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Emotion discrimination in humans: Its association with HSV-1 infection and its improvement with antiviral treatment

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ABSTRACT

Background: Herpes simplex virus, type 1 (HSV-1) infects over 3.4 billion people, world-wide. Though it can cause encephalitis, in the vast majority it is asymptomatic, with lifelong latent infection in neurons. HSV-1 infected individuals have greater cognitive dysfunction than uninfected individuals, particularly persons with schizophrenia – even without encephalitis. We investigated whether HSV-1 related cognitive dysfunction is progressive or remediable.

Methods: In a prospective naturalistic follow up sample (PNFU), temporal changes in cognitive functions were analyzed in relation to baseline HSV-1 infection in persons with/without schizophrenia (N = 226). Independently, in a randomized controlled trial (RCT), HSV-1 infected, clinically stabilized SZ outpatients received Valacyclovir (VAL, an HSV-1 specific antiviral, 1.5 G twice daily for 16 weeks) or placebo (PLA) added to standard antipsychotic treatment, using a stratified randomization design, following placebo run-in (N = 67). In both samples, HSV-1 infection (seropositivity) was estimated using serum IgG antibodies. Clinical evaluations were blinded to HSV-1 or treatment status. Standardized Z scores for accuracy on eight cognitive domains were analyzed for temporal trajectories using generalized linear models (PNFU) and VAL/PLA differences compared with intent to treat analyses (RCT).

Results: PNFU: At baseline, HSV-1 infected participants had significantly lower accuracy scores for Emotion Identification and Discrimination (EMOD), Spatial memory and Spatial ability, regardless of SZ diagnosis ($p = 0.025$, 0.029, 0.046, respectively). They also had significantly steeper temporal worsening for EMOD ($p = 0.03$). RCT: EMOD improved in VAL-treated patients ($p = 0.048$, Cohen's $d = 0.43$).

Conclusions: A proportion of age related decline in EMOD is attributable to HSV-1 infection.

1. Introduction

HSV-1 causes lifelong infection in approximately 3.4 billion people (Looker et al., 2015). It produces sporadic productive, lytic eruptions on mucosal surfaces, interspersed with latent, apparently asymptomatic infection restricted to neurons (Steiner et al., 2007). HSV-1 induced encephalitis is rare (0.004%) (Steiner et al., 2007), but many cross-sectional studies indicate cognitive dysfunction in working memory, attention and related domains in seropositive persons (Dickerson et al., 2003; Dickerson et al., 2004; Dickerson et al., 2008; Dickerson et al., 2012; Prasad et al., 2007; Prasad et al., 2012; Schretlen et al., 2010; Shirts et al., 2008; Strandberg et al., 2003; Tarter et al., 2014; Thomas et al., 2013; Watson et al., 2013; Yolken et al., 2011). Among healthy children, HSV-1 seropositivity is associated with lower reading and spatial reasoning test scores (Tarter et al., 2014). The associations are detectable among persons without a history of encephalitis and after accounting

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for potential socio-economic and infectious confounding factors (Studies cited above). Fruchter et al. (2015) studied associations between cognitive function and HSV-1 exposure among healthy young soldiers and found that HSV-1 exposed individuals were significantly more impaired. Other studies of non-psychiatric samples also reported that cognitive functions were more significantly impaired among HSV-1 exposed persons (Strandberg et al., 2003; Tarter et al., 2014; Jonker et al., 2014).

Cortical volume reductions in frontotemporal regions are also detectable in HSV-1 infected persons (Prasad et al., 2007). Though HSV-1 has not been etiologically linked with SZ (Thomas et al., 2013), the cognitive dysfunction is observed frequently among persons with SZ (Dickerson et al., 2003b; McGrath et al., 1997; Yolken et al., 2011). In sum, the cognitive dysfunction associated with persistent HSV-1 infection is distinct from the global, severe cognitive dysfunction among survivors of HSV-1 encephalitis (Hokkanen and Launes, 2007; McGrath et al., 1997; Prasad et al., 2007). It is reminiscent of 'cognitive aging', i.e., minor cognitive dysfunction among otherwise healthy adults that can compromise or magnify other physical and mental disabilities (Blazer et al., 2011). Like cognitive aging, varying trajectories of temporal cognitive decline have also been reported (Table 1). To test whether the HSV-1 associated cognitive dysfunction is remediable, we previously conducted a small randomized controlled adjunctive trial (RCT, N = 24) among US SZ patients with HSV-1 infection and found that 18-week adjunctive treatment with valacyclovir (VAL), an antiviral drug with high specificity for HSV-1 infection significantly improved verbal memory, working memory and visual object learning, compared with placebo augmentation of antipsychotic treatment (Prasad et al., 2013). Valacyclovir is highly specific as an antiviral agent, and studies have shown that it is very safe drug (Tyring et al., 2002). To evaluate the prognosis of HSV-1 associated cognitive dysfunction, we used a prospective, naturalistic follow up (PNFU) design to assess patterns of temporal change in cognitive functions among persons with and without HSV-1 infection. As our initial RCT was relatively small (Prasad et al., 2013), we separately evaluated a larger, independent sample using the same protocol.

2. Methods

The study was conducted at Dr. Ram Manohar Lohia Hospital, Delhi, India (RMLH). All participants were assessed with the Diagnostic Interview for Genetic Studies and consensus diagnoses were assigned as described (Thomas et al., 2013). Cognitive functions were assessed using the validated Penn Cognitive Neuropsychological Battery (PennCNB), which estimates accuracy and speed estimates for ten cognitive domains (Gur et al., 2001a; Gur et al., 2001b; Watson et al., 2013). As the accuracy and speed estimates are correlated, only age standardized accuracy scores were analyzed here (Bhatia et al., 2012).

HSV-1 infection was estimated using standard immunoassays at certified clinical laboratories. Highly specific IgG antibodies are normally produced following HSV-1 infection, so elevated HSV-1 antibody levels in the serum were used to assess HSV-1 exposure. Antibodies to HSV-1 were assayed using Euroimmun anti-HSV-1 Type specific glycoprotein C1 Elisa (IgG) kits by certified laboratories (SRL and Quest Diagnostics, India (http://www.srl.in/srl/srl.asp) (www.QuestDiagnostics.in). The reference ranges were: for SRL; <16.0 international units (IU, HSV-1 seronegative), 16 to 100 (ambiguous) and above 100 (seropositive, HSV-1 infected). At Quest diagnostics, the cutoff values were: <0.9 units (negative, HSV-1 uninfected), 0.9 to 5.0 (ambiguous) and above 5 (positive, HSV-1 infected). Data from patients with ambiguous exposure were not analyzed in either sample.

2.1. Quality control for serological assays

Randomly selected samples were analyzed in duplicate (N = 28). The duplicate samples matched completely with regard to HSV-1 seropositive status using the reference ranges for positive, negative or equivocal results. There were significant correlations for quantitative antibody titers between the pairs of samples, all of which were analyzed blind ($r = 0.92$, $p < 0.001$). Samples with equivocal antibody titers based on pre-determined cutoff values were not analyzed further (SZ, N = 9, non-psychotic, N = 10).

2.2.1. Sample 1, PNFU

Individuals with SZ and individuals without psychoses were included and re-assessed after 1–3 years (ages 18–50 years). Persons with substance abuse, medical or neurological disorders and those unable to complete cognitive tests were excluded.

2.2.2. Sample 2, RCT

All inclusion/exclusion criteria and RCT protocols were identical to our earlier US study (Prasad et al., 2013) (Fig. 1). The sample comprised

Table 1
HSV-1 exposure and temporal trajectory of cognitive function in published studies.

First author/reference	Study sample (N)	Cognitive tests	Follow up duration	Key results
Strandberg (Strandberg et al., 2003)	Random sample of Helsinki residents with cardiovascular disease (383)	MMSE, CDR	1 year	Reduction in MMSE scores proportional to viral burden due to HSV-1, CMV and HSV-2
Aiello (Aiello et al., 2008)	Community-dwelling elderly Latino sample (1204)	MMSE, episodic memory (word list-learning test)	4 years	Rate of cognitive decline significantly related to CMV titers, but not HSV-1 titers
Prasad (Prasad et al., 2012)	First-episode antipsychotic-naive SZ patients (26); Healthy subjects (38)	WCST	1 year	Greater reduction in perseverative errors in HSV-1 seronegative SZ patients than in the HSV-1-seropositive patients. No significant associations with CMV, or in healthy subjects.
Barnes (Barnes et al., 2014)	3 cohorts of elderly community members (N = 849)	MMSE, tests of working memory, episodic memory, visuospatial function	5 years	No significant temporal associations with HSV-1 status. CMV seropositivity associated with greater risk of Alzheimer disease and faster rate of cognitive decline in global cognition.
Nimgaonkar (Nimgaonkar et al., 2016)	Representative community sample of elders	MMSE, tests of complex attention, executive functions, memory, language, visuospatial function	5 years	IgG titers of antibodies to CMV, HSV-2 and Tox associated with differing patterns of greater cognitive decline. No temporal associations with HSV-1.

MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating scale; HSV-1: herpes simplex virus, type 1 (HSV-1); CMV: cytomegalovirus; HSV-2: herpes simplex virus, type 2 (HSV-2); Tox: Toxoplasma Gondii.

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