Case Study

Neuropsychological Consultation in Infectious Diseases: Pathogenesis and Neuropsychological Sequelae in Herpes Simplex Encephalitis

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Abstract

Herpes simplex encephalitis (HSE) is an acute or subacute sporadic encephalitic illness. It has a predilection for the medial temporal lobes, the orbital surface of the frontal lobes, and subcortical structures such as the hippocampus. Sequelae may include seizures and neuropsychological impairment. The present case study involves a 66-year-old, retired, Caucasian male diagnosed with herpes simplex encephalitis. Evaluation methods consisted of electrophysiological, laboratory, and radiological testing. Comparison of neuropsychological test results yielded high agreement in terms of site of lesion as documented by MRI and EEG findings. Neuropsychological test findings are described in detail. This case study serves to underscore the clinical utility of neuropsychological testing in infectious disease consultations, specifically in herpes simplex encephalitis.

Keywords herpes simplex encephalitis; herpes simplex virus—type 1; seizure; neuropsychological testing; temporal lobe; neurocognitive rehabilitation

1 Introduction

Neuropsychologists have recently found new avenues of consultation—liaison in the area of infectious diseases (known in the vernacular as “ID”). Very challenging and complex consultation—liaison cases may surface for the practicing clinician, which are also rich in teaching possibilities for students such as practicum students, externs, interns, and postdoctoral fellows or residents. Some of the pathological conditions that may be of interest are the infectious diseases involving the brain. These conditions include: brain abscess, thrombosis of the dural sinuses and cavernous sinus thrombosis, meningitis, neurosyphilis, chronic basal meningitis, cysticercosis and neurocysticercosis, cryptococcus neoformans, histoplasmosis, aspergillosis, toxoplasmosis, cerebral malaria, trypanosomiasis, echinococcosis, schistosomiasis trichinosis, viral encephalitides, rabies, herpes simplex encephalitis, coxsackie viral infections, cytomegalovirus infection, poliomyelitis, measles encephalitis, Jakob-Creutzfeldt, and Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome [26]. The present article describes a case study based on information presented at the 2006 National Academy of Neuropsychology Grand Rounds [23]. This case study underscores the clinical utility of neuropsychological testing in the diagnosis, localization of lesion or trauma, and treatment planning of infectious diseases, specifically herpes simplex encephalitis.

Herpes simplex encephalitis (HSE) is an acute or subacute sporadic encephalitic illness that affects all age groups and is the most common fatal necrotizing focal encephalitis in adults [3,18,22]. It is important to note that untreated patients with HSE caused by herpes simplex virus—type 1 (HSV-1) have a 70%–80% mortality rate [3,22,26]. Among the treated survivors, more than 50% are left with moderate to severe neurological deficits [3]. This disease can affect any age group, but is most common in those under 20 and over 40 years of age. In older children and adults, the majority of herpes encephalitis cases are caused by herpes simplex virus—type 1 (HSV-1; commonly called oro-facial herpes), which upon infection remains latent in the trigeminal nerve ganglion. In neonates and younger children, the majority of herpes encephalitis cases are caused by herpes simplex virus—type 2 (HSV-2; commonly called genital herpes), which is acquired through delivery. There appears to be no sex or race predisposition. The focus of this communication will primarily examine HSE in adults caused by HSV-1.

The pathogenesis of HSE is poorly understood. However, it is thought that transmission of HSV-1 spreads to the brain from structures in or around the base of the brain rather than through the blood stream. The neuronal transmission of the virus occurs from the peripheral neuron in retrograde fashion to the brain, usually through the
trigeminal or olfactory tract. HSE may also be caused by a reactivation of a latent peripheral infection in the olfactory bulb or in the trigeminal ganglion or a central infection in the brain itself. Once in the brain, the virus initiates a destructive hemorrhagic process. HSE has a predilection for the medial temporal lobes and the orbital surface of the frontal lobes, insular cortex, posterior occipital cortex, cingulated gyrus [22] as well as much of the subcortical structures of the limbic system such as the hippocampus, and has a tendency to produce marked necrosis of all tissue elements in the brain. It is not uncommon for one side of the brain to be considerably more involved than the other, and this localization may be related to the path of entry. The lesions may begin either unilaterally or bilaterally in the medial temporal cortex and then spread along the limbic pathways to the orbital frontal lobe and insular cortex [35]. The reverse pattern of category-specific deficits (semantic naming of nonliving stimuli) has also been found in this population with damage to the inferomedial temporal lobe associated with impaired performance for living stimuli (i.e. animals, plants) [10,21,34]. The reverse pattern of category-specific deficits (semantic naming of nonliving stimuli) has also been found in this population with damage to frontoparietal areas [11]. Additionally, there has been research to support that objects visually similar in presentation contribute to identification errors [28]. However, it is important to note that research has shown that items from different semantic categories can differ along stimulus variables (i.e. familiarity and visual complexity), which can influence recognition/naming performance [31]. Therefore, suggested dissociations between semantic categories can only be interpreted with confidence if these variables have been taken into consideration.

Neuropsychological testing has important clinical utility in the diagnosis and treatment of the neurocognitive and neurobehavioral manifestation of herpes simplex encephalitis.

2 Clinical presentation and course

A variety of neurological and neurobehavioral sequelae may occur as a result of herpes simplex encephalitis. It is important for the clinician to keep in mind that the clinical presentation is kaleidoscopic, varying with the manner and intensity of the HSV-1 transmission and the damage to neighboring tissues. The presentation of signs and symptoms can be multifocal in appearance. HSE may present with a short prodromal phase (3–5 days) of fever and headache [32]. It presents as signs of a focal encephalitis, often with seizures, vomiting, decreased level of consciousness, visual disturbances, memory problems, and vertigo [3,22]. Neurologic signs include aphasia, apraxia, agnosia, delirium, confusion, and behavioral changes [3,13,22,32]. Partial seizures that can secondarily generalize may take place and abnormal brain electrophysiology occurs in most patients. Hemiparesis is evident at presentation in approximately one-third of cases [3]. Psychiatric signs include irritability, distractibility, aggressive episodes, emotional blunting, psychosis, delusions, olfactory, gustatory, and auditory hallucinations, periods of apathy and depression, and episodes of restlessness. Other symptoms presented in the literature include: speech disturbances (some described above) and a partial or complete Kluver-Bucy syndrome may be seen [18,33].

It has been suggested that the diagnosis of HSE should be considered, “in any patient with a progressively deteriorating level of consciousness, fever, abnormal CSF findings, and focal neurologic abnormalities in the absence of any other causes” [3]. The primary indication to HSE rather than a different type of encephalitis is focality, especially to the temporal lobe [38]. The diagnosis of HSE is multifaceted and consists of lab studies (Polymerase chain reaction analysis [PCR] of cerebral spinal fluid and lumbar puncture and cerebral spinal fluid [CSF] analysis), imaging studies (magnetic resonance imaging [MRI] and computed tomography [CT] head scan), and electroencephalography (EEG).

Polymerase chain reaction is considered the standard criterion for diagnosis of HSE. PCR analyses the cerebral spinal fluid for HSV DNA. This technique is highly sensitive (94–98%) and specific (98–100%) [3] and results become positive within 24 hours of the onset of symptoms. The viral load in the cerebral spinal fluid is correlated with the clinical course and the presence of viral DNA at the end of antiviral therapy is linked with a poor outcome [3]. Lumbar puncture and cerebral spinal fluid analysis examines opening pressure (elevated in HSE), glucose (normal or mildly decreased in HSE), protein (mildly elevated in HSE), pleocytosis (10–1,000 cells/mm³ in HSE), and red blood cells (xanthochromia: frequently seen-presence or absence not diagnostic of HSE) [3,12,15].

MRI of the brain is the preferred imaging study and may show changes in the medial temporal and/or inferior frontal areas. Although an abnormal MRI of the brain is not enough to confirm a diagnosis of HSE, findings of localized temporal lobe abnormalities may be highly suggestive of further inquiry into the possible diagnosis of HSE. A CT scan of the head may show abnormalities of the temporal and/or frontal lobes with the most characteristic appearance of an area of low attenuation in the medial portion of the temporal lobe and undersurface of the frontal lobe [12]. However, it should
be noted that approximately one-third of individuals diagnosed with HSE will present with a negative head CT [3].

Finally, EEG can be analyzed and in fact may show changes earlier than the MRI. The EEG may show focal abnormalities over the involved temporal lobes with the earliest changes in focal-temporal or lateralized delta activity. EEG patterns include focal slowing, spiking, and characteristic repetitive slow wave lateralizing epileptiform discharges [10,15]. Pseudoperiodic complexes may appear over temporal regions and may rapidly change from day to day [4].

Treatment of HSE generally includes antiviral therapy. Individuals with whom treatment is instituted earlier generally have a better outcome than those with whom treatment is begun when they are in a semicomatose or comatose state. Research has suggested that cognitive outcomes are better in patients with a short delay between onset of symptoms and antiviral treatment (less than 5 days) compared to those with a longer delay between symptom onset and treatment [34].

3 Case study
The present case study involves a left-handed, 66-year-old, retired, married, Caucasian male, with 18 years of formal education who previously worked as an electrical engineer. He was discovered by his wife to be dry heaving and gagging. He then proceeded to have what was initially perceived as a syncopal episode, but then had some foaming at the mouth with jerking movements of his extremities. His wife immediately called 911 and the patient was brought to the hospital in a postictal state. Upon admission to the emergency department, the patient was confused and nonresponsive to verbal questioning. He became agitated necessitating the combined physical restraint of three male nurses and the emergency room physician to contain him. He required chemical restraint and eventually required physical placement in four leather restraints.

The patient was admitted to the neuro-intensive care unit and placed on a ventilator due to respiratory arrest. During the hospital course, his cerebral spinal fluid was analyzed by PCR analysis. Results from the PCR analysis of this patient’s cerebral spinal fluid were positive for detection of HSV DNA. Furthermore, the EEG revealed abnormal activity with 4 to 5 Hz background and diffuse slower 1 to 3 Hz activity consistent with a generalized cerebral process of nonspecific etiology. The CT scan revealed some motion artifacts at the base of the skull but no evidence for an acute hemorrhage, acute cortical infarct, edema, or mass effect. The pre and postcontrast MRI of the brain revealed abnormalities over the involved temporal lobes with the changes earlier than the MRI. The EEG may show focal slowing, spiking, and characteristic repetitive slow wave lateralizing epileptiform discharges [10,15]. Pseudoperiodic complexes may appear over temporal regions and may rapidly change from day to day [4].

Upon confirmation of HSE as the infecting agent, the patient was treated with antiviral therapy (intravenous Acyclovir), antibiotics (Rocephin and Doxycycline), anticonvulsant (Depakote) for seizure prophylaxis, and antipsychotic (Geodon) for cognitive impairment.

At the time of discharge, the patient’s speech had become somewhat more fluent; however, he continued to exhibit some word blocking, some difficulty with hesitance of speech, and some word retrieval difficulties. The patient was initially placed on Depakote but he was switched to Dilantin secondary to complaints of a Depakote-induced tremor. He then developed Dilantin toxicity and was placed back on Depakote (500 tid) with more optimal tolerance.

Referral for clinical neuropsychological testing was done over several testing sessions. The neuropsychological test battery was shortened secondary to the patient’s unrelated medical conditions (gastrointestinal and orthopedic), which limited the execution of a complete Halstead-Reitan neuropsychological battery, WAIS-III, and specialized frontal lobe testing. The neuropsychological tests were chosen to provide the most comprehensive profile of the patient’s cognitive functioning, while specifically examining the presenting complaints and referral questions surrounding memory and language issues. While some of the tests administered may overlap in general focus, they each provide information on specific cognitive functions and may act to support other clinical data, such as information provided in history gathering and collateral interviews. The neuropsychological testing included the following abbreviated battery: clinical diagnostic interview; Mini-Mental Status Exam (MMSE) [14]; selected tests from the Halstead-Reitan Neuropsychological Battery (HRNB) [27] including Trail Making Test (A & B), Strength of Grip, and Finger-Tip Number Writing; Boston Naming Test (BNT) [19]; Wechsler Memory Scale—3rd ed. (WMS-III) [36]; Mini-Inventories of Right Brain Injury—2nd ed. (MIRBI-2) [24]; Benton Visual Form Discrimination [9]; Rey-Osterrieth Complex Figure Test (ROCFT; copy, immediate recall, 30 minute delayed recall, and 30 minute recognition task) [20]; Wechsler Abbreviated Scale of Intelligence (WASI) [37]; Dementia Rating Scale—2nd ed. (DRS-2) [17]; Pocket Smell Test (PST) [29]; Computerized Assessment of Response Bias (CARB) [11]; Word Memory Test (WMT) [2]; Geriatric Depression Scale [30]; Beck Anxiety Inventory (BAI) [5]; Beck Depression Inventory—2nd ed. (BDI-2) [8]; Beck Hopelessness Scale (BHS) [7]; and Beck Scale for Suicidal Ideation (BSI) [6]. Significant highlights from the neuropsychological testing completed with this patient are listed in Table 1.

4 Discussion
During the neuropsychological testing, the patient put forth considerable effort and motivation. All of the scores on the
specific auditory memory weakness was characterized by memory deficit (General memory = 67, extremely low), and a 20-point gap between his Auditory immediate index (68, extremely low) and his Visual immediate index (88, low average), and a 24-point gap between his Auditory delayed index (64, extremely low) and his Visual delayed index (88, low average). This patient did not appear to benefit when given cues, as shown by his Auditory recognition delayed index (60, extremely low). On the Rey-Osterrieth Complex Figure Test (ROCF) his performance fell within the following percentiles: copy = 28/36 possible points, less than 2–5th percentile, immediate recall = 12/36 points, 27th percentile, and delayed recall = 12/36 points, 27th percentile [9]. His ability to recognize the figure was intact when asked to choose from a field of eight foils. The patient was given the DRS-2, in which he scored in the moderate range (Age and Education Correlated MOANS scaled score [AEMSS] = 4). He performed in the below average range on the Conceptualization subscale, in the moderate range on the Initiation/Perseveration subscale, and in the severe range on the Memory subscale.

The neuropsychological evaluation indicated that the patient’s brain injury appeared to specifically involve the left hemisphere with the preponderance of deficits suggestive of left temporal lobe dysfunction. His neuropsychological deficits ranged from mild to severe, with a predominance of amnestic and aphasic features. This is consistent and correlates with reported cognitive deficits in individuals with HSE [3,10,13,22,34]. This patient’s aphasia correlated with previous research [10,11,21,28,34]. The results of the neuropsychological testing, specifically the results of the Boston Naming Test and California verbal Learning Test, in addition to clinical behavioral observations further support his difficulties in retrieving words that are visually similar [28]. Additionally, he displayed the semantic naming differences found in previous research [10,11,21,34]. These findings clinically correlate with MRI and EEG findings. Additionally, these neuropsychological, imaging, and electrical findings are consistent with previous research that found memory performance was associated with retrosplenial and medial temporal lobe metabolism and executive function performance was associated with dorsolateral frontal metabolism [25].

Since the onset of his symptoms, the patient’s emotional functioning was characterized by performance anxiety and embarrassment. He did not score within the clinical range on either the BDI-II or GDS. He exhibited signs of sadness and frustration and depression secondary to his memory, language, and cognitive losses. He was specifically embarrassed and distressed over his inability to recall friends and family names, and would spend great amounts of time attempting to “drill” these names into his memory. His strengths included his high intelligence, drive, community support, and marital relationship, which was very supportive.

### Table 1: Significant highlights of neuropsychological testing.

| Test          | Description                                                                 |
|---------------|-----------------------------------------------------------------------------|
| WASI          | FSIQ = 109 (average) VIQ = 96 (average) PIQ = 124 (superior)               |
| HRNB (Heaton et al., 2004) | TMT—A = below average TMT—B = average Sensory perceptual—total = below average Sensory perceptual—right = above average Sensory perceptual—left = moderate impairment Grip strength—dominant hand = mild impairment Grip strength—non-dominant hand = mild impairment |
| Boston naming | 44/60 (Mean = 53.3, S.D. = 4.6), moderate impairment                         |
| WMS-III       | General memory index = 67 (extremely low) Immediate memory index = 73 (borderline) Aud. immediate index = 68 (extremely low) Visual immediate index = 68 (low average) Aud. delayed index = 64 (extremely low) Visual delayed index = 88 (low average) Aud. recogn. delayed index = 60 (extremely low) Working memory index = 81 (low average) |
| ROCF          | Copy = 28/36 (< 2–5th percentile) Immediate recall = 12/36 (27th percentile) Delayed recall = 12/36 (27th percentile) |
| DRS-2         | AEMSS = 4 (moderate impairment) Attention = 11 (average) Initiation/Perseveration = 5 (moderately impairment) Construction = 10 (average) Conceptualization = 9 (below average) Memory = 3 (severe impairment) |
Neuropsychological testing served to assist in treatment planning of this patient. Due to the cognitive deficits found in the neuropsychological assessment, the patient was referred for neurocognitive rehabilitation to specifically address the following: memory (encoding and storage strategies) and remediation of anomic aphasia (specifically word finding and language work, hand stabilization techniques and aids). His rehabilitation plan also recommended treatment with speech and language pathology, occupational therapy, and psychotherapy to address depression, anger, and adjustment issues in dealing with cognitive losses.

5 Conclusion

This case study provides an interesting example of the clinical utility of neuropsychological consultation in the diagnosis and treatment of infectious diseases in general and herpes simplex encephalitis (HSE) in particular. The results of the neuropsychological battery yielded high agreement in terms of site of lesion as documented by MRI and EEG findings. Left hemispheric deficits revealed in neuropsychological testing including auditory-verbal memory impairment and anomic aphasia correlated with left hemisphere lesion sites as shown by MRI and EEG, specifically, abnormal signal intensity in the left temporal lobe extending into the left hippocampus and insular cortex. Neuropsychological test results supporting a left hemispheric weakness included: the WASI in which there was a statistically significant 28 point gap between his VIQ (96) and PIQ (124); and the WMS-III in which the patient displayed an overall memory impairment but specific auditory-verbal memory impairment (e.g. a statistically significant \( p < .05 \) 20-point gap between Visual Immediate Index, 88, and Auditory Immediate Index, 68; and a statistically significant \( p < .05 \) 24-point gap between Visual Delayed Index, 88, and Auditory Delayed Index, 64). The patient also displayed a mild to moderate anomic aphasia as evidenced by: prominence of word-finding difficulty in the context of fluent, grammatically well-formed speech, absence of literal and verbal paraphasia, relatively intact auditory comprehension, confrontation naming failures, circumlocutions for missing words, emptiness of substantive words, and slightly compromised comprehension of isolated nouns and verbs. Neuropsychological testing proved to be of significant value in a multifaceted diagnostic approach to herpes simplex encephalitis (HSE) in particular and infectious diseases in general via the documentation and quantification of neuropsychological deficits and confirmation of lesion sites. These data also proved to be important in treatment planning.

It is hoped that neuropsychologists will find the avenue of consultation-liaison neuropsychology in infectious diseases to be a valuable, personally rewarding, and scientifically significant clinical endeavor.

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