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Synthetic cannabinoids impact on cognitive functions

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Abstract

Background Synthetic cannabinoids SC are now becoming progressively popular among young people worldwide; little is known about their negative effects. Anger, anxiety, hallucinations, and perceptual changes were the most common psychoactive findings. Substance abuse causes cognitive impairment (CI). This study's goal is to raise public awareness about the dangers that synthetic cannabinoid intoxication poses to public health. As well as the magnitude of CI in synthetic cannabinoids in comparison with healthy controls. The study included 30 synthetic cannabinoids SC addicts and 30 healthy people. The Wechsler memory scale (WMS), the Benton visual retention test (BVRT), and Trail Making Test (TMT) A and B were used to assess cognitive functions. Addiction Severity Index (ASI), Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I), and Structured Clinical Interview for DSM-IV Axis II Disorder (SCID II).

Results Using BVRT, (96.7%) of the SC use disorder cases had more impaired performance than controls (0%) ($P < 0.001$). Almost three quarters of the cases had impaired performance on the trail making tests A and B compared to none of the controls ($P < 0.001$). Similarly, there was a high statistically significant difference between SC use disorder cases and controls in all domains of the WMS. There was no statistically significant correlation between the cognitive scales (BVRT, WMS and TMT) results in relation to age of SC use patients or duration of use.

Conclusions Patients who used synthetic cannabinoids SC were more likely than controls to develop CI, which manifested as impaired visual, auditory, immediate, delayed, and working memory.

Keywords New psychoactive substances, Synthetic cannabinoids, Cognition, Dependence, Memory, Cognitive impairment, Egypt

Introduction

Cannabinoids and synthetic cannabinoids (SC) are widely used psychoactive substances nowadays. In Egypt, nicotine is the most commonly used substance over lifetime (9%), followed by benzodiazepines (5.1%), alcohol (3.3%), and cannabis 3.1% [1]. Similar rates were found by Kabbash et al. (2022) [2].

Recently, newer psychoactive substances became popular in Europe and USA, and they are increasingly finding their way to other countries. Synthetic cannabinoids (SCs)—the focus of our research—is considered one of these new psychoactive substances (NPS) [3].

Synthetic cannabinoids (SCs) are a large family of chemically unrelated structures. Like Δ 9-tetrahydrocannabinol (THC), the active component of cannabis, they interact with cannabinoid receptors (CB1 and CB2) to exert their psychoactive effects [4].

Strox and voodoo are the most popular street names for SCs in Egypt [5, 6]. "Spice," "K2," "Black Mamba," and

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"Scooby Snax" are some other brand names for these products [7, 8].

SCs use has many problems. First, due to lacking cannabidiol CBD (another component of cannabis, that reduces risk of psychosis) and due to their higher potency, SCs users are more prone to develop psychotic symptoms [9]. A second problem in SCs, is that the chemical components and compound concentrations varies between and within packages [10]. A third problem is that novel SCs have no urine metabolites. Therefore, SCs are undetectable by standard cannabis tests or immunoassays [11–13]. Finally, SC have a stronger affinity for CB1 and CB2 receptors than Δ THC. All leading to severer side effects than natural cannabis, for example, cardiovascular, gastrointestinal tract (GIT), neurological affection and more addictive properties [14, 15].

Toxicity of SC leads to life-threatening effects, including hyperarousal (19.1%), drowsiness (17.5%), hypertension (9.6%), nausea (9.3%), confusion (8.9%), dizziness, vertigo (8.1%), and chest pain (8.1%). SC can also cause ischemia, myocardial infarction, and tubular necrosis [16].

Moreover, SC has been linked to neuropsychiatric problems, such as seizures, psychosis, chronic insomnia, anxiety disorders, suicidal thoughts, or even catatonia [17–20].

On the long-term, emerging evidence show that SCs may cause cognitive decline, especially in executive functions, memory, and visuo-spatial skills. These findings were also associated with brain changes in SC users [21]. Miller et al. (2013) and Basavarajapp et al. (2014) found long-term potentiation (LTP) and white matter affection in the hippocampi of SC users [22–24]. A DTI study indicated that SC abusers have smaller corpus callosum and thalami than healthy controls [25]. In addition, another study demonstrated affection of the inferior fronto-occipital fasciculus (which regulates inhibition and attention), the temporal occipital fasciculus, and other social cognitive areas in SC users [26]. Given these widespread deleterious cognitive affections caused by SC, this study was set out to investigate the cognitive functions of SC-dependent male patients compared to healthy controls. This is one of the few studies discussing this important problem.

Methods

This is a cross-sectional case–control study. A convenient sample of 30 male patients with SC use disorder were included in the study. The study was conducted at the outpatient clinics of addiction unit of Ain Shams University psychiatry department, Okasha Institute, in the duration from October 2018 to August 2019.

Male patients aged between 18 and 45 years, fulfilling the diagnosis of SC-dependence disorder as outlined in the DSM-IV criteria, were included in the study. Only those who were only using SC as their main substance of abuse in the past 30 days were included (reported by the patient).

Thirty apparently healthy male smoker volunteers, aged between 18 and 45 years, were included as a control group; having no history of psychiatric diseases, substance use (except for smoking), or medical diseases. Controls were recruited from the employees and workers at the Institute of Psychiatry, Ain Shams University. They were matched for age to the case group.

Subjects were excluded from the study if they had any of the following conditions: chronic medical, or neurological disorders, or refused to sign consent.

The nature and scope of the study were discussed with each patient, and written informed consent was obtained. This study was reviewed and approved by the Ain Shams University ethics committee.

All eligible subjects (based on self-reports of drug use) were subjected to the following tools:

1. The psychiatric sheet of Ain Shams University, psychiatry department, including personal data and present psychiatric illness. In addition, an assessment of the concurrent medical conditions was done.
2. The Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I) was used for diagnosis of substance use disorder and any comorbid psychiatric disorder [27]. An Arabic version was used [28]
3. The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID II) was used for diagnosis of Axis II personality diagnoses [29]. Arabic version was used [30].
4. Participants in the case group only were evaluated using the Addiction Severity Index (ASI), a semi-structured interview designed to serve as quantitative measure of symptom and functional impairment due to drug disorders, it covers demographics, alcohol use, drug use, psychiatric status, medical status, employment, legal status, and family and social issues. It is formed of 142 items, including yes–no, multiple-choice and scaled items [31]. Arabic version was used (5th ed.) [32]
5. Cognitive Assessment tests include:
6. *Benton visual retention test-revised (BVRT)* [33]*:* An individually administered test for people aged from 8 years to adulthood that was used for assessing visual perception, visual memory, and visuo-constructive abilities. BVRT test is considered impaired if the difference between obtained error score and expected error score > 4.

7. *Trail Making Test (TMT) A and B* [34, 35]. The test provides information on visual search, scanning, processing speed, mental flexibility, and executive functions. The score represents the amount of time required to complete tasks [36]. Impaired Scoring of TMT part, A: complete test > 98 s. Impaired Scoring of TMT part, B: complete test > 233 s.
8. *Wechsler memory scale (WMS)* [37]*;* It is a neuropsychological test designed to measure different memory functions. Anyone aged between 16 and 90 is eligible to take this test. The functions assessed include memory for verbal and visual stimuli, meaningful and abstract material, and delayed as well as immediate recall. It was applied by a trained psychologist. Scores of impaired WMS subscales: Information > 14, Verbal paired association I > 24, Visual paired association I > 18, Digit span > 19, Visual Memory Span > 21, Verbal paired association II > 8, Visual paired association II > 6

Table 1 Demographic characteristics of the study group

Socio-demographic data	Control *n* = 30 (%)	SC *n* = 30 (%)	*P* value
Age (years) (Mean ± SD)	25.2 ± 3.9	23.6 ± 4.6	0.075$^{(T)}$
Education			
Illiterate	0 (0%)	1 (3.3%)	**< 0.001**$^{(F)**}$
High school	2 (6.7%)	24 (80%)	
High education	28 (93.3%)	5 (16.7%)	
Marital status			
Single	17 (56.7%)	29 (96.7%)	**< 0.001**$^{(F)**}$
Married	12 (40%)	1 (3.3%)	
Divorced	1 (3.3%)	0 (0%)	
Employment			
Unemployed	0 (0%)	21 (70%)	**< 0.001**$^{(C)**}$
Employed	30 (100%)	9 (30%)	

(F); Fisher exact test, (T); *T* test, C; Chi-square test

*Statistically significant < 0.05, **statistically highly significant < 0.001

SD, standard deviation, SC, synthetic cannabinoids

Statistical analysis

The processing of data was computed using statistical package for social Sciences (SPSS)-version 20 IBM (SPSS Inc., Chicago, Illinois, USA). Data were described in the form of number and percentage, and range and mean SD. To compare quantitative variables between two groups, the Student's *t* test (T) was applied. Chi-square (X^2) and Fisher's exact test were used to compare qualitative variables. Pearson correlations was used to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically 'r' defines the strength and direction of the linear relationship between two variables.

A *P* value of 0.05 or less was considered significant and *P* < 0.001 as highly significant.

Results

This study is a cross-sectional case–control study. During the study period, 32 met the eligibility criteria for the study: two patients refused to sign the consent, and there were no dropouts.

Table 1 shows the mean age of subjects were (23.6 ± 4.6) years for the SC group and (25.2 ± 3.9) years for healthy controls. There was a highly statistically significant difference between both as regard level of education, the SC group being less educated. In addition, more of SC group were single and unemployed.

In SC use patients, the average duration of addiction was (1.5 ± 0.5) years and age of onset was around (20.9 ± 3.5) years.

Table 2 Psychiatric disorders in the patients' group by SCID-I and SCID-II scales

SCID-I and SCID-II scales	SC *n* (%)
Schizophrenia	9 (30%)
Bipolar affective disorder	7 (23.3%)
Major Depressive disorder	1 (3.3%)
Antisocial personality disorder	19 (63.3%)
Borderline personality disorder	27 (90%)

SC, synthetic cannabinoids

Psychiatric disorders in the patients' group are shown in Table 2, with schizophrenia being the most common (30%), followed by bipolar affective disorder (23.3%). The most common personality disorder in our sample was borderline personality disorder. Clinical characteristics of SC use disorder are shown in Table 3.

Table 4 clarifies a high statistically significant difference between SC use disorder cases and controls in visual memory, visual reconstruction ability and processing and delayed memory using BVRT. The cases (96.7%) had more impaired performance than controls (0%) (*P* < 0.001).

There was also statistically significant difference between SC use disorder cases and controls in attention and processing speed using trail making test (TMT) A and B. Almost three quarters of the cases had impaired performance compared to none of the controls (*P* < 0.001).

Table 3 Clinical characteristics of synthetic cannabinoids use disorder cases using addiction severity index (ASI)

ASI subscales	SC *n* (%)
Medical	
Slight problem	13 (43.3%)
Moderate problem	15 (50%)
Considerable problem	2 (6.7%)
Employment	
Slight problem	1 (3.3%)
Moderate problem	14 (46.7%)
Considerable problem	9 (30%)
Extreme problem	6 (20%)
Drug	
No problem	9 (30%)
Slight problem	15 (50%)
Moderate problem	4 (13.3%)
Considerable problem	2 (6.7%)
Legal	
Slight problem	24 (80%)
Moderate problem	6 (20%)
Family	
Moderate problem	6 (20%)
Considerable problem	20 (66.7%)
Extreme problem	4 (13.3%)
Psychiatric	
Slight problem	7 (23.3%)
Moderate problem	5 (16.7%)
Considerable problem	9 (30%)
Extreme problem	9 (30%)

SC, synthetic cannabinoids

Similarly, a high statistically significant difference in visual, auditory, immediate, delayed and working memory using WMS between SC use disorder cases and controls in all domains.

Table 5 shows no statistically significant correlation between the cognitive scales (BVRT, WMS and TMT) results in relation to age of SC use patients or duration of use.

Table 6 shows a statistically significant correlation between (psychiatric dimension of ASI and Digit span of WMS) of SC use disorder cases. Otherwise, no significant correlations were found.

Discussion

This study compared an age and sex matched 30 SC users to 30 healthy controls, to investigate SC impact on cognitive functioning. This is one of the few studies discussing this important problem in Egypt.

The study found that participants engaged in SC substance use were around 23 years of age, with average duration of use of 1–2 years. Seventy percent of patients were unemployed, and they were less educated than controls. This agrees with other studies showing that non-recreational SC users were less educated, and with lower socioeconomic status than controls [25, 38].

In our sample, 30% of the SC use patients had schizophrenia, (23.3%) had bipolar affective disorders, and MDD cases (3.3%). This is comparable with pervious literature investigating psychiatric effects of SC on users, which reported found that 44.3% had psychotic disorders, such as schizophrenia or unspecified psychotic disorder [39].

This implicates endocannabinoid receptors in psychosis. This receptor is strongly expressed in psychosis pathophysiology, cognition, and behavior [39]. Men with SC-induced acute psychosis demonstrated similar cognitive deficits to schizophrenics. SC-induced behavioral and cognitive impairments in animals mirror schizophrenia. The users also reported utilizing SC. For SCs, the most prevalent adverse effect is agitation, followed by irritability, restlessness, depression and psychomotor impairments [40].

SCID II showed 63.3% of SC users had Antisocial personality disorder APD and 95% of SC users had Borderline personality disorder BPD. Goretti et al. 2017 reported Between similar data, 65% and 90% of substance abusers have personality disorders (PD), with cluster B personality disorders occupying 46.7% [41]. BPD was extremely common about 76% and 12% APD. All this data conclude that addiction is a risk factor for Cluster B personality disorders [41].

Previously, another study included 120 Egyptian of substance abusers at the Menoufia University Hospitals' Addiction Centre and Neuropsychiatry. Cluster B PDs and substance abuse were linked. Impulsivity and self-harm are important in cluster B PDs [42].

Using the ASI medical subscale, more than half of SC individuals experienced moderate to severe medical problems. SC use is associated with adverse effects [43]. Around 30% of the study population reported headache, 20% panic, 10% dizziness and fainting, 6% cardiovascular and respiratory symptoms, and 8% GIT symptoms. Substantial adverse effects and death connected to SCs were observed in the Midwest, Northeast, and West. About 11% of patients treated at the University of Mississippi Medical Center were admitted to general inpatient treatment, 10% to critical care services, and three died [43]. In April 2015, the Department of Mental Health reported 120 SC-related ED visits in a single week, six times gastrointestinal issues include hyperemesis [44, 45], severe rhabdomyolysis, hyperthermia, and seizures [46, 47].

Table 4 Comparing cognitive functions between tramadol group and healthy controls

	Control group $n=30$ (%)	SC group $n=30$ (%)	*P* value
Benton visual retention test (BVRT)			
BVRT (Mean ± SD)	0.5 ± 0.5	10.4 ± 3.2	**< 0.001$^{(T)}$****
Impaired BVRT (%)	0 (0%)	29 (96.7%)	**< 0.001$^{(c)}$****
Trail making test (TMT)			
Trail making test Part A (Mean ± SD)	28.9 ± 9.1	74.3 ± 18.5	**< 0.001$^{(T)}$****
Trail making test Part B (Mean ± SD)	58.7 ± 16.7	212.9 ± 35	**< 0.001$^{(T)}$****
Impaired Trail making test (%)	0 (0%)	22 (73.3%)	**< 0.001$^{(C)}$****
Wechsler memory scale (WMS)			
Information (Mean ± SD)	16 ± 0	12.9 ± 1.4	**< 0.001$^{(T)}$****
Information Impaired (%)	0 (0%)	16 (53.3%)	**< 0.001$^{(C)}$****
Verbal PAI (Mean ± SD)$^{\#}$	22.6 ± 1	11.5 ± 3.3	**< 0.001$^{(T)}$****
Verbal PAI Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****
Visual PAI (Mean ± SD)§	16.2 ± 0.9	6.6 ± 2	**< 0.001$^{(T)}$****
Visual PAI Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****
Digit span (Mean ± SD)	19.9 ± 1.9	7.1 ± 2.2	**< 0.001$^{(T)}$****
Digit span Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****
Visual MS (Mean ± SD)$^{£}$	18.7 ± 1.5	5.3 ± 1	**< 0.001$^{(T)}$****
Visual MS Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****
Verbal PAII (Mean ± SD)$^{\#}$	8.1 ± 0.3	4.6 ± 1.3	**< 0.001$^{(T)}$****
Verbal PAII Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****
Visual PAII (Mean ± SD)§	6 ± 0	2.9 ± 1	**< 0.001$^{(T)}$****
Visual PAII Impaired (%)	0 (0%)	30 (100%)	**< 0.001$^{(c)}$****

**Statistically highly significant < 0.001

SD, standard deviation; $^{\#}$Verbal paired association I and II; §Visual paired association I and II; $^{£}$Visual memory span; SC, synthetic cannabinoids

(C), Chi-square test; (T), *T* test

Table 5 Correlation between Benton visual retention test as well as Wechsler memory scale and trail making A and B in relation to age of SC use disorder cases and duration of use

SC group $n=30$ Pearson correlation	Age		Duration of addiction	
	r	*P* value	r	*P* value
Trail making A	− 0.221	0.240	− 0.239	0.203
Trail making B	− 0.070	0.713	0.128	0.501
Benton visual retention test	0.143	0.451	− 0.052	0.783
Information	0.025	0.895	0.071	0.710
Verbal PA1§	− 0.023	0.904	0.266	0.155
Visual PA1#	− 0.052	0.785	0.240	0.201
Digit span	− 0.176	0.352	− 0.231	0.220
Visual MS$^{£}$	− 0.050	0.793	− 0.166	0.381
Verbal PA2§	− 0.236	0.209	− 0.133	0.485
Visual PA2#	− 0.184	0.331	− 0.068	0.720

$^{\#}$ visual paired association I and II; § verbal paired association I and II; £ Visual memory span; SC, synthetic cannabinoids

* = statistically significant < 0.05, ** = statistically highly significant < 0.001

Almost three-quarters of the patients had cognitive impairment, compared to none of the controls. Using BVRT, SC exhibited significantly worse performance than controls in visual memory, visual reconstruction ability, and delayed memory. In addition, SC users exhibited poor attention, delayed processing speed, visual, auditory, immediate, delayed, and working memory compared to controls in all domains. An increase in attention difficulties and psychiatric symptoms was found by ASI and WMS Digit span in SC group.

Two studies tested executive function, inhibition, and long-term memory [25, 48]. A study by Altinas et al. (2016) used the Frontal Assessment Battery (FAB) to assess differences in executive function [48]. They detected cognitive impairment in Israeli and Hungarian synthetic cannabinoid users. This impacted CBT outcomes, because SC users had impaired working and long-term memory and executive function.

Similarly, SC eaters have reported fine motor, memory, and long-term cognitive impairments [20]. Drug users'

Table 6 Correlation between addiction severity index (ASI) of SC use disorder cases and BVRT, TMT A and B, as well as WMS

SC group $n=30$ Spearman correlation		TMT A	TMT B	BVRT	WMS						
					Information	Verbal PA1§	Visual PA1#	Digit span	Visual MS£	Verbal A2§	Visual A2
Medical	r	− 0.058	− 0.141	− 0.230	− 0.292	− 0.172	− 0.084	0.308	0.460	− 0.092	− 0.048
	P value	0.761	0.457	0.222	0.117	0.365	0.660	0.098	0.051	0.629	0.802
Employment	r	− 0.227	− 0.189	0.176	− 0.046	0.173	0.060	− 0.059	− 0.133	0.104	− 0.120
	P value	0.229	0.317	0.352	0.808	0.360	0.751	0.757	0.483	0.583	0.526
Drug	r	− 0.045	− 0.061	0.293	0.016	0.186	− 0.018	0.002	− 0.230	0.199	− 0.222
	P value	0.812	0.748	0.117	0.932	0.324	0.926	0.992	0.221	0.293	0.238
Legal	r	− 0.039	− 0.203	0.103	− 0.231	0.157	0.054	− 0.140	− 0.070	− 0.015	− 0.020
	P value	0.837	0.282	0.589	0.218	0.409	0.775	0.461	0.712	0.937	0.915
Family	r	0.066	0.278	0.264	− 0.124	− 0.196	− 0.224	0.155	− 0.098	− 0.029	− 0.285
	P value	0.729	0.138	0.159	0.512	0.299	0.233	0.413	0.608	0.879	0.126
Psychiatric	R	− 0.018	− 0.146	− 0.215	− 0.329	− 0.084	0.016	0.474	0.398	0.188	− 0.049
	P value	0.925	0.443	0.254	0.076	0.657	0.935	0.008	0.059	0.321	0.797

[#] visual paired association I and II; [§]verbal paired association I and II; [£]Visual memory span; SC, synthetic cannabinoids

*Statistically significant < 0.05

response inhibition is slower. Psychomotor, visual–spatial and cognitive mistakes. A few case studies have been reported on SC's effects on driving, including poor coordination, sedation, confusion, and motor skill impairment [49].

Many studies have explained this. In the hippocampus and prefrontal cortex, CB1 receptors are not surprising (WM). Strong cannabis agonists in SC products may impair WM function. Thalamus and left cerebellum of SC users had decreased grey matter [7].

Endocannabinoids and CB1R are known to be involved in many areas of central nervous system function and illnesses, such as addiction, memory, and schizophrenia [50]. CB1 receptors are involved in inflammation, glaucoma, cancer, liver, and musculoskeletal issues [51]. Studies on animals have indicated that activating CB1R improves memory and cognitive function [52].

Conclusions

Patients who used synthetic cannabinoids SC were more likely than controls to develop CI. The highly significant difference in cognitive performance between both groups invites for more meticulous wide-scaled study of this growing epidemic of SC use in Egypt. In addition, these results implicate that the assessment of cognitive impairment in this vulnerable group of patients may help in tailoring psychotherapeutic, academic, and vocational programs for these individuals.

Several important limitations should be borne in mind when interpreting these results: first, this sample may not represent all addiction treatment facilities in Egypt due to small sample size and non-random method of sampling. Second, the cross-sectional study design limits any causal inferences. Third, this clinical study included patients with drug-related problems with a high prevalence of comorbidities (specifically depression), which may constitute a potential confounder. As such, these findings await replication with a larger sample of synthetic cannabinoids use patients in a prospective study design.

Abbreviations

APD	Antisocial personality disorder
ASI	Addiction Severity Index
BPD	Borderline personality disorder
BVRT	Benton visual retention test
CBD	Cannabidiol
CB1 and CB2	Cannabinoid 1 and 2 receptors
CBT	Cognitive behaviour therapy
CI	Cognitive impairment
D2	Dopamine receptor 2
DEA	Drug Enforcement Administration
DSM-IV	Criteria Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DTI	Diffusion tensor imaging
ECS	Endocannabinoids
ED	Emergency department
FAB	Frontal Assessment Battery
LTP	Long term potentiation
NPS	New psychoactive substances
MD	Doctor of Medicine
MDD	Major depression disorder
PD	Personality disorders
PET	Positron emission tomography
SC	Synthetic cannabinoids
SCID II	Structured Clinical Interview for DSM-IV Axis II Disorder
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorder
SCRAs	Synthetic cannabinoid receptor agonists

SDAPA	Synthetic Drug Abuse Prevention Act
THC	Δ 9-Tetrahydrocannabinol
TMT	Trail Making Test
WM	Working memory
WMS	Wechsler memory scale

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Author contributions
HHE study concept, critical revision of the manuscript, and design. YAE and ZME study concept, and design, and critical revision of the manuscript. ATM recruitment of cases, analysis, interpretation of data, writing and editing the manuscript. MSA, interpretation of data, and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials
All data and materials are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Ain Shams University Hospital Ethics Committee, on the 13th of May 2017. A written informed consent was obtained from participants/their guardians before participation in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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