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Kawasaki Disease can Improve Autism: A Case Report and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

In this paper, we report a case of autism in a child who was cured of Kawasaki disease and the condition of autism was significantly improved. Kawasaki disease (KD), also known as cutaneous mucosal lymph node syndrome, was first reported by Japanese doctor Tomaku Kawasaki in 1967. In recent years, domestic and foreign studies believe that the pathogenesis of KD is significantly related to infection, genetic susceptibility and immune response, and its pathogenesis and treatment still need to be further studied. The occurrence of autism may be based on genetic predisposition and triggered by environmental factors during the critical period of immune establishment at the age of 1-3 years, which causes immune-mediated inflammation, changes the permeability of gastrointestinal tract and blood-brain barrier, and leads to chronic inflammation in the central nervous system, thereby affecting neurogenesis, migration and synaptic construction.

Keywords: Autism; gastrointestinal tract; lymph node syndrome; neurogenesis.

1. INTRODUCTION

Autism is a kind of autism Spectrum disease (ASD) [1], a generalized mental development disorder characterized by social and interpersonal communication disorders, abnormal verbal communication, stereotyped, and repetitive behaviors [2]. In the past 30 years, more than 100 susceptibility genes have been found in the study of pathogenic genes, and advances in the field of biomedicine suggest that vaccines, infection, stress and trauma may affect the pathogenesis of autism [3]. The immune system is an important

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component to maintain the stability of the immune internal environment, and immune dysregulation plays an important role in the pathogenesis of autism [4].

Kawasaki disease (KD), also known as cutaneous mucosal lymph node syndrome, was first reported by Japanese doctor Tomaku Kawasaki in 1967. The main clinical manifestations are persistent fever for more than 5 days, changes of the mouth and lip mucosa, pleomorphic rash, non-suppurative lymphadenopathy of the neck, conjunctival hyperemia of both eyes, rigid edema of the hands and feet, and peeling of the finger ends [5]. KD mainly occurs in children under 5 years of age. The incidence of KD in Asian children is higher than that in western countries, and there is a relatively obvious gender difference, with more males than females [5]. The standard treatment for KD is intravenous immunoglobulin combined with high-dose aspirin, which can significantly reduce the incidence of coronary aneurysms, but coronary artery injury still exists [6]. In recent years, domestic and foreign studies believe that the pathogenesis of KD is significantly related to infection, genetic susceptibility and immune response, and its pathogenesis and treatment still need to be further studied.

Because the etiology and pathogenesis of autism is still not clear, so it is lack of drugs for core autism symptoms, relies on special education and rehabilitation training method. It is urgent to find new treatments. When a two-year-old autistic child with Kawasaki disease was cured by intravenous human immunoglobulin, the condition of autism was significantly relieved.

Could human immunoglobulin be a new treatment for autism?

2. CASE PRESENTATION

In this paper, we report a case of autism in a child who was cured of Kawasaki disease and the condition of autism was significantly improved, as follows.

2.1 Clinical Data

2.1.1 Case data

A aged 2 years and 2 months boy was always unwilling to look at people, deaf to external sounds, and unable to express in words. He was diagnosed with autism in the local child health department.

The boy was admitted to Shenmu City Hospital on June 4, 2022 due to "fever for 2 days". Physical examination on admission: temperature 38.3℃, pulse 138 / min, respiration 34 / min, weight 15kg.He was conscious and in fair spirits. There was no abnormality in the skin of the whole body. Enlarged lymph nodes could be palpable in the neck of both sides, which were hard, with acceptable range of motion, and no obvious tenderness. There was no deformity of the cranial features, or cyanosis of the face or lips. There was no hyperemia in the pharynx, grade II enlargement of tonsils, a little pus moss covering, coarse breath sounds in both lungs, and no wet or dry rales. The heart boundary was small, the heart sound was strong, and no pathological murmurs were heard in each valve area of the heart. There were no abnormalities in the abdomen or nervous system. Outpatient cervical lymph node ultrasound showed bilateral cervical lymph node enlargement, the larger one on the left side was about 16x7mm, and the larger one on the right side was about 15x6mm, with regular shape and clear boundary. Admission diagnosis: acute suppurative tonsillitis.

2.1.2 Diagnosis and treatment

After admission, relevant examinations were completed. On June 5th (the second day of admission), blood routine +CRP: White blood cell count was 8.40x10^9/L, neutrophil percentage was 71.00%, lymphocyte percentage was 0.00%, hemoglobin concentration was 122.00g/L, platelet count was 287.00x10^9/L, CRP111.61 mg/L, high-sensitivity c-reactive protein (hs-crp) > 5mg/L. Procalcitonin assay (PCT) was 4.78ng/ml. Blood gas analysis: pH 7.37, partial pressure of oxygen $(pO)_2$56.60 mmHg, potassium ion (K^+4.70 mmol/L, actual base surplus (ABE)-5.90 mmol/L, standard base surplus (SBE)-6.80 mmol/L, glucose concentration (Glu)7.80 mmol/L, lactate concentration (Lac)3.30 mmol/L, oxygenation index $(pO)_2(a)/Fi0_2$) 270.N-terminal natriuretic peptide (NT-probNP) : 9957.95pg/ml. Four coagulation items: prothrombin time (PT) 13.7S, prothrombin percentage activity (PT %) 62.50%, and fibrinogen (FBG) 4.7g/L. Urine and fecal routine was normal. On June 6 (the third day of admission), the ESR was 71.00 mm/h. Rheumatism: rheumatoid factor (RF)10.50IU/ml, anti-0 (ASO)2.00IU/ml, CRP110.52mg/L, high-sensitivity c-reactive protein (hs-crp) > 5mg/L.B-

mode ultrasound of liver, bile, pancreas and spleen: no obvious abnormalities were found in the liver, bile and pancreas, and accessory spleen. Heart ultrasound: EF59%, left main coronary artery diameter 1.7mm, and the ratio of aortic diameter to aortic diameter 0.12.The inner diameter of the main right coronary artery was 1.9mm, and the ratio of the main right coronary artery to the aorta was 0.13. There were no obvious abnormalities in the cardiac structure, a small amount of tricuspid regurgitation, normal left ventricular systolic function and diastolic function, normal inner diameter of the left and right coronary arteries, and the ratio of the aorta to the aorta. After admission to give "ceftriaxone" static drop anti-infection treatment 3 days, children with high fever is not retreated, gradually cracked oral bleeding, strawberry tongue, conjunctival congestion, rash, hand, foot and hard swollen, membrane molting typical kawasaki disease such as performance, on June 7, 4 days (hospital) switch to "cefoperazone sodium shu ba temple" static drop check resistance to infection and peripheral blood smears: The number of white blood cells was high, the proportion of neutral lobulated nuclei was increased (70%), the proportion of eosinophils was high (6%), lymphocytes (20%), monocytes (4%), the nuclei of some neutrophils were swollen and dissolved, and toxic particles (+) were found in the plasma. Liver function: total bilirubin (TBiL) 42.50 umol/L, total protein (TP)63.27g/L, albumin (ALB) 40.60g/L, globulin (GLB)22.67g/L, alanine aminotransferase (ALT)229.70U/L, aspartate aminotransferase (AST)106.40U/L.On June 07 (the 4th day of admission), the diagnosis was revised: Kawasaki disease. He was given 30 aspirin enteric-coated tablets (Bayer) (base), 0.15g each, orally TID; A total of 12 doses of human immunoglobulin (PH4) 30g each time were intravenously injected for anti-inflammatory support therapy. Thirty-six hours after the end of intravenous infusion of human immunoglobulin, the patient still had fever, the body temperature was over 38℃, and the child was obviously agitated. Kawasaki disease complicated with coronary artery damage score: Liver function: Aspartate aminotransferase (AST)106.40U/L(2 points), C-reactive protein (CRP)189.17mg/L(1 point), platelet count (PLT)287.00x10^9/L(1 point), a total of 4 points. KDSS score: (1) male patients; (2) albumin (ALB)28.00g/L < 35g/L; (3) Hematocrit (HCT) 32.30% < 35%; (4) C-reactive protein (CRP)189.17mg/L, which met 4 out of 7 criteria, was considered as a high-risk population. On June 08 (the 5th day after admission), blood routine +CRP was reexamined: The white blood cell count was 8.54x10^9/L, the percentage of neutrophils was 56.80%, the percentage of lymphocytes was 27.10%, the hemoglobin concentration was 107.00g/L, the platelet count was 333.00x10^9/L, the CRP189.17mg/L, and the high-sensitivity c-reactive protein (hs-crp) > 5mg/L.Blood gas analysis: pH 7.38, partial pressure of oxygen $(pO)_2$)63.70mmHg, potassium ion (K^+3.60 mMO1 /L, actual base surplus (ABE)-3.00mmol/L, standard base surplus (SBE)-3.40mmol/L, oxygenation index $(pO)_2$(a)/$Pi0_2$)303.00, sodium ion (Na^+) 138.00 mmo1 / L. Liver function: albumin (ALB)28.00g/L, alanine aminotransferase (ALT)73.80U/L, AST 23.00U/L, electrolyte: potassium (K^+) 4.06 tendency for L, sodium (Na^+) 134.90 tendency for L, chlorine (CL^-) 106.90 tendency for L, calcium $(Ca)^{2+}$Tendency for 2.21 L.B ultrasound of gastrointestinal tract: intestinal flatulence; B ultrasound of appendix: no obvious abnormality. Abdominal position radiography: intestinal gas with intestinal gas-liquid plane. On June 10 (the 6th day of admission), he was given 12 intravenous immunoglobulin injections of 30g each time and intravenous fluids. The child still had fever, and the temperature was higher than 38℃, so he was given methylprednisolone sodium succinate 40 mg each time and intravenous infusion for anti-inflammatory treatment. The body temperature returned to normal on the same day, and repeated three days later: on June 13 (the 9th day of admission), abdominal ultrasound showed no obvious abnormal mass and effusion in gastrointestinal area. Echocardiography: EF67%, the inner diameter of the left main coronary artery was 1.7mm, and the ratio of the inner diameter to the aortic diameter was about 0.12. The inner diameter of the main right coronary artery was 1.9mm, and the ratio of the main right coronary artery to the aorta was 0.13. There were no obvious abnormalities in the cardiac structure, a small amount of tricuspid valve regurgitation, normal left ventricular systolic function and diastolic function, normal left and right coronary artery inner diameter, and normal ratio to the aorta. Routine blood test +CRP: The white blood cell count was 28.43x10^9/L, the percentage of neutrophils was 62.80%, the percentage of lymphocytes was 27.90%, the hemoglobin concentration was 122.00g/L, the platelet count was 866.00x10^9/L, the CRP was 24.16mg/L, and the high sensitivity c-reactive protein (hs-crp) was > 5mg/L. Procalcitonin (PCT) was 0.20ng/ml. N-terminal urinary natriuretic peptide (BNP)(NT-probNP) 611.21 pg/ml. Blood sedimentation

11.00 mm/h. Liver function: total bilirubin (TBiL)6.10umol/L, albumin (ALB) 33.50g/L, alanine aminotransferase (ALT) 40.90U/L, aspartate aminotransferase (AST) 39.80U/L.D-dimer (D-Dimer)) was 2.45mg/L.Blood coagulation was normal, renal function, electrolytes and glucose were normal. The anti-inflammatory treatment of reduced methylprednisolone sodium succinate 20g each time was given. He was cured of Kawasaki disease and discharged from hospital on June 16, 2022.After discharge, she continued her oral treatment with "prednisone tablets, aspirin tablets and dipyridamole tablets". One week later (June 22), Shenmu Hospital reexamined the echocardiography: EF63%, the inner diameter of the aortic root was 11mm, the inner diameter of the wider part of the main left coronary artery was about 3.2mm, the inner diameter of the opening was about 1.9mm, and the ratio of the inner diameter to the aortic diameter was about 0.29.Right coronary artery opening diameter 1.9 mm, opening is about 1.7 mm, with aortic ratio is about 0.17, roughly normal heart structure, a small amount of reflux, tricuspid valve, left ventricular systolic function and diastolic function is normal, the left coronary artery with local wide diameter, and increased aortic ratio, right coronary artery diameter is normal, and normal aorta ratio of high value. Routine blood test +CRP: The white blood cell count was 15.03x10^9/L, the percentage of neutrophils was 66.80%, the percentage of lymphocytes was 25.00%, the hemoglobin concentration was 116.00g/L, the platelet count was 836.00x10^9/L, the CRP was less than 5mg/L, and the high-sensitivity c-reactive protein (hs-crp) was 0.94mg/L. Blood sedimentation 33.00 mm/h. On August 11, the patient came to Xi 'an Children's Hospital for reexamination. Echocardiography showed EF61%, the inner diameter of the aortic ring was 11.5mm, the inner diameter of the left main coronary artery was dilated, the inner diameter of the right main coronary artery and the left anterior descending artery was normal, and the intima of both coronary arteries were less smooth. LCA/AO ring =2.7/11.5=0.23, LAD/AO ring =1.8/11.5=0.15, RCA/AO ring =1.7/11.5=0.14. The aorta relationship and inner diameter were normal, and the left aortic arch was continuous in the descending part. The inner diameter of the left main coronary artery was dilated, and the intima of both coronary arteries was less smooth. There were no obvious abnormalities in the rest of the heart structure and color blood flow. Left ventricular systolic function was within normal range.12-lead ECG: Sinus bradycardia with asymmetry, undeviated electrical axis, approximately normal ECG. Blood routine +CRP: white blood cell count 6.26x10^9/L, neutrophil percentage 28.1%, lymphocyte percentage 52.8%, hemoglobin concentration 115.00g/L, platelet count 332x10^9/L, CRP<5mg/L, high-sensitivity c-reactive protein (hs-crp)<0.5mg/L. Blood sedimentation 8.00 mm/h. Liver function, coagulation function and high-sensitivity troponin T were normal.

Table 1. Changes of main inflammatory indicators

Time / Project	The 2022-6-5	The 2022-6-8	The 2022-6-10	The 2022-6-22	The 2022-8-11
White blood cells x 10 ^ 9 / L	8.40	8.54	28.43	15.03	6.26
Neutral grain percentage %	71.00	56.80	62.80	66.80	17.6
Hemoglobin g/L	122	107	122	116	115
Platelet x10 ^ 9 / L	287	333	866	836	332
C-reactive protein mg/L	111.61	189.17	24.16	< 5	-
Procalcitonin ng/ml	4.78	-	0.20	-	-
Blood sedimentation mm/h	71	-	11	33	

What is exciting is that the symptoms of autism in children with Kawasaki disease are significantly reduced within two weeks after the onset of Kawasaki disease. Suddenly, children can understand commands, express their needs verbally, and begin to communicate with others.

3. DISCUSSION

At present, autism mainly depends on rehabilitation training and special education, and drug therapy is only an auxiliary symptomatic treatment.

Many domestic and foreign studies have shown the effectiveness of family intervention for ASD. The World Health Organization (WHO) recommends that caregiver parenting skills training for children aged 2-9 years with developmental disabilities and ASD be carried out in developing countries around the world [7-11].

However, the implementation of family intervention needs to be combined with natural situations and daily parenting process. Under the guidance and help of professionals, parents should build confidence in implementing family intervention, strive to learn the principles and strategies of family intervention, and actively carry out training as soon as possible. During this period, they should pay attention to their own physical and mental health, and realize effective family intervention. In order to promote children with ASD to maximize their potential and achieve the best outcome [12].

Research and clinical practice have confirmed that scientific and appropriate intensity of behavioral intervention using the neuroplasticity window in early development can effectively improve mental developmental deviation, promote the development of social skills, and reduce the harmful repetition and stereotypic behavior.

The boy's autism improved significantly two weeks after Kawasaki disease was cured by intravenous human immunoglobulin, which may be related to the following factors.

1. Immune abnormalities play an important role in the pathogenesis of autism, including cytokine imbalance, T cell and B cell abnormalities, natural killer cell function changes, decreased production and function of immunosuppressive factors, and increased production of autoantibodies. The occurrence of autism may be based on genetic predisposition and triggered by environmental factors during the critical period of immune establishment at the age of 1-3 years, which causes immune-mediated inflammation, changes the permeability of gastrointestinal tract and blood-brain barrier, and leads to chronic inflammation in the central nervous system, thereby affecting neurogenesis, migration and synaptic construction [13].

2. Blocking Fc segment antibody by infusion of "human immunoglobulin" can inhibit the immune damage of cerebral cortex and improve brain function, which may be the reason for the improvement of autism performance in this child.

4. CONCLUSION

A case of Kawasaki disease in an infant was cured by immunoglobulin, and the subsequent autism situation was significantly improved, which provides a new direction for the drug treatment of autism, but more clinical data are needed to support it.

CONSENT

As per international standard or university standard, patient (s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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