

## Correlation between Herpes Simplex Virus Type-1 Incidence and Mental Disorders

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### Abstract

Recent research has focused on Herpes simplex virus 1 (HSV-1) infectious agent as potential players in the etiologic pathway of chronic diseases, including psychiatric illnesses. Due to their potential neurotropism and latency, viral organisms in particular are considered possible agents in many chronic central nervous system disorders. The study was aimed to assess HSV-1, IgG antibody titer among patients with mental disorder, and to identify the relation between recurrent cold sore of HSV-1 and the mental disorders. Fifty patients with mental diseases and twenty five healthy individuals as a control were included in this study. Serum samples were collected and examined by Eliza, using HSV-1 IgG ELISA test for the detection of IgG antibodies to Herpes Simplex Virus type- 1 in Human serum. Records of patients' age, sex, clinical features, type of mental disorder and medications used in comparison with healthy control were collected. The majority of patient was male with age of 35 (63.90 %). The significant of increasing incidence of sero-positivity showed in the viral infections within the schizophrenia and depressive disorders patients. Antibodies against herpes simplex virus (HSV-1) showed highly significant increasing in the schizophrenia (P= 0.004). The treatment of mental disorders revealed a highest percentages of sero-positivity for HSV IgG Abs was with Chlorpromazine (87.5%) used for treatment of Schizophrenia, and Fluoxetine (83.3%) used for treatment of Depressive Disorder. The higher percentages for systemic diseases were with Schizophrenia (62.50%) and Depressive Disorder (41.67%). While Depressive Disorder showed the highest percentages rate (75%) and (66.67%) in anemia and leucopenia respectively, followed by Schizophrenia was (66.67%) and (31.25%) in the anemia and leucopenia cases respectively. In Conclusion, The outcome of this study emphasizes on the association between infectious agent of HSV-1 and psychiatric diseases of schizophrenia, depressive disorders, chronic depression.

**Key words:** HSV-1, Mental disorders, HSV-1, IgG Antibodies, Cold sore, Schizophrenia.

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## Introduction

Herpes simplex virus type -1, (HSV-1), is a large enveloped DNA virus, it is one member of the herpes virus family, Herpesviridae, that infect humans and cause different diseases. HSV-1 might produce most of cold sores, which is ubiquitous and contagious, can be spread when an infected person is producing and shedding the virus [1]. After infection the viruses attached themselves to, and penetrate the cells, then use them to reproduce and remain latent for long period of time. The virus can become active when triggered by stress and other infection or environmental factors [2]. Exposure to the common virus may be partially responsible for shrinking regions of the brain and loss of concentration skills memory and these widely seen in patient with some mental disease, and recent research has focused on infectious agents as potential players in the etiologic pathway of chronic diseases, including psychiatric illnesses such as schizophrenia and other syndromes [1,3]. Due to their potential neurotropism and latency, viral organisms in particular are considered possible agents in many chronic central nervous system (CNS) disorders [2]. There are several infectious agents in the environment that can cause persistent infections in the host, they usually cause their symptoms shortly after first infection and later persist as silent viruses or bacteria within the body [3].

After viral reactivation the virus becomes active in a nerve cell and is transported via the neuron's axon [2-4], and might caused central nervous system inflammatory changes that can present with symptoms indistinguishable from schizophrenia. HSV-1 appears to be particularly damaging to the nervous system and increases one's risk of developing Alzheimer's disease [5,6]. The virus interacts with the components and receptors of lipoproteins, which may lead to the development of Alzheimer's disease schizophrenia and other mental diseases [7]. Encephalitis and other conditions leading to CNS inflammatory changes often present with symptoms that are difficult to distinguish from new-onset schizophrenia [6,8]. The present study was aimed to correlate between HSV-1 and patients with mental disorders, by detecting IgG antibody in the serum of those patients in regard to the age, systemic diseases, some hematological criteria and medications used.

**Materials and methods:** Fifty five patients with mental diseases and twenty five cases as a control were included in this study. Serum samples (5ml) were collected and examined by Enzyme Linked Immuno Assay (ELISA), using HSV- 1, IgG ELISA test for the detection of IgG antibodies to Herpes Simplex Virus type-1 in Human serum. The test was performed according to "Demedilec Diagnosis Gmbh / Germany". EDTA Blood samples were collected from those patients for estimation of hemoglobin (Hb) and white blood cells (WBC) count. Control cases that have no mental diseases also subjected to the serum and the whole blood evaluation.

## Results

The mean age of the participants was ranged between 20 to 70 years old, and the majority of patient 35 (63.90 %) was male (Table 1). The important results of this study showed that there is a higher incidence of sero-positivity for viral infections in Schizophrenia, and Depressive disorders with significant association at  $P= 0.039$ . The chronic depression (42%), psychosis (50%), dementia (25%), epilepsy (50%) and bipolar disorder (25%) showed no significant changes. Antibodies against herpes simplex virus (HSV-1) was over represented highly significant increasing in the schizophrenia (87.5%) at  $P = 0.004$  (Table 2) (Figure 1).

**Table 1: Distribution of study sample according to Age and Gender with comparison significant**

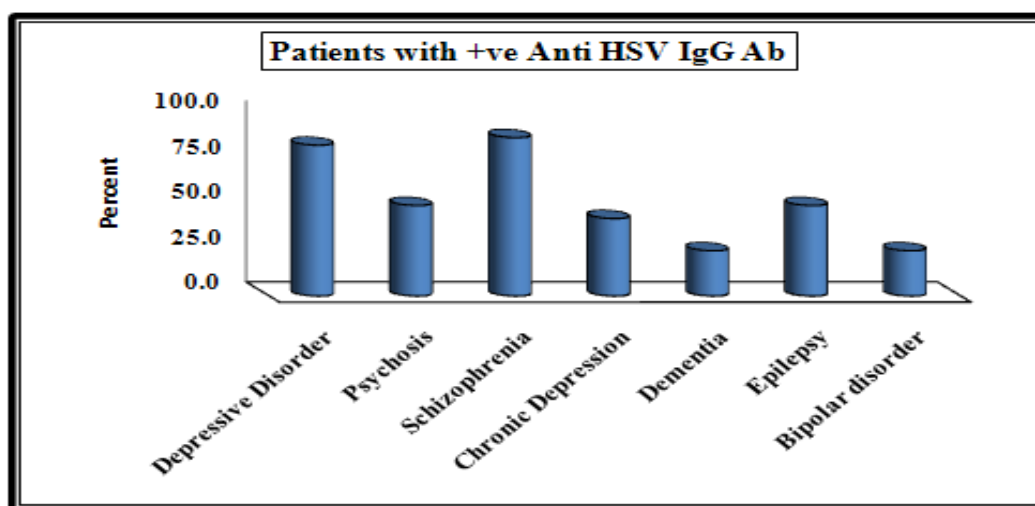
Age & Gender	Patients	Healthy	C.S. <sup>(*)</sup> /P-value
<u>Age</u>			$t = -2.007$
Range /yrs.	20 – 70	25 –70	$P < 0.05$
Mean $\pm$ Std. Dev.	45 $\pm$ 9.5	50 $\pm$ 10.5	S
<u>Gender</u>			FEPT
Female	20 (36.10 %)	15 (60%)	$P = 0.318$
Male	35 (63.90 %)	10 (40%)	NS
(Female /Male) : Ratio	1 : 1.7	1.5 : 1	(1 : 0.88)
Odds Ratio			
Total	55	25	-

<sup>(\*)</sup>FEPT Fisher Exact Prob. Test; S: Sig. at  $P < 0.05$ ; NS: Non Sig. at  $P > 0.05$

**Table 2: Distribution of HSV-1 IgG /Abs in the serum of study sample according to the type of Mental Disorder with comparison significant**

Type of Mental disorder	No.	No. Patients with +ve Anti HSV IgG Ab	% with Positive	CS <sup>(*)</sup> P-value
Depressive Disorder	12	10	83.3%	P=0.039 (S)
Psychosis	6	3	50.0%	P=0.508 (NS)
Schizophrenia	16	14	87.5%	P=0.004 (HS)
Chronic Depression	7	3	42.8%	P=1.000 (NS)
Dementia	4	1	25.0%	P=0.625 (NS)
Epilepsy	6	3	50.0%	P=1.000 (NS)
Bipolar disorder	4	1	25.0%	P=0.625 (NS)
Total	55	35	-	P=0.059 (NS)
Multiple Z -test		MZ=13.380		: P<0.05 (S)

(\*) Binomial test; NS: Non Sig. at P>0.05; S: Sig. at P<0.05; HS: Highly Sig. at P<0.05



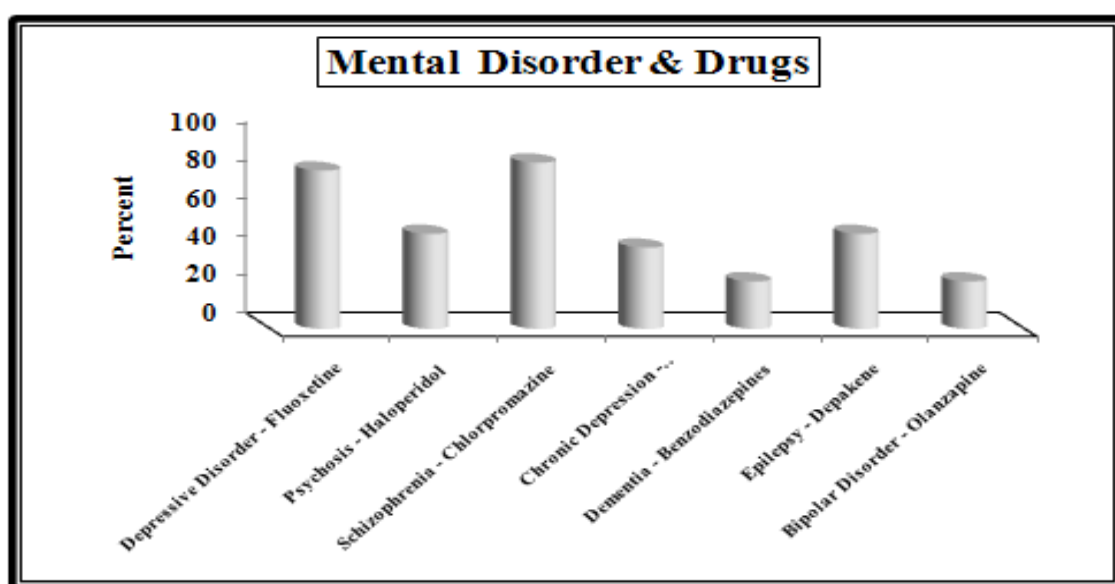
**Figure 1: Bar Chart for the distribution of HSV-1 in the serum of study sample according to the type of Mental Disorder.**

In regard to the medication used for treatment of Mental Disorders, the results revealed that the higher percentages for sero-positivity For HSV IgG Ab was with Chlorpromazine (87.5%), used for treatment of Schizophrenia, and with Fluoxetine (83.3%), used for treatment of Depressive Disorder (Table 3, Figure 2).

The highest percentages for systemic diseases were with Schizophrenia (62.50%). While Depressive Disorder showed the highest percentages rate (75%) and (66.67%) in anemia and leucopenia respectively, followed by Schizophrenia was (66.67%) and (31.25%) in the anemia and leucopenia respectively (Table 4, Figure 3).

**Table 3: Distribution of HSV-1 in the serum of study sample according to the type of Mental Disorder and medication used**

Type of Mental Disorder	Patient NO.	Medication Used	Patients NO. with +ve Anti HSV IgG Ab	% positive
Depressive Disorder	12	Fluoxetine	10	83.3%
Psychosis	6	Haloperidol	3	50.0%
Schizophrenia	16	Chlorpromazine	14	87.5%
Chronic Depression	7	Benzodiazepines	3	42.8%
Dementia	4	Benzodiazepines	1	25.0%
Epilepsy	6	Depakene	3	50.0%
Bipolar Disorder	4	Olanzapine	1	25.0%
Total	55	-	35	



**Figure 2: Bar Chart for the distribution of HSV-1 in the serum of study sample according to the type of Mental Disorder.**

**Table 4: Distribution of patients with mental diseases according to other Health Problems**

Type of Mental Disorder	Systemic Disorder %	Patient with Anemia %	Patient with Leukopenia%
Depressive Disorder	5(41.67)	9(75.00)	8(66.67)
Psychosis	2(33.33)	4(37.50)	3(50.00)
Schizophrenia	10(62.50)	6(66.67)	5(31.25)
Chronic Depression	3(42.86)	2(28.57)	3(42.86)
Dementia	1(25.00)	1(25.00)	1(25.00)
Epilepsy	1(16.67)	2(33.33)	3(50.00)
Bipolar Disorder	1(25.00)	1(25.00)	1(25.00)
Total	23/55	25/55	24/55
Multiple Z -test	MZ=5.48 (P>0.05):NS	MZ=8.233 (P>0.05):NS	MZ=4.915 (P>0.05):NS

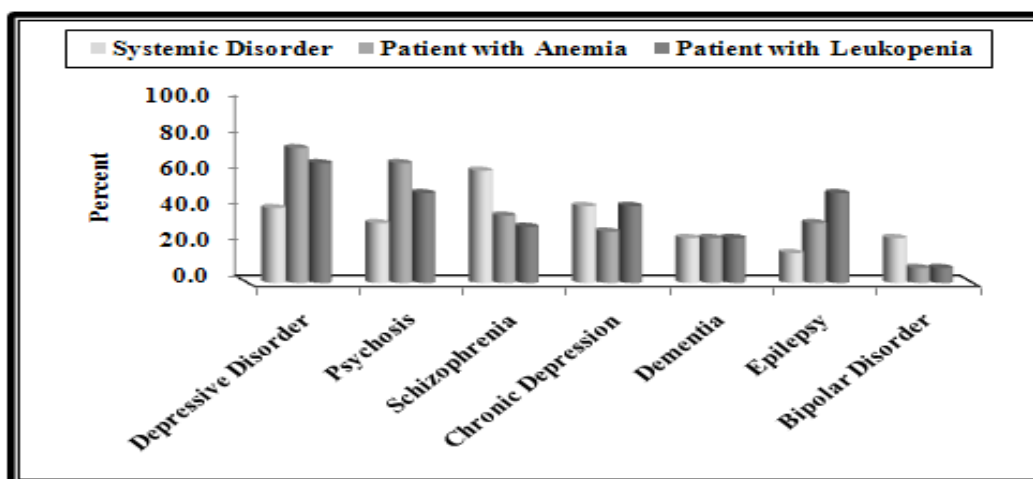


Figure 3: Cluster Bar Chart for the distribution of patients with Mental Diseases according to other Health Problems.

### Discussion

The present study revealed that the rate of positive antibodies against HSV-1 differs between groups of patients affected with mental disorders. The important results of this study showed that there is a higher incidence of sero-positivity for viral infections in the schizophrenia and depressive disorders with significant at  $P = 0.039$ . Antibodies against HSV-1 was over represented in schizophrenia (87.5%), with highly significant statistical association ( $P = 0.004$ ). In the total of bipolar disorders, the patients showed lower rates of antibodies to HSV-1 infectious agent. Bipolar disorder also known as manic depression that involves abnormally "high" or pressured mood states, known as mania or hypomania, alternating with normal or depressed mood [4,5,7].

The findings of current study are in line with previous studies that concluded that HSV-1 infection represents one risk factor for schizophrenia [6]. Schizophrenic patients were found to have a higher susceptibility to viral infections than individuals with other syndrome. This finding might point to a modification in special immune parameters in these diseases. Even so, total elevated vulnerability to HVS-1, might be explained by alterations within the immune status [6,8,9].

The present study found some indications that could point to a disturbed immune system in these diseases, the main findings was IgG antibodies elevated. IgG antibodies are involved in secondary immune responses and IgM antibodies appear already early in the course of an infection. This finding might be indicated that the infections have progressed to dormant infections with a persistent immune response. Previous studies mentioned that the involvement of the immune system in the

pathophysiology of psychiatric diseases has gained broad attention [2,5]. Little is known about the potential mechanisms of action for herpes family virus infections and risk of schizophrenia [5]. Studies of maternal infection provide some evidence that modulation of immune response and adverse effects on in utero maturation of critical brain structural and functional components may correlate with increased risk of schizophrenia in offspring [3,6,8]. Furthermore, signs of inflammation were found in the brains of schizophrenic patients [9,10].

Lea *et al.* [10] reported the status of seizures, focal neurological signs, systemic complications and in-hospital death were noted in the HSV group. Furthermore, mild cases of HSV might associated with meningo- encephalitis, traditionally considered a devastating infection were reported [10,11]. Daniela *et al.* [4] In their study for evaluation of infectious agents associated with psychiatric diseases including assessment of antibodies against cytomegalo virus (CMV), HSV, Epstein-Barr virus, Toxoplasmosis, Mycoplasmosis and Chlamydia trachomatis/pneumonia, the finding was higher prevalence of HSV (P=0.017) and CMV (P=0.017) antibodies in schizophrenic patients. The significant association between human herpes virus type 6 and schizophrenia was reported with 95% confidence interval. Women and blacks had significant negative associations with herpes simplex virus type 2 and cytomegalovirus, while among the blacks was a significant positive association with herpes simplex virus type- 1. Among men, there was a HHV-6 temporal effect with an HR of 1.41 (95% CI = 1.02, 1.96) for sera drawn 6–12 months before diagnosis [7,9]. Herpes encephalitis occurs sporadically and may be severe and multiple early seizures were characteristic [12,13].

There are some limitations of antipsychotic medication influences the immune system and therefore, the infectiousness might be affected. Psychiatric medications also have health effects, such as impaired glucose tolerance, effects on renal function, effects on liver function, and many others. Medications used to treat medical illness often have psychiatric effects, psychiatric patients often have limited access to medical care and are less likely to receive necessary medical care [14,15].

A wide range of comorbidity has been described between mental disorders with chronic medical illnesses such as hypertension, heart disease, pulmonary disease, and diabetes. The high rate of comorbid medical illness among psychiatric patients has



multiple etiologies. There may be specific associations between medical illnesses and psychiatric illnesses. For example, an association between manic-depressive illness and diabetes mellitus has been attributed to genetic relations between the diseases or to pathogenic mechanisms that are common to both. Another link is that psychiatric patients are less motivated to seek care for medical illness. They are often neglectful of their health and self-care [16-18]. Regardless of its cause, the association between psychiatric illness and medical comorbidity has important implications for patient care. The fact that comorbid medical illness is associated with worse medical outcomes is well established. The association between the disease-related, patient-related and physician-related with the latter is being the most important. For example, psychiatric patients are less likely to receive necessary medical care and have higher rates of morbidity and mortality from medical illnesses when compared with control populations [18]. Mortality rates from comorbid medical illness are especially high when the psychiatric illness involves substance abuse, when patients are elderly, or when they suffer from "organic brain syndromes." Therefore, the standard of care for the psychiatrically ill requires that the detection and treatment of comorbid medical illnesses be a high priority. The principal goal of this effort is to reduce medical morbidity and its associated mortality [11,17]. In Conclusion, The outcome of this study emphasizes on the association between infectious agent of HSV-1 and psychiatric diseases (schizophrenia, depressive disorders, chronic depression, psychosis, dementia, epilepsy and bipolar disorder). It highlights the differential distribution of sero-positivity to this agent in those patient groups.

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