Successful Treatment of Cognitive Decline in Sneddon Syndrome Associated with Hepatitis C with Cyclophosphamide

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Introduction

Sneddon syndrome (SS) is characterized by livedo reticularis, central nervous system (CNS) vasculitis and multifocal cerebral infarctions, which may result in dementia. The treatment of SS has been proposed as either chemotherapy or warfarin to prevent strokes and improve skin findings. However, no reports have demonstrated an effective treatment of cognitive decline for this disease or the association of SS with hepatitis C. We report a case with SS and cognitive decline in a patient with hepatitis C who was successfully treated with cyclophosphamide for 8 months with significant cognitive function improvement.

Case

A 36-year-old, right handed Caucasian woman with a history of hypertension, livedo reticularis in the abdomen and feet (Figure 1A), and hepatitis C presented with acute onset of left-sided hemiparesis and sensory loss. Brain CT revealed multifocal subcortical hypodensities. DWI confirmed multifocal subcortical strokes (Figure 2A). Four vessel cerebral angiogram showed distal narrowing of intracranial blood vessels consistent with vasculitis (Figure 2B-D). Echocardiogram showed normal left heart function without thrombus or patent foramen ovale. However, right atrium and right heart were dilated with high pulmonary artery pressure consistent with pulmonary hypertension. ESR and CRP were not elevated, and cryoglobulins were absent in the serum. Antiphospholipid antibodies were absent, and further hypercoaguable workup was unremarkable. Additionally, the patient complained of poor attention and concentration. She also demonstrated impulsivity and irritability with the medical team. Neuropsychological testing demonstrated impaired visual memory, poor performance on verbal learning, and moderate levels of depression (Table 1-2).

Figure 1

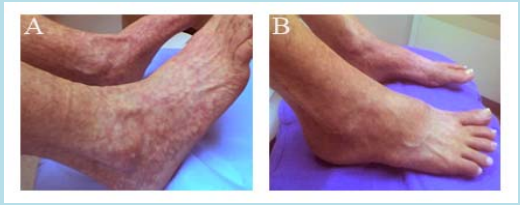
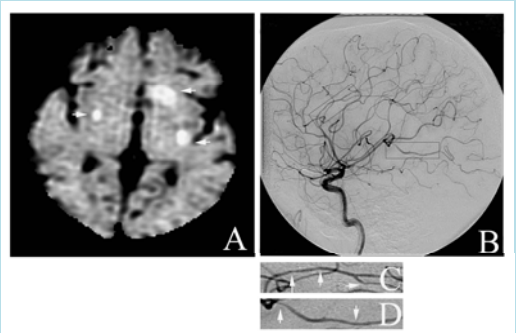


Figure 2



The patient was initially treated with steroids, but she developed hyperglycemia. She was subsequently treated with IV cyclophosphamide for 3 days and then monthly for 8 months.

Following her 8 month treatment, she experienced improvements from the average to the above average range on both verbal and visual learning (Table 2). All other cognitive scores remained stable. Her muscle strength and livedo reticularis also improved (Figure 1B). Repeat brain MRI did not show any new strokes.

Table 1: Administered Neuropsychological Measures

Domain	Test
Mental Status	Mini-Mental Status Exam (MMSE)
Pre-morbid IQ Estimate	WAIS-III Similarities*
Attention	Trail Making Part A (Trails A) WAIS-III Digit Span Test of Sustained Attention (TSAT)
Language	Verbal Fluency (FAS) Category Fluency-Animals Boston Naming Test (BNT)
Memory	Hopkins Verbal Learning Test-Revised (HVLT-R) Brief Visual Memory Test-Revised (BVMT-R)
Executive Functioning	Wisconsin Card Sorting Test (WCST) Trail Making Part B (Trails B)
Visuospatial	Clock Drawing WAIS-III Block Design Rey-Osterrith Complex Figure (ROCF)
Mood	Beck Depression Inventory-II (BDI) Beck Anxiety Inventory (BAI)
WAIS-III=Wechsler Adult Intelligence Scale; *baseline only	

Discussion

The hallmark feature of Sneddon syndrome is CNS vasculitis with livedo reticularis. It typically occurs in females between the ages of 30-40 and is associated with obesity and hypertension. About half of SS patients have antiphospholipid antibodies. Our case is the first report to associate SS with hepatitis C. The neuropathological findings of SS are controversial. Some report focal small vessel hyperplastic changes with thrombosis, while others report inflammatory changes. Therefore, the rationale for the treatment of SS is either anticoagulation/antiplatelet therapy for thrombosis or chemotherapy for vasculitis.

Several reports have described SS as a cause of progressive dementia of the young. The pathogenesis is proposed as multi-focal subcortical infarcts causing a vascular type of dementia. Other neurological symptoms associated with SS include seizure, chorea, migraine-like headache, and encephalopathy.

Table 2: Neuropsychological Scores before and after cyclophosphamide treatment

Measure	Before		After	
	Raw	Norm	Raw	Norm
Mental Status				
MMSE (0-30)	28	NA	29	NA
Pre-morbid IQ Estimate^				
WAIS-III Similarities (0-33)	20		NA	
Verbal Memory				
HVLT-R Total (0-36)	25	T=43	34	T=63
HVLT-R LTM (0-12)	11	T=55	11	T=55
Visual Memory				
BVMT-R Total (0-36)	21	T=42	30	T=60
BVMT-R LTM (0-12)	7	T=38	11	T=59
Language				
BNT (0-60)	51	T=36	51	T=36
COWA-FAS (no max)	37	T=41	38	T=44
Category Fluency-Animals (no max)	18	T=38	16	T=42
Visuospatial				
Clock Drawing (0-10)	9	NA	10	NA
Block Design (0-68)	30	SS=8	28	SS=8
ROCF (0-36)	34	Z=-0.91	35	Z=-0.11
Attention/Info. Processing				
Digit Span (0-30)	17	SS=10	16	SS=9
Trails A (0-300 seconds)	29	T=41	27	T=46
TSAT (0-480 seconds)	66	Z=0.55	57	Z=1.05
Executive Functions				
Trails B (0-300 seconds)	61	T=47	56	T=47
WCST Persev Errors (0-64)	4	T=55	5	T=53
Affective Functioning				
BDI (0-63)	18	Mild	6	Mild
BAI (0-63)	10	Minimal	4	Minimal

However, no effective treatment has been proposed to treat the dementia due to SS and generally, the previous therapeutic attempts have been disappointing. We chose cyclophosphamide as the treatment for this patient based on 1). the lack of antiphospholipid antibody, 2). the possible association of SS with hepatitis C, and 3). the distal arteriopathy demonstrated on cerebral angiogram. In this patient with SS and hepatitis C, cyclophosphamide was an effective treatment for the patient's cognitive decline and her livedo reticularis.

Longitudinal neuropsychological and neurological follow-up evaluations will be conducted to continue to investigate changes in her cognition and medical condition. The influence of practice effects on neurocognitive function will also be evaluated.