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The impact of Herpes simplex virus type 1 on cognitive impairments in young, healthy individuals — A historical prospective study

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ABSTRACT

Herpes simplex virus (HSV) is a highly prevalent neurotropic virus. Although on the whole, chronic, latent or persistent infection is considered to be relatively benign, HSV infections can cause cognitive impairment during and after acute encephalitis. Some studies have documented cognitive impairment in exposed persons that is untraceable to encephalitis. Most studies have focused on these impairments in the mentally ill, mostly among individuals with schizophrenia, and only recently have studies begun to examine the impact of HSV infection on the cognition of healthy individuals.

Subjects were a representative, random sample of 612 soldiers before active duty in the Israeli military (Israeli defense force — IDF), 62.2% HSV positive (n = 381) and 38.8% HSV negative (n = 231). Cognitive functioning and language abilities were compared between these groups, controlling for years of education, immigration status, and gender.

Compared to soldiers who were sero-negative, soldiers who were sero-positive for HSV had significantly lower IQ scores (IQ = 97.96, SD = 15.19 vs IQ = 103.23, SD = 14.23; $p \le 0.001$, effect size (ES) = 0.2), and significantly lower Hebrew language scores (ES = 0.1, $p \le 0.01$). The results remained significant after removing subjects with mild depression, anxiety or personality disorders. Although we could not control for socio-economic status directly, our findings indicate that infection with HSV-1 is associated with reduced cognitive functioning in healthy individuals. This finding adds to the growing number of studies in the schizophrenia literature and indicates that many research findings seemingly characteristic of schizophrenia are related to the association between HSV exposure and cognitive functioning in general, and are not illness specific.

1. Introduction

Herpes simplex virus, type 1 (HSV-1) causes specific infections in the majority of US children and adults (http://www.cdc.gov/nchs/nhanes.htm). This double stranded DNA virus infects mucosal membranes, corneal tissues and the central nervous system (CNS). HSV-1 exposure can occur intrauterinely, and the rates of infection increase cumulatively with age, exceeding 90% in some African and South American countries, and 70% exposure rates in North American adults over 40 years of age (Smith and Robinson, 2002; Thomas et al., 2013). Following primary infection through mucosal membranes, HSV-1 virions migrate to the trigeminal ganglion, located within the blood-brain barrier, culminating in lifelong cycles of latent infection and reactivation in the CNS (Cleator and Klapper, 2004). The latent phase is asymptomatic and is considered harmless. The reactivation phase causes viral replication and migration along sensory nerves leading to recurrent mucosal and skin lesions such as 'cold sores'. Rarely, the virus replicates in the brain, causing encephalitis (Steiner et al., 2007). Encephalitis may cause extensive cognitive impairment, and post-encephalitic sequela characterized by seizures, deferent neurological problems, behavioral abnormalities, cognitive impairments and even anecdotal cortical blindness (Hokkanen and Launes, 2000; Nalini et al., 2000). Yet, encephalitis is a rare outcome (~0.04%) of herpetic infection (D'Aiuto et al., 2015; Prasad et al., 2012). Importantly, viral DNA has been detected in 35% of non-encephalitic postmortem brain tissues (Baringer and Pisani, 1994; Karatas et al., 2008), suggesting that HSV-1 often spreads to the brain during persistent infection. Recent studies (e.g., Bruder et al., 2005; D'Aiuto et al., 2015; Diaz-Asper et al., 2008; Dickerson et al., 2008; Schretlen et al., 2010; Thomas et al., 2013; Weinberger et al., 2001; Yolken et al., 2011) have suggested an

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association between schizophrenia, positive HSV-1 serology, and cognitive impairment. A review of these studies by Prasad et al. reported that schizophrenia patients who were HSV-1 positive without a history of encephalitis, had significantly poorer cognitive abilities compared to schizophrenia patients who were HSV-1 negative, and this finding remained significant after adjusting for age, gender, and socio-economical-status (SES) (Schretlen et al., 2010). Similar results were found in patients with bipolar disorder (Dickerson et al., 2003). Most findings have shown mild–moderate impairments in attention, working, and verbal memory (D'Aiuto et al., 2015). The estimated ORs for cognitive impairment among HSV-1-exposed young adults suffering from schizophrenia are 1.25–3.2 (Dickerson et al., 2008; Watson et al., 2013). Although there is knowledge on the effect of HSV-1 infection in patients with psychiatric disorders, there is little evidence regarding the effect of HSV-1 infection on cognitive abilities in healthy individuals. The little evidence that does exist, for the most part, though not unequivocally (Aiello et al., 2006), indicates that healthy HSV-1 positive individuals have poorer cognitive abilities compared to HSV-1 negative individuals (reviewed by Prasad et al., 2012). However, many of these studies were based on small samples not representative of the general population. In this historic prospective study, we attempt to add to current knowledge by examining possible associations between cognitive functioning and HSV-1 infection in a random sample of healthy soldiers, representative of the general population in Israel.

2. Materials and methods

2.1. Sample and laboratory methods

Data on HSV-1 serology were available from a study of a sample of Israeli defense force (IDF) recruits (see Davidovici et al., 2006 for details on the sampling method and laboratory procedures). Sera were kept frozen (−20 °C) until tested. HSV-1 type-specific antibody assays were performed with indirect enzyme-linked immunosorbent assay (ELISA) IgG assay (HerpesSelect; Focus Diagnostics, Cypress, CA). The reported sensitivity and specificity for HSV-1 were above 90%., sera with ELISA index values between 0.9 and 1.1 were defined as having equivocal results (as advised by the manufacturer) and these were re-tested. Seventeen samples remained unequivocal after re-testing and were excluded from the analysis.

After receiving approval from the IDF Medical Corps' ethical committee (IRB), data on HSV exposure were linked with cognitive and psychiatric military data using the military ID number. After the data were linked, identifiers were deleted, and the data set used in the analyses was unidentified. Six hundred and twelve (612) soldiers (59.2% male and 40.8% female; aged 17 at the draft board examination and aged 19–21 at the time that they were tested for HSV-1, Table 1) on active duty in the Israeli military were randomly sampled. Sixty-two point two percent (62.2%) were HSV positive (n = 381) and 38.8% were HSV negative (n = 231).

2.2. Cognitive and psychiatric assessments

Israeli law requires that the entire, unselected population of Jewish Israeli adolescents between the ages of 16 and 17 years undergo a pre-induction medical and psychiatric assessment of their eligibility to serve in the military. The screening procedure includes a medical and psychiatric history conducted by a physician, tests of Hebrew language abilities and intelligence testing. This assessment is administered through regional draft board centers located throughout the country. A detailed account of the draft board procedure is available elsewhere (Gal, 1986; Tubiana and Ben-Shakhar, 1982).

2.2.1. Cognitive assessment

Cognitive assessment includes four tests: a modified Otis-type verbal intelligence test, which measures the ability to understand and carry out verbal instructions; Similarities-R, a modified version of the 'similarities' subtest of the Wechsler Adult Intelligence Scales (WAIS) that assesses verbal abstraction and categorization; Arithmetic-R, which is similar to the 'Arithmetic' sub-test from WAIS which measures mathematical reasoning, concentration and concept manipulation; and non-verbal analogies, a modified version of Raven's Progressive Matrices (RPM) that measures non-verbal abstract reasoning and visual–spatial problem-solving abilities. A detailed account of the cognitive tests is available elsewhere (Gal, 1986; Rabinowitz et al., 2000). The sum of the four scores is a validated measure of IQ, scoring on a nine-point scale (scaled between 10 and 90, with a 10-point increment at each score). The 95th percentile of this IQ measure was equivalent to an IQ above 135, and its correlation with the WAIS total IQ was above 0.90 (Gal, 1986). The sum of the 4 scores was transformed into IQ scores with a mean of 100 and standard deviation of 15 using z-scores (Weiser et al., 2007).

2.2.2. Hebrew language score

The Hebrew language test assesses the level of knowledge and control of the Hebrew language and has four different parts: reading, writing, reading comprehension, and speech. A composite score ranges from 2 (low) to 9 (high). A more detailed account of the test is available elsewhere (Reichenberg et al., 2002).

2.2.3. Psychiatric screening in the military

An interview assessing personality and behavioral traits is administered by college-aged individuals who participated in a 4-month-long training course on the administration of the interview. Based on the interview and on findings from the physician's examination, adolescents who are suspected of having behavioral disturbances or mental illness are referred for an in-depth mental health assessment by a

Table 1
Distribution of sex, education level and immigration among the entire sample and among soldiers who are HSV positive vs. HSV negative.

Variables	Entire sample (N = 631)	HSV− (N = 231)	HSV+ (N = 381)	Comparison
Sex				$\chi^2(1) = 1.34$, $p > 0.05$
Male	N = 463 (59.4%)	N = 144 (62.3%)	N = 220 (57.6%)	
Female	N = 249 (40.6%)	N = 87 (37.7%)	N = 162 (42.4%)	
Education				$\chi^2(2) = 12.92$, $p \leq 0.01$
1–11 years	N = 80 (13.1%)	N = 19 (8.2%)	N = 61 (16.0%)	
12 years	N = 462 (75.4%)	N = 175 (75.8%)	N = 287 (75.1%)	
13± years	N = 71 (11.5%)	N = 37 (16.0%)	N = 34 (8.9%)	
Immigration status				$\chi^2(2) = 2.41$, $p > 0.05$
Immigrant	N = 74 (12.0%)	N = 34 (14.7%)	N= 40 (10.5%)	
Native-born	N = 539 (88.0%)	N = 197 (85.3%)	N = 342 (89.5%)	
Psychiatric diagnoses	N = 16 (2.6%)	N = 7 (3.0%)	N = 9 (2.3%)	$\chi^2(2) = 2.00$, $p > 0.05$
Personality disorders	N = 11 (1.8%)	N = 6 (2.6%)	N = 5 (1.3%)	
Neurosis	N = 5 (0.8%)	N = 1 (0.4%)	N = 4 (1.0%)	

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