly important to choose the opportunity of psychological intervention rea-

sonably. At present, ASD score is used as an indication of psychological intervention clinically, but the research results show that ASD score alone has low accuracy in judging autism, so it is necessary to combine children's physiological indicators (16) and carry out the psychological intervention in time before autism is serious (8). Studies have shown that autism occurs in children with low birth weight, premature birth, respiratory distress and feeding methods. Low body weight and premature birth are congenital deficiencies, and the fetal development cycle is short, which will cause problems such as autoimmunity and neurological dysfunction, resulting in respiratory diseases after birth (17), or cognitive problems. Some scholars believe that brain problems such as craniocerebral injury, convulsion and high fever will cause cognitive and nervous system disorders and induce autism, which is consistent with the results of this study (18).

Correlation between Hcy, 5-HT, vitamin B12 levels and autism

The results of this study show that 5-HT, Hcy, vitamin B12 level and febrile convulsion are the main risk factors of autism in children. It has been reported that the autism rate of children with high 5-HT is 15 ~ 19% (9), mainly because 5-HT belongs to neurotransmitters and plays an important role in brain development, cognitive function regulation and emotional control, which directly acts on the central nervous system. Animal experiments have shown that the increase of 5-HT will lead to slow response, lack of desire, fear, nervousness and other reactions, and even increase the pain threshold. There are also clinical studies that too little 5-HT will destroy synaptic connections in the sensory cortex of the brain, resulting in loneliness, abnormal perception, decreased ability of smell and taste, etc. (20), and too much 5-HT will cause symptoms such as stiffness, convulsions, fever, emotional MoMo, convulsions, etc., which is consistent with the results of this study (21).

Vitamin B12, also known as cobalamin, is an important substance for the development of the nervous system, which cannot be synthesized by the human body and needs external intake. The deficiency of vitamin B12 can cause the development disorder of the nervous system and lead to Alzheimer's disease. It promotes the utilization of protein and nucleic acid through helper enzymes, improves the utilization rate of folic acid, and has the effect of protecting the nervous system. The results of this study show that the serum vitamin B12 level of autistic children is low, which is consistent with the above research (22).

Hcy is a cytotoxic sulfur-containing amino acid, which can induce apoptosis and interfere with the normal cycle of the embryonic system. If Hcy is at a high level, it will lead to an abnormal metabolic pathway, increase Hcy content in vivo and induce hyperhomotype Hcy. Hcy is metabolized by the methylation pathway and sulfur transversion pathway, and the methylation pathway is related to the vitamin B12 helper enzyme, which forms S-adenosylmethionine under the action of S-adenosylmethionine synthetase; The sulfur transfer pathway is cystathionine synthetase to form cystathionine, and then cysteine. The growth of Hcy can produce oxygen free radicals (23) and hydrogen peroxide, and can also inhibit the activities of other antioxidant enzymes and promote lipid peroxidation. Therefore, a higher Hcy level will lead to autism, and the serum Hcy level of autistic children will be higher than that of normal children, which is consistent with the results of this study (24).

Timing of autism intervention

After autism is diagnosed, intervention measures should be taken, and psychological intervention should be decided according to the development of the disease. However, there is no consensus on the timing of psychological intervention for children with autism. Studies have shown that children's ASD score decreases, Hcy level and 5-HT level increase, which may be the best time for psychological intervention (25). Clinically, the ASD score is the main basis for diagnosing the severity of children's autism. Before ASD score drops, children have undergone significant changes, but the evaluation of changes belongs to the subjective judgment of clinicians and cannot be used as the basis for accurately judging children's autism. Therefore, the timing of children's psychological intervention is controversial in the clinic, which affects the quality of autism. Studies have shown that early psychological intervention has a positive role in promoting the improvement of children's autism. Because children with autism have a high change rate within 14 days (16), this paper divides them into study groups I and II as the division standard and observes the psychological intervention effect and prognosis of different groups. The results show that the ASD score growth rate, ASD score change rate and overall ASD score of a study group I are lower than those of study group II, while the Hcy and 5-HT change rates are significantly higher than those of study group II, with significant differences. Psychological intervention for children with autism is mainly observation, and it is common for ASD scores to increase in a short time. However, changes in ASD scores increased Hcy and 5-HT levels, and deficiency of vitamin B12 levels will aggravate autism and even cause other serious consequences. Studies have shown that early psychological intervention can minimize damage to the nervous system, reduce the degree of cognition and perception, and improve the prognosis of children with autism. Psychological intervention can improve the level of neurotransmission in children, while late psychological intervention can not improve the level of neurotransmission, affect the absorption of vitamin B12, strengthen the damage to the nervous system, and have a poor prognosis and high recurrence rate. The research in this paper is consistent with the above results (26).

To sum up, 5-HT, feeding methods, Hcy, vitamin B12 level and febrile convulsion are the main risk factors of children's autism. Psychological intervention is an effective means to improve children's autism, but for early psychological intervention, the effect of late psychological intervention is poor. Early psychological intervention can effectively reduce the recurrence rate, ASD score growth rate, Hcy and 5-HT levels, and the prognosis of children is better.

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