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High prevalence of Human Herpesvirus 8 in schizophrenic patients

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ABSTRACT

Many studies have reported an association between Herpes family viruses and an increased risk of schizophrenia, but the role of Human Herpesvirus 8 (HHV8) has never been investigated. This study aimed to assess HHV8 prevalence in schizophrenic patients as well as the possible association between HHV8 infection and schizophrenia clinical features. We consecutively enrolled 108 patients meeting fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of schizophrenia and 108 age and sex matched controls. Data about a number of demographic characteristics and potential HHV8 risk factors of infection were collected. Standardized psychopathology measures, disease severity and functioning level were obtained using Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), Clinical Global Impressions (CGI) and Global Assessment of functioning (GAF). The presence of anti-HHV8 antibodies was analyzed using an indirect immunofluorescence assay. A higher prevalence of HHV8 infection in schizophrenic patients than in controls was found. Marital status, having children, sexual behavior and risk factors of blood transmission were not associated with HHV8 prevalence. However, among schizophrenic patients, HHV8 prevalence was statically associated with positive symptoms. To our knowledge, this would be the first report of a possible role of HHV8 in the pathogenesis of schizophrenia. To prove this hypothesis, further investigation of HHV8 in schizophrenia with larger samples is needed.

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1. Introduction

Most psychiatric diseases have multifactorial etiology as both genetic and environmental factors play important roles in the manifestation of symptoms (Cowan et al., 2002; Tomonaga, 2004). Several working hypotheses propose that viral infection contributes to the induction of neural cell dysfunction, resulting in a wide range of behavioral abnormalities, including cognitive, motor and social behavioral impairments (Tomonaga, 2004). In recent years, the role of viral infection in the pathogenesis of schizophrenia has garnered increased attention (Fruntes and Limosin, 2008; Fatemi and Folsom, 2009; Brown, 2011). Among a large number of microorganisms studied, interest in members of the Herpesviridae family has risen. Human Herpes viruses (HHVs) are double stranded DNA viruses that can establish latent infection in the nervous system and lymphoid tissue (Pellet and Roizman, 2007). Eight viruses belong to the family of human Herpesviridae: Herpes simplex virus type 1 and type 2 (HSV1 and HSV2), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella-Zoster (VZV) and Human herpes virus 6, 7 and 8 (HHV6,7 and 8). The role of HHVs in serious acute and chronic neurological disease of the central and peripheral nervous system had been established in immunocompetent and immunosuppressed individuals (Gilden et al., 2007). With the exception of HHV8, the role of HHVs in schizophrenia has been suggested. Even if results are often contradictory, a growing body of evidence suggests that individuals exposed to HHVs have a higher risk of developing schizophrenia. A substantial association between infection and schizophrenia was shown for HSV1, HSV2 and CMV (Dickerson et al., 2006; Brown, 2011; Yolken et al., 2011; Prasad et al., 2012).

Abbreviations: HHV8, Human Herpesvirus 8; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; CGI, Clinical Global Impressions; GAF, Global Assessment of functioning; HHVs, Human Herpes viruses; HSV 1, Herpes simplex virus type 1; HSV2, Herpes simplex virus type 2; CMV, Cytomegalovirus; EBV, Epstein-Barr virus; VZV, Varicella-Zoster virus; KS, Kaposi sarcoma; vIL-6, viral Interleukin-6; hIL-6, Human Interleukin-6; CNS, central nervous System

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A recent meta-analysis of studies that have assessed the possible association between detection of different infectious agents and schizophrenia supported the idea that there is a statistically significant association between schizophrenia and HSV 2, but no significant overall association between infections by HSV1, CMV, VZV, EBV, HHV6 and schizophrenia (Arias et al., 2012).

Despite the abundance of data on the relation between HHVs and schizophrenia, no study has assessed the possible role of HHV8 in this disease. HHV8 is the most recently discovered Human Herpes virus and has been associated with the development of Kaposi sarcoma (KS), primary effusion lymphomas, and multicentric Castleman disease (Cannon et al., 2003). HHV8 is not a ubiquitous virus. The highest prevalence of HHV8 infection (between 10% and 70%) was observed in Africa and the Mediterranean areas; in these countries the viral transmission seems to occur via close contact, through saliva. In areas with a low viral seroprevalence ($<5\%$) such as the USA, Northern Europe and Asia, infection appears to essentially concern groups at risk for sexual transmitted diseases (Edelman, 2005; Plancoulaine et al., 2002). HHV8 also appears to be transmissible, although less frequently, via exposure to blood (Cannon et al., 2003). HHV8 shares many biological properties with other HHVs such as the phenotypic structure and having genes that code for proteins involved in two major stages: latency and lytic growth. But HHV8 has a large arrangement of gene not shared by other HHVs. The virus has, in particular, an important number of human host gene homologs including genes encoding chemokine analogs. These genes seemed to have been acquired from the human cellular genome. The diversity of the HHV8 genes has an important role in human diseases and malignancies, and allows the virus to assault and modulate its human host with many strategies (Edelman, 2005). Being a gammaherpesvirus, this virus is predominantly, but not exclusively, lymphotropic (Chang et al., 1994). While the spectrum of in vivo tropism of HHV8 has yet to be fully elucidated, reports of detection of HHV8 in the nervous system suggest a neuroinvasive potential of this novel virus (Chan et al., 2000). Besides belonging to HHVs and its neurotropism, the hypothesis of a link between HHV8 and schizophrenia is supportable by the fact that the genome of HHV8 encodes a viral form of Interleukin-6 (vIL-6), which shares structural and functional identities with human Interleukin-6 (hIL-6) (Neipel et al., 1997). As the role of hIL-6 between inflammatory cytokines is largely documented in the literature as a part of the pathophysiology of schizophrenia (Potvin et al., 2008; Watanabe et al., 2010; Miller et al., 2011), hypothesis of a role of vIL6 in schizophrenia is plausible. In this work, we aimed to study the hypothesis of an association between HHV8 and schizophrenia by a seroepidemiological study of case-control type.

2. Subjects and methods

2.1. Subjects

2.1.1. Patients

One hundred and eight patients with schizophrenia were enrolled among patients attending the Department of Psychiatry of Sousse Farhat Hached hospital (Central East of Tunisia) during a 12 month period (December 2008 to November 2009). All patients met the following inclusionary criteria: (1) aged 18–65 years; (2) diagnosis of schizophrenia after clinical evaluation according to the criteria of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994) and validation using a structured interview schedule (MINI) and (3) the absence of severe mental retardation that may impair verbal communication. In addition, patients gave informed consent after the procedure had been fully explained.

Psychopathology standardized assessment was performed by a trained psychiatrist and was based for all patients on the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), the scale for the Assessment of Positive Symptoms (SAPS) and the scale for the Assessment of Negative Symptoms (SANS). We also used the Clinical Global Impressions (CGI) and the Global Assessment of Functioning (GAF) to respectively determine the disease severity and the functioning level.

2.1.2. Healthy controls

As controls, we enrolled 108 voluntary blood donors (as blood donation in Tunisia is anonymous, voluntary, and compensation-free). They were free from any psychotic disorder (MINI), with matched age and sex. Data about some demographic characteristics and potential HHV8 risk factors of infection were collected: Age, have been married, having children, residence (rural/urban), educational level, professional activity, surgical history, blood transfusion history, intravenous drug abuse, presence and stability of sexual partner. Standard economic measures of socio-economic status (SES) such as use of monetary information, income or consumption expenditure were not available.

2.2. Serological analysis

Blood samples were collected from patients and controls. Sera were separated and stored at $-20\ ^{\circ}C$ until testing. All samples were tested for the presence of antibodies against HHV-8 lytic antigens using an indirect immunofluorescence assay according to the manufacturer's instructions (Kit Biotrin HHV-8-IgG-IFA, Dublin, Ireland). The sensitivity and specificity were 100% and 94%, respectively, as reported in the manufacturer's catalog.

2.3. Statistical analysis

For univariate analysis, continuous variables were expressed as mean standard deviations (S.D.) and compared using the independent *t*-test. Categorical variables were expressed as numbers and percentages and compared between 2 groups using the χ^2 test. A logistic regression model (Wald Stepwise) was performed to analyze HHV8 status among schizophrenic patients, including potential confounding parameters (variables from the univariate analysis with $p<0.2$) and variables that showed significant differences between patients and controls. *P* values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 11.0.

Table 1
Demographic characteristics and potential risk factors of HHV8 infection in schizophrenic patients and controls.

Demographic characteristics/risk factors of HHV8 transmission	Schizophrenic patients ($n=108$) (%)	Healthy controls ($n=108$) (%)	*p*
Sex			
Male	71 (65.70%)	76 (70.40%)	NS
Female	37 (34.30%)	32 (29.60%)	
Have been married	38 (35.20%)	61 (56.50%)	0.02
Having children	29 (26.90%)	49 (45.40%)	0.05
Rural residence	51 (47.20%)	51 (47.20%)	NS
Absence or low level of scholar education	57 (52.80%)	43 (39.80%)	NS
Absence of professional activity	75 (70.10%)	21 (19.40%)	$<10^{-3}$
Surgical history or dental procedures	7 (6.5%)	34 (31.5%)	$<10^{-3}$
Blood transfusion history	1 (0.9%)	2 (1.8%)	NS
Intravenous drug abuse	4 (3.7%)	0 (0%)	NS
Presence of sexual partner	45 (41.7%)	85 (78.7%)	$<10^{-3}$
Instability of sexual partner	21 (19.4%)	27 (25%)	NS

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