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Original Article

Pattern of Auditory and Cognitive Impairment in Children with Sickle Cell Disease: Single Center Experience

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Abstract:
Background: The relationship between sickle cell disease (SCD), hearing and cognitive impairment is intertwined due to the vaso-occlusive, vascular insults and tissue hypoxia associated with sickle cell disease.
Aim of the work: To assess the hearing ability and cognitive functions in patients with SCD.
Material and methods: a cross sectional case-control study included 41 children with SCD who presented to Pediatric Hematology Clinic, Children Hospital, Cairo University. They were screened for auditory impairment using tympanometry and pure tone audiometer (PTA), they were also assessed for cognitive impairment using the Stanford-Binet Intelligence Scale, 4th Ed, and P300 event related auditory evoked potential. Another 41 healthy age and gender matched children were enrolled as controls for P300 data.
Results: The age of the children with SCD ranged from 6-17 years (mean± SD= 10.4±3.3 year), 15 (36.6%) were males and 26 (63.4%) females. Nine (22%) had impaired hearing detected by PTA. The cognitive dysfunction was encountered in 33 (80.5%) patients with SCD. The greater impairment was observed in older patients (p=0.082), and in those with hemoglobin SS type (p<0.05). Twelve (29.3%) patients had abnormal P300 latency. P300 latency was higher (p=0.002) and amplitude was lower (p=0.008) in patients aged <10 years compared to their controls. 33 (80.5%) patients had low IQ (<89), they had a significant lower P300 amplitude (p=0.004) but comparable latencies (p=0.3) to patients with normal IQ. Only one third of patients with low IQ had abnormal P300 values. Receiver operating (ROC) curves showed that area under the curve (AUC) of P300 latency was 0.632 indicating that overall predictability of cognitive dysfunction by P300 latency was not significant (p=0.243) and agreement between P300 latency and IQ test was low. No significant differences were found between patients with auditory dysfunction and patients who had normal hearing, regarding the IQ scoring (p=0.61), P300 latency (0.595) or amplitude (0.322).
Conclusion: Both cognitive and auditory impairments were prevalent among children with SCD. IQ tests were superior to P300 in the evaluation of cognitive impairment.

Level of Evidence of Study: IV (*1*).
Keywords: Sickle cell disease; cognitive; auditory impairment; children.
Abbreviations: dB: decibel; Hb: hemoglobin; Hz: hertz; IQ: intelligence quotient; PTA: pure tone audiometry; SB-IV: Stanford-Binet Intelligence Scale, Fourth Edition; SCD: sickle cell disease; SNHL: sensory-neural hearing loss.

Introduction

Sickle cell disease (SCD) is characterized by chronic hemolytic anemia, high propensity to infections and intermittent episodes of vascular occlusion causing acute and chronic pain. SCD complications are frequent and include bone disease, splenic dysfunction, pulmonary complications, skin ulceration, behavioral disorders, neurologic, cognitive deficits and impairments of vision or hearing (*2*). One of the reported complications of SCD is impairment in

global cognitive functions, that leads to reduced lifetime capacities of reading achievement, increased absences from school, and lower performance on intelligence quotient (IQ) tests (*3*).

Cognitive impairment is part of the spectrum of neurological consequences of SCD that result from complications associated with hemolytic anemia, cerebral hypoxia, vaso-occlusive nature of sickle cell disease (*4*) and to a lesser extent stenosis of major cerebral arteries (*5*). In addition to the silent or overt brain insults, the auditory impairment might be another risk factor of cognitive impairment. The SCD associated hearing loss is not limited to the vaso-occlusive crises but also to the high prevalence of adenotonsillar hypertrophy and otitis media among subjects with SCD (*6*). Hence, the potential for auditory damage is not unexpected (*7*).

Children with hearing loss, specifically senso-neural hearing loss (SNHL), frequently experience speech-language deficits, lower academic achievements, impairment of attention, calculation difficulties and poor socio-emotional development than peers of the same age where they are frequently referred for neuropsychological evaluation (*8*). Impairment of long latency auditory evoked P300 potentials, also contribute to impaired mental processing (*9*).

The present study aimed to assess the pattern, frequency and possible risk factors of auditory and cognitive impairments in children with SCD and to determine the association between the hearing and cognitive impairment among them.

Subjects and Methods

This was a prospective case-control study conducted at Pediatric Hematology Unit, Faculty of Medicine Pediatric Hospitals, Cairo University. It included 41 children with sickle cell disease diagnosed according to clinical and hematologic criteria (*10*) and 41 healthy age and gender matched control group. The study was approved by the Higher Committee for Research, Faculty of Medicine, Cairo University, Egypt. Written informed consent from care giver of each patient was obtained after proper orientation regarding the objectives of the study. Data and identity confidentiality were maintained throughout the study, were coded and accessed by the investigators only. The study complied with the Helsinki Helsinki- Ethical Principles for Medical Research Involving Human Subjects (*11*).

Participants

The study included 41 children with confirmed SCD (*10*). Patients older than 18 years old, those with history of perinatal complications as hypoxic ischemic encephalopathy, traumatic brain injury, as well as patients with diabetes mellitus, chronic otitis media, previous exposure to any ototoxic medications, or family history of hearing loss were excluded from the study.

Methods

The data of the 41 children with confirmed SCD were collected including their medical records, laboratory assessments; complete blood count, reticulocyte count, and serum levels of ferritin by Enzyme Linked Immuno-Sorbent Assay (ELISA), lactate dehydrogenase (LDH), and hemoglobin electrophoresis. All enrolled cases underwent imaging studies; trans-cranial doppler using Toshiba Doppler Ultrasound Machine (Xario100, Japan), magnetic resonant Image (MRI) and magnetic resonant arteriography (MRA) (by Siemens Healthineers, Germany).

Auditory functions assessment:

Auditory functions were assessed by the same specialist.

- Tympanometry using GSI audiometer model 1761, (manufactured by Grason-Stadler Inc., Denmark) was done at varying pressures ranging from +200 to - 400 mm H_2O with 226 hertz (Hz) of the generated sounds. Acoustic reflex threshold measurements using pure tones of (500-4000Hz) were elicited ipsi and contra-laterally. Abnormal tympanogram was considered as abnormal anatomy of the middle ear but not as sensorineural hearing loss. The resulting curves were interpreted as follows: A wave: normal middle ear system, free of fluid or physiological anomalies, B wave: middle ear pathology such as fluid or infection behind the ear drum, and C wave: often consistent with sinus allergy congestion, or Eustachian tube dysfunction (*12*).

- Pure tone audiometry (PTA) was performed using GSI audiometer model 1761, (manufactured by Grason-Stadler Inc., Denmark) in a sound treated cabin. PTA of air conduction for octave frequencies of (250-8000 Hz) and bone conduction for octave frequencies of (500-4000 Hz) was performed using a descending- ascending technique. Hearing threshold (intensity) was measured at different given frequencies to detect abnormal hearing threshold (Normal 0-15 decibel (dB)) and degree and type of hearing loss. Hearing loss was classified as: slight (16-25

dB), mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB), and profound (more than 90 dB) (*13*).

Cognitive functions assessment:

- IQ testing was performed using The Arab version of Stanford-Binet Intelligence Scale, Fourth Edition (SB-IV) (*14*). Patients IQ range of 89 to 110 was considered normal.

- Cognitive functions were assessed using The Arab version of Stanford-Binet Intelligence Scale, Fourth Edition (SB-IV) (*14*). SB-IV was used to assess intelligence and cognitive abilities and provide an overall test composite score and standard age scores. The test consisted of 15 subtests, grouped into four area scores: The verbal reasoning, the short term memory, the quantitative reasoning and the abstract/visual reasoning. Each correct answer increased the patient's score based on the patient's chronological age. The resulting score was a crude assessment of each patient intellectual ability. Based on norms, SB-IV has an average score of 100 and a standard deviation of 11.

- P300 event related auditory evoked potential was performed (*9*) to further assess cognitive functions for all subjects and controls. Recording were preformed using two-channel device (Amplaid model MK12, manufactured by Diatec Diagnostic Ca., Italy). Stimuli were delivered binaurally with intensity corresponding to 80dB and frequent and rare stimulus frequencies to 1000 Hz and 2000 Hz, respectively. The stimuli were presented at a rate of 1/second using evoked potential response audiometer (GSI audiometer model 1761, manufactured by Grason-Stadler Inc., Denmark). All subjects were tested while lying comfortable in a sound treated room, they were instructed to count the number of high pitched or "rare tone" they hear, electrodes were placed as follow: Fpz (ground electrode), Cz (active electrode), M1 and M2 (reference electrodes) for the purpose of measuring electrical potentials that arise from the central nervous system in response to the auditory stimulus. If no change to stimulus was detected only sensory evoked potentials were recorded, if a new auditory stimulus was detected, attentional processes govern a change and P300 were observed. P300 was observed as a vertex positive wave. If the wave was bifurcated the largest peak was marked as the (P300b) to separate it from an earlier occurring non attentive waveform (P300a). If the wave appeared as plateau, the point with the highest amplitude was marked and latency was measured.

Amplitude refers to the difference between the pre-stimulus baseline voltage and the largest positive-going peak of the evoked response potential (ERP) waveform within a time window (measured by microvolt), while latency refers to the time from stimulus onset to the point of maximum positive amplitude within a time window (*9*). P300 amplitude reflected the quality of information processing influenced by attention while P300 latency measures the speed of processing incoming information incorporated into working memory. Impaired cognitive abilities were considered in case of amplitude reduction and/or increasing latency**.** Impaired cognitive abilities were considered in case of amplitude reduction and/or increasing latency compared to that of the control group (*15*).

Statistical Analysis

Data was analyzed by Statistical Program for Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA). Non- parametric data was expressed as frequencies and compared by Chi square $\chi 2$ test or Mann Whitney test. Parametric numerical data were expressed as mean (± standard deviation) and compared using t- test and analysis of variance (ANOVA) test. Pearson's correlations were used to explore associations between numerical variables. Stepwise Regression Analysis was done, p value and 95% confidence intervals (95% CI) to detect the possible risk factors. P300 latency cutoff value was calculated as mean ±2 SD; this could not be done for P300 amplitude as the data was not normally distributed. Receiver operating characteristic (ROC) curve was used to assess the predictability of P300 in cognitive impairment. P- value less than 0.05 was considered statistically significant. (*16*)

Results

Our study included 41 SCD patient with mean age± standard deviation (SD) of 10.4±3.3 years, of them 15 (36.6%) were males and 26 (63.4%) females, 27 (65.9%) were of sickle cell anemia (SS) type and 14 (34.1%) were sickle beta-thalassemia (S-Beta), with the mean level of hemoglobin (Hb) S of 73.20 ±15.28% with a range of (35% -98.2%) and a mean Hb F of 18.35

±10.9% with a range of (1.8% - 34.8%). Thirty-three (80%) of our patients were on hydroxyurea (HU) for a duration of (3.00±2.83) years at a dose of (18.59±4.70) mg/kg/day, while 7 (17%) where on iron chelator (Deferiprone) for a duration of (3.74± 4.00) years. Among all our patients only one had silent stroke where MRI showed left frontoparietal area of encephalomalacia denoting an old ischemic insult and MRA showed normal lateral circulation apart from non-visualized left internal carotid artery, this patient was male aged 15 years, with SS-type, his tympanometry, PTA were normal, his IQ score was 55 with significant impairment in abstract visual learning.

Auditory dysfunction in children with SCD:

Six (14.6%) patients had middle ear affection, 4 (9.76%) had type B wave (indicating the presence of otitis media) and 2 (4.88%) patients had type C wave (indicating Eustachian tube dysfunction), while 35 (85.4%) patients had normal test results (A wave). The frequency of hearing loss by PTA was 22% (9 patients), conductive hearing loss was seen in 4 (9.76%) patients, sensorineural hearing loss (SNHL) in 3 (7.32%); 2 had high frequency hearing loss and 1 had flat frequency, while mixed hearing loss of moderate severity was seen in 2 (4.88%) patients. None of the studied cases showed severe or profound hearing loss. Median PTA for the 9 children with hearing loss was 22.49 dB (range 21.43-24.29 dB), compared to 14.75 (range 10-15.55 dB) among those with intact hearing (Figure 1).

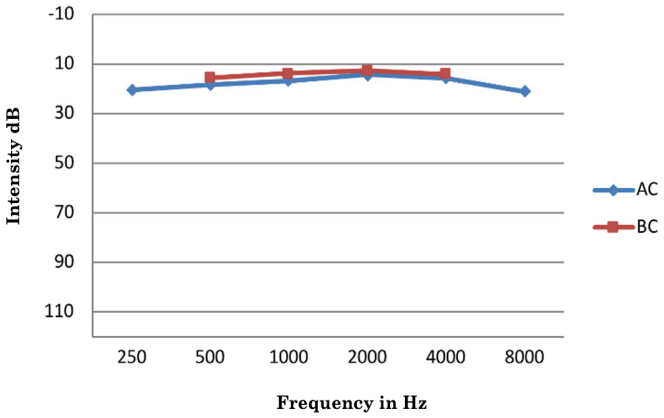

Figure 1. Mean Pure Tone Audiometry of Both Ears in sickle cell disease studied patients. AC: air conduction, BC: bone conduction.

Cognitive dysfunction in children with SCD:

According to SB-IV the frequency of cognitive dysfunction among our SCD children was 80.5%, with nearly 40% of total patients being slow learners. Mean IQ was 77.3±18.1 (range 44 to 147; median score 76). The most frequently affected specific cognitive ability was abstract visual learning in 6 (18.2%) patients (figure1). Patients with cognitive dysfunction were insignificantly older (p=0.082), and of SS type (p<0.05). This Hb SS type was proved to be a significant risk factor of cognitive impairment by Stepwise regression analysis (p=0.04). No significant associations were found between the presence of cognitive impairment and other disease parameter like the frequency (p=0.768) and severity (p=0.563) of vaso-occlusive crises, dose (p=0.805) and duration of hydroxyurea therapy (p=0.751), the intake of iron chelators (p=0.533), or serum ferritin level (p=0.052).

Table 1. Distribution of IQ among the studied cases according to The Stanford-Binet Intelligence Scale, Fourth Edition (SB-IV):

	General IQ % score (reference range)	Studied cases (n=41)
		Number (%)
Normal cognition	High average (IQ: 111-120)	1 (2.4)
	Average (IQ: 89-110)	7 (17.1)
Cognitive dysfunction	Low average (IQ: 79-88)	7 (17.1)
	Slow learner (IQ: 68-78)	16 (39.0)
	Mild Mental Retardation (IQ: 52-67)	7 (17.1)
	Moderate Mental Retardation IQ: (36-51)	3 (7.3)

IQ: Intelligence Quotient

IQ scoring and P300 in relation to hearing loss:

The frequency distribution of patients according to IQ is illustrated in table 1. No significant differences were found between the nine patients who had hearing loss and the patients who had normal hearing regarding the IQ scoring (p=0.61), P300 latency (0.595) or amplitude (0.322). (Table 3).

P300 and Cognitive impairment:

Table 2 illustrates P300 latency and amplitude of cases and controls. Patients with SCD had prolonged P300 latency (394.6±53.1 with a range of 339.8-440 MSc) and lower P300 amplitude (15.6±8.55 with a range of 9.25-29.25 mV), compared to controls (latency of 359.37±32.56 with a range of 326.3-392.4 MSc and latency of 22.1±10.65 with a range of 12.1-33.1 mV). According to the calculated reference range of P300 latency and amplitude, there were 12 patients (29.3%) with abnormal P300 latency. P300 amplitude correlated positively with hydroxyurea dose (r=0.51, p=0.003), and Hb F% (r=0.52, p=0.024). (Figure 2).

Table 2. P300 latency and amplitude of cases and controls and distribution of the studied cases according to the calculated reference range of P300 latency.

Age groups	P300 Latency/ms		P value	P300 Amplitude /mv		P value
	Cases (n=41)	Control (n=41)		Cases (n=41)	Control (n=41)	
Less than 10 years (n=20)	394.6 ± 45.9	355.5±30.7	0.002*	14.8±7.2	24.0±13.6	0.008
Ten years or more (n=21)	394.6 ±60.2	363.2±35.4	0.062	16.4±9.9	20.3±7.7	0.051

ms: millisecond, mv: millivolt

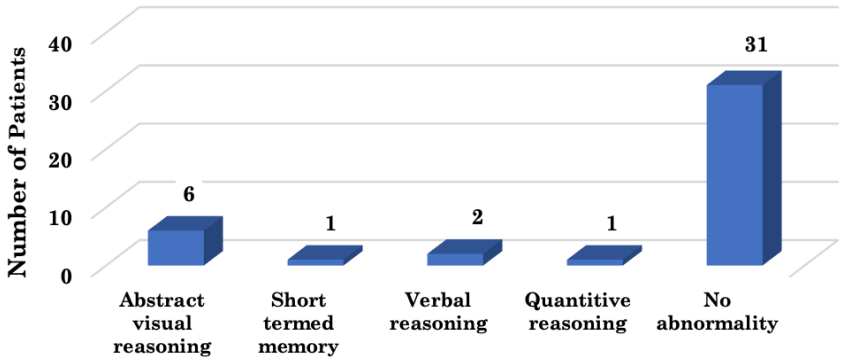

Figure 2. The distribution of the cognitive abilities among the studied SCD cases.

Table 3. P300 Latency and amplitude among the studied patients according to IQ.

	Impaired IQ score (n=33)		Normal IQ score (n=8)		P value
	Number (%)		Number (%)		
P300 Latency (ms)					
Normal	22 (66.7%)		7 (87.5%)		0.398
Impaired	11 (33.3%)		1 (12.5%)		
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
P300 Latency (ms)	400.06 ±54.50	402.0 (373.5-440.0)	378.75± 44.78	370.5 (339.8-423.0)	0.313
P300 Amplitude (mv)	13.19±5.13	12.00 9.25 -17.25)	24.63 ±12.65	23.5 (13.50-29.25)	0.004

IQ: Intelligence Quotient; IQR: Inter Quartile Range; ms: millisecond, mv: millivolt

Patients with low IQ (<89) had lower P300 amplitude (p=0.004) but comparable P300 latencies (p=0.3) to patients with normal IQ. Eleven out of 33 patients with low IQ (33.3%) had abnormal P300 values while 22 (66.7%) had normal P300 readings (0.398) (Table 4). P300

amplitude correlated positively with mental age as well as IQ scores (r=0.46, p=0.003, r=0.49, p=0.001 respectively). The auditory impairment was not a risk factor of cognitive impairment. IQ testing was assumed to be the standard test in the assessment of cognitive impairment. Further evaluations were carried out at different cutoff values for P300 latency by receiver operating (ROC) curves and area under the curve of P300 latency was 0.632, p=0.243; indicating that overall predictability of cognitive dysfunction by P300 latency is low and not significant, at a cut off value of ≥378 P300 test has a sensitivity of 72.7% and a specificity of 62.5% in prediction of cognitive impairment. Further analysis using *Cohen's kappa testing* showed no agreement between P300 latency and IQ test (kappa was 0.1 (p=0.2)).

Table 4. IQ scoring and P300 test results among the studied patients with hearing.

	Patients with hearing loss (n=9)		Patients with normal hearing (n=32)		P-value
IQ scoring: Normal (n (%) Impaired (n (%)	3 (33.3) 6 (66.7)		5 (15.6) 27 (84.4)		0.236
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
IQ scoring (%)	76.56±18.44	75.5 (68-82)	80.11±17.62	87 (67-93.5)	0.610
Mental age (yrs)	8.11 ±2.10	7.80 (6.35 -9.75)	7.64±2.31	7.70 (5.43 -9.23)	0.648
Chronological age (yrs)	10.27 ±3.23	9.5 (8- 12)	11.06±3.36	11 (8-14)	0.53
P300 Latency (ms)	404.3±33.7	402.0 (373.5 -432.0)	393.5± 57.4	400.5 (345.0 -438.0)	0.595
P300 Amplitude (mv)	15.78 ±5.89	13.00 (12.00-18.00)	15.39 ±9.12	12.00 (9.00 -20.00)	0.322

IQ: Intelligence Quotient; IQR: Inter Quartile Range; Ms: millisecond, mv: millivolt; yrs: years

Discussion

In our study the overall frequency of hearing loss by pure tone audiometry was 22% among children with SCD and more than three quarters of our patients, mostly of Hb SS subtype, had cognitive impairment that deteriorates as the patient gets older. This frequency of hearing loss necessitates analysis to find and treat the possible associated risk factors.

On evaluating the auditory functions amongst our cohort, we found evidence of middle ear pathology in the form of middle ear effusion (Type B tympanogram) in nearly 10% of patients and Eustachian tube dysfunction (Type C tympanogram) in 5%. The frequency of middle ear pathology was much lower among our patients compared to a study in the early 1980s that reported abnormal tympanometric results in 34% out of 54 Hb SS patient, aged 12 years (14% with type B and 20% with type C) (*17*). Later in the year 2000, another study reported abnormal tympanometry among 6 of 28 (21%) patients with SCD, aged from 6 to 55 years (*18*). The latter results are similar to our study results. The lower percentage might be explained by the exclusion of some confounding factors such as chronic otitis media or previous exposure to ototoxic medications, or true drop in rates of otitis media due to mass vaccination against *Hemophilus influenzae*, less exposure to ototoxic drugs and prompt management of vaso-occlusive crises.

Pure tone audiometry (PTA) is considered the gold standard test and the best option for pediatricians to screen peripheral hearing loss when hearing threshold is less than or equal to 20 dB (*19*). In our study, the overall frequency of hearing loss was 22%. The reported prevalence of hearing loss among patients with SCD -regardless of its type- was reported globally with nearly similar frequencies that ranged from 20% (*20*) to 24% (*21*). On the contrary, zero percent frequency was reported in a previous study in the USA (*22*); and much higher frequencies ranging from 45.6% in France (*23*), to 66% in Ghana (*24*) were reported. Regular screening for hearing loss is mandatory among children with SCD. It is known that impaired hearing early in life hinders brain development, hence the name hearing loss is a neurodevelopmental emergency (*25*). More studies are needed to define the age at which hearing impairment sets in and the guidelines of the intervals at which screening should be implemented.

Our work suggests that damage in the auditory system in SCA patients may be present involving retro-cochlear structures, causing functional deficits without deterioration of auditory sensitivity. In addition to the middle ear pathology, the occurrence of hearing loss in patients

with SCD may be related to cochlea sensitivity to anoxia due to diminished capacity of anerobic metabolism, increased oxygen utilization, and delicacy of cochlear blood vessels, this also may be related to the persistent inflammatory process in sickle disease (*26*). Hence, the importance of prompt oxygenation, vigorous hydration and timely management of vaso-occlusive and pain crises in SCD. The hearing loss among our studied children with SCD was slight and progressive with age, hence it can pass unnoticed, and unmanaged. Screening for hearing loss periodically among children with SCD seems to be mandatory to allow timely diagnosis and management.

According to SB-IV the frequency of cognitive dysfunction among our children with SCD was up to 80.5%, with nearly 40% of total patients being slow learners. This renders cognitive dysfunction a frequent hidden disability among children with SCD irrespective of the hearing impairment. In our study, the median global cognitive IQ score was 76 and this was similar to that reported in previous studies which reported mean scores of ranging from 75.6 to 82 (*27*–*30*). Higher scores were reported in other studies and reached up to 101 (*31*). Impairment of the cognitive functions is frequently associated with reduced overall quality of life as a result of reduce school and work performance, poor social life, increase risk of being bullied, and high incidence of depression (*32*). The variation in the reported scores might reflect ethnic variation, variation in severity of disease or variation in care between different centers, which may lead to silent neurological insults that may affect their intellectual abilities. Our work urges prospective studies of impact of cognitive impairment in children with SCD on their learning, school performance, proneness to accidents, quality of life and social adaptation.

We failed to find the risk factors for cognitive dysfunction among our studied children with SCD other than the Hb SS-type, which was the most significant risk factor for cognitive dysfunction. Yet this finding is controversial (*28*, *33*–*35*). Patients of Hb SS genotype are more prone to disease related complications due to lack of fetal hemoglobin which ensures better oxygenation of the brain. They might develop silent infarctions and brain structural abnormalities which make them more sensitive to brain perfusion changes (*36*).

P300 is an auditory evoked potential that can test some aspects of cognition as the degree of attention, sound discrimination, and memory. It is an indicator of cortical processing and speed recognition (*37*). In this study, abnormally long P300 latency was found in 29.3% of the studied patients and none of the controls. Unfortunately, little information is available on P300 test results in SCD children (*20*, *38*). The lack of association of P300 latency, and all the disease severity parameter, suggest a silent disease-specific change in the cerebral cortex of affected patients, which may be related to the chronic state of hypoxia due to persistent low Hb, or the persistent inflammatory reaction in SCD patients. Also the lack of correlation with the presence of silent infarction may suggest the presence of diffuse brain injury that results in neuronal damage. Fetal hemoglobin (Hb F) prevents sickling of RBCs; hence it increases the amount of oxygen distribution to the body including the brain. Hb F is considered the most critical lab parameter for clinical severity of SCD. In our study, significant positive correlation was found between P300 amplitude and Hb F ($p=0.02$), that might be related to its role in preserving working memory (*39*).

P300 amplitude showed significant positive correlation with HU dose, which supports previous findings (*40*). This might be explained by the reduction of the inflammatory process of SCD caused by HU treatment which in turn reduces the adhesion of erythrocytes and leukocytes to the vascular endothelium, reduces myelosuppression and induces vasodilation through the release of nitric oxide.

In this study, only one third of SCD children with abnormal IQ scores had abnormal P300 readings ($p=0.4$). However, patients with low IQ had lower P300 amplitude ($p=0.004$), but comparable P300 latencies ($p=0.3$) to patients with normal IQ. Moreover, P300 amplitude had a weak positive correlation with the IQ scores and mental age. The correlation between neurocognitive function by Evoked Response Potentials (P300) and neuropsychological tests like IQ in SCD children has not been investigated. However, number of studies not related to SCD demonstrated direct relation between P300 amplitude and IQ scores, an inverse relation with P300 latency (*41*, *42*), and a significant correlation between P300 amplitude and cognitive abilities (*43*). The lack of consensus of the role of P300 in diagnosis of cognitive impairment highlights the superiority of The Arab version of Stanford-Binet Intelligence Scale, Fourth Edition (SB-IV) in cognitive assessment, and that P300 should be part of the assessment but cannot be relied upon solely (*44*). Investigation of relation between P300 latency/ amplitude and difference in neuropsychological testing has revealed complex yet contradictory results, we suggest that this discrepancy may be dependent on the cognitive area affected in a specific disease needed to be examined by the targeted task of the neurophysiological test chosen. We speculate that the IQ-P300 amplitude correlations were likely present due to the high affection

of attention domain in SCD. In this study, evaluations were carried out at different cutoff values using ROC curve, which indicated that the accuracy of P300 latency in predicting or diagnosing cognitive impairment among SCD patients was low. Further evaluation using Cohen's *kappa* testing revealed a low insignificant agreement between P300 latency and IQ test. IQ is a more reliable tool for IQ assessment among children with SCD.

On studying the cognitive functions among our patients with abnormal hearing (nine patients), six patients had a low IQ score compared to patients with normal hearing, although it was statistically insignificant (p=0.61). In this study, the P300 results showed that patients with abnormal hearing had insignificantly longer P300 latency and an increased P300 amplitude compared to patients with normal hearing (p=0.6, p=0.3 respectively).

Our study had some limitations as the small number of patients, and the cross-sectional nature of the study that may impair the interpretations of the results, also the lack of studying the effect of impaired congestion on school performance, social and psychological wellbeing. We did not study the effect of interventions to improve the hearing and cognition of our studied cohort as it was beyond the scope of this study. Further studies with larger sample size might be helpful in addressing these aspects. Longitudinal study to follow up the effect of auditory impairment in patients with SCD will be more informative. We recommend routine screening of auditory and cognitive functions to be implement as important points of care in young SCD children.

Conclusion

In conclusion, cognitive impairment and auditory impairment are frequent among SCD children. P300 test alone is neither specific nor sensitive for the diagnosis of cognitive impairment. P300 amplitude correlated positively with mental age as well as IQ scores. IQ is a more reliable tool for IQ assessment among children with SCD. There's no direct relationship between auditory and cognitive impairment.

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Author Contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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