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Diminished somatostatin gene expression in individuals with HIV and major depressive disorder

Abstract—In analyzing the expression of 15 candidate genes for HIV encephalitis (HIVE) by the presence or absence of major depressive disorder (MDD), we noted significant reductions in the expression of four cytoskeletal genes and somatostatin. Whereas disruption of cytoskeletal genes has been noted in HIVE, dysregulation of somatostatin has not, indicating that dysregulation of somatostatin is part of the molecular pathologic process of MDD in the setting of HIV.

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The frequency of major depressive disorder (MDD) is significantly elevated in people with HIV infection,¹ which may increase nonadherence to antiretroviral therapy and potentially lead to treatment failure and mortality. It is not clear whether the excess MDD in the HIV-infected population represents recurrence of mood disorder that antedated HIV or is a reflection of the stress of living with a life-threatening illness or whether there is a pathologic mechanism resulting from HIV brain infection that results in enhanced vulnerability to psychiatric morbidity. Previously, we analyzed the gene expression of 15 genes during an investigation of gene dysregulation in HIV encephalitis (HIVE).² We noted four of these individuals had a history of MDD. In this group there was significant down-regulation of somatostatin and four cytoskeletal genes. Dysregulation of the cytoskeletal genes had also been noted in HIVE; however, decrease in gene expression of somatostatin was limited to MDD in the setting of HIV infection.

Neuropathologically, in primary MDD there is reduced cortical glial cell density and neuronal volume, which is thought to include dendritic simplification.³ In HIV infection there are dendritic and synaptic simplification and selective neuronal loss associated with HIV neurocognitive disorder.⁴ At the gene level, we have recently observed that in HIVE, there is dysregulation of several sets of genes including neuronal, dendritic, synaptic, and cell-cycling genes, all of which are involved in the maintenance of the cytoskeleton.⁵ Quantitative real time (qRT)-PCR of 15

identified genes revealed that HIVE was characterized by decreases in the gene expression of microtubule-associated protein 1B (*MAP1B*) and mitogen-activated protein kinase kinase 1 (*MAPKK1*).⁵

Methods. In the current study, we assessed somatostatin gene expression by qRT-PCR, as described in our previous study,⁵ on 21 cases; 5 of these had no HIV brain pathology, 8 had HIVE, and none had opportunistic infections or anoxic brain injury. Utilizing the prospectively acquired clinical data of the California NeuroAIDS Tissue Network,⁵ we identified within this group seven individuals who had a lifetime diagnosis of MDD, three of whom also had HIVE. In most cases, patients died as a result of acute bronchopneumonia or septicemia, and postmortem interval was within 24 hours of death (average approximately 12 hours). Risk factors for HIV infection included men who had sex with men, heterosexual transmission, and in one case IV drug use. In performing several statistical tests simultaneously, we considered the possibility of chance capitalization of type I error. To account for this, a more stringent definition of significance was adopted, where *p* values of 0.01 or below were considered significant. There were no statistical differences in the mean age, log plasma viral load, or plasma CD4 count of the group without a history of MDD (43.2 [6.5] years, 4.7 [0.7] copies/mL, and 115 [65] cells/mL) compared with those with a history of MDD (46.5 [9] years, 4.88 [0.98], 113.6 [58.3]). Of the seven cases with MDD, three also had HIVE.

Results. In our previous study of 13 individuals with HIV, some of whom had HIVE,⁵ we had undertaken qRT-PCR on 15 candidate genes derived from microarray analysis.⁵ Recently we found that 4 of these original 13 cases had a documented history of MDD, and when we reanalyzed the 15 candidate genes in relation to the presence of MDD (table), we found that there were significant decreases in gene expression in the group with MDD of 5 genes. The most dramatic was a 75% fall (*p* = 0.0087) in relative amount of the somatostatin gene. There was a 60% decrease (*p* = 0.0013) in the expression of synapsin II, approximately 40% reduction in tetraspan 5 (*p* = 0.0072), and approximately 35% diminution (*p* = 0.0065) in *PAK1* and *MAPKK1* (*p* = 0.0034).

In the light of these findings, in the current study, we sought to validate the significant reduction in somatostatin in a larger series of cases. We identified 21 cases, matched by age and sex, 14 of whom had no documented history of MDD and 7 of whom had a recorded lifetime event of MDD. In this extended series, we found that the mean relative amounts of somatostatin, by qRT-PCR was 15.9 ng (SEM 3.9 ng) in the no-MDD group vs 5.1 ng (SEM 4.7 ng) in the lifetime-MDD group. This was a (Wilcoxon

*See the appendix for a complete list of Group members.

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Table qRT-PCR-determined gene expression for 15 genes in HIV-infected cases with and without a history of MDD

Gene	No MDD	MDD	% Change	<i>p</i>	Gene	No MDD	MDD	% Change	<i>p</i>
Synapsin II (U40215)	34.4 (6.7)	14.0 (7.7)	-60	0.0013	<i>SMST</i> (J00306)	37.7 (23.4)	9.6 (10.1)	-75	0.0087*
<i>MAP1B</i> (L06237)	31.5 (8.5)	18.7 (5.4)	-41	0.025	Tetraspan 5 (AF065389)	61.4 (16.5)	36.7 (8.3)	-40	0.0072*
<i>Cdc42</i> (M35543)	58.0 (14.5)	40.0 (14.9)	-31	0.065	<i>IFITM1</i> (9-27) (J04164)	47.9 (33.5)	18.9 (16.3)		NS*
<i>MAPKK1</i> (L05624)	82.4 (12.5)	54.2 (13.1)	-34	0.0034	<i>PAK1</i> (U24152)	71.2 (10.8)	46.3 (15.8)	-35	0.0065
Vimentin (Z19554)	30.9 (11.6)	26.9 (12.3)		NS	<i>Tyro3</i> (U18934)	78.8 (39.6)	55.7 (17.4)		NS*
<i>SLC1A2</i> (U01824)	64.5 (16.4)	54.5 (19.9)		NS	<i>ISG15</i> (M13755)	119.1 (1524)	48.3 (39.5)		NS*
Connexin 43 (X52947)	69.2 (17.0)	62.3 (21.3)		NS	<i>IFP35</i> (U72882)	252.5 (202.3)	116.3 (81.7)		NS*
<i>STAT1</i> (M97935)	579.5 (421.7)	265.6 (360.2)		NS					

RNA ng brain tissue amounts for 15 candidate genes with SD in parentheses. Gene names are followed by their accession number. Statistical analysis was performed using one-way analysis of variance (*performed on log-transformed data).

qRT = quantitative real time; MDD = major depressive disorder; *MAP1B* = microtubule associated protein 1B; *cdc42* = cell division cycle 42 (GTP-binding protein, 25 kd); *MAPKK1* = mitogen-activated protein kinase kinase 1; *SLC1A2* = solute carrier family 1 (glial high affinity glutamate transporter), member 2; *STAT1* = signal transducer and activator of transcription 1, 91 kd; *SMST* = somatostatin; *IFITM1* (9-27) = interferon-induced transmembrane protein 1 (9-27); *PAK1* = p21/Cdc42/Rac1-activated kinase 1; *ISG15* = interferon-stimulated gene 15 kd; *IFP35* = interferon-induced protein, 35 kd.

rank sum, $p = 0.044$) 68% reduction in somatostatin gene expression levels in the MDD group.

Discussion. Our findings highlight a number of issues. First, the approximately 70% reduction in somatostatin gene expression noted in both the original four cases and the expanded series presented here indicate that this gene is involved in the pathophysiology of MDD in the setting of HIV. Second, as the other four genes that were down-regulated in the first four cases, but not pursued in the expanded series, were mainly related to the maintenance of the cytoskeleton, these genes may represent an overlapping dysregulation by both HIV and MDD. Genes previously shown to be dysregulated by HIV (*synapsin II*, *MAP1B*, *MAPKK1*, and *PAK1*) are generally involved in cytoskeletal maintenance.⁴ Synapsin II is a member of a family of synaptic vesicle phosphoproteins that regulates neurotransmitter release and both *MAP1B* and *PAK1* are involved in neurite outgrowth.⁵ *PAK1* and *MAPKK1* also function in cell signaling, adhesion, and cycling. Although *cdc42* gene down-regulation was a nonsignificant trend, this gene activates *PAK1*, which was significantly down-regulated. The activities of these genes suggest that diminution in the ability of dendrites and synapses to remodel may contribute to MDD in HIV-infected adults.

The substantial decrease in somatostatin RNA levels in the MDD group may play a primary role in the evolution of MDD in the setting of HIV. Low levels of somatostatin, a neuromodulatory transmitter found in a distinct population of interneurons arising from the medial ganglionic eminence, have been correlated with cognitive deficits. Furthermore, somatostatin has been found to have its highest levels of concentration located within the amygdale,

which is a cortical structure well documented for its extensive role in emotional processing.⁶ Previous research has also documented that somatostatin can cause a potent increase in striatal dopamine levels, which also suggests a potential functional role in mood regulation.⁷ Alongside this, the somatostatin analogue vapreotide antagonizes neurokinin receptors and antagonism of neurokinin receptors is the target of a new generation of antidepressants.

Although the precise pathways determining the expression of these dysregulated genes remain to be elucidated, mechanisms to explore include 1) the possibility that the promoter region of the genes dysregulated in this study have similar elements that could all be affected by a polymorphism of a key transcription factor and 2) the gene changes are secondary to alterations of a trophic factor or neurotransmitter. Future studies to define the mechanisms are required to increase our understanding.

In this analysis we were not able to account for potential effects of psychotropic medication. Further characterization of the somatostatin and cytoskeletal gene dysregulation in HIV-infected MDD, including medication effects, will clarify their role in the molecular pathology of depression both in and outside the context of HIV infection.

Appendix

The San Diego HIV Neurobehavioral Research Center (HNRC) Group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the San Diego Veterans Affairs Healthcare System and includes the following: director: Igor Grant, MD; co-directors: J. Hampton Atkinson, MD, and J. Allen McCutchan, MD; center manager: Thomas D. Marcotte, PhD; Naval Hospital, San Diego: Mark R. Wallace, MD (P.I.); neuromedical component: J. Allen McCutchan, MD (P.I.), Ronald J. Ellis, MD, Scott Letendre, MD, Rachel Schrier, PhD; neurobehavioral component: Robert K. Heaton, PhD (P.I.), Mariana Cherner, PhD, Joseph Sadek, PhD, Steven Paul Woods, PsyD; imaging component: Terry Jernigan, PhD (P.I.), John Hesselink, MD, Michael J. Taylor, PhD; neuropathology component:

Eliezer Masliah, MD (P.I.), Ian Everall, MD, PhD, Dianne Langford, PhD; clinical trials component: J. Allen McCutchan, MD, J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, Scott Letendre, MD; data management unit: Daniel R. Masys, MD (P.I.), Michelle Frybarger, BA (data systems manager); statistics unit: Ian Abramson, PhD (P.I.), Deborah Lazzaretto, MS, Tanya Wolfson, MA.

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