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IMPROVEMENT OF SACCADIC EYE MOVEMENTS AFTER HEAD-EYE VESTIBULAR MOTION (HEVM) THERAPY AND NEURO-PSYCHIATRIC CONSIDERATIONS

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SUMMARY

Introduction: *Eye movement pathology can assist in the identification, diagnosis and treatment of mental health disorders. Eye-tracking paradigms have been utilized to provide greater ecological validity, and directly capture the detailed sequence of processes in perception and attention, while quantifying classifiers in mood, anxiety, and psychotic disorders. Saccadic eye movements serve as an endophenotype for various mental health disorders.*

Subjects and methods: *Patients suffering from post-concussive syndrome and mental health concerns performed saccadic eye movements that were quantified for amplitude, velocity, latency and accuracy before and after Head-Eye Vestibular Motion therapy (HEVM).*

Results: *HEVM therapy is associated with statistical and substantive significant improvements in mental health and in saccadic metrics.*

Conclusions: *Oculomotor dysfunction is related to the symptom dimensions of mental health disorders that may be treated with physical rehabilitation modalities. We feel it reasonable to suggest that psychiatrists and others involved in the treatment of mental health disorders quantify eye movements and use them as biomarkers in the evaluation of the outcomes of varied therapies.*

Key words: *mental disorders - behavior outcomes – concussion - mild traumatic brain injury – psychiatry - saccades*

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INTRODUCTION

Eye movement pathology can assist in the identification, diagnosis and treatment of mental health disorders. Eye-tracking paradigms have been utilized to provide greater ecological validity, and directly capture the detailed sequence of processes in perception and attention, while quantifying classifiers in mood, anxiety, and psychotic disorders (Kerr-Gaffney et al. 2018). The complexities of mental health demand an understanding of the principles of operation of neural systems. The integration of brain models to neuro-muscular biomechanical models providing relevant visual and proprioceptive feedback signals facilitate the understanding of complex brain function as a controller for movement and behavior (James et al. 2018). Cortical and subcortical structures involved in controlling behavior also act as the neural controllers of saccadic eye movements and visual fixation. The analysis of eye movements (EM) by eye-tracking has been carried out for several decades to investigate mood regulation, emotional information processing, and psychomotor disturbances in depressive disorders and can be used to discriminate patients with depressive disorders from controls, as well as patients with bipolar disorder from patients with unipolar depression (Carvalho et al. 2015).

Oculomotor dysfunction is one of the most replicated findings in schizophrenia with relations between the symptom dimensions of schizophrenia and saccadic task performances in both clinical (schizophrenia) and pre-clinical (clinical high risk) populations (Obyedkov et al. 2019). As well as the functional observations of eye movement characteristic of schizophrenia, there are also structural changes in cortical thickness (Morita et al. 2019). Antisaccade error rate is an endophenotype for schizophrenia patients because they engage different cognitive processes in the antisaccade task when compared to healthy individuals (Thomas et al. 2018). These patients make significantly more errors associated with increased severity of hallucinations, and smaller amplitudes, less accurate final eye positions and slower latencies of their correct responses in comparison to healthy controls (Subramaniam et al. 2018). While impaired eye movements are one of the cognitive hallmarks of schizophrenia patients, they are also found to be pathological in their relatives with a phenotype of error rates between patients and healthy controls (Myles et al. 2017).

Suicide is a major public health problem, and it remains unclear which processes link suicidal ideation and plans to the act of suicide. Affective temperaments, especially depressive and irritable, are strongly associated with suicidal risk (Vazquez et al. 2018) and the majority of suicidal patients diagnosed with major depression or bipolar disorder report repetitive suicide-related images and thoughts that may be reduced in frequency and intensity by Eye Movement Dual Task (EMDT) (van Bentum et al. 2019).

Current evidence suggests a link between mood disturbance and sports-related concussion with noted depression symptoms in elite athletes (Rice et al. 2018). There is a consistent positive association between a history of concussion and depression among former athletes with public concern catalyzing research investigations addressing the potential long-term negative health consequences associated with sport-related concussion and sub-concussive impacts (Hutchison et al. 2018). Although one concussion may be associated with mental health impairment, multiple concussions appear to be a significant risk factor for cognitive impairment and mental health problems (Manley et al. 2017).

Our group reported that head-eye vestibular motion (HEVM) therapy is associated with improvement of the mental and physical health of post-concussive syndrome (PCS) patients that had been severely impaired for greater than 6 months after a mild traumatic brain injury (Carrick et al. 2017). Saccadic eye movements are an endophenotype for mental health disorders. HEVM therapy does not include strategies specific to saccadic eye movement retraining but is associated with amelioration of mental health conditions. We were therefore interested in measuring saccadic eye movements before and after HEVM therapy to see if a non-saccadic rehabilitation regime would change the endophenotype of saccades associated with mental health syndromes.

SUBJECTS AND METHODS:

This study was a single-center, retrospective review of records performed at our Institutional Brain Injury Clinic conducted in accordance with the Declaration of Helsinki with equipoise. The Carrick Institute Institutional Review Board approved the records review and written informed consent was obtained from each patient prior to his or her examination and treatment. We identified patients that were disabled from work or school for a period of time exceeding 6 months after suffering a sports concussion and depression. These subjects all were enrolled in a 5-day HEVM rehabilitation program at our Institutional Brain Center with pre- and post- saccadic eye movement outcomes. Blinded investigators that were not involved in the treatment of subjects nor had any interaction with them or the treating physicians did the review.

Saccadic eye movements were measured by the Ober Saccadometer (Consulting 2017) a FDA registered Class II Medical Device that perform strict quantitative evaluations of saccadic dynamic performance (latency and velocity), using micro-miniature equipment. The Ober Saccadometer utilizes the method of Direct Infra-Red Oculography, which is embedded in the Cyclop ODS type sensor (ODS- Oculus Dexter Sinister) and measures the resultant rotations of the left and the right eye taken together. Due to the conjugacy and synchronicity of the saccadic eye movements, the rotation of left and right eyes, can be added and averaged. The inner canthi of the left and right eyes are illuminated with the low intensity IR light (irradiance below 1 mW/cm^2 (operating condition)) and the difference between the amounts of IR reflected back from the eye surfaces carries the information about the eye position changes. The measuring rate is ±35 degress with a band width of 9.200 HZ and a noise level of 0.5 arc min (peak to peak) with a signal to noise ratio (SNR) of 41.6 dB (referenced to a 10 degree saccade). The average linearity error is in the range ±15 deg: 1.4 deg; maximal error: 2.9 deg.

The protocol used to acquire saccadic data in this investigation required the subject to be comfortably seated 1 m from a wall (with uniform texture and neutral gray color to reduce scatter of the laser beams hitting the wall). After calibration, 100 saccades (alternated 50 to the right and 50 to the left) were performed by the subjects between two peripheral targets (at 10° amplitude each from the midline, for a total saccade amplitude of 20°). The pace was random between 1.3 s and 2.3 s. The software (LatencyMeter v 6.6 - Ober Consulting – Poznań, Poland) recorded for each eye movement the position of the eyes (relative to the beginning of the saccade) and calculated, for each movement, the latency, duration, amplitude, peak velocity, mean velocity (calculated as amplitude over duration) and Q factor. As output, the latency versus time (showing each eye movement position using as origin of the time scale the presentation of the target), and the velocity versus time were also provided. Graphs and numerical results could be also subdivided based on the direction of the saccade (left or right).

The primary treatment was gaze stabilization exercises administered with coordinated HEVM at positions and speeds associated with a decomposition of head and eye tracking movements. Subjects would attend to a visual target that would move in a plane at a velocity approximating the speed of head–eye decomposition while moving their head in combinations of pitch, yaw, and roll. The visual target underwent a gradual increase of its velocity and amplitude until head–eye movements further degraded or became synchronous at which time the session would stop. These sessions had durations of 3 min at a time followed by a 3-min rest and then repeated three times. The sessions would be scheduled five times per day with a rest period of a minimum of 1.5 h between sessions over 5 days.

A secondary treatment of vestibular and somatic stimulation was administered by placing the patient in an accelerated rotation in a multi-axis rotational chair (MARC) (Centers 2017) from 0 to 60°/s over 15 s about a plane opposite to the plane of head movements that were slower than coordinated eye movements in combined slow visual pursuits. Subjects underwent 3–30 s acceleration–deceleration rotations with the accelerated rotations beginning at 0 and terminating at 60°/s over 15 s followed by a 15-s deceleration from 60 to 0°/s. The acceleration–deceleration was linear and followed by a 2-min break between each rotation and repeated two times per day over 5 days. Subjects were also rotated in a unique Roll plane combination with the same acceleration/deceleration paradigm as in Pitch and Roll and at the same time resulting in a novel 3-axis rotation of the subject.

A tertiary treatment of somatic sensory motor movements involved subject complex movements of the upper and lower extremity, both passively with a therapist and actively (right arm, left arm, right leg, and left leg) and in combination (right arm-left leg, left arm-right leg, right arm-right leg, and left arm-left leg). Subjects participated in somatic sensory motor movements for three sessions per day. The eye should not move if the head moves at the same speed of a slow-moving target while fovealizing on the target. Neck musculature that exhibits increased tone or resistance to stretch and movement results in a sensory mismatch between head and eye movement. Manipulation of the cervical spine was administered to all patients on the side opposite the greatest eye movement observed with coordinated head eye targeting of slow pursuit targets in the horizontal plane.

Statistical Analysis

Statistical analysis was performed with STATA 14, Statacorp LP, College Station, TX, USA. Two sample paired t tests with equal variances were calculated for each variable (pre and post treatment intervention) independent of other variables. The effect size was calculated by Cohen's d to indicate the standardized difference between two means. A Cohen's d of 0.2 is considered to be a small effect size, 0.05 a medium effect size, and 0.08 a large effect size.

RESULTS

The review of records of patients was limited to those that had suffered from post-concussion syndrome for a duration greater than 6 months with documented mental health issues including depression, traumatic stress, increased or decreased emotionality, irritability, sadness and anxiety. The normality of the distributions of data was verified using Kolmogorov-Smirnov with Lilliefors Significance Correction and Sharpiro-Wilk tests of normality. We identified 154 subjects, 91 males and 63 females with a mean age of 36.73 years (Std. Dev 21.58 minimum age of 5 years and maximum age of 91 years). There was no difference between male and female performance, therefore they were combined in the analysis. We analyzed saccadic performance including amplitude, velocity and latency.

The amplitude of the total saccade was 20°. We defined hypometria as an amplitude that was ≤19° and hypermetria as an amplitude that was ≥21°. We found statistical and substantive significance in the performance of saccades before and after HEVM treatment. Table 1 summarizes the differences between saccadic performance before and after treatment.

Figures 1 & 2 are scatterplots of the Pre and Post HEVM treatment for all saccadic metrics.

DISCUSSION

The endophenotype of saccadic performance and mental health issues is becoming an interesting biomarker that might demonstrate the consequence of a variety of treatment modalities. We have quantified the standard characteristics of saccades including the amplitude, velocity, direction, latency and accuracy and measured them before and after HEVM treatment that has been associated with the amelioration of some mental health syndromes.

Disorders of midbrain, cerebellum, or basal ganglia can lead to prolonged transition time during gaze shift with an associated decreased saccade velocity (Puri and Shaikh 2017). We have observed these phenomena and the resultant changes in metrics that suggest HEVM treatment affects neurological integration in these areas. The mental health concerns of structural and physiological changes in these areas of the brain are well established.

The cerebellum guarantees the precision of ocular movements to optimize visual performance and occupies a central role in all classes of eye movements both in real-time control and in long-term calibration and learning (i.e., adaptation) (Beh et al. 2017). It is logical to assume that the consequences of HEVM therapy have a significant cerebellar component. The caudal fastigial nucleus (cFN) of the cerebellum is the output nucleus that influences the brainstem saccade generator. An imbalance in the intrasaccadic activity between the two caudal fastigial nuclei impairs the amplitude of saccades resulting in dysmetria (Goffart et al. 2003). Our observations suggest that HEVM therapy results in decreasing a mismatch between cFN resulting in improvements in saccadic accuracy and decreased dysmetria. We found changes in saccadic accuracy after HEVM therapy that must influence the control signal sent to the motor neurons to bring the fovea to the target requiring changes in cerebellar circuitry located in the posterior vermis and fastigial nucleus.

Table 1. Paired T tests of difference in saccadic eye movements and their statistical and substantive significance after a 5-day program of HEVM before and after HEVM Treatment. P values <0.05 are in *italics.* A Cohen's d is considered to be small (0.2), medium (0.5) and large (0.8)

Saccade Metrics	N	Mean	Std Dev	95% CI		T	P	Cohen's d
Pre Amplitude Left ≤ 19°	99	14.61	3.98	13.81607	15.40413	0.02	*0.0183*	-0.2239
Post Amplitude Left		15.58	4.67	14.64996	16.5157			
Pre Amplitude Right ≤ 19°	113	14.91	3.73	14.21678	15.608	-4.14	*0.0001*	-0.3942
Post Amplitude Right		16.48	4.20	15.69617	17.26489			
Pre Amplitude Left ≥ 21°	12	23.94	1.45	22.82782	25.06107	2.17	0.0609	1.2660
Post Amplitude Left		21.47	2.35	19.6558	23.27753			
Pre Amplitude Right ≥ 21°	12	25.62	3.11	23.23076	28.01369	4.77	*0.0040*	2.080
Post Amplitude Right		18.08	4.08	14.9425	21.21305			
Pre Velocity Left ≤ 350°/s	27	266.89	71.58	238.5706	295.1998	-2.98	*0.0061*	3.057
Post Velocity Left		363.67	149.69	304.4514	422.8819			
Pre Velocity Right ≤350°/s	30	274.49	72.46	247.4283	301.545	-4.90	*0.0000*	2.908
Post Velocity Right		0.17	1.38	-0.1582953	0.5011524			
Pre Latency Left ms	154	210.18	90.97	195.7069	224.6698	2.38	*0.0188*	0.1325
Post Velocity Left ms		197.81	95.80	182.5544	213.056			
Pre Latency Right ms	154	217.75	110.24	200.2033	235.3032	1.91	*0.0288*	0.1193
Post Velocity Right ms		205.18	100.15	189.2389	221.1247			
Pre Latency Left ≥ 200 ms	64	280.75	102.97	255.0297	306.4703	2.47	*0.0164*	0.1936
Post Latency Left ms		0.58	1.70	0.1787652	0.9926633			
Pre Latency Right ≥ 200 ms	56	309.05	139.69	271.6435	346.4636	2.61	*0.0117*	0.3045
Post Latency Right ms		266.91	137.06	230.2045	303.6169			

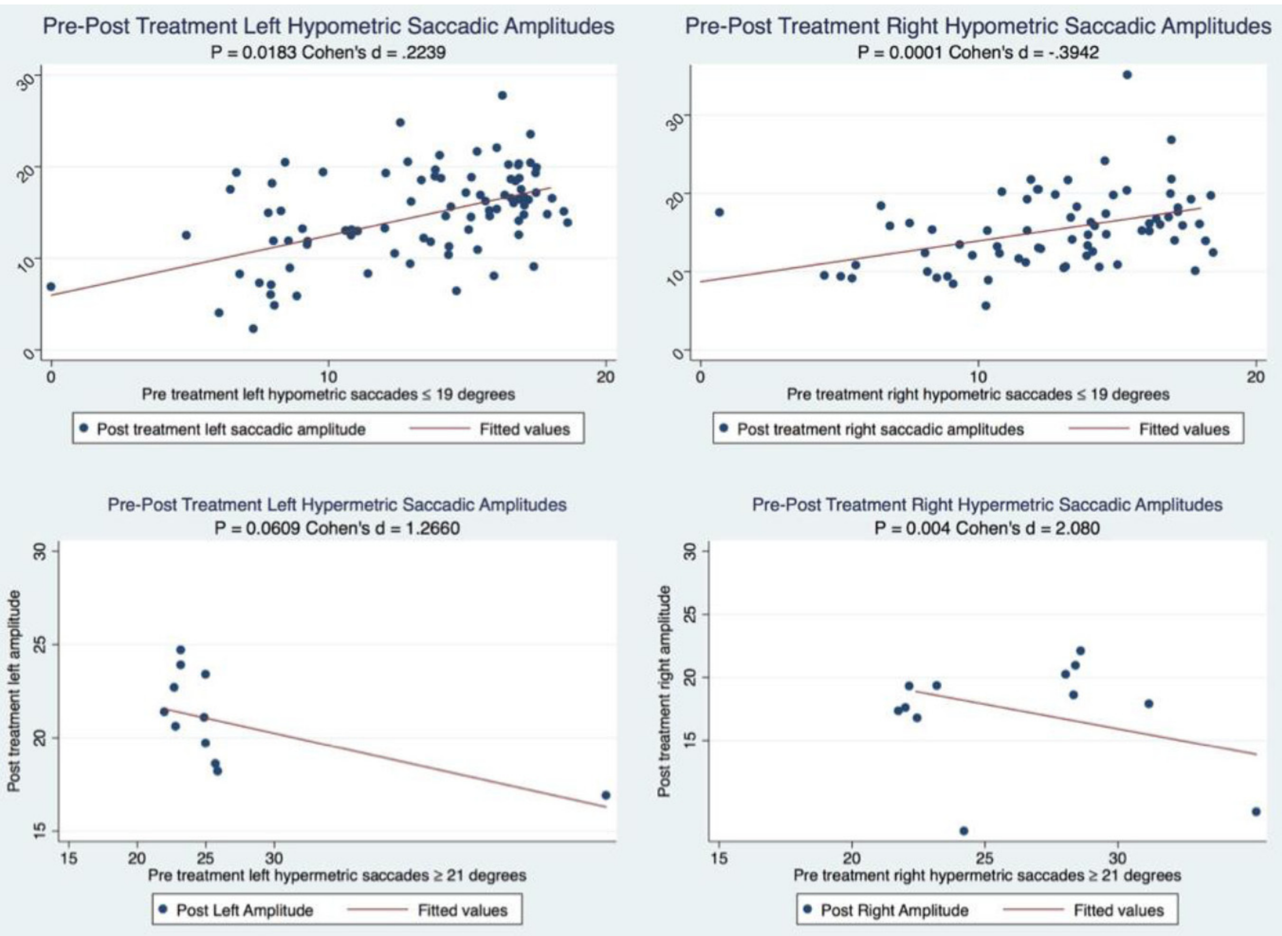

Figure 1. Scatter plots of hypo and hypermetric saccadic eye movements before and after HEVM Treatment

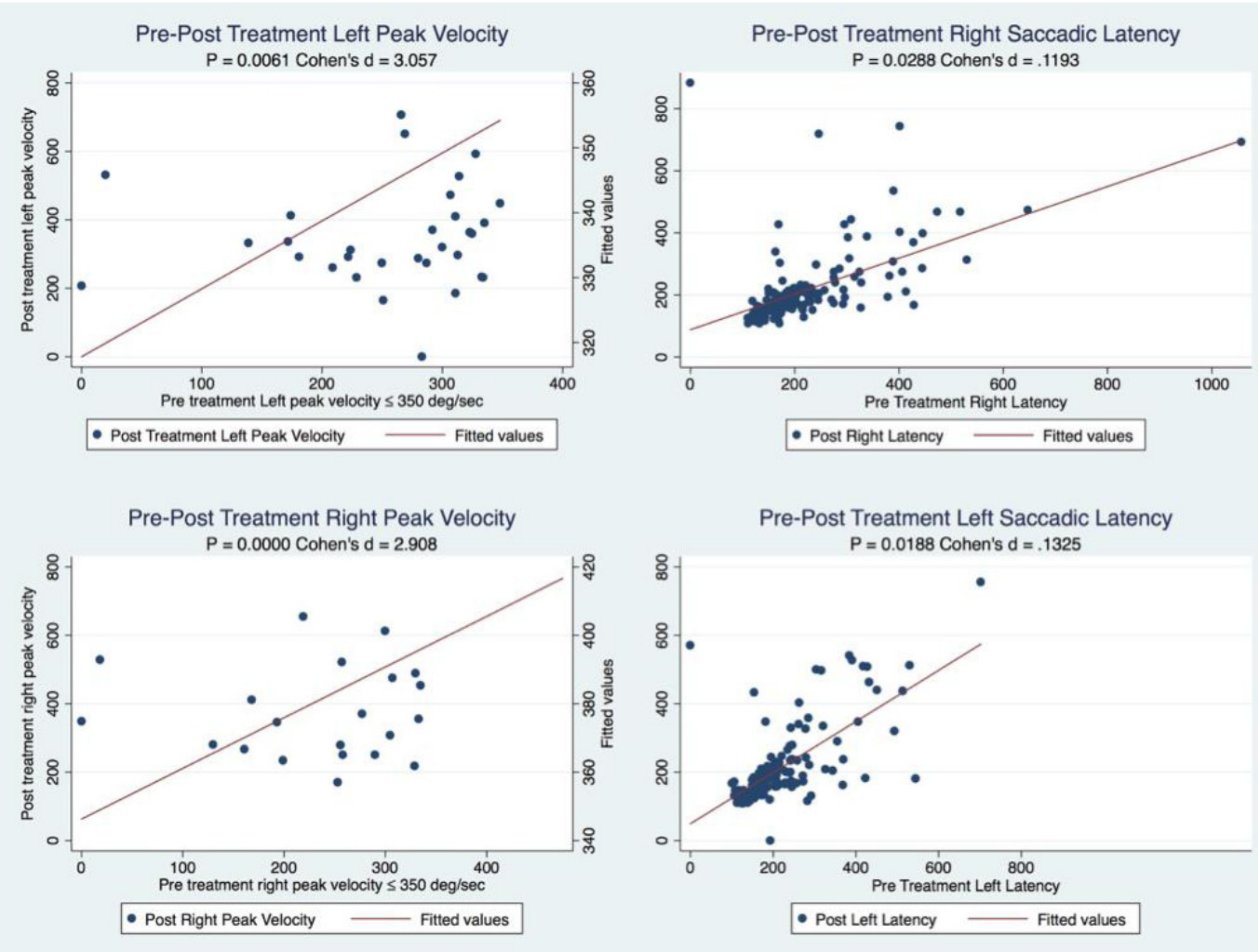

Figure 2. Scatter plots of peak velocity and latency of saccadic eye movements before and after HEVM Treatment

The neural control of saccades is initiated by the deep layers of the superior colliculus and terminated by the cerebellar fastigial nucleus involving circuitry in the paramedian pontine reticular formation, vestibular nucleus, abducens nucleus, oculomotor nucleus, cerebellum, substantia nigra, nucleus reticularis tegmenti pontis, thalamus, deep layers of the superior colliculus and the oculomotor plant for each eye (Enderle & Engelken 1996). Clearly these structures are involved in the integration of higher cognitive function associated with psychiatric applications and affected by HEVM therapy. The seminal paper by Paul Dean and colleagues gives a robust overview of a model of brainstem-cerebellar interactions affecting learning and saccadic accuracy of how the cerebellum adaptively controls it (Dean et al. 1994). It is reasonable to suggest that HEVM therapy involves this interaction.

Gaze is oriented to a target by combined displacements of the eye and head using a feedback system that is internally created and fed back to the superior colliculus controlling gaze (Guitton 1992). The changes in accuracy of gaze after saccadic eye shifts to targets were quantified in this review. We feel it reasonable to suggest that psychiatrists and others involved in the treatment of mental health disorders quantify eye movements and use them as biomarkers in the evaluation of the outcomes of varied therapies. As patients with depressive disorders demonstrate significantly abnormal eye movement indices compared to healthy controls (Li et al. 2016) we find that therapy addressing eye movement not customarily associated with psychiatry may have great applications in the treatment of a variety of neuropsychiatric syndromes.

CONCLUSIONS

This study has confirmed that rehabilitation strategies that involve subjects in procedures involving HEVM therapy can affect saccadic metrics with statistical and substantive significance. These metrics are associated with a variety of mental health conditions and suggest that impairments in the cognitive-behavioral flexibility associated with saccade generation may be used to guide further research and therapeutic applications.

Limitations

This is a single clinical location study that may not be generalized to a general population.

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Conflict of interest: *None to declare.*

Contribution of individual authors:

Frederick R. Carrick, Rashid Zaman, Matthew M. Antonucci, Guido Pagnacco, Sergio Azzolino & Elena Oggero conceived the idea of the study, contributed to the literature review and revised the manuscript.

Ahmed Hankir organised the study, collected the data, and contributed to the literature review and revised the manuscript.

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