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Middle East Research Journal of Medical Sciences
ISSN: 2789-7699 (Print) & ISSN: 2958-2024 (Online)
Frequency: Bi-Monthly
DOI: https://doi.org/10.36348/merjms.2025.v05i02.007

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Study of Reduced Severity of Health Conditions in Autistic Affected by Herpes Viruses 1, 2, and 6

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Abstract: Despite the same name, the Herpes Simplex Virus (HSV) has two types of viruses that spread in different ways, type 1 herpes simplex virus/HSV-1 and type 2 herpes simplex virus/HSV-2, with around 417 million people having the virus present in their blood. Herpes simplex is the most common viral disease in modern man, excluding respiratory infections. In immunocompromised patients, herpes infections can cause several complications. Herpes simplex is also classified as a sexually transmitted disease, affecting only men and without seasonal variations. Overall, primary HSV-6 infection is among the most prevalent causes of acute febrile illness in young children. It is also a significant cause of emergency room visits and hospitalizations. The manuscript aims to verify the reduction in the severity of health conditions in autistic individuals affected by herpes viruses 1, 2, and 6. The methodology used an integrative literature review and a synthesis process to develop the study to expand the understanding of knowledge and achieve the expected results.

Keywords: Epstein-Barr, Genital, IgE, Immuno-compromised, Patients, Ruseola.

Research Paper

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How to cite this paper:
Marco Vinícios de Oliveira Santana *et al* (2025). Study of Reduced Severity of Health Conditions in Autistic Affected by Herpes Viruses 1, 2, and 6. *Middle East Res J. Med. Sci*, *5*(2): 178-198.

Article History:
| Submit: 18.03.2025 |
| Accepted: 17.04.2025 |
| Published: 24.04.2025 |

1.0. INTRODUCTION

According to data released by the World Health Organization (WHO), together with the Brazilian Society of Dermatology, more than 90% of the adult Brazilian population already has the herpes virus in their bodies. However, only 10-15% exhibit symptoms. Despite sharing the same name, Herpes Simplex Virus (HSV) comprises two distinct types of viruses that spread in different ways. Herpes simplex is modern man's most common viral disease, excluding respiratory infections (Silverman *et al.*, 2004; Neville *et al.*, 2004; Consolaro and Consolaro, 2009).

In immune-compromised patients, herpes infections can cause several complications. Herpes simplex is also classified as a sexually transmitted disease, affecting only men and without seasonal variations. Overall, primary HHV-6 infection is among the most prevalent causes of acute febrile illness in young children. It is also a significant cause of emergency room visits, hospitalizations, and febrile seizures (Trindade *et al.*, 2007; Santos *et al.*, 2012; De Clercq, 2013).

Despite being part of the same family, the 8 types of human herpes virus can act in different ways in the body. Above all, contact with these viruses can occur to anyone before the age of 5. “For this reason, seroprevalence is high. Primary infections depend on each type of virus in the family and can range from subclinical infections to serious infections, such as encephalitis, meningitis, and lymphomas” [Dra Meri Bordignon Nogueira, professor of virology at UFPR and pharmacist-biochemist at the virology laboratory of the Hospital de Clínicas da UFPR]. After infection, the virus can remain latent in the body, that is, without presenting any type of manifestation. However, it can cause serious problems in patients with a weakened immune system [Dra Meri Bordignon Nogueira] (Freitas, 2018; Kaye, 2023; Wald *et al.*, 2025). “Viruses of the Herperviridae family have the property of remaining latent after causing the primary infection and can be reactivated in immunosuppressed or immunocompromised patients, upon exposure to UV light, stress, and hormonal changes. For this reason, they are called opportunistic viruses” [Dra Meri Bordignon Nogueira] (Silverman *et al.*, 2002; Neville *et al.*, 2004; Santos *et al.*, 2012).

A. Herpes Simplex Virus Type 1 (HSV-1)

HSV-1 is one of the most common types of herpes in men and women worldwide. Studies state, for example, that 90% of the Spanish population expresses antibodies against this virus, and around 40% suffer recurrent infections. It is the agent responsible for the

clinical manifestations of labial herpes, small vesicles in groups, burning, and itching in the area.

B. Herpes simplex virus type 2 (HSV-2)

Herpes simplex virus type 2 is a large DNA virus with characteristics very similar to HSV-1. It is the main cause of genital herpes and is, therefore, the most common sexually transmitted disease in developed countries. It is usually acquired.

C. Varicella-zoster virus (VZV)

The varicella-zoster virus is one of the types of herpes with an affinity for cells in the skin and nervous system. Epstein-Barr virus (EBV) type 3.

D. Epstein-Barr

The Epstein-Barr virus is also called human herpes virus type 4. It is responsible for infectious mononucleosis or kissing disease, which manifests fever, pharyngitis, and enlarged lymph nodes.

E. Cytomegalovirus (CMV)

Cytomegalovirus is one of the most common types of herpes virus in people of all ages. It is also known as human herpes virus type 5 and is responsible for several infections, the severity of which depends on the immune status.

F. Human herpes virus type 6 (HHV-6)

HHV-6 is one of the types of herpes with an affinity for T lymphocytes. This virus is usually acquired during childhood and is widely distributed throughout the world. Some studies claim that the most frequent manifestations occur in children under 2 years of age, of whom 90% develop a sudden rash or roseola.

G. Human herpes virus type 7 (HHV-7)

Human herpes virus type 7 is a very common agent. It has a similar structure to HHV-6 and is usually transmitted through saliva. The submaxillary gland, parotid gland, and minor salivary glands are its main sites of replication.

H. Kaposi sarcoma-associated herpes virus (KSHV)

It is also called human herpes virus type 8 (HHV-8). It is currently believed that this virus is responsible for the development of Kaposi sarcoma (KS). It is a tumor pathology that generally occurs in immunocompromised people, whose proliferation occurs in the blood and lymphatic vessels (Silverman *et al.*, 2002; Neville *et al.*, 2004; Santos *et al.*, 2012).

1.1. OBJECTIVE

The manuscript aims to verify the reduction in the severity of health conditions in autistic individuals affected by herpes viruses 1, 2, and 6.

2.0. METHODS

The methodology used an integrative literature review and a synthesis process to develop the study to expand the understanding of knowledge and achieve the expected results. Regarding the inclusion criteria, national and international articles were used in full, in Portuguese, English, and Spanish. The exclusion criteria were articles that were presented as duplicates and did not meet the objectives of the investigation. In this way, the reviewer/researcher can prepare an integrative review with different purposes. This can be directed towards defining concepts, reviewing theories, or methodological analysis of included studies of a particular topic. In its construction process, it is necessary to go through six distinct stages, which are: identification of the theme and selection of the hypothesis or research question; establishment of criteria for inclusion and exclusion of studies or literature search; definition information to be extracted from selected categorization of studies; evaluation of included studies; interpretation of results; and presentation of knowledge review/synthesis.

3.0. SELECTED STUDIES

3.1. Herpes types 1 and 2

Type 1 (HSV-1), which occurs in the region of the lips and face with the appearance of blisters and vesicles, is usually transmitted through kissing or sharing cutlery and drinks, through saliva; type 2 (HSV-2), on the other hand, appears in the genital region and is transmitted through sexual contact with an infected person. Stress and low immunity are the main factors that can influence the manifestation and reappearance of the virus in infected patients. HSV consists of a DNA molecule, surrounded by an icosahedral capsid, a fibrillar tegument structure, and an envelope consisting of a lipid bilayer of cellular origin and viral glycoproteins. Because they are acellular, human herpes viruses need cells to reproduce, and transmission is through direct or indirect contact with contaminated fluids (Figure 1) (Trindade *et al.*, 2007; Nicoll *et al.*, 2012; Vadlapudi *et al.*, 2013).

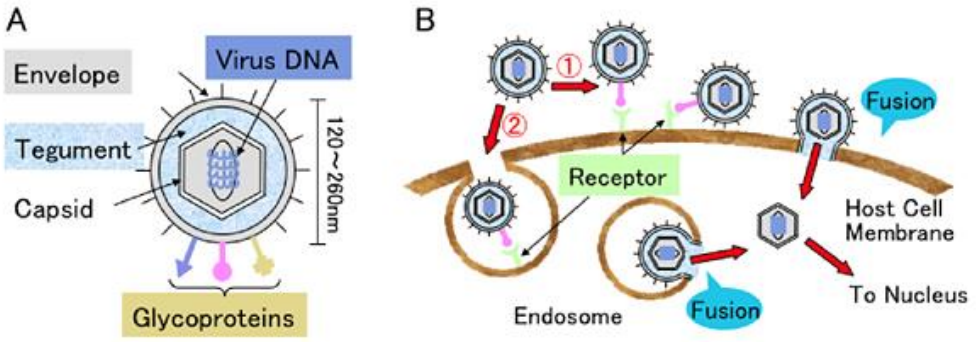


Figure 1: (A) Scheme of the human herpes virus. (B) Enveloped viruses have two routes. ① Direct fusion of virus envelope with host cell membrane. ② Fusion of virus envelope with endosomal membrane after endocytosis to enter host cells. Fusion caused by the association of glycoprotein on the envelope with the receptor on the cellular membrane is indispensable for virus entry, whichever route the virus takes
Source: https://x.com/NEJM/status/1657445659744813056?mx=2

After penetrating the cell, the virions can cause a primary infection, causing the occurrence of symptoms in varying degrees and types, which depends on the type of virus and the host's immune response, or they can enter a dormant state and establish themselves in the cytosol as an episome extrachromosomal DNA molecule, a phase known as latency, not being detected and being able to remain there for long periods, varying according to each subtype (Trindade *et al.*, 2007; Nicoll *et al.*, 2012; Vadlapudi *et al.*, 2013).

HSV belongs to the Herpesviridiae family and the Alphaherpesviridae subfamily and is characterized by its propensity to infiltrate the central nervous system, by its latent incubation period, and by its reactivation in immunosuppressed individuals. Only humans are natural reservoirs. The pathogen is transmitted by person-to-person contact, and infection occurs by inoculation of the virus into susceptible mucosal surfaces such as the oropharynx, cervix, and conjunctiva or through small lesions on the skin. The virus is inactivated immediately at room temperature, and therefore, transmission by aerosol and fomites is rare (Figure 2) (Miranda-Saksena *et al.*, 2018; Senne Licor Diagnóstico, 2023; Fleury, 2025).

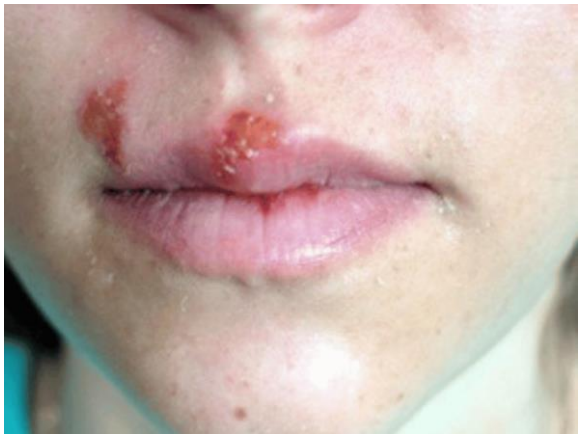


Figure 2: Sores from a primary HSV-1 infection usually heal completely. They rarely leave a scar. However, it is important to remember that the HSV-1 virus infection remains in the body. It moves to centrally localized nerve cells, where it remains in a resting state
Source: https://www.derminstitutemd.com/services/medical/herpes-simplex/

After the initial infection, all herpes viruses remain latent within specific host cells and can subsequently reactivate. The clinical syndromes resulting from primary infection can vary significantly from those caused by the reactivation of these viruses. Herpes viruses do not survive long outside a host; therefore, transmission usually requires close contact. In individuals with latent infection, the virus can reactivate without causing symptoms; in these cases, asymptomatic shedding occurs, and individuals can transmit the disease. Although herpes viruses are genetically and structurally similar, they cause a wide variety of clinical syndromes that are generally nonoverlapping (Figure 3) (Consolaro and Consolaro, 2009; Shang *et al.*, 2007; Wald *et al.*, 2025).

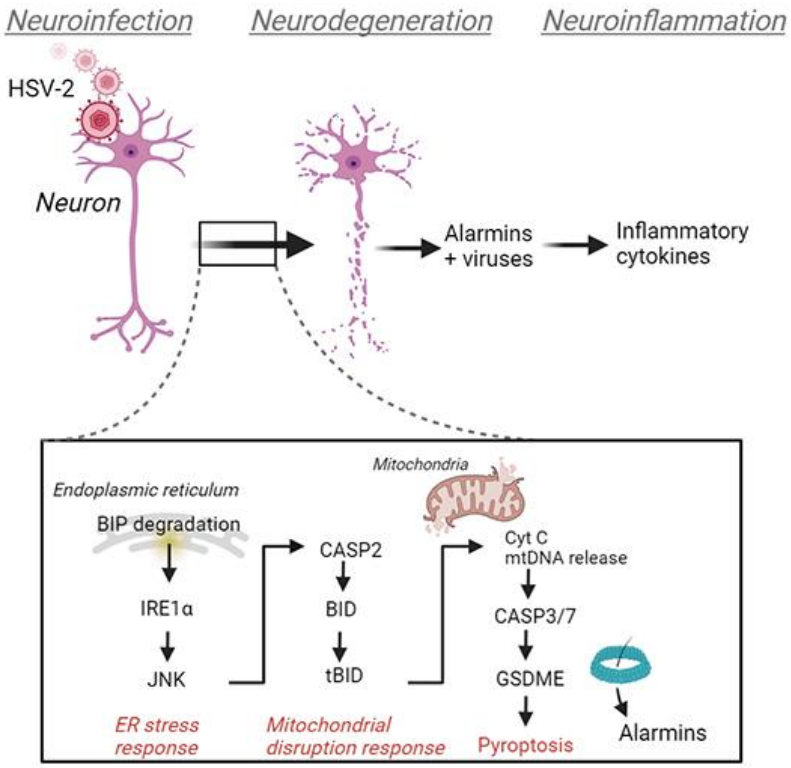


Figure 3: Neurons can be infected by a panel of viruses, but how this induces cell death remains unknown. Here, neuronal cells lytically infected with herpes simplex virus type 2 (HSV-2) are found to undergo cell death through a mechanism triggered by ER stress and executed by gasdermin E

Sources: https://www.glycoforum.gr.jp/article/15A3.html and 10.3Q389/fmicb.2024.1415417

HSV-2 infections are more frequent in the perinatal period and at the beginning of active sexual life. Advanced age after the onset of sexual life and the number of partners are factors associated with the seroprevalence of HSV-2 antibodies. Clinical manifestations depend on age, the host's immune system, the anatomical site involved, and the type of virus, and can range from stomatitis to encephalitis and neonatal herpes, the latter being fatal in 70% of cases (Figure 4) (Ducoulombier *et al.*, 1998; Consolaro and Consolaro, 2009; De Clercq, 2013; Wald *et al.*, 2024).

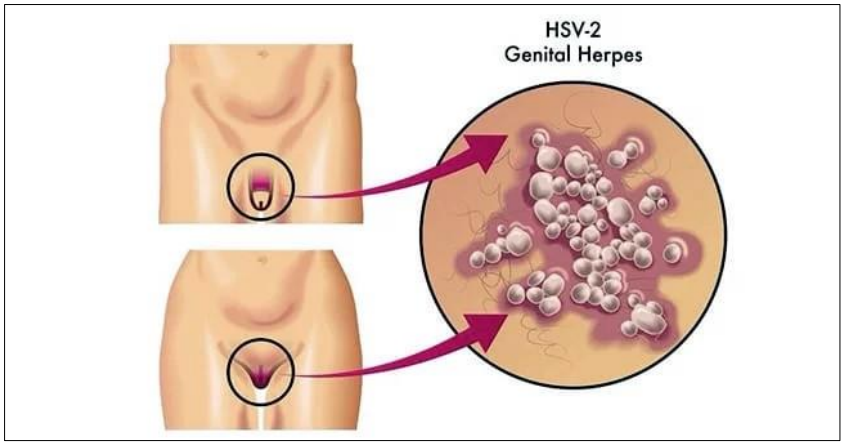


Figure 4: HSV type 2 will affect the genital area, causing genital herpes. Generally, the virus may affect the genitalia, anal region, mucosal surfaces, and other skin surfaces

Source: https://premier-clinic.com/skin-and-body-problems/herpes-simplex-virus-infection-causes-symptoms-treatments/

Diseases caused by herpes simplex virus -HSV-1 or HSV-2: (**1).** Diseases include Mucocutaneous infection, including genital herpes. (**2).** Eye infection (including herpes keratitis). (**3).** Infection of the central nervous system (CNS). (**4**). Neonatal herpes. HSV rashes may be followed by erythema multiforme, possibly due

to an immune reaction to the virus. Eczema herpeticum is a complication of HSV infection in which patients present severe herpes disease in areas of the skin with eczema (Amir *et al.,* 1997; Ducoulombier *et al.,* 1998; Cernik, 2008).

Lesions can appear anywhere on the skin or mucosa but are most common in the following locations: Mouth or lip perioral infection and genitals. Conjunctival and corneal tingling, discomfort, or itching, and clusters of small, tense vesicles appear on an erythematous base. Injuries to the nose, ears, eyes, fingers, or genitals can be particularly painful. The blisters often persist for a few days and then dry out, forming a thin, yellowish crust (De Clercq, 2013; Wald *et al.,* 2024).

Acute herpetic gingivostomatitis is usually the result of primary infection with HSV-1, typically in children. Herpes pharyngitis can occur in both adults and children. Through oral-genital contact, the cause may be HSV-1 or HSV-2. Oral and gingival vesicles rupture, usually within several hours to 1 or 2 days, forming ulcers. Fever and pain often occur. Difficulty eating and drinking may cause dehydration. After resolution, the virus resides in an inactive form in the semilunar ganglion. Cold sores are usually a recurrence of HSV (Figure 5) (Spruance *et al.,* 1990; Jensen *et al.,* 2004; Gilbert, 2007; Cernik *et al.,* 2008; De Clercq, 2013).

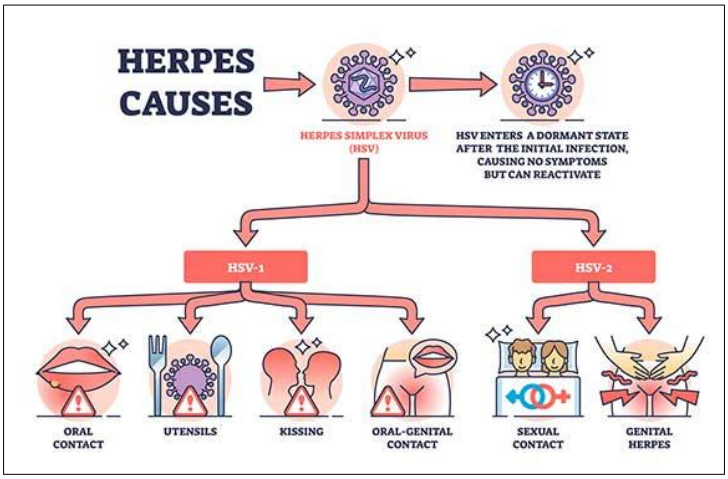


Figure 5: Herpes 1 and 2 belong to the herpes virus family, and they are very similar. HSV-1 and HSV-2 differ in several ways. However, the differences are not clinically significant enough to warrant different treatments or result in a different prognosis

Source: Slava Fuzayloff/Published on May 31, 2024

It develops as ulcers on the edge of the lips, cold sores, or, less frequently, as ulcerations of the mucosa of the hard palate oral herpes. Herpes simplex I/II, IgG and IgM antibodies, serum. HSV I and II, IgG (Figure 6) (Cernik, 2008; De Clercq, 2013).

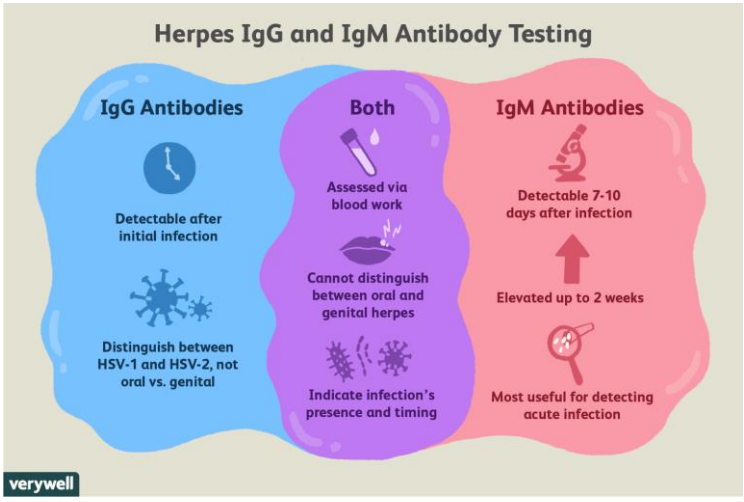


Figure 6: Herpes simplex 1+2 virus (HSV), antibodies panel, IgG & IgM, serum

Source: https://k-lab.com.np/product/herpes-simplex-12-virus-hsv-antibodies-panel-igg-igm-serum/

It is not just a Sexually Transmitted Infection (STI). There are other ways of transmitting the virus, usually through direct contact with the consultation. A person can be a carrier of the virus without ever having developed lesions. Although transmission is more important during direct contact with lesions, unprotected sexual intercourse with carriers, even without lesions, can also cause infections (Spruance *et al.*, 2006; Gilbert, 2007; Cernik *et al.*, 2008).

Direct contact through kissing only if there are visible lesions; the saliva is not an infectious material. However, oral herpes lesions may occur that have already dried but have not yet healed completely and still have active viruses on their surface or even atypical herpes lesions on the mucosa that can be mistaken for canker sores. Indirect contact through sharing objects of common use. Active oral lesions rich in viruses can be transmitted indirectly to susceptible people if there is sharing of kitchen utensils such as cutlery and glasses for washing, drinking from the same bottle, or using the same object (Jensen *et al.*, 2004; Spruance *et al.*, 2006; Gilbert, 2007; Cernik *et al.*, 2008).

Vertical transmission from mother to child during pregnancy. There is no need for visible lesions, but it usually only occurs when the pregnant woman has the first infection during pregnancy. Learn more about herpes gestations and neonatal herpes here. Perinatal transmission occurs from mother to child when the baby passes through the birth canal during normal birth, and the mother has active lesions at this time (Figure 7) (Jensen *et al.*, 2004; Gilbert, 2007; Cernik, 2008; Yin *et al.*, 2024).

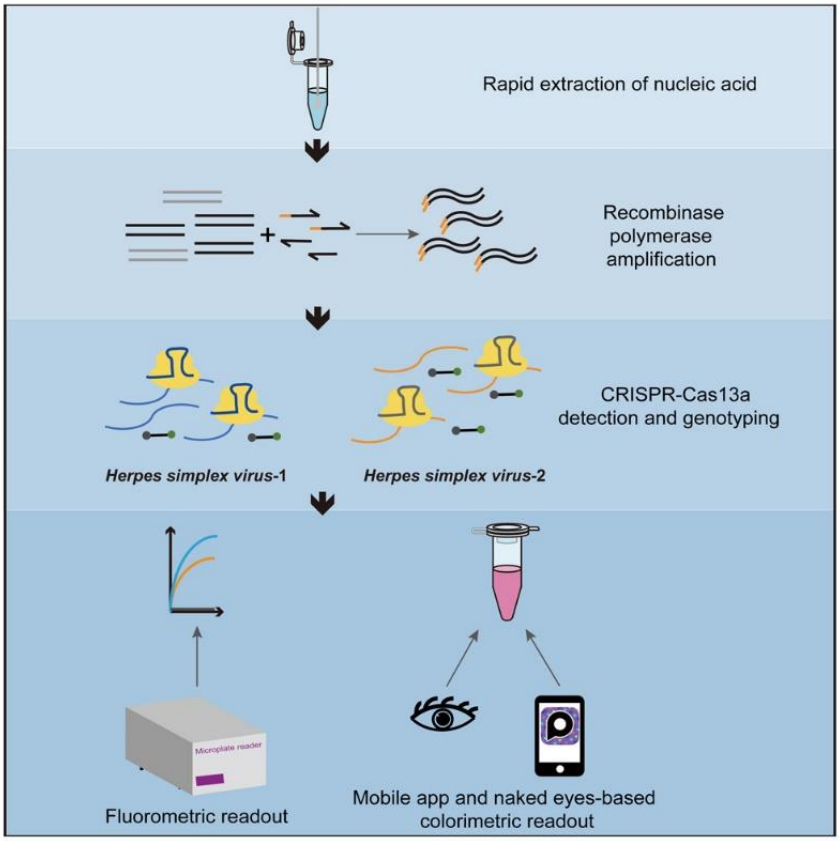


Figure 7: Prompt diagnosis is essential for managing herpes simplex virus types 1 and 2. Existing diagnostic CRISPR-Cas13a-based assay for the detection and genotyping of HSV. Our assay demonstrated a high sensitivity of 96.15% and 95.15% for HSV-1 and HSV-2

Sources: iScience, 2024, 27(1), 108581 and https://www.sciencedirect.com/journal/iscience/vol/27/issue/1

The test is useful for the diagnosis of herpes infection, which can be caused by both HSV-1 and HSV-2, including the specific search for antibodies of the IgG class directed against HSV-1 and HSV-2. The presence of IgG antibodies does not allow a distinction to be made between a current and a previous infection, except when an increase in titters is detected between two successive measurements (Spruance *et al.*, 1990; Spruance *et al.*, 1997).

The test also investigates IgM antibodies against HSV, which are associated with recent infection, but cannot distinguish between virus types 1 or 2, due to the extensive cross-reactivity between them. The final diagnosis of a probable HSV-1 or HSV-2 infection depends on the oscillation of IgG class antibody titers directed against each of the two agents separately (Spruance *et al.*, 2003; Jensen *et al.*, 2004; Spruance *et al.*, 2006; Gilbert, 2007).

Current antiviral treatments do not eradicate HSV infection, and treating a first oral or genital infection does not prevent chronic nerve infection. However, during relapses, antiviral medications such as acyclovir, valacyclovir, or famciclovir can relieve discomfort and help resolve symptoms a day or two earlier. Treatment is most effective when starting early, within a few hours of symptoms appearing, preferably at the first sign of tingling or discomfort, before blisters appear (Marcocci *et al.,* 2001; Voineagu *et al.,* 2011).

For people who have frequent painful flare-ups, the number of flare-ups can be reduced by taking antiviral medications every day for an indefinite period, which is called suppressive therapy. However, taking antiviral medications does not necessarily prevent infected people from spreading the infection. Most antiviral medications are available only by prescription (Sacks *et al.,* 2001; Spruance *et al.,* 2002).

A penciclovir ointment, applied every two hours during waking hours, can shorten the time and duration of cold sore symptoms by about a day. Over-the-counter ointments containing docosanol applied 5 times a day may cause some problems. Acyclovir, valacyclovir, or famciclovir taken by mouth for up to a few days may be the most effective treatment for recurrent cold sores. Antiviral agents for HSV infection include acyclovir, valacyclovir, and famciclovir (Sacks *et al.,* 2001; Ozonoff *et al.,* 2005).

Metabolites of these nucleoside derivatives interfere with viral DNA synthesis by inhibiting viral DNA polymerases. Of all human herpes viruses, acyclovir has the greatest in vitro activity against HSV-1 and HSV-2. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, have greater oral bioavailability than acyclovir and are administered less frequently (Sacks *et al.,* 2001; Ozonoff *et al.,* 2005; Santos, 2010; XGEN Mobius, 2024).

Oral anti-HSV agents are generally very well tolerated; however, gastrointestinal side effects or headaches may occasionally occur. The margin of safety and tolerability of these oral antiviral drugs is excellent since these drugs are selectively converted to active compounds only within virus-infected cells. With all of these agents, dosage adjustment is necessary for moderate to severe renal impairment since the clearance of acyclovir and its analogs is dependent on renal function (Figure 8) (Santos, 2010; Senne Licor Diagnóstico, 2024).

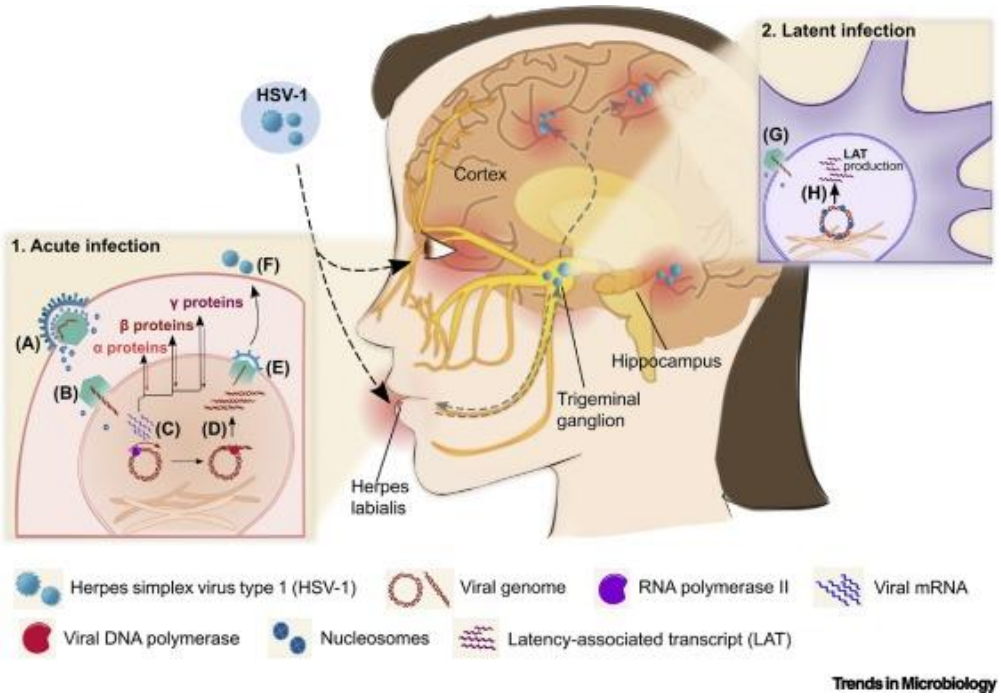


Figure 8: Schematic representation of acute and latent herpes simplex virus-1 (HSV-1) infection in humans the outermost layer of hsv is the lipid bilayer envelope, which contains at least 12 viral membrane proteins (gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, gM, and gN)

Source: https://www.creative-diagnostics.com/blog/index.php/what-is-herpes-simplex-virus/

Oral infection - Primary infection**:** The classic clinical manifestation of primary oral HSV-1 infection, i.e., initial HSV infection in a seronegative host, is gingivostomatitis, which may be associated with pharyngitis. Although gingivostomatitis and pharyngitis are self-limiting diseases, severe infection can cause significant oral pain and dehydration. Symptomatic primary HSV infections are associated with an increased risk of constitutional symptoms, a longer duration of lesions, and prolonged viral shedding compared with

recurrent disease (Freitas, 2023; Ozonoff *et al.*,2005; Santos, 2010).

Antiviral therapy: This is recommended for patients with evidence of primary gingivostomatitis who presented within 72 hours of symptom onset. Early antiviral therapy results in faster healing of lesions, decreased pain, and shorter duration of fever. However, antiviral therapy should still be offered if the patient presents with new lesions and/or significant pain after this time (Senne Licor Diagnóstico, 2024; XGEN Mobius, 2024).

Dosage of antiviral therapy**:** Oral treatment options for adolescents and adults with primary infection include Acyclovir: 400 mg orally three times daily or 200 mg five times daily. Famciclovir: 250 mg three times daily or 500 mg twice daily. Valacyclovir: 1g twice daily. Most of the data evaluating treatment efficacy was with acyclovir, as described above. However, for patients who can tolerate oral medications, it may be preferable to use an agent such as valacyclovir, which has greater bioavailability than acyclovir and therefore requires less frequent dosing (Freitas, 2023; Rebello *et al.*, 2003; Senne Licor Diagnóstico, 2024; XGEN Mobius, 2024).

Dose adjustments for patients with reduced renal function. Patients with severe odynophagia may sometimes require hospitalization for intravenous therapy with acyclovir 5 mg/kg every eight hours in patients with normal renal function and intravenous fluids. These patients may be switched to oral therapy to complete treatment when they can swallow comfortably (Santos, 2010; Senne Licor Diagnóstico, 2024).

Sunlight exposure**:** In some patients, intense sunlight exposure can lead to HSV-1 reactivation. Several treatment strategies have been evaluated to prevent these recurrences, including zinc-based sunscreens and topical and oral antiviral therapies, although no studies have directly compared any of these strategies (Figure 9) (Rebello *et al.*, 2003; Thomasini *et al.*, 2008; Santos, 2010).

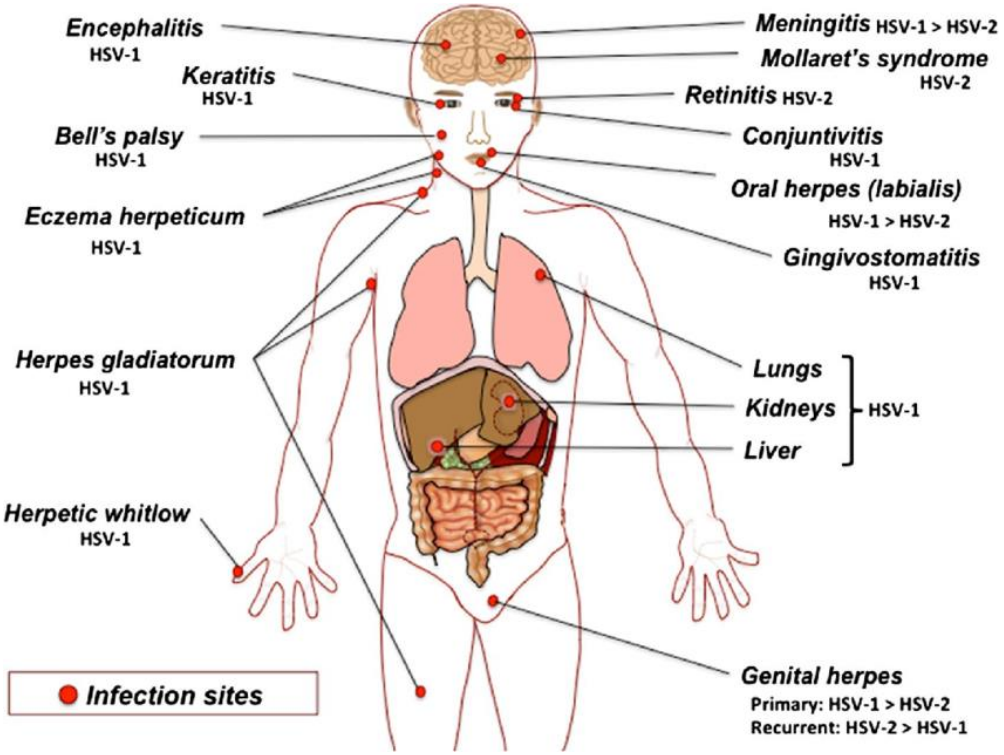


Figure 9: Clinical manifestations produced by herpes simplex viruses: the sites of infection by herpes simplex viruses include brain meningitis and encephalitis, infections in the ocular area eyes: keratitis, retinitis and conjunctivitis; mouth: lips and gingivostomatitis; facial nerves: facial paralysis, torso, limbs and genitals neck, arms, hands, fingers, legs, legs, genitals and internal organs, such as lungs, kidneys and liver
Source: https://www.researchgate.net/figure/Clinical-manifestations-produced-by-herpes-simplex-viruses-the-sites-of-infection-by_fig1_265558901

Surgical procedures HSV reactivation may be seen in the context of surgical procedures such as trigeminal nerve root decompression and ablative laser facial dermabrasion; in some reports, the risk of recurrent oral herpes has been reported to be as high as 50 to 70 percent. Given the high risk of HSV reactivation associated with these procedures, we typically administer antiviral prophylaxis at the time of surgery, even for those with no known history of HSV (Porter *et al.*, 2000; Santos, 2010; Voineagu *et al.*, 2011).

3.2. Herpesvirus type 6, IgG, and IgM antibodies

Other names: Herpes 6 serology, Anti-HHV6 antibodies, HHV6 serology, Exanthema subitum serology, Infant Roseolovirus serology. Overall, primary HHV-6 infection is among the most prevalent causes of acute febrile illness in young children. It is also a significant cause of emergency room visits, hospitalizations, and febrile seizures. HHV-6 belongs to the subfamily Betaherpesvirinae and the genus *Roseolovirus* (Herpesvirales: Orthoherpesviridae) (Rebello *et al.*, 2003; Thomasini *et al.*, 2008; Voineagu *et al.*, 2011).

The virion particle has the characteristic structure of a herpes virus, with a central core containing the viral DNA, a capsid, and a protein-rich coat that is surrounded by a membrane. HHV-6A and HHV-6B are double-stranded DNA viruses in the subfamily Betaherpesvirinae and the *Roseolovirus* (herpes virus). HHV-6A and HHV-6B have infected nearly all human populations that have been tested (Figure 10) (Voineagu *et al.*, 2011; Senne Licor Diagnóstico, 2024).

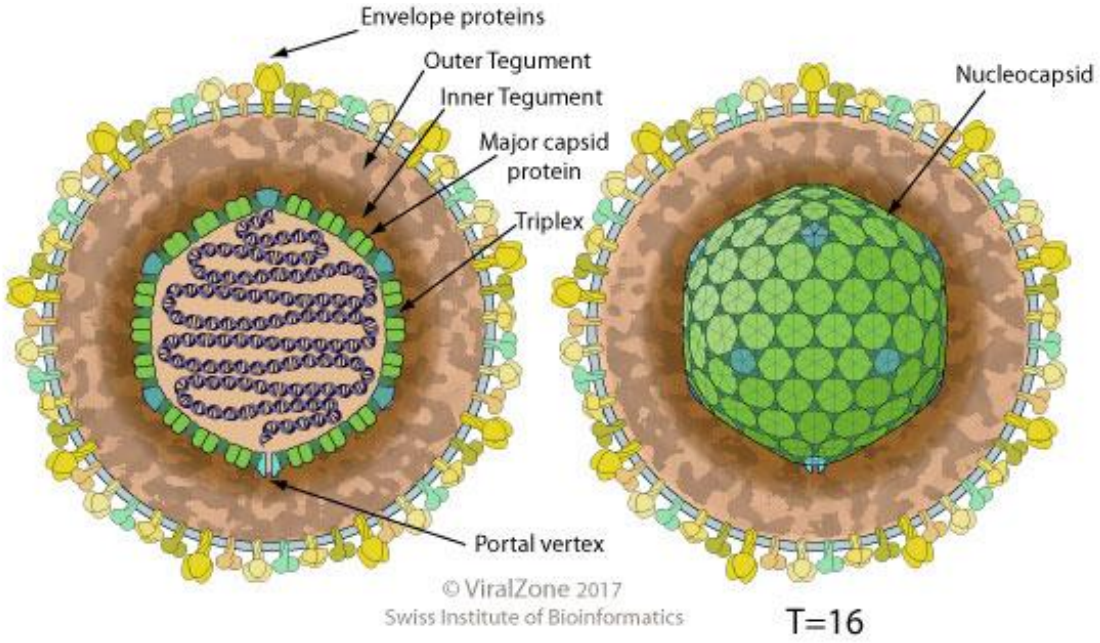


Figure 10: Herpesvirus type 6 (HHV)
Source: https://viralzone.expasy.org/5796

Human herpesvirus 6 (HHV-6) is the common collective name for Human betaherpesvirus 6A (HHV-6A) and Human betaherpesvirus 6B (HHV-6B). These closely related viruses are two of the new herpes viruses known to have humans as their primary host. Three stages can be recognized in the natural history of HHV-6 infection. The first is represented by acute primary infection in infants. The second stage occurs in healthy children and adults; the virus replicates in the salivary glands and is secreted into saliva as HHV-6B without inducing any obvious pathology, remains latent in at least lymphocytes and monocytes, and persists in various tissues, possibly with low-level replication (Porter *et al.*, 2000; Caserta *et al.*, 2001; De Bolle *et al.*, 2005; Despensa and Medveczky, 2017).

The third stage occurs infrequently, usually in immunocompromised individuals, and is associated with the reactivation of the virus by latency or reinfection. Other pathological conditions, notably multiple sclerosis, tumors, and CFS, have been associated with HHV-6 (De Bolle *et al.*, 2015; Despensa and Medveczky, 2017; Despensa and Medveczky, 2017).

HHV-6A has been described as more neurovirulent and, as such, is more frequently found in patients with neuroinflammatory diseases such as multiple sclerosis. It infects approximately 90% of the population before the age of two. Most infections occur in healthy children, causing exanthema subitum Infant Roseolovirus. In approximately 6% of infected children, the virus can lead to encephalitis and meningitis. Some case reports have also reported the association of fulminant hepatitis, thrombocytopenic purpura, myocarditis, and hemophagocytic syndrome. HHV-6 levels in the brain are also elevated in people with Alzheimer's disease (Figure 11) (Caserta *et al.*, 2001; De Bolle *et al.*, 2005; Despensa and Medveczky, 2017).

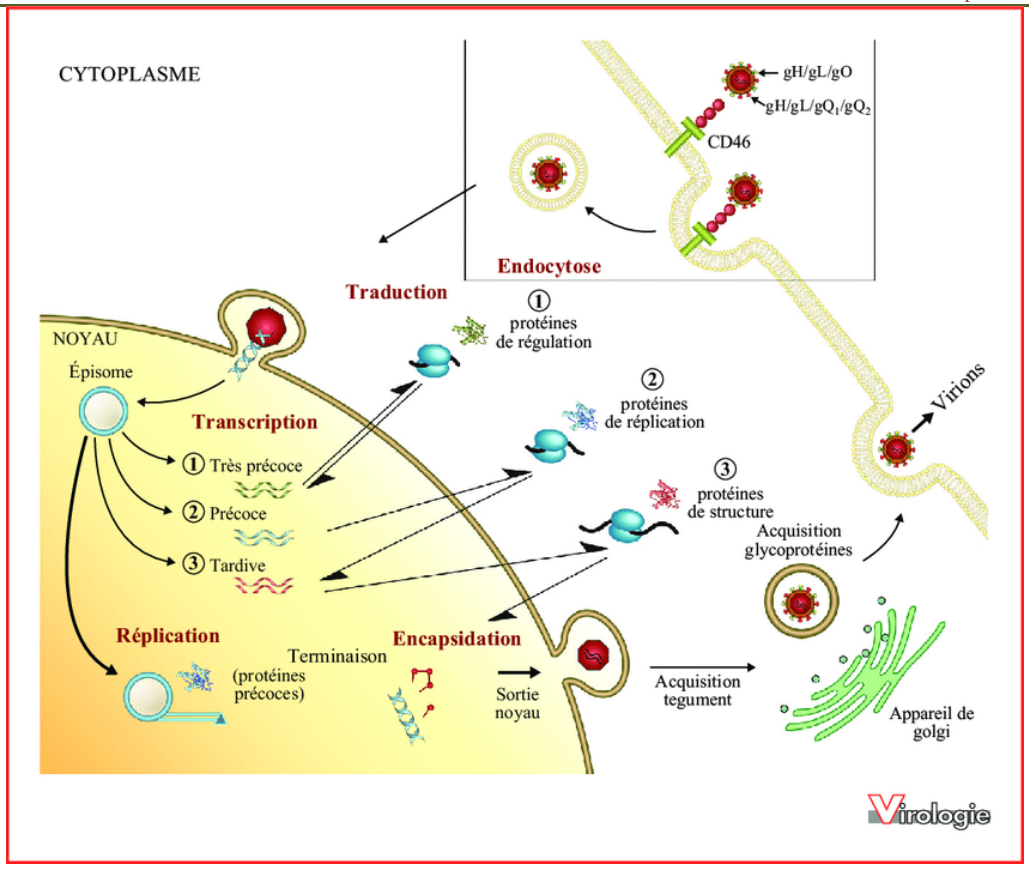


Figure 11: First, the virus enters the target cell by endocytosis through its binding to the cellular receptor CD46. Second, the virus releases its genomic DNA into the nucleus, where it circularizes to form a viral episome, followed by the sequential production of proteins essential for the lytic cycle. Third, the viral genome is replicated and encapsidated, and the newly formed viral particle is transported via the exocytosis pathway
Sources: Figure adapted from De Bolle *et al.*, and Doi: 10.1128/CMR.18.1.217-245.2005

In transplant patients, some of the clinical complications that may arise due to infection or reactivation of the virus are bone marrow suppression, encephalitis, encephalopathy, fever, actual betrayal, organ infection, and in severe cases, can lead to death. In patients with AIDS, the viral load is increased, spreading the virus throughout the body and to the lymph nodes, causing infection in several organs, pneumonia, retinitis, and active infection of the Central Nervous System (CNS) and can result in death (Thomasini *et. al.*, 2008; Despensa and Medveczky, 2017).

Primary HHV-6 infection is asymptomatic and very common in children up to two or three years of age. HHV-6 infection is the most common cause of febrile seizures between the ages of 6 and 24 years. It is rare in immunocompetent adults. When it occurs, it manifests as fever, lymphadenopathy, hepatitis, or encephalitis. After primary infection, HHV-6 remains latent until the immune system is compromised, at which point the virus may reactivate. The main target cell of HHV-6 is the mature CD4+ T cell (Braun *et al.*, 1997; Mandell *et al.*, 2009).

The virus has demonstrated pleiotropic effects on the immune system, including modulation of natural killer cell function. In vivo, HHV-6 infects and replicates primarily in CD4 lymphocytes after binding to the CD46 cellular receptor. Through receptor-mediated endocytosis, HHV-6 enters cells with subsequent viral replication Ablashi. After primary infection, the virus DNA lives in Peripheral Blood Mononuclear Cells (PBMC) (Prichard and Whitley, 2014; Yavarian *et al.*, 2014; Eliassen *et al.*, 2018).

The best-known route of transmission is horizontal, through saliva, as the salivary glands function as a very important reservoir for this virus. Infant Roseolovirus is a primary infection, described by a sudden rash, accompanied by a high fever, above 40º C, lasting three to five days. Then, rashes are noticed spread over the trunk, although never applied to the face (Prichard and Whitley, 2014; Yavarian *et al.*, 2014).

The child's clinical condition may be complicated by seizures and CNS symptoms. In adults, it is considered rare, but if it does occur, it is characterized by a mononucleosis-type liver infection. Human herpesvirus type 6 (HHV-6), in rarer cases, is also associated with meningitis in combination with sudden (Yavarian *et al.*, 2014; Agut *et al.*, 2015; Eliassen *et al.*, 2018).

Although the exact mechanism of HHV-6 transmission is still under investigation, several studies have elucidated viral transmission via saliva. It appears that transfer via mother-to-child saliva is the most common route. Several early reports described infectious HHV-6 as being present in the saliva of nearly all individuals tested. Furthermore, salivary samples from 90% of individuals tested contained HHV-6 DNA, whereas, in another PCR-based study, only 3% of individuals tested positive, although 63% of salivary gland biopsy samples tested positive (Mandell *et al.*, 2009; Caserta *et al.*, 2014; Yavarian *et al.*, 2014).

The HHV-6 genome has also appeared in the CSF of children during primary and latent infections, as well as in the brain matter of normal adults at autopsy, pointing to both the CNS and salivary glands as reservoirs for viral latency and persistent infection. There is currently no approved formulation exclusively for the treatment of HHV-6, and there is no vaccine available. Providing antiviral prophylaxis for HHV-6 infection is generally not recommended. Instead, early antiviral treatment is advisable, especially in cases of HHV-6 encephalitis. First-line therapy with intravenous ganciclovir and foscarnet is recommended, with a 3- to 4-week course of treatment (Rentz *et al.*, 2007; Prichard and Whitley, 2014; Agut *et al.*, 2015).

In patients undergoing stem cell transplantation, treatment with ganciclovir has documented benefits and is the suggested antiviral of choice. Treatment for this condition involves a combination of antivirals and antipyretics, in addition to frequent hydration of the patient. The disease is self-limiting and resolves spontaneously without sequelae. Antibody testing is useful for the diagnosis of acute infection, marked by the detection of IgM (Mandell *et al.*, 2009; Caserta *et al.*, 2014).

In our case, it has little diagnostic value in reactivations since the presence of IgG is very prevalent and does not discriminate between latent and active infection. For the diagnosis of reactivation in immunosuppressed patients, the molecular test (PCR) is suggested without blood and/or without liquor (Figure 12) (Agut *et al.*, 2015; Young, 2016).

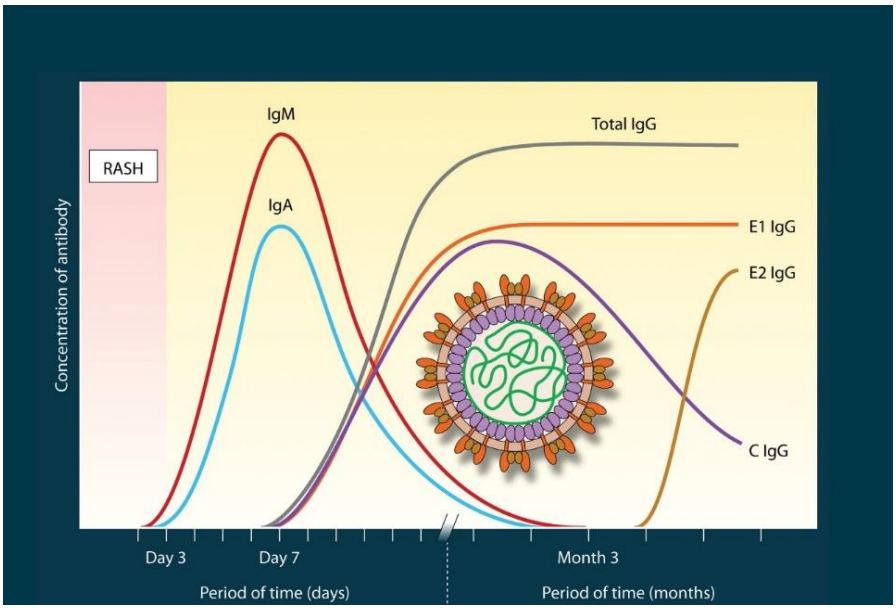


Figure 12: Current concepts for genital herpes simplex virus infection: diagnosis and pathogenesis of genital
Source: https://doi.org/10.1128/cmr.00093-15

The diagnosis of primary infections in childhood is based on clinical findings. Laboratory investigation is rarely used since the disease is self-limited in immunocompetent children with the classic presentation. However, it is always necessary to be alert to atypical manifestations. Etiological identification is recommended in children with atypical manifestations or immunodeficiency, allowing for early and appropriate treatment. HHV-6 infection is often underdiagnosed because it has nonspecific symptoms that suggest the condition is related to the disease (Irving *et al.*, 1990; Campadelli-Fiume *et al.*, 1999).

However, its recognition is important, given the cases related to central nervous system infection, such as the meningitis described in this report, in which inadequate treatment could result in irreversible damage to the development and life of patients. Laboratory identification of the virus is necessary for children with atypical manifestations or immunocompromised children, allowing for the initiation of the correct treatment as soon as possible to avoid complications (Dewhurst, 2004; Mandell *et al.*, 2009; Casertaet *et al.*, 2014).

3.3. Autism (ASD)

High levels of antibodies against herpes simplex-2 in the blood of pregnant women have been associated with an increased risk of autism in male infants. This association was observed with the increase occurring in mid-gestation rather than at the time of delivery. Autism spectrum disorders (ASDs) comprise a spectrum of neurodevelopmental syndromes with varying degrees of social impairment, language and communication deficits, and stereotyped and repetitive behaviors (Campadelli-Fiume *et al.,* 1999; Elsabbagh *et al.,* 2012; American Psychiatric Association, 2013).

There are no definitive biomarkers for ASD; therefore, diagnosis relies on clinical criteria. The prevalence of ASD is estimated at 1–2% in high-income countries in Asia, Europe, and North America and is higher in males than in females. The pathogenesis is, in most cases, unexplained; however, both genetic and environmental factors are implicated (Figure 13) (Voineagu *et al.,* 2011; Werling and Geschwind, 2013; Mahic *et aI.,* 2017).

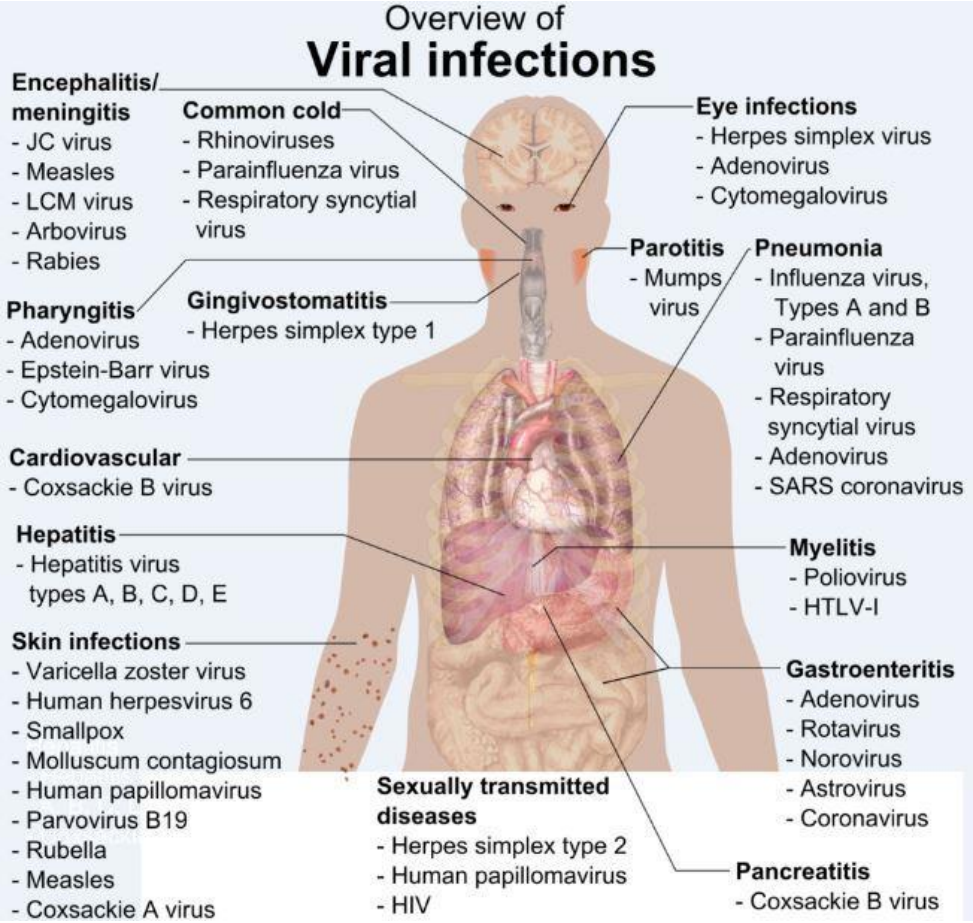
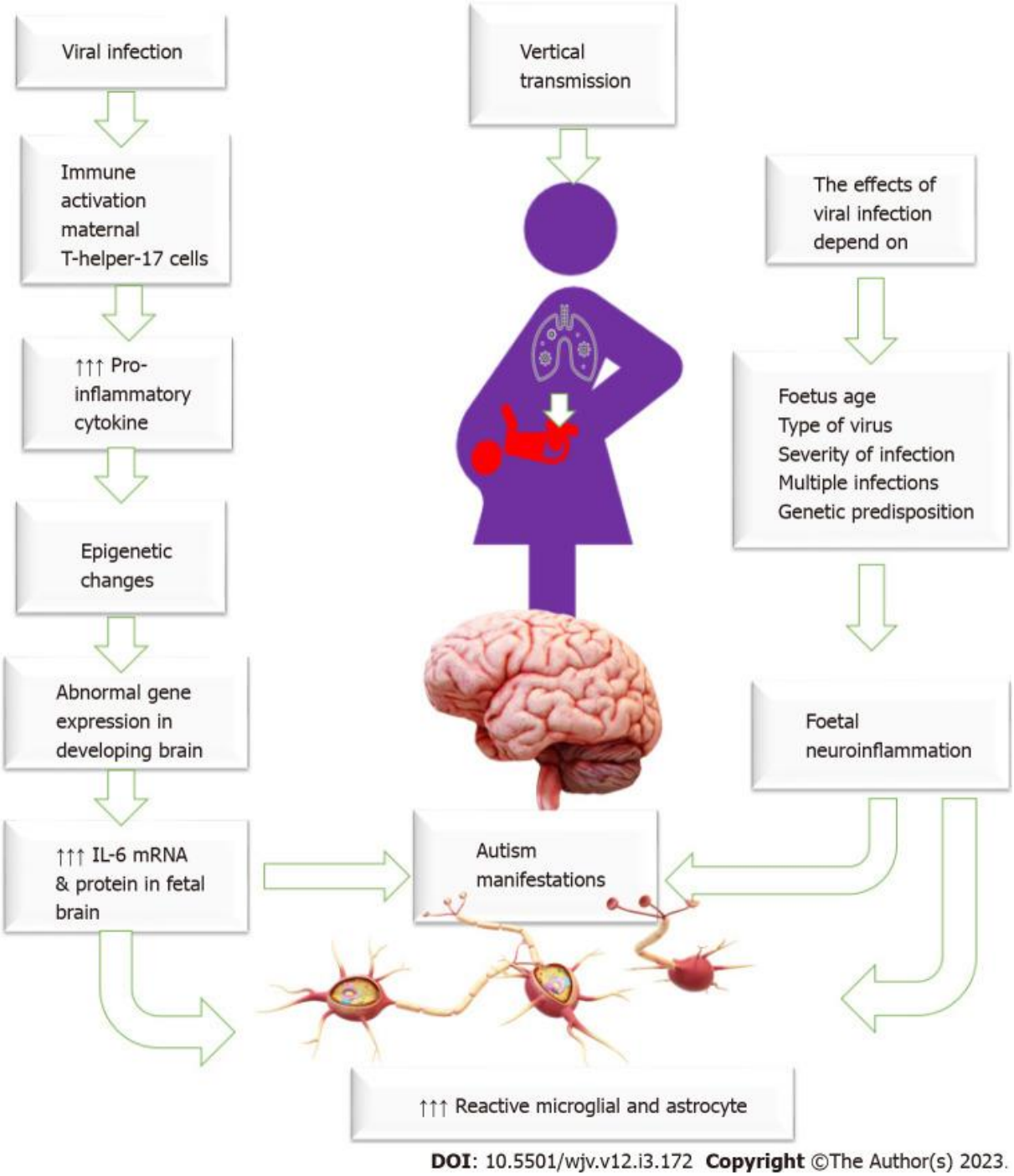


Figure 13: Herpes virus may be a trigger for autism ScienceMag. Herpes simplex virus type 2 (HSV-2), the primary cause of the blistering genital disease that infects roughly one in five U.S. women of childbearing age, may play a role in autism, according to a new study. Herpes virus infection while pregnant increases Autism risk
Source: Vitamin DWiki

Infections during pregnancy have been suggested to be a risk factor for several neurodevelopmental disorders, including ASD. Proposed mechanisms of damage include placental inflammation, maternal or fetal production of proinflammatory cytokines, and maternal autoantibodies that bind to the fetal brain. Evidence from epidemiological studies and work in animal models of neurodevelopmental disorders suggests that genetic and environmental factors may be involved (Hallmayer, 2011; American Psychiatric Association, 2013).

Based on the study of gestational infection and immune activation, high levels of IgG antibodies related to herpes simplex virus 2 in maternal plasma in midgestation but not at delivery were associated with an increased risk of autism spectrum disorder in male infants. It is believed that the mother's immune response to the virus may compromise the development of the fetal central nervous system (Figure 14) (Voineagu *et al.,* 2011; Werling and Geschwind, 2013; Mahic *et al.,* 2017; Al-Beltagi *et al.,* 2023).



DOI: 10.5501/wjv.v12.i3.172

Figure 14: That maternal viral infection could reach the virus through vertical transmission and affect the placenta. It also causes maternal immune reactivation with the activation of the maternal T-helper -17. This immune hyperactivation leads to a marked increase in the pro-inflammatory cytokines, causing epigenetic changes in the fetus, which causes abnormal gene expression in the developing brain with overactivation of astrocytes and glial cells and the development of autistic manifestations
Source: Doi: 10.5501/wjv.v12.i3.172

Researchers in the Autism Birth Cohort (ABC) study, conducted by the Norwegian Institute of Public Health, examined blood samples from 442 mothers of children diagnosed with autism spectrum disorder and 463 mothers of children without the disorder, who were included in the study. Maternal blood samples were obtained around 18 weeks of gestation and at the time of delivery (Elsabbagh *et al.,* 2012; Werling and Geschwind, 2013)

The Columbia team then assessed possible links between maternal exposure to five pathogens: *Toxoplasma gondii* (Nicolle & Manceaux, 1908) (Eucoccidiorida: Sarcocystidae), Rubella virus,

Cytomegalovirus, HSV-1, and HSV-2 (ToRCH). Laboratory analyses: ToRCH. Levels of IgG antibodies to *T. gondii*, Rubella virus, CMV, HSV-1, and HSV-2 in plasma were measured using the Zeus AtheNA Multi-Lyte ToRCH IgG Plus test system Athena; Zeus Scientific, Inc., NJ, EUA (Vinters and Willey, 1993; Hallmayer, 2011; Lyall *et al.*, 2014; Mahic *et aI.*, 2017).

They found that during pregnancy, the risk of autism spectrum disorder in the fetus was not associated with autism spectrum disorder and the presence of IgG antibodies to the other four pathogens. The researchers noted that high levels of antibodies against HSV-2 may indicate a recent primary infection or reactivation of latent infection. Only 12% of herpes simplex virus 2-seropositive mothers reported herpetic lesions before or during the first trimester of pregnancy, indicating that most HSV-2 infections were asymptomatic. The effect of early anti-HSV-2 antibodies on the risk of ASD was only observed in children. Due to the small sample size of the study, there is not enough evidence to conclude that the effect is specific to males, although ASD is generally more common in males (Figure 15) (Kimberlin and Rouse, 2004; Hallmayer, 2011; Lyall *et al.*, 2014; Freitas, 2023; Torres *et al.*, 2023).

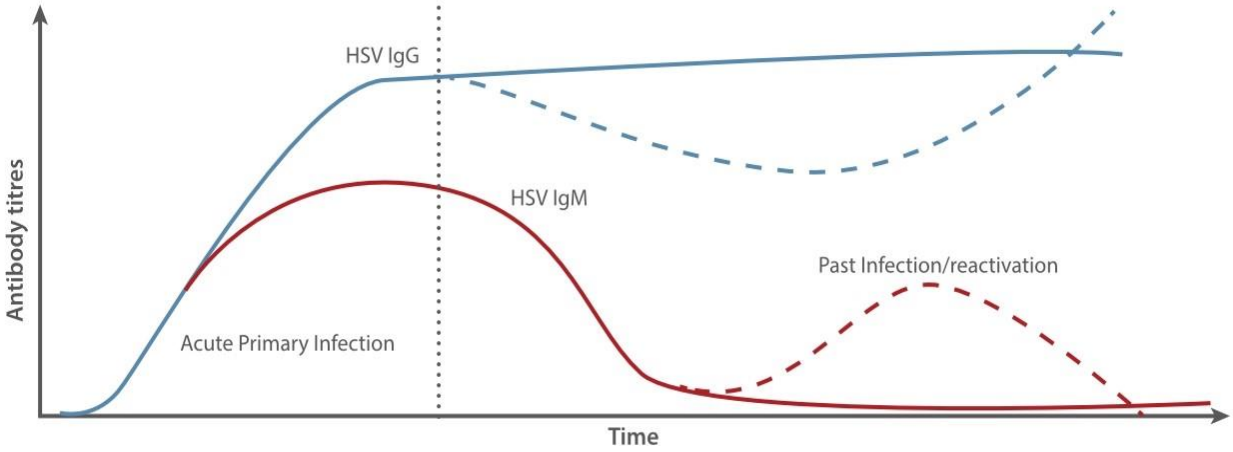


Figure 15: Serological changes of herpes simplex virus in infection ca ters to the increasingly diverse clinical requirements. Mindray has launched a series of HSV assays, including HSV-1 IgG, HSV-2 IgG, HSV-1+2 IgG, and HSV-1+2 IgM

Source: Doi: 10.1056/NEJMcp023065. PMID: 15128897

The causes of autism spectrum disorder remain poorly understood, and scientists believe the condition is caused by some combination of genetic and environmental influences. The researchers believe that the risk of autism in children is not directly linked to infection of the fetus, which could be fatal in this case. They believe that the risk is linked to a reaction in the mother's body or to a reactivation of the infection coupled with inflammation near the uterus. This is the first study to report an association between maternal levels of anti-HSV-2 antibodies and the risk of ASD in offspring. Our data suggest that high levels of anti-HSV-2 antibodies in mid-pregnancy increase the risk of ASD in boys (Torres *et al.*, 2006; Hallmayer, 2011; Lyall *et al.*, 2014; Freitas, 2023; Torres *et al.*, 2023).

A study carried out at Columbia University in the United States indicated that a pregnant woman who carries the herpes virus has a greater chance of giving birth to a child who may later be diagnosed with autism. The problem, in theory, is caused by the future mother's immune system's response to the infection, which interferes with the development of the fetus's central nervous system. However, there is still much divergence in the scientific community regarding the discovery (Marcocci *et al.*, 2001; Torres *et al.*, 2006; Bom, 2012).

"There is still no established relationship between herpes and autism. Further studies are needed," he says. "In pregnant women, the virus can cross the placenta and cause a generalized infection in the child, which is usually life-threatening, and in the mother herself, who may have generalized herpes," warns the professional [Fernando Maia]. Another complication is poor neurological development of the fetus, which can cause cerebral palsy (Figure 16) (Goodin, 2012; Marcocci *et al.*, 2020; Torres *et al.*, 2023).

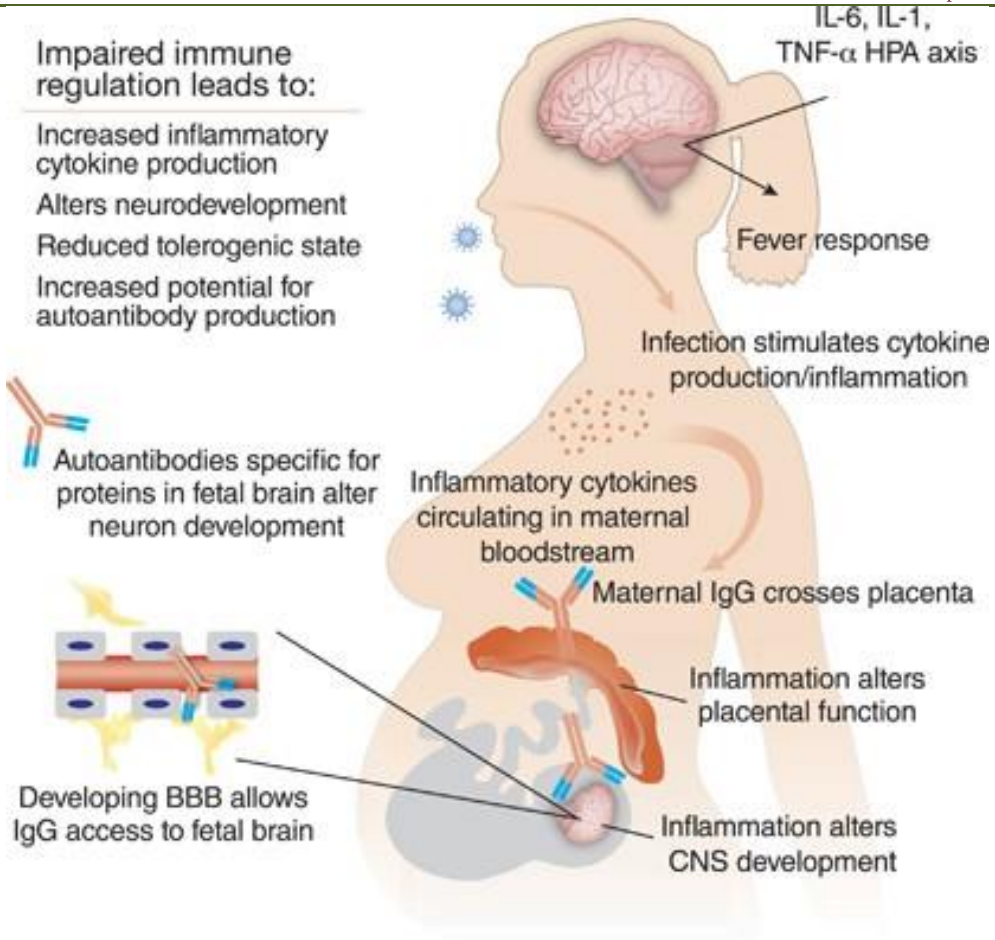


Figure 16: Maternal immune dysregulation during gestation is a risk factor for autism, and numerous interrelated factors may lead to dysregulation of the maternal immune system. Infections during the pregnancy, such as by rubella or influenza virus, can create an inflammatory immune environment and spur the production of maternal cytokines, which can not only directly affect the placenta but also to a limited degree may cross the placenta and enter the fetal compartment to have lasting effects on the development of the fetus
Source: https://doi.org/10.1038/npp.2016.158

Pregnant women with herpes simplex are at high risk of fetal and neonatal complications, especially when the infection occurs in the last trimester of pregnancy. Therefore, newborns have orolabial manifestations as their primary infection, with the rate varying between 33% in the population with low socioeconomic status. Neuropsychomotor development is the progress of motor, cognitive, linguistic, and psychosocial skills, and can be influenced by environmental, social, and biological factors, which can cause changes in DNPM brain disorders in children, which lead to disturbances in normal maturation, with consequent delays in neuro psychomotor development typical (Torres *et al.,* 2006; Theodore *et al.,* 2008; Bom, 2012; Goodin, 2012; Torres *et al.,* 2023).

Biomarkers for ASD note that a pro-inflammatory cytokine causes TNF-α stimulation in neural stem cells and has an effect on the GRID2 gene expression. Increased caspase-3 protein dependent on TNF stimulation has shown that caspase-3 activates apoptotic cascades and induces neurodegeneration. Increased production of pro-inflammatory cytokines could play a role in the pathophysiology of autism. Identifying cytokines that play a key role may help determine the direction and lead to an understanding of autism spectrum disorders. In addition to TNF-α affecting Caspase-3 directly, it leads to neuronal apoptosis, and this may lead to autism (Figure 17) (Vinters *et al.,* 1993; Jacobson, 2006; Chang *et al.,* 2008; Theodore *et al.,* 2008; Nisar and Haris, 2023; Torres *et al.,* 2023).

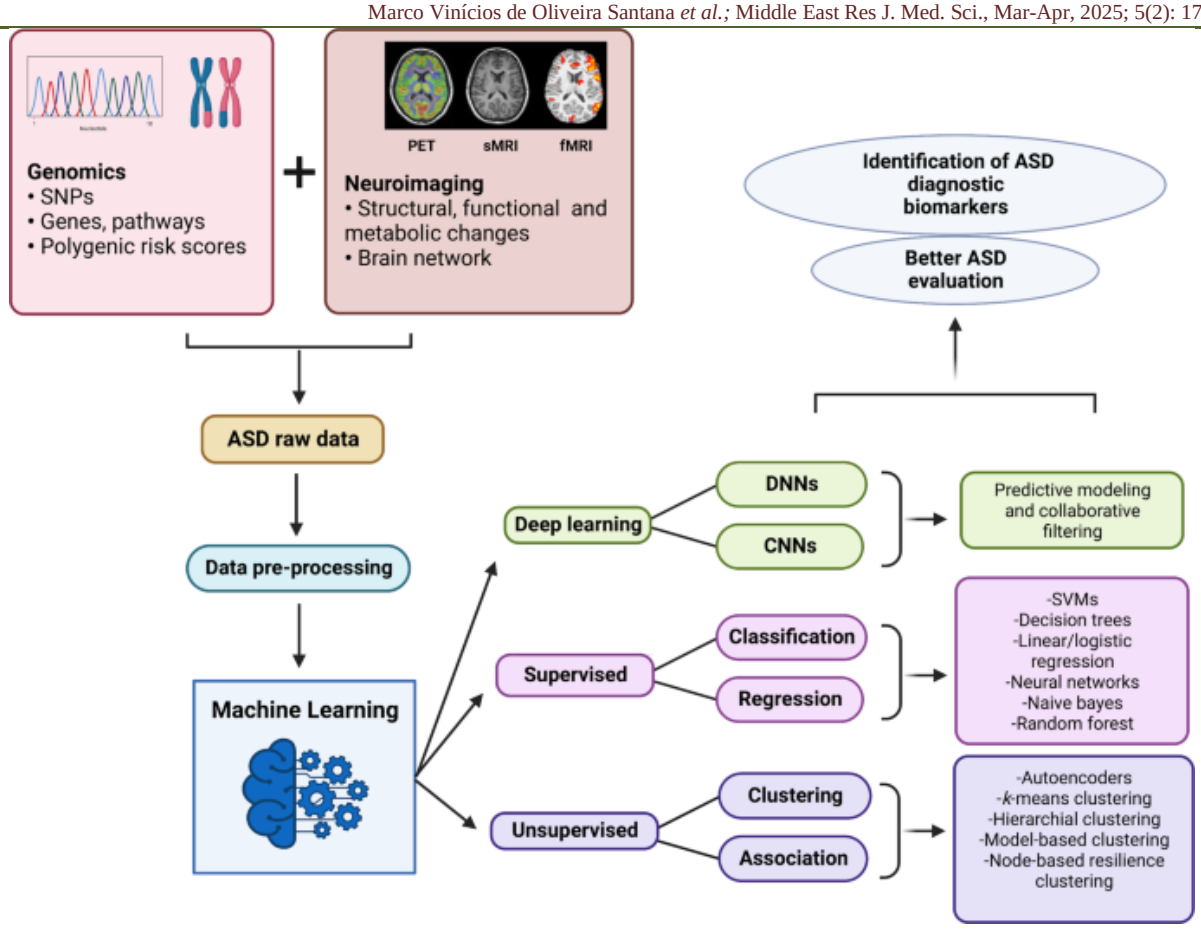


Figure 17: Machine-learning (ML) approaches for early diagnosis and better evaluation of autism spectrum disorder (ASD). ML methods or techniques can be applied to ASD raw data obtained from genomics and neuroimaging approaches. ML uses supervised and unsupervised learning methods to classify and distinguish clusters in ASD. Deep-learning techniques, such as deep neural networks (DNN) and convolutional neural networks (CNN), can be applied to diagnose ASD
Source: https://doi.org/10.1038/s41380-023-02060-9

Healthy children, who begin without any cause with febrile convulsions, encephalopathy, and subsequent cognitive deterioration that is confused with the characteristics of the autistic spectrum (ASD) when at older ages, the child shows a regression in cognitive development may resemble those presented in developmental disorders and some older children with ASD (Libbey *et al.,* 2005; Fotheringham *et al.,* 2007; Singh, 2007; Eliassen *et al.,* 2018; Torres *et al.,* 2023).

Neurodevelopmental delays are defined as alterations or setbacks in the development of functions linked to the maturity of the central nervous system, which may be compromised by the presence of the HHV-6 virus, and in some cases the damage may be present in a specific location, as in the case report by Henduld (Unilateral hippocampal sclerosis with subdural recording of contralateral temporal seizures: case report) which analyzes the sclerosis produced in the hippocampus due to an infection by HHV-6. which are autistic spectrum disorders, which are a set of developmental and behavioral syndromes that result from disorders in different cognitive areas (Bale, 2006; Singh, 2007; Shukla and Prasad, 2012; Osaghae *et al.,* 2011; King ad Khalili, 2024).

3.4. Antiviral IgE

The development of anti-respiratory syncytial virus IgE antibodies has been reported in children after infection with this virus. In experimental studies, the presence of specific IgE antibodies against HSV has been demonstrated in rabbits and mice. Furthermore, it has been shown that frank viral infection or the use of viral vaccines can lead to elevations in specific serum IgE. Patients suffering from recurrent HSV-induced lesions five or more times per year have elevated serum IgE levels compared with patients suffering from relatively mild disease (Figures 18-19) (Donati *et al.,* 2003; Voineagu *et al.,* 2011; Granata *et al.,* 2011; Senne Liquor Diagnosis, 2023).

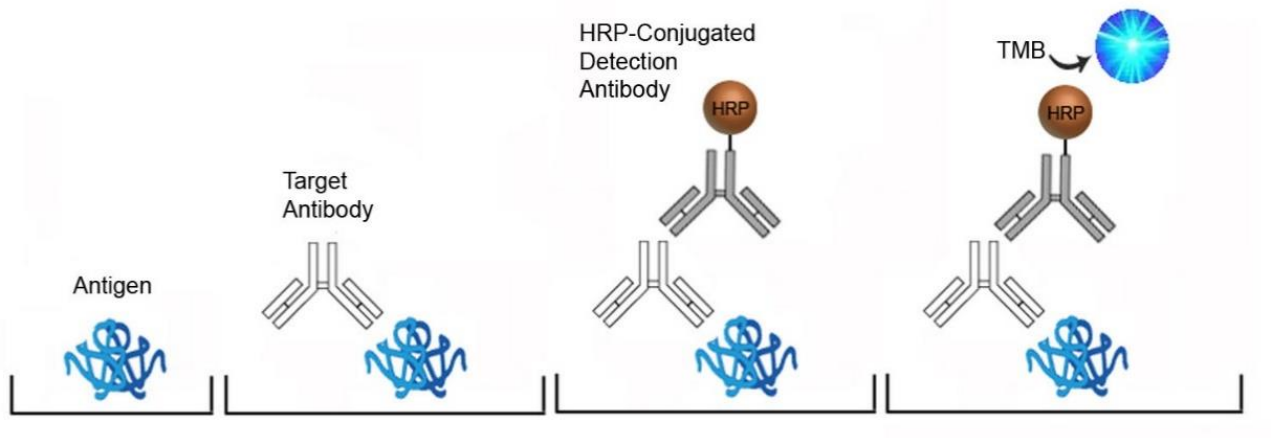


Figure 18: Human Anti-Respiratory syncytial virus (RSV) antibody (IgG) (Direct ELISA) ELISA Kit - LS-F10362
Source: https://www.lsbio.com/elisakits/human-anti-respiratory-syncytial-virus-rsv-antibody-igg-direct-elisa-elisa-kit-ls-f10362/10362

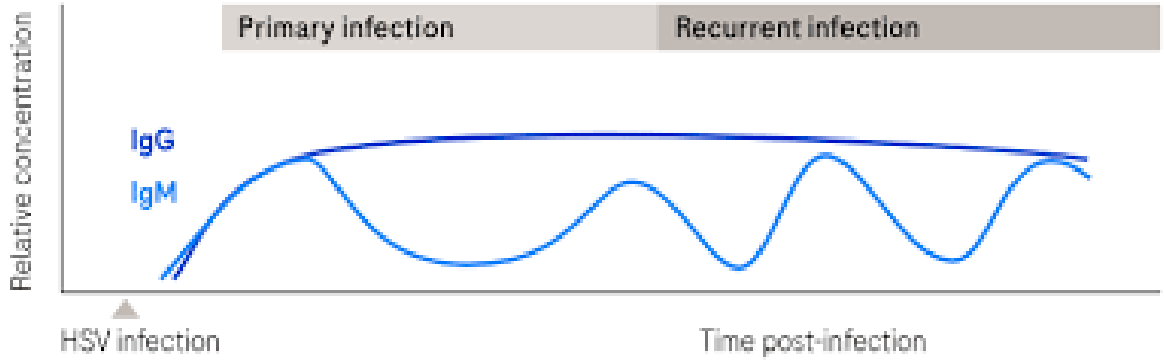


Figure 19: Antibodies to HSV are detected 2 weeks to 6 months after primary exposure. A substantial proportion of newly infected patients are positive for IgG and IgM, or IgG alone
Source: https://infectious-diseases-testing-guide.roche.com/test-hsv-adults

Active disease was considered the period during which patients continued to have lesions attributable to HSV and usually lasted between 3 and 7 days. Serum IgE levels in international units per milliliter were measured with ELISA Enzygnost-IgE, Behring Institute, Marburg, W. Germany. All samples were examined in duplicate. The mean variation in duplicates was <5% (Rentz *et al.*, 2007; Meltzer and Water, 2017; Zhao, 2024).

Serum IgG and IgM levels were monitored by ELISA procedures that involved the use of bound rabbit antibodies against human IgG and IgM, respectively. In these cases, the relative amounts of antigen-antibody complex formation, and thus IgG and IgM, were determined by reading the optical density of the supernatants spectrophotometrically at 492 nm (Rentz *et al.*, 2007; Meltzer and Water, 2017; Zhao, 2024).

3.5. Acyclovir Medication

The medication is indicated for the treatment of infections caused by herpes on the skin and mucous membranes, as well as initial genital herpes or in recurrent conditions. The cream is indicated for treating skin infections caused by the herpes simplex virus, both genital and labial, whether in its initial or continuous form. Once the tablet is disseminated through the bloodstream, its use is broader (Figure 20) Rentz *et al.*, 2007; Voineagu *et al.*, 2011; Meltzer and Water, 2017; Zhao, 2024).

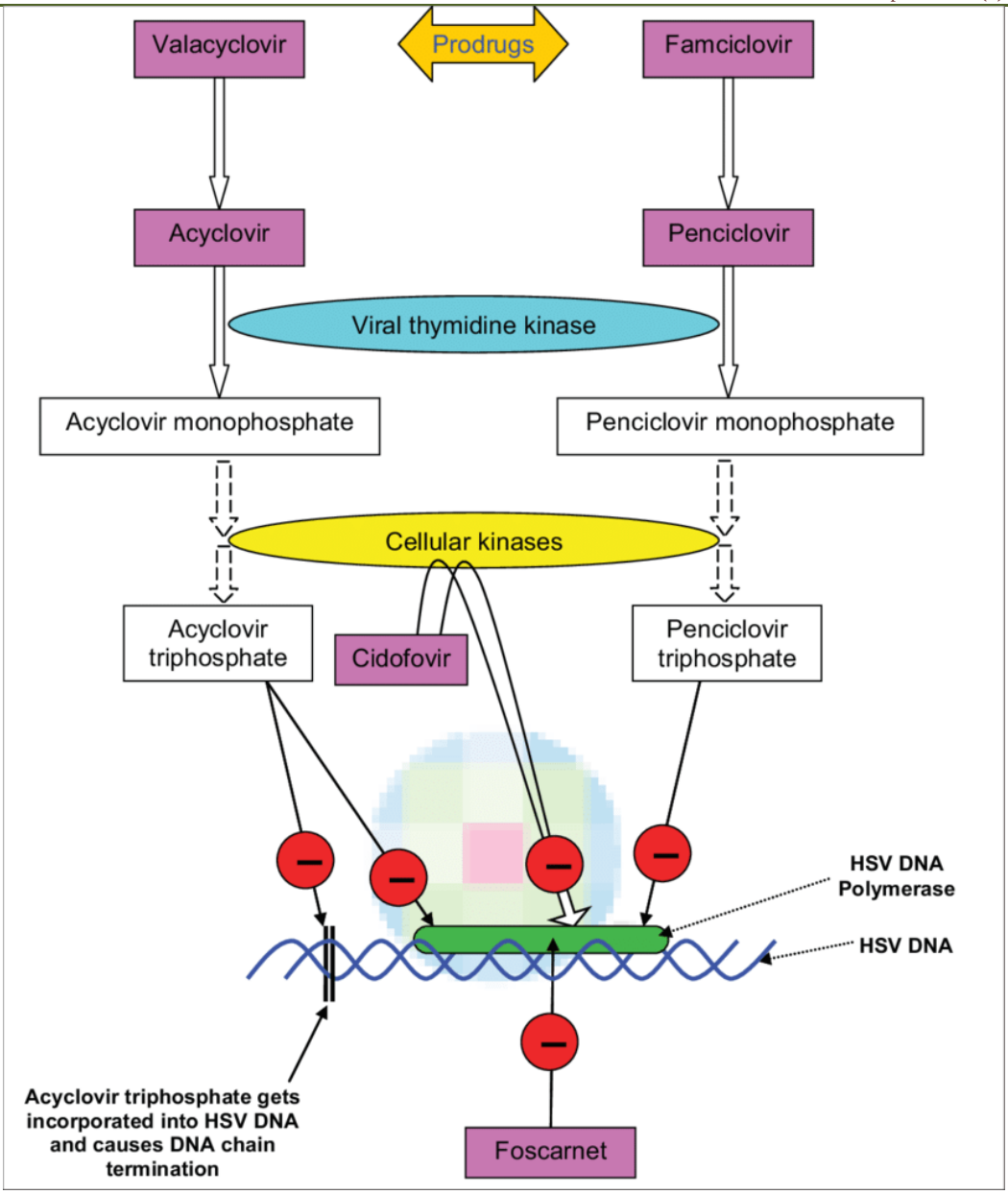


Figure 20: Major mechanisms of action of anti-herpes simplex virus antiviral drugs
Source: Doi: 10.4103/0378-6323.57716

The ointment has a local action, mainly in preventing and treating visible lesions. There is also an ophthalmic ointment indicated for treating keratitis and intravenous injection. This is an inflammation of the cornea associated with herpes simplex infections **(**Cernik *et al.,* 2008; Zhao, 2024)

5. CONCLUSION

Permanent brain injury is the most feared complication. Biochemical indicators of neuronal death appear promising in this scenario. In this context, NSE has been studied in patients resuscitated from cardiac arrest, and elevated levels of this enzyme suggest more extensive brain injury and are associated with unfavorable clinical outcomes. Outcomes after cardiac arrest are determined primarily by the degree of ischemic brain injury, and early measurements of serum NSE may be a valuable adjunct method in the prognostic assessment of these patients. Treatment involves the use of antiviral drugs when indicated; otherwise, it is supportive.

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