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DEMENTIA FOLLOWING HERPES ZOSTER ENCEPHALITIS:

Grand Rounds

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Abstract

We studied the rare case of an older adult with dementia following herpes zoster encephalitis (HZE). This 71-year-old woman presented to us approximately 1 year following resolution of a rapid-onset episode of HZE, and subsequently underwent neuropsychological and neuroimaging examinations. Cognitive assessment revealed impairments in general cognitive functioning, verbal and nonverbal memory, executive functions, speed of information processing, attention/working memory, and motor skills. The patient's neuroimaging data, when compared to a demographically similar healthy control sample (n = 9), demonstrated moderate central and perisylvian brain volume loss, several subcortical lesions in the white matter, and resting state whole brain and hippocampal hypoperfusion. These findings highlight neuropsychological changes evident in a dementia syndrome of this type, and they suggest that early identification and treatment of HZE has implications for the preservation of long-term cognitive functioning.

Keywords

Herpes zoster; Encephalitis; MRI; Cognition; Dementia

INTRODUCTION

Herpes zoster (HZ), or shingles, is caused by the varicella-zoster virus (VZV; Weller, 1953). It typically affects middle-aged and older adults and is more common and severe in immunocompromised individuals (Kupperman et al., 1994; Mazur & Dolin, 1978; Merselis, Kaye, & Hook, 1964). The annual incidence of HZ in population-based studies has ranged from 3.6/1000 to 14.2/1000 in the oldest individuals (Thomas & Hall, 2004), affecting up to 50% of those who live to 85 years old (Schmader, 2001). Encephalitis is a rare but serious complication of herpes zoster (Appelbaum, Kreps, & Sunshine, 1962). Its annual incidence

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is not well understood (e.g., Appelbaum et al., 1962), although it is thought to be rare but may occur in up to 5% of patients who require hospitalization (Mazur & Dolin, 1978). Few studies have examined the brain changes and cognitive outcomes associated with herpes zoster encephalitis (HZE). Existing HZE studies show considerable variability in terms of the brain regions affected, severity of neurologic damage, and cognitive domains preferentially affected. In addition, the symptoms associated with HZE are thought to be variable, although it often begins with a clearly defined constellation of symptoms of sudden onset such as headache, vomiting, fever, and altered sensorium. Generally, the course of HZE is short, lasting only 1–3 weeks (Appelbaum et al., 1962).

In terms of mental status, HZE patients often present as disoriented and confused and may demonstrate cognitive deficits during the acute encephalitic phase; however, this clinical presentation typically improves dramatically over the course of a few weeks (Jemsek et al., 1983). Given that there exist few data describing the neuropsychological sequelae beyond the acute stage, and that the few existing studies report inconsistent findings, debate remains as to whether HZE appreciably modifies cognitive or brain functioning after the acute stages. Further, to our knowledge, no other studies have focused on the effects of HZE on neuropsychological functioning in older adults. We therefore performed neuropsychological and neuroradiological examinations of an older adult with HZE approximately 1 year after onset and treatment of HZE.

CASE REPORT

A 71-year-old right-handed, English-speaking, Caucasian woman with 12 years of education was referred to our neuropsychology clinic with a 10-month history of memory complaints following HZE. Approximately 10 months prior to the current neuropsychological exam and 13 months prior to the neuroimaging exam the patient acutely developed a backache, nausea, and mental confusion, and within a couple of days she had developed a left-sided rash on and around her chest, rib cage, arm, and back. Symptoms continued to worsen and the patient presented to the emergency department 10 days after symptom onset at which point she was diagnosed with HZE, hospitalized, and treated with antiviral medication. Of note, antiviral medications have been shown to be effective when initiated within 72 hours of lesion onset (see Whitley, 2009, for review), and our patient's relatively late intervention may have impacted her prognosis. Indeed, in a study of encephalitis due to another virus in the same group, herpes simplex virus (HSV), time from symptom onset to antiviral treatment was the best predictor of cognitive outcome (Kaplan & Bain, 1999). Despite this, delayed treatment or, in relatively mild cases, lack of treatment is not uncommon (Cunningham & Dworkin, 2000). In fact, in one study of 957 HZ patients only two-thirds of participants received antiviral treatment within 72 hours of the onset of rash (Oxman et al., 2005).

Prior to the onset of HZE, according to both the patient and family, she reportedly was functioning normally in all aspects of her daily life. Her cognition was purportedly intact and an objective neuropsychological measure estimated her premorbid intellectual functioning to be in the high average range (American version of the National Adult Reading Test [ANART] standard score = 112). She performed both basic and complex instrumental activities of daily living independently, and she maintained a vigorous schedule of volunteer activities in the community. Both the patient and her family denied any memory problems prior to the onset of HZE. Since her hospitalization, however, both the patient and her husband reported acute, striking impairments in her ability to perform activities of daily living, and she no longer performs a number of previously independent activities such as driving, finances, yard work, and cooking. The patient and her husband reported lingering difficulties in memory as their primary concern since her hospitalization, which prompted

her referral for neuropsychological assessment. These memory problems reportedly had remained stable since her illness. In addition to these cognitive difficulties, the patient reported suffering from postherpetic neuralgia as a complication of her HZ illness.

In terms of the patient's other relevant medical history, she reported a cardiac arrhythmia beginning 9 years ago as well as hypertension that is well controlled with medication. She denied a history of any other vascular risk factors including diabetes, high cholesterol, or cigarette smoking. Family history, per the patient, is positive for cardiovascular disease (in the patient's mother and father) but negative for dementia, stroke, or other neurological problems.

METHOD

Neuropsychological testing

The patient underwent neuropsychological testing including assessment of *global cognitive functioning* (Wechsler Adult Intelligence Scale – 3rd edition [WAIS-III; Wechsler, 1997; normative data for all WAIS-3 scores drawn from Wechsler, 1997] Full Scale IQ and Mattis Dementia Rating Scale [DRS; Mattis, 1976; normative data drawn from Mattis, 1988]), *verbal memory* (California Verbal Learning Test – II [CVLT- II; Delis, Kramer, Kaplan, & Ober, 2000; normative data drawn from Delis et al., 2000] and Wechsler Memory Scale – Revised [WMS-R; Wechsler, 1987; normative data drawn from Wechsler, 1987] Logical Memory subtest), *visual memory* (WMS-R Visual Reproduction subtest), *executive functions* (Wisconsin Card Sorting Test [WCST 64-card version; Kongs, Thompson, Iverson, & Heaton, 2000; normative data drawn from Heaton & PAR Staff, 2003], Trail Making Test and Color-Word Interference subtests of the Delis-Kaplan Executive Function System; [Delis et al., 2001; normative data drawn from Delis et al., 2001]), and *verbal fluency* (letter and category fluency; normative data drawn from Heaton, Miller, Taylor, & Grant, 2004), *speed of information processing* (WAIS-III Digit Symbol and Symbol Search subtests, Digit Vigilance Test [Lewis, 1995; normative data drawn from Heaton et al., 2004]), *attention/ working memory* (WAIS-III Digit Span, Arithmetic, and Letter-Number Sequencing subtests), *spatial skills* (WAIS-III Block Design and Picture Completion subtests), *verbal/ academic skills* (WAIS-III Vocabulary subtest and Boston Naming Test [BNT; Kaplan, Goodglass, & Weintraub, 1983; normative data drawn from Heaton et al., 2004]), and *motor skills* (Finger Tapping, Hand Dynamometer, and Grooved Pegboard; normative data drawn from Heaton et al., 2004). Her score on the Beck Depression Inventory-2 (3) was within the range suggestive of a minimal level of self-reported depression.

Neuroimaging

MR exams were performed on a 3.0 Tesla General Electric Medical Systems EXCITE whole-body imager with an eight-channel receive-only head coil (General Electric Medical Systems, Milwaukee, WI, USA). Nine cognitively normal older women who were demographically similar to the patient (mean age of control group = 77.8, range = 66–87; mean education of control group = 13.7 years, range = 8–18 years) also underwent neuroimaging exams. The data from these control participants were used as reference material to aid in interpretation of the patient's neuroimaging data. Hippocampal regions of interest were manually delineated for use in analyses using a method published previously (Jak, Houston, Corey-Bloom, Nagel, & Bondi, 2007; see Figure 1). The patient's neuroimaging exam was performed 3 months after the neuropsychological evaluation. All of the control participants gave their informed consent to participate in the study and the patient assented to the study (and her husband provided surrogate consent).

Per the patient's medical records, a neuroimaging examination involving magnetic resonance imaging (MRI) and computed tomography (CT) scans at the time of her acute presentation with HZE revealed bilateral temporal lobe encephalomalacia, small bilateral cerebellar infarcts, and periventricular deep white matter changes. As mentioned above, the infarctions and deep white matter changes were not thought to represent acute processes. However, of note, on neuroimaging (e.g., Reshef, Greenberg, & Jankovic, 1985) and neuropathological examination (e.g., Horten, Price, & Jimenez, 1981), lesions of the white matter or at the white–gray matter junction are often found after HZE. Three additional clinical neuroimaging examinations performed 6, 14, and 16 months after the patient's acute presentation were stable with no changes, as compared to the scans performed during her illness.

RESULTS

Neuropsychological assessment

A neuropsychological assessment demonstrated deficits in several cognitive domains including general cognitive functioning, verbal and nonverbal memory characterized by deficits in both encoding/storage and retrieval, executive functions, speed of information processing, attention/working memory, and bilateral motor skills with relative preservation of visual-spatial abilities and verbal/academic skills (see Table 1).

Neuroradiological examination

The MR angiogram showed that the patient had normal intracranial arteries. However, findings from the axial fluid-attenuated inversion recovery (FLAIR) images revealed several small lacunar infarcts present in the subcortical white matter, right thalamus, and basal ganglia. In addition, subcortical lesions that likely represent chronic changes of microvascular ischemia were observed (Figure 1). Corroborating this observation, quantification of deep white matter lesion (DWML) pathology demonstrated greater burden in the HZE patient relative to the control group. Moreover, the T1-weighted anatomical scan showed moderate central and perisylvian brain volume loss greater than would be expected for the patient's age. Finally, findings from arterial spin labeling (ASL) showed reduced whole brain and bilateral hippocampal resting cerebral blood flow (CBF; see Table 2).

DISCUSSION

The effects of HZE on cognition and brain functioning after the acute stages are still poorly understood. In fact, to our knowledge, there are only two published studies examining the neuropsychological sequelae following acute HZE. Hokkanen et al. (1997) reported a pattern of neuropsychological performance in nine HZE patients that resembled a subcortical cognitive impairment characterized by poorer processing speed and memory as well as mood changes and behavioral disinhibition in the absence of aphasia, agnosia, or apraxia. However, the neuropsychological findings were noted to be very mild and, with the exception of one patient who was re-examined 7 months after the initial exam, there was no long-term follow-up.

Hokkanen and colleagues (1997) also reported normal brain computed tomography (CT) scans in five of their patients and mild diffuse cortical and central atrophy in the other four patients. The authors generally attributed these findings to age-related brain changes. They also administered single photon emission computed tomography (SPECT), which predominantly showed bilateral frontal hypoperfusion. Taken together, Hokkanen and colleagues suggested the pattern of perfusion and cognitive changes distinguished HZE from encephalitis due to HSV. Specifically they commented that, unlike HZE, encephalitis due to

HSV is often accompanied by focal hyperperfusion (e.g., Launes et al., 1988) and memory impairment that is global and severe in nature.

Hokkanen et al. (1997) also reported infarct-like hypodense lesions in two of their nine HZE patients. As they noted, previous studies of herpes zoster patients have shown MRI and CT findings of lesions within the subcortical white matter of regions including the frontal lobe, basal ganglia, caudate nucleus, internal capsule, and thalamus as well as cortical regions (e.g., see Reshef et al., 1985). However, such studies were based on individuals who were immunosuppressed prior to the onset of HZE and did not receive antiviral treatment. Hokkanen and colleagues speculated that differences in patient characteristics between their study and prior studies may contribute to the variability in findings. They concluded that tissue damage and cognitive deficits may be less extensive/severe in individuals who were otherwise relatively healthy, although our results suggest that this may not hold true in older adults.

In another study, Wetzel et al. (2002) reported that eight HZE patients examined 4–52 months after symptom onset performed significantly more poorly on the copy condition of the Rey-Osterreith Complex Figure (ROCF), although the HZE patients performed comparably to their demographically matched normal control sample on all other cognitive measures. In our patient, executive but not visual-spatial skills were impaired, although some commonalties between our patient and the findings observed by Wetzel et al. are plausible if one assumes the ROCF assesses both visual-spatial perception as well as executive functions related to organization and planning.

In contrast to these studies that reported no or relatively mild neuropsychological deficits, the patient with HZE that we studied demonstrated severe cognitive impairment across several neuropsychological domains. This finding indicates that HZE can result in relatively severe, long-term cognitive deficits in an individual who was immunocompetent and otherwise healthy at the time of infection. In addition, our findings demonstrating that both verbal and visual memory were impaired and that hippocampal volume was reduced stand in contrast to the findings of Hokkanen and colleagues (1997) who proposed that a lack of a global memory deficit can distinguish HZE from HSV encephalitis. It is well known that encephalitis due to HSV results in temporal lobe damage and subsequent severe memory impairment. Indeed, a review of cognitive outcomes in encephalitis found that an anterograde memory deficit is the most common neuropsychological consequence of HSV encephalitis, although retrograde amnesia is also common (Hokkanen & Launes, 2000).

Our results may have varied from those of Hokkanen et al. (1997) and Wetzel et al. (2002) for several reasons. First, those studies included young participants (e.g., in their teens or twenties) in their sample and thus the impact of HZE may not have been as profound in the acute stage. Indeed, both advanced age (Hope- Simpson, 1965) and postherpetic neuralgia (Johnson, 2002) are associated with increased severity of HZ infection. Given our patient's age and history of postherpetic neuralgia, it is possible that she experienced a more severe infection relative to the participants in prior studies. A more severe infection as well as a relatively late intervention with antiviral medications may also have resulted in greater neural and cognitive deficits. Second, neither study involved the assessment of multiple cognitive domains as was done in the current study. Brief batteries assessing gross cognitive function likely limit the ability to fully detect and describe the extent, nature, and severity of resulting cognitive impairment. Third, we employed a much more thorough and detailed imaging protocol, allowing us to better appreciate and describe brain changes in structure and blood flow associated with HZE.

Given our patient's age, as well as her cognitive changes and neuroradiological findings that are not necessarily specific, we must consider whether our patient was experiencing a dementing process independent of HZE. Consistent with a progressive neurodegenerative condition, such as AD, our patient demonstrated rapid forgetting and decreased hippocampal volumes. However, several other findings are inconsistent with AD, including the patient's abrupt onset of cognitive deficits that occurred during her acute HZE phase as well as the static nature of these deficits since testing. Further, she demonstrated impairments in motor skills, which are not typically observed in early AD. Finally, per the patient's medical records, there was no evidence of progressive atrophy as indicated by stable serial structural MRI exams conducted over a 16-month period when compared to scans acquired during the acute encephalitic period.

Similarly, given that our patient presented with some vascular risk factors and documented white matter changes, we must consider the possible influence of vascular processes. However, she had relatively few vascular risk factors and these white matter changes were not thought to be an acute process at the time of the onset of her cognitive problems. Nonetheless, it is possible that the patient's reported preexisting white matter changes may have lowered the threshold of acute damage required for striking cognitive and functional changes following HZE. Further, given that the patient did not demonstrate symptoms of Parkinsonism or a hyperkinetic movement disorder, changes in personality, or prominent psychiatric symptoms, several other forms of dementia (e.g., Parkinson's disease, Huntington's disease, frontotemporal dementia) can be tentatively ruled out. In addition, there were no suggestions of other viral (e.g., HIV) or autoimmune disorders (e.g., lupus, multiple sclerosis) during her hospitalization or following her discharge. Taken together, the patient's abrupt onset of cognitive deficits coinciding with the acute phase of HZE and the static nature of these deficits suggest a pattern of cognitive impairment consistent with dementia following HZE. Furthermore, stable serial MRI examinations and lack of further decline noted by the family provide additional support for the role of HZE as the primary cause of her neurocognitive profile.

In sum, our patient was immunocompetent at the time of HZE onset and received effective antiviral treatment approximately 10 days after symptom onset. Despite treatment, she demonstrated a significantly poor outcome at follow-up characterized by the following: (1) impairments in multiple cognitive domains; (2) greater brain atrophy than expected for her age; (3) increased deep white matter lesion volume; and (4) resting state whole brain and hippocampal hypoperfusion. Due in part to its rarity, HZE may lead to diagnostic and therapeutic challenges. Given that treatment with antiviral medications appears to be effective (e.g., Peterslund, 1988), this case demonstrates the clinical importance of early detection and treatment of HZE with the goal of preservation of cognitive and brain function. Although this is the first detailed case study to assess a patient with HZE using a detailed neuropsychological battery and neuroradiological protocol, larger studies are needed in order to further elucidate the specific brain changes and cognitive outcomes associated with HZE.

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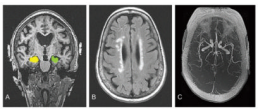

Figure 1.
MRI scans of herpes zoster encephalitis (HZE) patient. (A) Coronal section displaying the manually-outlined hippocampal region of interest (ROI) used in the volumetric and regional CBF analyses. (B) Axial section of FLAIR scan revealing periventricular and deep white matter lesions. (C) Axial section of angiogram demonstrating normal intracranial arteries.

Table 1

Neuropsychological test scores of herpes zoster encephalitis patient

Cognitive measure	Raw score	T-score/scaled score (SS)/Z-score
Global cognitive functioning		
WAIS-III FSIQ	82	T = 34
Dementia Rating Scale	127/144	T = 35
Verbal episodic memory		
WMS-R Logical Memory 1 (Immediate Recall)	15/50	SS = 5
WMS-R Logical Memory II (Delayed Recall)	7/50	SS = 3
WMS-R LM Percent Savings	47%	
CVLT-II Learning Trials (1–5)	31	T = 38
CVLT-II Long Delay Free Recall	0	Z = −2.5
CVLT-II Total Recognition Discriminability	1.5	Z = −1.5
CVLT-II Forced Choice Recognition	16/16	92.5% of normative sample in patient's age group performed at 100% accuracy
Visual episodic memory		
WMS-R Visual Reproduction I (Immediate Recall)	20	SS = 5
WMS-R Visual Reproduction II (Delayed Recall)	5	SS = 3
WMS-R Visual Reproduction Percent Savings	25%	
Executive functions		
WCST-64 Perseverative Responses	21	T = 43
WCST-64 Categories	1	11–16 percentile
WCST-64 Set Losses	0	
WCST-64 Total Errors	36	T = 35
Trail Making Test Part B	300″	T = 18
Letter Fluency – F, A, and S words	28	T = 39
Category Fluency – Animals	7	T = 19
D-KEFS Color-Word Interference – Inhibition/Switching Trial	180″	SS = 1
Speed of information processing		
Trail Making Test Part A	88″	T = 23
Digit Vigilance-Time	908″	T = 32
WAIS-III Digit Symbol	36	SS = 7
WAIS-III Symbol Search	12	SS = 6
Attention/working memory		
Digit Vigilance-Errors	23	T = 33
WAIS-III Digit Span	15	SS = 10
WAIS-III Arithmetic	7	SS = 6
WAIS-III Letter–Number Sequencing	3	SS = 4
Spatial skills		
WAIS-III Block Design	20	SS = 8
WAIS-III Picture Completion	11	SS = 7
Verbal/academic skills		
WAIS-III Vocabulary	30	SS = 8

Cognitive measure	Raw score	T-score/scaled score (SS)/Z-score
Boston Naming Test	50	T = 44
Motor skills		
Finger Tapping – Dominant hand	27.8	T = 36
Finger Tapping – Non-dominant hand	23.2	T = 31
Hand Dynamometer – Dominant hand	16.5	T = 39
Hand Dynamometer – Non-dominant hand	13.0	T = 35
Grooved Pegboard – Dominant hand	152″	T = 28
Grooved Pegboard – Non-dominant hand	158″	T = 33

SS=Scaled score (mean=10; *SD*=3). T-score (mean=50; *SD*=10). Z-score (mean=0; *SD*=1). WAIS-III=Wechsler Adult Intelligence Scale – 3rd edition. WMS-R=Wechsler Memory Scale – Revised. WCST-64=Wisconsin Card Sorting Test – 64 Card Version. CVLT-II=California Verbal Learning Test – 2nd edition. D-KEFS=Delis-Kaplan Executive Function Scale.

Table 2

Patient–control comparisons of brain volume and perfusion indices

Brain measures	HZE patient	Control group Mean (*SD*)	Z-score of HZE patient*
DWML (mm^3)	5613.41	1443.73 (2592.56)	1.61
Whole Brain Gray Matter Volume	0.45	0.44 (0.02)	0.33
Bilateral Hippocampal Volume	0.45	0.48 (0.05)	−0.75
Whole Brain CBF	30.35	51.34 (13.60)	−1.54
Bilateral Hippocampal CBF	42.63	61.37 (15.32)	−1.22

DWML = deep white matter lesion volume. CBF = cerebral blood flow measured in mL/100 g tissue/minute. Note: Whole brain gray matter and bilateral hippocampal volumes were normalized by dividing the structure volumes by the whole brain volume to correct for intersubject differences in overall brain size. Hippocampal volume values were multiplied by 100.

*Z-scores for the HZE patient are based on the mean and *SD* of control group.