Review Article

Neurocognitive Changes in Sickle Cell Disease: A Comprehensive Review

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Abstract

Background: Sickle cell disease (SCD) is a type of hemoglobinopathy characterized by abnormal hemoglobin molecules, which includes numerous acute and chronic complications. Ischemic stroke, silent cerebral infarction, headache, and neurocognitive impairment are the most common neurological complications associated with SCD.

Summary: Acute anemia because of SCD can cause cognitive impairments because of cerebral hypoxia. Cognitive abnormalities in SCD manifest in various aspects such as working memory, verbal learning, executive functions, and attention. These neurocognitive impairments have been associated with poor functional results, such as transitioning from juvenile to adult care, adherence to medications, and unemployment.

Key message: In this review, we focus on neurocognitive aspects of SCD patients based on different imaging techniques, psychological batteries, associated neuromarkers, and interventions for managing of cognitive deficiencies.

Keywords

Sickle cell disease, Cognition, Neurocognition, Neuroimaging

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Introduction

Sickle cell disease (SCD) is a category of disease affecting hemoglobin molecule. Hemoglobin in SCD is called sickled hemoglobin or HbS, abnormal hemoglobin, because of which the shape of red blood cells (RBCs) becomes crescent or sickle-shaped. These sickled-shaped RBCs get stuck in the capillaries which leads to episodes of acute pain because vaso-occlusion gradually leads to organ damage over time. It is one of the world's most typical severe monogenic diseases, most prevalent in wide regions of sub-Saharan Africa, the Mediterranean Basin, the Middle East, and India.[1,2] SCD is characterized by single nucleotide substitution in the gene encoding hemoglobin subunit beta. Substitution of adenine to thymine results in the replacement of glutamic acid to valine. This mutation leads to the polymerization of hemoglobin molecules inside the RBCs, which leads to the crescent shape of RBCs. Patients with SCD have limited oxygen-carrying capacity because of low hemoglobin levels, which can be exacerbated by acute medical conditions like acute chest syndrome or vaso-occlusive crisis. RBCs in SCD patients are more sticky than normal RBCs, which can cause occlusion in blood vessels. Increased blood viscosity, related to HbS, may further restrict blood flow via constricted blood vessels or in normal brain capillaries.[3–7]

Neurological complications such as ischemic stroke, silent cerebral infarction (SCI), headache, and cognitive dysfunction are also very common in SCD. Cognitive abnormalities in SCD manifest in various aspects such as working memory, verbal learning, visuomotor function, inadequacies in general intellectual functioning, executive functions, language, and attention.[8,9] Initially, overt stroke was regarded as the predominant cause of cognitive impairment in SCD. But

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latest evidence has shown that overt stroke and SCI are usually linked with cognitive decline. Recent data also revealed that neurocognitive abnormalities could occur in children with SCD even if there is no indication of a stroke on magnetic resonance imaging (MRI).[10,11]

In this review, we attempt to demystify all the vital areas of the brain responsible for cognitive processing and discuss them in light of alterations reported in SCD. We have included the majority of the imaging studies, associated neuromarkers/biomarkers, and their correlation with various aspects of cognition. Later, we also discussed enhancing the cognitive abilities of individuals with SCD through pharmacological and nonpharmacological interventions.

Neural Substrates of SCD Induced Hypoxic Brain Injury

Neuroimaging Studies

Neuroimaging studies are different imaging techniques that directly or indirectly examine the brain's anatomy and functioning. It is a relatively recent field of study within medicine, neurology, and psychology. Out of the two broadly classified categories of neuroimaging techniques, positron emission tomography (PET), near-infrared spectroscopy (NIRS), transcranial Doppler (TCD) ultrasonography and functional magnetic resonance imaging (fMRI), etc. assesses the alteration in blood flow in relation to brain activity, while electroencephalography (EEG) based techniques work with the principle of measuring the electrical activity of the brain. Table 1 provides an outline of imaging studies done on SCD patients.

Transcranial Doppler (TCD) Ultrasonography

TCD ultrasonography has recently gained popularity in medical science as a noninvasive, low-cost, secure, and accessible method of assessing cerebrovascular function. It allows for consistent and bidirectional monitoring of cerebral hemodynamics, and pulsatility across the significant cerebral vasculature (central, frontal, posterior, and basilary arteries). It is also free of movement artifact and demonstrates high test-retest reproducibility. The distal internal cerebral artery (ICA) and the adjacent sections of the middle cerebral artery (MCA) and anterior cerebral artery (ACA) are involved in SCD.[12,13] Studies on infants with sickle cell anemia reported higher cerebral blood flow velocities (systolic and mean) in the basilar artery (BA), MCA, and ICA, which was linked to a medium to a high probability of neurodevelopmental delays.[14] Analysis revealed that children and adolescents with SCD with aberrant systolic velocities (maximum velocity more than 200 cm/s in the MCA and ICA) performed worse cognitively than those with SCD who had usual systolic velocities (maximum velocity 170–200 cm/s).[15–17] Kral et al. also discovered a link between cerebral hemodynamics and cognition in SCD patients. Children with SCD with higher and mid-range systolic velocities performed better in verbal recall tasks than those with SCD with normal TCD velocities.[18] Krejza et al. used the Kaufman Brief Intelligence Test (K-BIT-IQ) and TCD to assess cerebral hemodynamics and pulsatility indexes (PI) in the middle cerebral arteries (MCA). Lower PI in the right MCA was linked to a lower K-BIT-IQ component and language scores in 46 SCD children. Furthermore, they discovered that interhemispheric disparities in PIs were much more significantly connected to neuropsychological ability, while flow velocities were unrelated to the K-BIT-IQ score.[19] According to Strouse et al., cognitive function and cerebral blood flow (CBF) have a significant inverse association.[20] Whereas, Onofri et al. and Aygun et al. found no association between mean velocities and cognitive performance.[21,22] A recent Nigerian study suggests that SCD children with high TCD velocity are at risk for deficiencies in executive planning, specifically males with higher TCD velocity are at a higher risk for complications in auditory working memory.[23] Apart from the above studies, adult SCD patients have lower TCD velocities than pediatric SCD patients.[24,25]

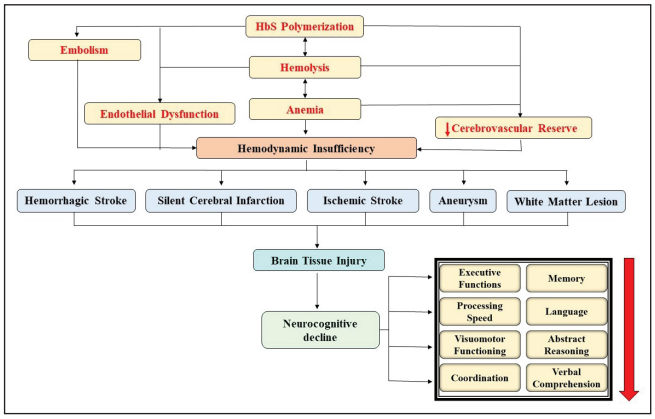

Figure 1. Mechanisms Behind Neurocognitive Decline in SCD.

MRI/fMRI/MRA Studies

MRI may produce crisp, high-resolution images of the brain's anatomical structure and identify abnormalities or lesions in the brain. To increase picture contrast, a dye or tracer, like gadolinium, may be injected into a vein in the arm. However, the use of gadolinium contrast agents is gradually reduced, primarily for SCD patients with renal disease, which can impair gadolinium clearance from the body. Variations in the intensity of the nuclear magnetic resonance signal retrieved from different sites in the brain can improve the quality of images. After the scanner's pulse sequence, the relaxation periods, T1, T2, and fluid-attenuated inversion recovery (FLAIR), are assessed and selected to look at exact tissue inside the brain. Magnetic resonance angiography (MRA), on the other hand, gives crucial information on the state of the microvasculature and has largely supplanted intra-arterial

catheter angiography as a precise and noninvasive method of identifying cerebral artery abnormalities.[26,27]

The relationship between MRI results and cognitive functioning was assessed by Kugler et al.,[28] and found that 50% of patients demonstrated progressive MRI abnormalities and had bad scores in one or more cognitive functioning domains. Armstrong et al.[29] and Gold et al.[30] found central nervous system (CNS) abnormalities on MRI in children with SCD having a clinical history of cerebrovascular accident (CVA). These SCD children had smaller frontal lobe infarcts and were considerably weakened on measures of intellect, memory, and frontal lobe function compared with standard MRI scans of sibling controls.[31,30] Previously, quantitative MRI investigations in SCD children with cerebral infarction discovered a substantial link between the level of visible tissue injury and cognitive impairments. Schatz et al. discovered differences in left vs. right hemisphere damage in children with SCD stroke by conducting tests that assess particular visual-spatial skills. Further, T2-weighted MRI scan was done to assess midsagittal corpus callosum (CC) size and its relationship with cognitive functioning. Posterior CC size decreased among SCD children, but no association could be found with cognitive functioning because of less sample size.[31,34,35] Other studies also show that intracranial volume is smaller in SCD patients and has significantly more lacunae, mainly in the frontal lobe, parietal lobe, and basal ganglia. Lacunae are supposed to be caused by the obstruction of a penetrating branch of one of the main cerebral arteries. They are defined as a small cystic infarct in the cerebrum and brainstem's deeper (noncortical) regions. The authors discovered an apparent association between lacunae and IQ, but after controlling for age, this link became nonsignificant.[36,37] Individuals with SCD also had thinner frontal lobe cortex and smaller basal ganglia and thalamus sizes compared to healthy controls. The authors stated that cognitive impairment might be exacerbated by the reduced volume of the basal ganglia and aberrations in the thalamus.[38]

In addition, resting-state fMRI analysis in SCD patients reported lower functional integration in the sensory-motor, auditory, salient, and subcortical networks when compared to controls, and a more significant proportion of white matter oxygen extraction was linked to reduced connectivity in these networks. These findings propose that increased oxygen extraction and impaired functional connectivity may serve as neuroimaging biomarkers for cognitive deficiency in SCD.[39,40] According to Novelli et al.,[41] cerebral vascular anomalies have also been associated with cognitive decline in SCD patients. Patients with SCD had considerably lower long venule density and higher short venule density than controls, which is inversely associated with cognitive ability. Whole-brain examination of the amplitude of low-frequency fluctuations (ALFF) in resting-state fMRI revealed lower ALFF in the frontal lobe, cerebellum, and medial superior frontal gyrus, as well as existence of white matter hyperintensities which were related to decreased frontal and medial superior frontal gyri activity in SCD subjects. Reduced ALFF in the frontal lobe was associated with lower verbal fluency and cognitive control.[42] Zou et al.[43] employed blood oxygenation level-dependent (BOLD) and cerebral blood flow (CBF)-based fMRI to examine primary visual cortex reaction to visual stimulus in children with SCD and discovered that BOLD responses were decreased. Nocturnal hemoglobin oxygen desaturation and sleep fragmentation can also contribute to cognitive dysfunction in SCD patients.[44] A study by Andreotti et al. proposes a link between cytokine levels and decision-making function in SCD children, implying that inflammatory processes may have a role in cognitive outcomes in these children. They examined verbal and nonverbal abilities, mental flexibility, inhibition, and verbal fluency, in relation to plasma levels of different cytokines like IL-4, 5, 8, and 13 and found that there were substantial negative correlations between cytokine levels and various measures of executive function skills.[45]

PET Scan Studies

MRI provides a high-resolution anatomical description, whereas Positron emission tomography (PET) is the only imaging technique that can display tissue function and structure by utilizing a metabolically active tracer molecule labeled with a positron-emitting isotope. Although there is very scarce literature on PET and cognition in SCD, some data shows anomalies in glucose metabolism and microvascular blood circulation, notably in the frontal lobes. Further study requires a correlation between PET abnormalities and progressive neurologic dysfunction.[46,47]

Single-photon emission computed tomography (SPECT) study by Al-Kandari et al. revealed a perfusion deficiency mainly in the frontal lobe of SCD patients, either alone or in collaboration with the temporal and parietal lobes. The results suggest that SPECT was beneficial in the detection of brain perfusion deficiency in persons with SCD and that such primary identification may be potentially valuable in the future follow-up of such patients because cerebral perfusion deficiency is expected to develop silent infarction and overt stroke, that ultimately declines cognitive abilities.[48]

EEG-ERP Studies

EEG is another brain imaging technique that primarily detects the currents which occur during synaptic excitations of several pyramidal neurons in the cerebral cortex and measures scalp electrical activity generated by brain regions. EEG is sensitive to various states, including stress, attentiveness, resting state, hypnosis, and sleep. Because the EEG technique is noninvasive and painless, it is commonly used to investigate the brain physiology of cognitive functions such as perceptions, memory, attention, language, and emotions in healthy individuals and infants. Another variant of EEG, i.e., ERPs, are extremely tiny voltages produced in brain areas in

response to certain events or stimuli. EEG changes are time-locked to particular stimuli such as sensory, motor, or cognitive events. It offers a noninvasive and secure method for studying the psychophysiological aspects of brain function.[49,50] EEG is widely used in the early diagnosis and management of neurological and cognitive involvement of SCD. Early case reports by L. Neidengard and E. Niedermeyer revealed a large amount of slow-wave activity in SCD patients. The degree of slowing in the EEG was much more significant than one would have expected from the clinical state.[51] Resting-state EEG frequency analysis in SCD children showed a higher amount of slow-wave activity in occipital-parietal and temporal-frontal brain areas. Although the authors failed to suggest a strong reason behind that, it may be because of a lack of oxygen-carrying capacity or obstruction in blood flow in brain regions.[52] Studies by Case et al. revealed strong evidence of EEG changes in pain processing regions in SCD. In comparison to controls, SCD patients showed higher theta and lowered beta power. Source localization demonstrated that locations with higher theta band activity were associated with pain processing. On EEG-fMRI data, spontaneous power and microstate analyses were also done. Independent component analysis revealed that patients had no activity in the default mode network (DMN) and executive control network (ECN) as compared to the control group.[53–55] EEG power measures are also associated with cognitive functions like global cognition, memory, language, and executive functioning. These EEG power measures might prove helpful in prospective studies to predict longitudinal cognitive decline.[56] Downes et al. recorded auditory ERP in SCD children and compared it with age-matched controls. They observed more positive amplitudes by 100 ms in attended stimuli in healthy children but not in SCD children, indicating their attention deficits.[57] Correct response negativity (CRN) and error-related negativity (ERN) were reduced in SCD patients with unilateral and bilateral frontal white matter injuries. Further, it was also observed that SCD patients show executive function deficits.[58] Patients with SCD were found to have deteriorated cognitive abilities; cognitive responses to an auditory stimulus are delayed in SCD patients. The precuneus, which is interconnected to various cortical and subcortical areas of the brain and is involved in episodic memory, visual-spatial abilities, motor activity, coordination strategies, self-perception, executive and working memory, was not activated in SCD patients when compared to controls during stimulus presentation.[59]

Neuromarkers and Biochemical Basis

Biomarkers are measurable biological characteristics that are an indicator of normal biological processes. Anemia is a major factor in the pathophysiology of SCD and might be a source of cognitive impairment. Hemoglobin deficiency is a sign of inadequate brain oxygenation, which might explain poor cognitive performance. A wide variety of studies have tried to associate neurocognition with markers of anemia, like hemoglobin or hematocrit.[9,14,20,36,60,61] Ruffieux et al. disclosed a significant association between low hemoglobin F (HbF) levels with lower executive functioning.[16] According to Boehme et al., inflammatory markers such as IL-22 were associated with neurocognitive dysfunction alone. In contrast, cytokine levels such as CXCL8, CXCL1, IFNg, TNFa, sFasL, IL18, IL22, sICAM1, and VEGFA were associated with abnormal TCD (or stroke) plus neurocognitive dysfunction.[62] Cytokine levels were found to be inversely related to each of the conditions mentioned in all cases. Although hydroxyurea therapy is expected to improve neurocognition, studies have found no negative correlation between hydroxyurea administration and neurocognition.[63,64] Glial fibrillary acidic protein (GFAP) is a brain-specific intermediate filament protein expressed in glial cells (astrocytes) and is a known biomarker of acute stroke and head trauma in adults. Savage et al. reported a negative correlation between GFAP levels and IQ in children with SCD.[65]

Impact of SCD Induced Hypoxia on Neurocognition

Neural Substrates of Cognition

Neurocognition is the ability to relate and decipher the information, which encompasses various cognitive domains, e.g., working memory, speed of processing, attention, and/or executive functions.[66] Various brain areas function in coordination for better cognitive outcomes.[67,68] Worsening of working memory has been reported to be associated with derangement in cortical and subcortical structures at the distal distributions of the anterior and middle cerebral artery, which disturbs oxygen delivery to deep white matter, basal ganglia, middle and superior frontal gyrus, and dorsal parietal regions.[46,69,70] Besides, faster performers have efficient interactions between brain regions and increased neuronal activity in the prefrontal cortex (PFC) compared to slow performers for any executive function.[71] Performance relating to general intelligence has been observed to be dependent upon the parieto-frontal structurally intact axonal fibers, which help in fast information processing.[72] Thus, these facts delineate the dynamic interactions between various neural substrates for efficient cognitive outcomes.

SCD and Neurocognition: Cause and Effect Relationship

SCD is characterized by chronic and acute anemia, low baseline Hb (≤10 g/dL), hypoxia, and intracranial stenosis.[73] Various studies showed that SCI is the primary risk factor for neurocognition deficits in SCD patients, including children, adolescents, and adults, compared to patients without SCI.[74,75] There is increased cerebral blood flow,

Table 1. Outline of Imaging Studies Done on SCD Patients.

S. No.	Type of Imaging studies	Sample Size	Age	Imaging Protocol	Measure(s) of Cognitive Function	Findings	Reference
1.	TCD	28	Infants (3, 9, and 12 months)	Resting TCD	BINS	Increased SV and MV were associated with a higher risk of neurodevelopmental delay at 9 months of age	14
2.	TCD	60	Children (mean age 121 months)	Resting TCD	IQ-WASI; academic achievement-WJ-R; visual sustained attention-CPT-II; working memory-CMS	Children with abnormal TCD (velocity >200 cm/s) had lower verbal IQs than children with conditional TCD (velocities between 170 cm/s and 200 cm/s), who further performed worse than children with normal TCD on measures of executive function.	15
3.	TCD	96	6 to 24 years	Resting TCD	Motor Skills-PPT; memory-CVLT; executive functions; attention-CPT	37.5% of SCD patients had mild-to-severe cognitive deficits with a significant association between severe anemia, history of cerebrovascular accidents vs. lower executive functioning	16
4.	TCD, MRI	173 (TCD=143, MRI=144)	5 to 15 years	Resting TCD, MRI-noncontrast; 3-D MRA	WISC-III, WIPPSI-R	Lower IQ scores with abnormal TCD (velocity >200 cm/s) and MRI (increased signal on T2 weighted pulse sequences) (21% had abnormal MRI, 8.4% had abnormal TCD)	17
5	TCD, MRI, MRA	27	6 years 0 months to 16 years 11 months	MRI-without contrast and FLAIR, 3-D MRA TCD-Resting	IQ-WASI; academic achievement-WJ-R; attention-CPT-II; working memory-CMS; executive functioning-BRIEF	Abnormal TCD (velocity >200 cm/s) and MRI (increased signal on FLAIR and T2 weighted pulse sequences) patients had lower cognitive performance; with the association between low hemoglobin and neurocognitive impairment	18
6	TCD	46	47-166 months	Blood flow velocities and PI in MCA	KBIT	Lower PI in the right MCA was associated with lower K-BIT-IQ	19
7	TCD, CASL-MRI	24	6 to 12 years	TCD-resting MRI-1.7 Tesla, FLAIR CASL	IQ-WASI	Inverse relationship between performance IQ and CBF	20
8	TCD	88	4 years	TCD-Resting	BPS-II	No association between TCD measures and cognitive performance	21
9	TCD	35	4 to 16 years	TCD-Resting ICA MRI-1.5 Tesla, Axial FLAIR	WISC III—for 6 to 16 years age; WPPSI-for four to six years age	No significant differences in the altered TAMM velocities and cognitive performance	22
10	TCD	83	5 to 12 years	Resting TCD-MCA	Reasoning-RSPM; problem solving-TOL; IQ-WISC-IV	Risk for deficits in executive planning, with boys at increased risk for auditory working memory deficit	23
11	MRI, rCBF	16	11 to 29 years	MRI-1.5 Tesla; rCBF-xenon 133 inhalation method	Neuropsychological battery for memory, attention, executive function, motor speed, language, visuospatial abilities, and abstract reasoning	Cognitive abnormalities in SCD, even in the absence of MRI abnormalities or clinical stroke.	24
12	MRI	135	6 to 12 years	MRI-1.5 Tesla, T2-weighted	Global intellectual functioning and specific academic and neuropsychological functions	Poor cognitive performance with silent infarcts on MRI	29
13	MRI	65	7 to 17 years	MRI-without contrast	WISC-III, WJ-R, PPT, BTP	Poor cognitive performance with CVA	30

(Table 1 continued)

(Table 1 continued)

S. No.	Type of Imaging studies	Sample Size	Age	Imaging Protocol	Measure(s) of Cognitive Function	Findings	Reference
14	MRI	41	5.9 to 16.7 years	MRI-1.5 Tesla, T2-weighted	IQ-WISC-III, WPPSI-R; frontal lobe/executive function-WCST	Significantly impairment in measures of intelligence, memory, and frontal-lobe function in SCD patients with stroke	31
15	MRI	28	7 to 21 years	MRI-1.5 Tesla, T1-, T2-weighted, and proton-density	Neuropsychological battery of tests for four major domains of ability: attention/executive skills, spatial skills, language and memory	Volume of cerebral infarction was associated with spatial and language performance	32
16	MRI	27	12 years	MRI-1.5 Tesla, T2-weighted	WASI	Large tissue loss associated with lower Wechsler Full-Scale IQ in SCD children with silent cerebral infarcts	33
17	MRI	25	12 years	MRI-1.5 Tesla, T2-weighted	Visual-spatial ability-DAS, JOLO test; language ability- PPVT–R; cognitive ability-revised (WJ–R)	Injury of right-hemisphere associated with deficiency in global processing and spatial judgments while left-hemisphere injury resulted in relatively intact local versus global processing and categorical versus coordinate judgments; Bilateral injury caused relative deficits in global-level processing and spatial judgments.	34
18	MRI	28	12 years	MRI-1.5 Tesla, T2-weighted	IQ-WISC-III; SOPT	Decreased corpus callosum size in SCD children associated with cognitive decline	35
19	MRI	149	19 to 55 years	MRI-1.5 Tesla, T1-, T2-weighted	IQ-WAIS-III PIQ	Poor cognitive performance associated with anemia and age	36
20	MRI	120	Adult (age not mentioned)	MRI-1.5 Tesla, T1-weighted	WASI-III	Reduced volume of the basal ganglia and thalamus significantly associated with lower performance IQ and lower perceptual organization and working memory scores	38
21	TCD; MRI, MRA, fMRI	40	8 years	Resting TCD MRI-1.5 Tesla, T1-weighted, FLAIR, fMRI-resting state	IQ-WISC-III, WPSSI	SCD Patients with low neurocognitive scores presented higher brain connectivity in DMN	39
22	MRI	7	(Age not mentioned)	MRI-7 Tesla, T1, T2-weighted 3d orientation	HVLT-R	Lower density of long venules and greater density of short venules which was inversely related to cognitive performance and hemoglobin	40
23	MRI/fMRI, ALFF	20	12.4–34.4	MRI-3D T1, T2-weighted; fMRI-Resting state	WASI-II, WISC-IV, WAIS-IV, D-KEFS, CVLT, BASC 2	Decreased ALFF in the frontal lobe was correlated with decreased verbal fluency and cognitive flexibility.	41
24	fMRI	23	12 years	MRI-1.5 Tesla, T1, T2-weighted, FLAIR; BOLD response	WASI	BOLD responses were diminished in SCD children	42
25	MRI, Poly-somnography	10	-	MRI-1.5 Tesla, T2-weighted	Executive function-D-KEFS, BRIEF; intelligence-WASI	Decreased oxygen saturation and/or increased sleep arousals are associated with reduced cognitive performance	43
26	MRI, PET	6	10 to 29 years	MRI-1.5 Tesla, T2-weighted; PET-Approx. 5-10	Global intellectual functioning and specific academic and neuropsychological functions	PET showed a corresponding metabolic abnormality with cognitive dysfunction in all patients	47
27	fMRI, EEG	15	18 to 24 years	MRI-3D T1, T2-weighted; fMRI-Resting state, BOLD EEG- 64 channel	–	Reduced activity of DMN and increased activity in pain processing regions during rest in SCD	53

(Table 1 continued)

(Table 1 continued)

S. No.	Type of Imaging studies	Sample Size	Age	Imaging Protocol	Measure(s) of Cognitive Function	Findings	Reference
28	EEG-ERP	12	5 years	Auditory-ERP paradigm	IQ-WPPSI-III	Diminished and variable ERP responses for executive skills associated with lower performance intellectual quotient.	57
29	MRI, EEG-ERP	11	11 to 23 years	MRI-1.5 Tesla, T1,T2-weighted, FLAIR; ERP-visual	TEA-adults/children; WCST; SOPT	CRN and ERN diminished in SCD patients; with a deficit in cognitive performance	58
30	EEG-ERP, LORETA	12	11 years	Visual ERP paradigm for P3 wave	ERP	Delayed cognitive evoked potentials and altered cortical sources of P3 in SCD	59
31	MRI	49	4 to 19 years	MRI-1.5 Tesla,T1, T2-weighted,	WISC-R,WISC-III	Focal brain injury and diffuse brain injury were associated with cognitive impairment	60

Abbreviations: Cognitive Tests: BINS, Bayley Infant Neurodevelopmental Screener; WASI, Wechsler Abbreviated Scales of Intelligence; WJ-R, Woodcock Johnson psychoeducational battery revised; WAIS-III, Wechsler Adult Intelligence Scale-III; WISC-II/WISC-III, Wechsler Intelligence Scale for Children; WPPSI-III/WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence; BRIEF, behavior rating inventory of executive functioning; BPS-II, Brigance preschool screen-II; CVLT, California verbal learning; CMS, Children's Memory Scale; CPT-II, Conners's Continuous Performance Test-II; PPT, Purdue Pegboard Test; KBIT, Kaufman Brief Intelligence Test; RSPM, Raven's Standard Progressive Matrices; TOL, Tower of London–Drexel University; BTP, Benton Tactile Perception Test; DAS, Differential Abilities Scales; JOLO, Benton's Judgment of Line Orientation test; PPVT-R, Peabody Picture Vocabulary Test-Revised (PPVT–R); SOPT, Self-Ordered Pointing Test; HVLT-R, Hopkins Verbal Learning Test–Revised; D-KEFS, Delis-Kaplan Executive Function System; BASC 2, Behavior Assessment System for Children, Second Edition; TEA-ch, test of everyday attention for children; TEA-ad, test of everyday attention for adults; TCD, transcranial Doppler; MRA, magnetic resonance angiography; PI, pulsatility indexes; PMCA, proximal middle cerebral artery; PACA, proximal anterior cerebral artery; DICA, distal internal carotid artery; ICA, internal carotid arteries; rCBF, regional cerebral blood flow; CVA, cerebrovascular accident.

and decreased cerebrovascular reserve because of low baseline Hb, hypoxia caused by fever, and seizure, which leads to SCI, whose severity is increased by comorbidities like hypertension, diabetes, hyperlipidemia, and renal disease.[76,77] The prevalence of SCI has been documented ≥ 20% of SCD children that showed an increasing trend with age.[75,78,79] The other risk factors for SCI are male gender, high SBP, and previous seizures.[74]

SCIs are more in brain areas with low cerebral blood flow, hindering the proper oxygen supply in these patients. Reduced oxygen delivery was observed in white matter (WM), specifically in regions of high risk for silent strokes.[80] The cerebral blood flow was found to be inversely related to cerebral infarcts density obtained through the Silent Infarct Transfusion (SIT) Trial Infarct density map of 286 SCD children.[81] It was reported that in around 90% of children, the cerebral infarct density was more in the deep white matter of the frontal and parietal lobes with lower cerebral blood flow.[81]

Pegelow et al.,[82] documented in SCD patients of 6 to 19 years that stroke occurred more frequently in the frontal lobe than the parietal lobe, followed by subcortical nuclei and temporal lobe, and a few lesions in the occipital lobe or cerebellum. In children with SCD, the frontal cortex has been observed to be affected with or without the manifestation of tissue injury.[31,83–85] The frontoparietal regions and the associated internal carotid artery, the middle and anterior cerebral arteries are injured by a stroke in SCD.[78] Focal brain injuries such as clinical stroke and silent stroke result in small lesions in the brain that cause structural and volumetric changes in patients as reported through MRI in SCD.[73,86]

The occurrence/density of silent cerebral infarcts has been associated with cognitive impairment in SCD. The hemoglobin oxygen saturation levels[87] and hematocrit[60] are identified as biological factors linked to cognitive functions in children with SCD. Increased cerebral blood flow and oxygen extraction fraction have been positively associated with lower executive functions and increased silent cerebral infarcts in individuals with SCD.[88] It has been examined that SCI-generated lesions in subcortical areas alter the functional memory status via deteriorating processing speed.[89] Figure 1 depicts the mechanisms behind neurocognitive decline in SCD.

Cognitive Domains and Associated Neural Substrates in SCD

Executive Functions

Existing reports on the cognitive attributes and their neural bases showed that executive function is the most explored cognitive domain in relation to SCD. This domain is predominantly affected as a consequence of disease.

Working memory, a widely studied executive function, is associated with the temporary storage and processing of information. The working memory performance is mediated by two attributes, viz. central executive function and processing speed.[69] Thus, better central executive functions

reflect better working memory as observed through prompt addition related problem-solving capacity.[90] The Theta oscillations in prefrontal, parietal, temporal, and occipital cortical regions of the brain during the audiovisual working memory task show that multiple brain regions are associated with working memory.[91]

DeBaun et al.[74] reviewed that SCI in sickle cell patients is associated with worse cognitive performances in domains like executive functions (selective attention, card sorting, working memory), processing speed, visual-motor speed and coordination, vocabulary, visual memory, abstract reasoning and verbal comprehension. A reduced performance was also noted in an array of executive functions like nonverbal reasoning and visual-spatial skills, working memory, and processing speed in nonsymptomatic SCD adult patients.[18,36–38,92] Lower intelligence quotient (IQ) level in SCD patients and deterioration in cognitive functions like memory, language, learning, attention, retrieval, and overall executive functioning visible through WAIS-III verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) index in older patients has been linked to anemia.[36] Children with SCD showed low IQ and dysfunctions in executive tasks such as visuospatial working memory, sustained attention, and planning capacity.[93,94] The adolescent SCD patient also showed neurocognitive problems such as poor performance in verbal IQ scores, mathematical problem-solving capacity, and deteriorated visual-motor functions.[95] Children with infarcts in the frontal cortex showed reduced working memory span compared to SCD children without infarcts.[96] The visual-spatial skills, processing speed, and working memory have also been linked with the structural changes in the brain, including reduced volume in the basal ganglia and thalamus in SCD adults compared to non-SCD.[38]

The cognitive impairment occurred more in individuals with damaged white matter.[97,98] Thus, SCI damages the white matter and causes a reduction in global white matter volume in both the right and left cerebral hemispheres, specifically in the regions where anterior and middle cerebral artery distributed along with the corpus callosum, right brainstem, and right cerebellum as documented in adolescent and adult SCD patients compared to control. They also discovered that white matter injuries in the frontal, parietal, and temporal lobes were associated with low hemoglobin levels, platelet volume, chronic microvascular insufficiency, and hypoxia.[99] Steen et al.[100] found slow volumetric growth of brain gray matter in children compared to controls, affecting neurocognitive development. In individuals with SCD, there is increased cerebral blood flow; however, diminished blood supply is one of the prime causes of white matter loss[101–103]. The decreasing oxygen saturation has also been related to abnormal white matter in the corpus callosum in SCD, confirming that acute and chronic hypoxia negatively impact the neurocognition capacity.[104] The severity of chronic anemia has been considered one of the most vital factors of hypoxic-ischemia-related damage or loss of white matter in SCD patients. The severity of anemia is the strongest predictor of whole-brain white matter volume loss.[74,99]

Craft et al.[32] have alleged that lesion location is more related to attention and executive function problems than lesion volume. The overall IQ level of children with larger lesion volume showed more deterioration than children with less lesion volume.[84] Further, children with left cortical infarct also reported impaired IQ on a full scale, verbal and performance scale (FSIQ, VIQ, and PIQ), while children with right cortical infarct were poor in FSIQ and PIQ only. The SCD children with clinical or silent infarct were more prone to make errors on a cancellation task.[105] A meta-analysis study showed that SCD patients with a history of stroke have more cognitive deficits than those without infarcts, and SCD patients mainly have a problem with verbal reasoning, perceptual reasoning, and executive function.[95]

Recently, tract-specific analysis and white matter tract studies revealed the microscopic injury in white matter associated with the deterioration in processing speed and response inhibition executive functions in SCD patients.[106] Chai et al.[106] found white matter damage in "genu of the corpus callosum, corticospinal tract, inferior frontal-occipital fasciculus, right inferior longitudinal fasciculus, superior longitudinal fasciculus, and left uncinate fasciculus." Corpus callosum has been suggested to be essential for processing speed, working memory and executive functions related to cognitive skills.[106] Reduced fractional anisotropy (FA) values and an increase in apparent diffusion coefficient values in the corpus callosum and corticospinal tracts also indicate structural changes in these regions in SCD patients, resulting in neurocognition performance deterioration.[107] In SCD patients, SPO_2 was found to correlate with cerebral blood flow velocity in the right and left middle cerebral arteries, which was found to be negatively associated with IQ; thus, chronic anemia, low hematocrit, and hypoxia cause chronic cerebral ischemia and, ultimately, impaired neurocognitive functions.[60,108,109] Diffuse brain injury and focal brain injuries such as lacunar infarction, encephalomalacia, or leukoencephalopathy have been shown to cause neurocognitive dysfunction in verbal intelligence quotient and verbal comprehension.[60]

Memory

Memory seems to alter to a lesser degree in SCD patients.[31,110] Cohen et al.[111] examined that children diagnosed with left cortical infarct reported auditory-verbal memory and visual-spatial memory deficits; however, patients diagnosed with right cortical infarct were deficits only in visual-spatial memory.[111] Children having anterior lobe infarcts also showed poor performance on both short- and long-delayed free recall tasks compared to children without cortical infarcts,[96] though children with diffuse infarcts or their siblings without SCD showed similar cognitive performance.[32,112]

Visuomotor Functioning

SCD children have impaired visuomotor functioning compared to control, while with increasing age, visuomotor functioning improved. Visuomotor functioning-related cognitive abilities have been more susceptible to alteration because of disease compared to auditory-verbal skills in children with SCD.[93] Schatz et al.[110] reported that 30% of children with silent infarcts and 33% without infarcts displayed deficits in visuomotor functions compared to siblings without SCD.[110]

Language

Children having clinical infarcts as detected in MRI committed more errors while doing the rapid naming test compared to children without MRI abnormalities for clinical infarcts.[105] It has been suggested that language problems in SCD children are linked to the degree and lateralization of neurological injuries.[94]

Methodological Constraints of the Reports

Methodological variations relate to subject selections of varied ages and are not gender matched. Siblings with similar family or developing environments are preferred as controls, since family environment, education, and economic status have an impact on cognitive development trajectories and functions. Ethnicity also influences cognitive functions. Most of the studies are conducted in the USA, a developed country with better education, health facilities, and economic standard; however, similar parallel studies in other countries also revealed other socio-economic factors impacting the cognitive functions in SCD children.[9]

Interventions and Future Perspectives

The SIT Trial has been considered an effective blood transfusion therapy to prevent recurrent silent cerebral infarcts in participants with SCA. SIT Trial with brain MRIs in 169 children of the 5 to 14 years age group showed progressive brain volume changes in SCD children and no change in brain volume in children without SCD.[113] Regular monthly blood transfusion therapy has been suggested as a promising intervention to maintain the optimal transcranial Doppler (TCD) velocities for cerebral blood flow in addition to hydroxyurea administration, specifically at an early age to prevent the risk of SCI and stroke.[76] However, hydroxyurea, the approved therapy to prevent a secondary stroke and treat anemia in SCD,[114] may increase SCI-related complications.[115] Hematopoietic (blood-forming) stem cell transplantation (HSCT) has been purported to reduce the deformed RBC in children <16 years of age; and is the only known treatment for SCD that reduces or eliminates the sickling of RBC.[115] Stem cell therapy could also suggest an effective way to alleviate the consequence of disease that enhances the cognitive status of SCD individuals.[116]

Educational interventions such as training and a friendly and homely environment from childhood improve the cognitive-developmental trajectory. Cognitive-behavioral therapy can be used to improve any cognitive function by managing pain in childhood and preventing further cognitive decline in secondary cognitive processing, such as the central executive function, which is the component that primarily affects working memory in SCD children.[69,117] Thus, facilitating central executive function could improve working memory status in SCD children. Slow and deep breathing techniques, meditation, and yoga practices are also helpful, acceptable, and feasible nonpharmacological interventions in enhancing cognitive abilities and pain management in patients with SCD.[118,119] Figure 2 outlines the investigations done during different events of cerebral injury in SCD and various interventions for their management.

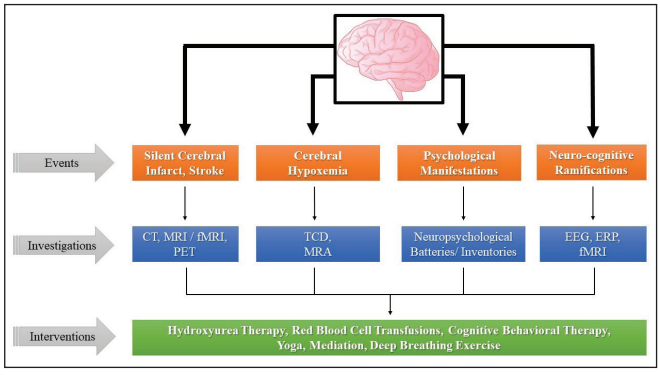

Figure 2. Different Events of Cerebral Injury, Their Investigations, and Interventions in SCD.

Summary

Various neurological complications, i.e., ischemic stroke, SCI, headache, and cognitive dysfunction, are commonly seen in SCD, which can be evaluated by different techniques like PET scan, NIRS, TCD, MRI, and EEG. SCD patients have multifaceted hemodynamic dysregulations, i.e., abnormal systolic velocities in the MCA and ICA in TCD, MRI abnormalities such as cerebrovascular accident, frontal-lobe infarcts, decreased CC size, and smaller intracranial volume with cognitive impairment. PET scan reveals anomalies in glucose metabolism and microvascular blood circulation in frontal lobes. Whereas, EEG-ERP studies show higher slow-wave activities and lesser positive amplitudes for auditory stimuli suggestive of cognitive decline in these patients. Further, SCD patients exhibit worse cognitive performances in domains like executive functions, processing speed, visual-motor speed and coordination, vocabulary, visual memory, abstract reasoning, and verbal comprehension. Inadequate brain oxygenation because of

hemoglobin deficiency is believed to be linked to poor cognitive performance in these patients.

The primary risk factor for neurocognition deficits in SCD patients is SCI which causes a reduction in global white matter volume both in the right and left cerebral hemispheres, specifically in the regions of the distribution of anterior and middle cerebral artery, along with other areas such as corpus callosum, right brainstem, and right cerebellum. Also, low hemoglobin levels, platelet volume, chronic microvascular insufficiency, and hypoxia cause white matter injuries in the frontal, parietal, and temporal lobes. Besides, cerebral hemodynamic insufficiency (oxygen demand exceeds supply) and reduced oxygen saturation in SCD patients are other reasons for white matter loss. In addition, decreased size of the corpus callosum with damage of white matter in the genu of the corpus callosum, corticospinal tract, inferior frontal-occipital fasciculus, right inferior longitudinal fasciculus, superior longitudinal fasciculus, and left uncinate fasciculus are other causes for cognitive abnormalities in SCD patients.

The only known treatments for SCD are regular blood transfusion, hydroxyurea therapy, and hematopoietic stem cell transplantation that reduces or eliminates the sickling of RBC. Besides, nonpharmacological interventions, i.e., educational interventions, cognitive-behavioral therapy, slow and deep breathing techniques, meditation, and yoga practices, might also prove useful in pain management and enhancing cognitive abilities in SCD patients.

Conclusion

In conclusion, this review provides evidence that patients with SCD are at increased risk of neurocognitive abnormalities across multiple domains throughout their lifespan. These neurocognitive impairments are related to the degree of anemia, suggesting that decreased oxygen transport to the brain is a pathogenetic cause. The neurocognitive deficiencies may explain why these patients have such high rates of intellectual disability. The current findings highlight the significance of regular cognitive examinations, pharmacological and nonpharmacological interventions, and potential neurocognitive rehabilitation programs for persons with SCD.

Authors' Contribution

TS and MS designed the review. TS, BP, and HKV performed the literature search, collected and assembled the data, and wrote the manuscript. TS, MS, and RS analyzed the obtained articles. MS and RS revised the manuscript critically. All authors have read and agreed to the published version of the manuscript. The complete article was made under the supervision of MS.

Statement of Ethics

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