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Clinical Observation of Tic Disorders and Persistent Replication of Cytomegalovirus Infection

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Abstract: *Objective*: To investigate the causal relationship between tic disorders (TD) and their behavioral problems with persistent replication of cytomegalovirus (CMV) infection (i.e., persistent positivity for CMV-IgM antibodies). *Methods*: 1. A highly specific serological micro-enzyme-linked immunosorbent assay (ELISA) was used for antibody detection, with persistent positivity for CMV-IgM antibodies as an indicator of active CMV infection and replication; 2. Serum CMV-IgM antibody tests were conducted sequentially on 96 patients with TD, their parents, and healthy individuals; 3. Follow-up CMV-IgM antibody tests were performed on children and mothers with a history of abnormal medical conditions during pregnancy and infancy; 4. CMV-IgM antibody tests were conducted on 46 patients at admission, during treatment, and after discharge to observe the relationship between changes in antibody titers and the improvement or disappearance of clinical symptoms; and treatment outcomes were compared among 18 patients with comorbid obsessive-compulsive disorder (OCD) and 16 patients with a positive family history. *Results*: 1. The IgM positivity rate among children was 90.6% (87/96); the IgM positivity rate among healthy children was 17.8% (13/73), with a significant difference between the two groups ($P < 0.01$). The IgM positivity rate among fathers was 72.4% (21/29), while that among healthy males was 11.4% (4/35), showing a significant difference ($P < 0.01$). The IgM positivity rate among mothers was 89.9% (62/69), while that among healthy women was 15.6% (7/45), with a significant difference ($P < 0.01$). There was a significant positive correlation between the IgM positivity rates in the child and parent groups, which differed significantly from the IgM positivity rate in the healthy group. 2. During treatment, as the clinical manifestations of tics and behavioral problems gradually decreased or disappeared, the CMV-IgM antibody titers in patients also decreased synchronously or converted from positive to negative; 3. The cure rates in this group of TD patients, those with comorbid OCD, and those with a positive family history were 58.7% (27/46), 55.6% (10/18), and 53.3% (8/15), respectively, showing a significant positive correlation among the three groups. 4. Patients with a long disease course and complex conditions who adhered to antiviral treatment showed a gradual decrease in antibody titers or conversion from positive to negative, along with significant improvement in clinical symptoms. *Conclusion*: 1. Tic disorders and their behavioral problems are closely associated with active CMV infection and persistent replication; 2. CMV infection in children is closely related to infection in their parents; 3. A positive family history is a manifestation of familial aggregation due to CMV infection; 4. The timing of infection, duration, and differences in the autoimmune

response in children can lead to significant variations in the pathological damage caused by viral replication to patient organs and tissues, as well as in clinical manifestations and outcomes.

Keywords: Tic disorders; Cytomegalovirus; Infection; Replication; Antibodies; Immune response; Mother-to-child transmission

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1. Introduction

At present, the treatment of many patients with tic disorders remains highly challenging, particularly in cases involving self-harm, self-injurious behavior, and compulsive symptoms. The etiology and pathogenesis of tic disorders are still not fully understood. Although family history, twin studies, and genetic research suggest a hereditary component, inconsistencies remain between these findings and clinical observations. For example, some children with tic disorders may experience spontaneous remission without treatment. Likewise, many infectious diseases also demonstrate familial clustering, which may complicate the interpretation of genetic associations. Differences observed following twin infections may, in some cases, produce effects similar to those attributed to genetic factors in twin studies. Since 1995, researchers have investigated the potential relationship between tic disorders, CMV infection, and maternal–fetal transmission through clinical observations and related studies. The findings suggest that some patients with tic disorders show evidence of CMV infection with persistent viral replication (CMV-IgM positivity) and that these infections appear to be closely associated with parental CMV infection [1–4].

2. Materials and methods

2.1. General information

(1) From April 1996 to 2000, 96 patients (81 males and 15 females) diagnosed with tic disorders according to the ICD-10 or CCMD-2-R criteria by experts from multiple tertiary hospitals across 17 provinces and municipalities were sequentially tested for CMV-IgM antibodies; among them, 52 had chronic tic disorders (TD) and 44 had vocal tics (TS); comorbid conditions included mental retardation in 9 cases, schizophrenia in 5 cases, enuresis in 4 cases, and autism in 2 cases; the age at consultation ranged from 5 to 27 years, with an average age of 11.3 years; the shortest disease history was 3 weeks, and the longest was 21 years. (2) Behavioral problems in 56 patients included learning difficulties (LD) in 35 cases, emotional disorders (ED) in 27 cases, attention deficit hyperactivity disorder (ADHD) in 26 cases, obsessive-compulsive disorder (OCD) in 18 cases, sleep disorders (SD) in 8 cases, and self-injurious behavior (SIB) in 3 cases; LD, ED, and ADHD were the most common comorbid conditions, while SIB posed the greatest harm. (3) Treatment outcomes were compared between TD patients with comorbid OCD and those with a positive family history.

2.2. Serum CMV-IgM antibody detection

A highly specific Chai's micro-ELISA method was used for CMV-IgM antibody detection (1). Five milliliters of venous blood were collected, and the serum was naturally separated in a refrigerator and numbered for testing. The reagents included high-titer antigen prepared from human embryonic lung cells (diploid) infected with the CMV standard strain AD 169 and an enzyme conjugate (1:4000). The dilution factor of the tested

serum ranged from 1:500 to 1:8000. Samples were sent to the Biological Research Laboratory of the Chinese Academy of Military Medical Sciences (CAST) in Beijing for testing.

3. Results

3.1. Reporting of CMV-IgM antibody test results and titers in patients with tic disorders

3.1.1. CMV-IgM antibody test results and antibody titers

The titer of a specimen was determined by the highest dilution factor at which a positive reaction occurred in the serum; the results were reported using a ＋ / － notation to indicate the titer range of the corresponding serum specimen. CMV-IgM antibody test results for 96 patients at the outpatient clinic are shown in **Table 1**.

Table 1. CMV-IgM antibody test results and antibody titers

CMV-IgM Antibody Titer	<1:500 (--)	≥1:500 (±)	≥1:1000 (+)	≥1:2000 (++)	≥1:4000 (+++)	≥1:8000 (++++)	Total Positive Rate
Detected/Total	- 9/96	6/96	7/96	8/96	29/96	37/96	87/96
IgM Antibody Positive Rate	- 9.38%	6.25%	7.29%	8.33%	30.20%	38.54%	90.62%

In this group of 96 patients, the positive rate of CMV-IgM antibodies (titer ≥ 1:500) was 90.62%, with 77.08% having IgM antibody titers ≥ 1:2000. This indicates that patients with tic disorders not only have a high positive rate of CMV-IgM antibodies but also exhibit high antibody titers. In this group, 9 patients tested negative for CMV-IgM antibodies (all titers < 1:500). Among them, the IgM antibodies of the parents of 7 children were all positive (all antibody titers ≥ 1:4000), and the IgM antibodies of the parents of 1 child with autism were strongly positive (titer of 1:8000). In contrast, the CMV-IgM antibodies of the other 2 patients and their parents tested negative in both initial and follow-up tests (titer < 1:500), warranting further investigation.

3.1.2. Comparison of CMV-IgM positivity rates between the children and parents group and the healthy control group

CMV-IgM antibody test results for the group of 96 children and their parents versus the healthy control group are shown in **Table 2**.

Group	Children and Parents Group			Healthy Examination Group		
	Patient Group	Father Group	Mother Group	Examined Children	Examined Males	Examined Females
Number of subjects / Mean age (years)	96 / (11.3)	29 / (41.2)	69 / (38.4.)	73 / (10.8)	35 / (39.3)	45 / (37.6)
IgM positive / Number of subjects	87 / 96	21 / 29	62 / 69	13 / 73	4 / 35	7 / 45
IgM positive rate (%)	90.6%	72.4%	89.9%	17.8%	11.4%	15.6%

The positive rate of CMV-IgM antibodies in the child patient group was 90.6%, while the positive rates of IgM antibodies in their parents were 72.4% and 89.9%, respectively. In the healthy control group, the positive rate among children was 17.8%, the positive rate of IgM antibodies among male participants was 11.24%, and the positive rate among female participants was 15.55%. There was a significant positive

correlation between the positive rates of IgM antibodies in children with tic disorders and their parents. This represents a significant difference compared to the healthy control group.

3.1.3. Follow-up testing of CMV-IgM antibodies during maternal pregnancy, infant period, and at onset of tic and behavioral disorders

Follow-up testing for CMV-IgM antibodies in relation to abnormalities during the mother's pregnancy and the child's infancy, as well as tic and behavioral issues, is shown in **Table 3**.

Detection of abnormal CMVIgM antibodies during mother's pregnancy/delivery and patient's infancy						Detection of CMVIgM antibodies at the onset of tic disorders and behavioral problems						
Group	**Mother**	**Pregnancy & Delivery**	**Neonatal Jaundice**	**Enuresis**	**Frequent Fever**	**Tic Disorder**	**ADHD**	**LD**	**ED**	**OCD**	**SIB**	**SD**
Examined/ Required	34/46	21/56	6/56	3/46	24/56	46/56	26/56	35/56	27/56	14/56	3/56	8/56
Positive/ Examined	29/34	21/21	6/6	3/3	23/24	44/46	25/26	34/35	27/27	14/14	3/3	7/8
IgM Positive Rate (%)	85.3%	100%	100%	100%	95.8%	95.7%	96.1%	97.1%	100%	100%	100%	87.5%

The follow-up test results for symptoms and signs such as miscarriage during pregnancy, tocolysis, and neonatal jaundice, as well as CMV-IgM antibodies, suggest intrauterine CMV infection in the affected children [3–5]. Clinical symptoms commonly observed in these children, such as neonatal pneumonia, frequent fevers, and enuresis, are associated with persistent active CMV infection (i.e., continuous replication of CMV infection) [3–5]. The positive rates of CMV-IgM antibodies in various groups with tic disorders and behavioral issues, as shown in the table, all indicate a close association between the onset of these conditions and CMV infection.

3.2. Differences between anti-CMV viral infection treatment and antipsychotic medication for symptomatic treatment of tic disorders (TD) and behavioral issues

3.2.1. CMV-IgM positivity and antiviral treatment outcomes in patients with tic disorders, comorbid obsessive-compulsive disorder (OCD), and positive family history

CMV-IgM antibody testing and antiviral treatment for patients with tic disorders and comorbid obsessive-compulsive disorder (OCD), as well as those with a positive family history, are shown in **Table 4**.

Table 4. CMV-IgM positivity and antiviral treatment outcomes in patients with tic disorders, comorbid obsessive-compulsive disorder (OCD), and positive family history

Group		Tic Disorder			Obsessive-Compulsive Disorder				Positive Family History			
Indicator	**Lgm positive**	**Cured**	**Markedly effective**	**Effective**	**Lgm positive**	**Cured**	**Markedly effective**	**Effective**	**Lgm positive**	**Cured**	**Markedly effective**	**Effective**
Number	44/46	27/46	9/46	8/46	16/16	10/18	3/18	3/18	15/16	8/15	3/15	4/15
Result	95.7%	58.7%	19.6%	17.4%	100%	55.6%	16.7%	16.7%	93.8%	53.3%	20%	26.7%

In this group of patients with tic disorders (TD), the IgM positive rate was 95.7%, and the cure rate was 58.7%. Among them, patients with obsessive-compulsive disorder (OCD) and those with a positive family history had IgM positive rates of 100% and 93.8%, respectively, with cure rates of 55.6% and 53.3%. There was a significant positive correlation between their IgM positive rates and cure rates, suggesting that the onset of these conditions is related to CMV infection.

3.2.2 Comparison of psychotropic drug (dopamine/serotonin-based) versus nucleoside antiviral (ganciclovir-based) treatment for TD, OCD, and related conditions

Differences between the treatment of TD and OCD with psychotropic drugs such as dopamine and 5-hydroxytryptamine and antiviral nucleoside drugs are shown in **Table 5**.

Item	Purpose, method, and effects of antipsychotic drugs such as dopamine and serotonin	Purpose, method, and effects of ganciclovir-based nucleoside antiviral drugs
Names of treated conditions	TD, TS, enuresis, OCD, SIB, LD, ED, SD, ADHD	TD, TS, enuresis, OCD, SIB, LD, ED, SD, ADHD
Purpose and method of treatment	Antipsychotic drugs such as dopamine and serotonin: regulate neurotransmitter imbalance, control or alleviate clinical symptoms; select different drugs and dosages based on patient condition.	Nucleoside antiviral drugs: inhibit viral replication, block immunopathological damage to target tissues, eliminate or reduce neurotransmitter metabolic disorders, allowing patient symptoms to naturally resolve; dosage calculated by body weight.
Conditions with rapid response	No clear pattern; treatment is difficult for complex cases such as SIB and OCD, with significant side effects.	SIB and OCD often respond within 1–2 weeks of treatment, with potential for clinical cure, and no side effects associated with antipsychotics.
Duration of treatment required	Controlling and alleviating symptoms involves regulating neurotransmitter imbalance, with no defined time limit; patients may be treated for months or years without certainty, and some cases are difficult to cure.	Anti-CMV treatment generally takes 3–6 months; longer treatment and recovery time is needed for complex cases. Antiviral treatment duration is determined by the decline of CMV-IgM antibody titer to approximately 1:500.
CMV-IgM testing	Antipsychotic treatment with dopamine, serotonin, etc., does not require CMV-IgM antibody testing.	Anti-CMV antiviral treatment requires the biological indicator of positive CMV-IgM antibodies.
Efficacy evaluation criteria	The primary criterion is the degree of improvement in clinical symptoms, with no biological indicator requirement.	The criteria for cure or recurrence are based on both the degree of symptom improvement and the biological indicator of IgM antibody titer levels.

Antipsychotic drugs such as dopamine and serotonin have been used for many years to treat TD (Tic Disorder). However, treating complex conditions and behavioral issues can be challenging, with numerous side effects from the medications. Anti-infective therapy aims to suppress the body's immune response to persistent CMV (Cytomegalovirus) infection replication, thereby preventing immunopathological damage to target tissues and organs and addressing neurotransmitter metabolic disorders. Its characteristics include significant improvement in antiviral therapy for TD and comorbid conditions like behavioral issues (e.g., SIB - Self-Injurious Behavior) within 1–2 weeks, with the potential for cure. Children who were forced to leave school due to vocal or behavioral issues affecting others or themselves can return to campus. During treatment, common side effects of antipsychotic drugs are absent, allowing most patients to complete treatment successfully.

3.2.3. Evaluation criteria for the efficacy of antiviral therapy in tic disorder and behavioral issues

The primary evaluation criteria are based on the degree of improvement in tic symptoms and behavioral issues after antiviral therapy, treatment duration requirements, the decline in CMV-IgM antibody titers, and whether the condition relapses after discontinuation. Cure: (1) Complete disappearance of tic symptoms, self-injurious behavior, and obsessive-compulsive behavior; (2) CMV-IgM antibody titers decline to around 1:500, with a treatment duration of 3–6 months or more; (3) No relapse after 6 months of discontinuing antiviral therapy, allowing return to school or normal life. The cure rate in this group was 58.69% (27/46). Significant improvement: The patient's tic symptoms, obsessive-compulsive behavior, learning disabilities, and other behavioral issues improve by 70%, with a treatment duration of about 3 months and antibody titers declining to ≤1:1000 (+). This standard was met by 19.56% (9/46). Effective: Significant clinical improvement after more than 3 weeks of antiviral therapy, but withdrawal for some reason. This group accounted for 17.39% (8/46). Ineffective: Withdrawal from treatment for some reason (1 case due to significant pathological changes found in head imaging, another case withdrew for other reasons). This group accounted for 4.34% (2/46).

3.2.4. Insights from antiviral therapy

(1) Immediate effects after 1-2 weeks of treatment are often observed in the last-appearing clinical symptoms, such as self-injurious behavior, obsessive-compulsive behavior, enuresis, and sleep disorders. The efficacy of the first-appearing tics, hyperactivity, and learning difficulties manifests later, fully reflecting the pathological characteristics and repair patterns of infection and immune damage. (2) Patients with complex conditions and longer disease durations need confidence and determination to persist with treatment and rehabilitation to achieve significant progress. (3) Provides new treatment methods and hope for a cure for patients with refractory comorbid conditions. (4) Follow-up after more than 20 years: No cases of impaired fertility due to antiviral therapy have been found, making such concerns unwarranted.

4. Discussion

With the increasing prevalence of chronic and vocal TD, especially comorbid conditions like SIB, Obsessive-Compulsive Disorder (OCD), Learning Disability (LD), Sleep Disorder (SD), and Attention Deficit Hyperactivity Disorder (ADHD), they have become severe chronic diseases harming children's physical and mental health. The etiology of TD remains unclear, with research primarily focusing on biological factors such as genetics, immunity, and neurobiochemistry.

CMV is one of the most common congenital infectious pathogens in humans, infecting fetuses and children through vertical and horizontal transmission during intrauterine, perinatal, and growth periods, causing various infectious syndromes [1, 3–4]. Wu Shengling used PCR to examine organ tissue samples from congenitally malformed fetuses and found the highest positivity rates for CMV-DNA in the thymus, brain, and liver, with a brain positivity rate of 53.9%. Liu Lanqing et al. used virus isolation, serum antibody determination, and molecular biology methods to find a 51.4% (36/70) positivity rate for CMV infection-induced nervous system damage in children, indicating CMV infection as a significant pathogen causing severe central nervous system damage in infants and children. Yow et al. found a 59% positivity rate for urinary CMV isolation in children within 5 years of birth [6]. Hou Zhifu et al. detected urinary CMV-DNA in

160 children, with a positivity rate of 18.8%, the highest in children aged 1-5 years [7]. The high incidence age of CMV infection in children is similar to the age characteristics of TD onset.

Based on the theory of viral maternal-fetal transmission, combined with family aggregation phenomena and twin studies related to genetic factors, the authors believe that family aggregation phenomena and twin effects can also occur in the occurrence and development of infectious diseases. Therefore, the authors initiated clinical research and observation on the relationship between CMV infection and TD onset in 1996 [8].

To clarify the causal role and exact criteria of infectious agents in diseases, infectious agents can be isolated from patients, and antibodies against these pathogens, especially recent IgM antibodies, can be monitored to determine the role of single infectious agents in the development of autoimmune diseases [2]. IgM antibodies are specific antibodies produced by the infected body during the active or latent phases of viral infection [2, 9]. Accordingly, this article selects CMV-IgM antibody positivity as an observational indicator for clinical research.

In this group of 96 TD patients, the CMV-IgM antibody positivity rate was 90.6% (87/96), with parent antibody positivity rates of 72.4% and 89.9%, respectively, significantly different from the healthy control group. The results also showed a significant positive correlation between CMV infection in children and their parents [1, 3, 4–5].

Among the 46 patients treated for anti-CMV infection, the IgM antibody positivity rate was 97.7%, with a cure rate of 58.7%. The cure rates for patients with comorbid OCD and positive family history were 55.6% and 53.3%, respectively, showing a significant positive correlation between infection rates and cure rates, all closely associated with CMV infection. Treatment revealed that behavioral issues like SIB, SD, and OCD, appearing later in the disease course, showed the earliest treatment effects. For example, two children with chronic TD who developed severe self-injurious behaviors like eye-gouging and tongue-biting stopped these behaviors after one week of antiviral therapy, with immediate improvement in anxiety and depression. Antiviral therapy not only brings hope for a cure to patients with complex and refractory TD and behavioral issues but also lacks the side effects of antipsychotic drugs. Based on the medical history of some children during maternal pregnancy and growth and the curable results of patients with positive family history, it suggests the etiological role of CMV maternal-fetal transmission in the disease's occurrence and development, providing new insights for etiological research on related neuropsychiatric diseases in children.

During treatment, to clarify the relationship between CMV infection and TD and comorbid conditions, excluding interference from other factors, early treatment only used nucleoside antiviral drugs for observation. For patients unable to stop taking large amounts of antipsychotic drugs, during antiviral therapy, antipsychotic medications should not be arbitrarily increased, decreased, adjusted, or suddenly stopped to avoid interfering with the treatment process and clinical observation. After symptoms are basically controlled, the dosage of psychiatric drugs should be gradually reduced under the guidance of a professional physician, and rehabilitation treatment time should be extended. Antiviral therapy has strict treatment duration requirements, not only requiring symptom reduction and disappearance but also needing CMV-IgM antibody titers to meet standards (generally 3–6 months). Treatment for patients with complex conditions may take about a year. Treatment is difficult for patients with clear pathological changes in brain tissue. During more than 20 years of follow-up, no cases of impaired fertility in male or female patients due to antiviral therapy have been found, making premature withdrawal from treatment unnecessary.

5. Conclusion

This clinical observation suggests that TD and its comorbid behavioral issues are primarily chronic infectious autoimmune diseases that gradually develop through CMV maternal-fetal transmission. It is likely the result of CMV infection and persistent replication, where blood antibodies penetrate the damaged blood-brain barrier and bind to similar antigens in neural tissue, affecting neurotransmitter metabolism.

Disclosure statement

The authors declare no conflict of interest.

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