

Role of Immunity in Pediatric Drug Resistant Epilepsy: Clinical, Neurophysiological, Neuroimaging and Immunological Study

Abstract

Introduction: Autoimmune epilepsy was an under-recognized condition, and its true incidence was unknown in pediatrics. Serum antibodies suggesting a potential autoimmune etiology were detected in 34.8% of patients presented by epilepsy of unknown etiology. Diagnosis of autoimmune epilepsy would be of great value in the search for potential preventive treatments for disabling seizures and cognitive impairment.

Autoimmune epilepsy was characterized by a depressed or altered level of consciousness, lasting more than 24 h, lethargy, or change in personality or behavior and at least one of the following features: neuropsychiatric symptoms, seizures, movement disorder, or cognitive dysfunction. Patients were excluded if an alternative diagnosis was made. The presence of neuronal antibodies and MRI changes supported the diagnosis. This study aimed to assess the possible role of immunity in the pathogenesis of pediatric drug resistant epilepsy through clinical electroencephalographic, neuroimaging and neuro-immunological testing.

Subjects and Methods: This study was conducted on twenty-four drug resistant epileptic children with suspected autoimmune etiology over the period from 2016-2018. The control group comprised twenty four children with idiopathic controlled epilepsy matched to the drug-resistant epilepsy sample for age and gender. Both groups were subjected to clinical examination, neuronal antibodies in serum and CSF, Mini-Mental State Examination (MMSE), Chalfont seizure severity scale (CSSS), EEG, and brain MRI studies.

Results: There was a large percentage of autoimmune epilepsy in pediatric cryptogenic drug-resistant epilepsy. 55% of DRE cases presented with mild pleocytosis and elevated CSF proteins. Serum and CSF neuronal antibodies were positive in about 66.63% and 65% of cases respectively. Serum neuronal antibodies to GAD were positive in 8.33%, NMDA Abs were positive in 33.3%, and VGKC Abs were in 25.0% of cases. In the CSF, GAD antibodies were positive in 10%, NMDA antibodies in 40%, and VGKC antibodies in 20% of cases. Seizures reduction was achieved with immunotherapy, also was prevalent in seropositive cases.

Conclusion: Pediatric patients presented by drug-resistant epilepsy should receive immunotherapy for a definite diagnosis. MRI changes in

the form of temporal hyperintensity, claustrum, cortical hyperintensities were a common finding in pediatric patients presented by drug-resistant epilepsy. CSF changes in the form of elevated proteins and /or mild pleocytosis signified inflammatory changes in the CNS and blood brain barrier (BBB) disruption. Steroid responsiveness played a major role in the diagnosis of autoimmune epilepsy, especially seronegative cases.

Keywords: GAD, VGKC, NMDA antibodies, drug-resistant epilepsy, autoimmune epilepsy in children.

UNDER PEER REVIEW

Introduction:

Drug-resistant epilepsy is defined as “a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom” [1].

The etiologies of drug-resistant epilepsy are numerous. One of its causes is abnormal autoantibodies [2]. Autoantibodies to surface proteins that influence neuronal excitability have been found in the serum and cerebral spinal fluid of over 10% of patients with epilepsy, whether the epilepsy was newly-diagnosed or established [3].

The most frequent or recently reported antibodies in association with seizures are directed against the various following targets: N Methyl D Aspartate (NMDA) receptors, Glutamic Acid Decarboxylase (GAD), and Voltage-Gated Potassium Channels (VGKC) [4].

The diagnosis is aided by detecting autoantibodies specific for neural intracellular or plasma membrane antigens. Testing for a single autoantibody is not advised because autoantibody specificities are informative and limited testing may miss an autoantibody marker with high predictive value for an occult systemic cancer (e.g. paraneoplastic cases) [5].

Because of the potential benefit of early-initiated immunotherapy, it is essential that an autoimmune etiology be considered in the initial differential diagnosis of new onset epilepsy. Autoimmune epilepsy is defined as epilepsy which is the exclusive or predominant symptom with a suspected autoimmune pathogenesis based on detection of neural autoantibodies, inflammatory cerebrospinal fluid or magnetic resonance imaging changes (T2 hyperintensity, contrast enhancement, or restricted diffusion) [6].

The aim of this study is to assess the possible role of immunity in the pathogenesis of pediatric drug resistant epilepsy through clinical electroencephalographic, neuroimaging and neuroimmunological testing.

Patients and methods:

This study was prospective observational study, conducted in the Neuropsychiatry Department and the Center of Neuropsychiatry and Neurosurgery, Tanta University Hospitals from July 2016 to July 2018. Written informed consent for participation in the study was obtained from the patients’ first degree relatives. The studied groups were pediatric patients suffering from epilepsy. They were divided into 2 groups:

Group I drug-resistant group (DRG): This group included 24 children presented with drug-resistant epilepsy which was defined as a failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. The endpoint was seizure freedom or tolerable seizure frequency ^[7].

This group was subdivided into 3 subgroups:-

- **Seropositive subgroup:** included children who have positive antineuronal antibodies titre
- **Seronegative immune subgroup:** included children who had negative antineuronal antibodies titre and showed improvement with immunomodulatory therapy.
- **Seronegative non-immune subgroup:** included children who have negative antineuronal antibodies titre and showed no improvement with immunomodulatory therapy.

Group II control group (CG): This group included 24 patients presented by **controlled primary epilepsy** either on medication or finished medical treatment matched with the group I regarding age and gender for comparison of the results.

Inclusion criteria:

- Pediatric patients aged from 3-year to 18 years.
- Patients presented by drug-resistant epilepsy according to the task force of international league against epilepsy

Exclusion criteria:

- Clinical and /or radiological findings suspect structural brain abnormality
- False refractoriness
- Acute symptomatic etiology for epilepsy.
- Febrile seizure and febrile seizure plus.
- Drugs that can lower the seizures threshold.

Methodology, diagnostic criteria, and assessment:

Both patients groups were exposed to:-

1. Full history taking including seizure semiology, general examination, and full neurological examination
2. Seizures severity assessment by Chalfont Seizure Severity Scale (CSSS) was used. This scale measured the components of seizures that cause a functional disturbance. It relied on the loss of awareness, presence of warning, drop a held object, injury, incontinence, automatism, convulsion, duration of seizures, and time to return to normal from onset ^[8].

3. **Mini-Mental State Examination (MMSE):** It aimed at identifying epileptic patients with cognitive impairment. The lower normal limit of the total score was 25 ^[9].

4. **Investigations:**

- Routine laboratory investigations.
- Standard EEG and/or long term video EEG recording using 21 channel scalp EEG NIHON KOHDEN model JE-921A, SN 00558 (2006).
- Chemical and physical analysis of CSF for drug-resistant group only.

5. **Neuroimaging study** in which all patients had subjected to Brain MRI at least (1.5 tesla) using multiple pulse sequences in different planes emphasizing on coronal FLAIR film using General Electric scanner (GE Medical Systems, Milwaukee) with quadrature head coil (8 channel).

11. **Antineuronal antibodies in serum** by ELISA kits supplied by Usen Life Science INC. Cat. No. E3245Hu:

a) **Anti N Methyl D Aspartate (NMDA) receptor antibodies:-**

Assay range (normal titre range): 0.5ng/ml -----150ng/ml

NMDA seropositive cases: if the titre was above 150ng/ml

Seronegative cases: if the titre was less than 150ng/ml

b) **Anti Glutamic Acid Decarboxylase (GAD) antibodies:**

Assay range: 2.5ng/ml-----750ng/ml

GAD seropositive cases: if the titre was above 750ng/ml

Seronegative cases: if the titre was below 750ng/ml

c) **Anti-Voltage-Gated-Potassium Channels (VGKC) antibodies:**

Feminine determinant (seronegative cases) if the sample OD value was less than the critical value.

Masculine determinant (seropositive cases) if the sample OD value was more than or equal to the critical value.

Immunotherapy (corticosteroids or plasmapheresis) were given as a therapeutic test.

Follow-up was performed after 3 months for the drug-resistant group, a 50% reduction of seizure frequency was considered a favorable clinical outcome and was termed as the “responder rate” ^[10].

Statistical Analysis

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer package version 20 ^[11]. For quantitative normally distributed data, the range, mean and standard deviation were calculated. For quantitative non-normally distributed data, median and interquartile range were used for data presentation. Qualitative data were presented as number and percent. For qualitative data, the comparison between two groups and more was done using Chi-square test (X²) and Fisher Exact test (FE). For comparison between

means of two groups, an independent student t test was used. It was replaced by a non-parametric test, Mann Whitney U test for non-normally distributed data. Correlation between variables was evaluated using Pearson's correlation coefficient. Significance was adopted at $p < 0.05$ for the interpretation of results of tests of significance.

Results:

Age and gender showed no significant difference between both DRG and CG while the level of education was significantly low in the drug-resistant group **Table (1)**.

Seizures severity assessed by the Chalfont Seizure Severity Scale (CSSS) showed that drug-resistant group had a significantly higher seizures severity compared to the control group regarding focal to GTC seizures and GTC seizures. Total CSSS was higher in DRG than control group. No significant difference in seizures severity was detected between the two groups regarding other seizures types **Table (2)**.

Impaired cognition was present in 91.67%, encephalopathy in 75.0% of the drug resistant group and absent in the control group. Provocation of seizures by fever was significantly present in 66.7% of the drug-resistant group and psychiatric manifestation in the form of apathy, mood changes, irritability, violence, and bizarre behavior were significantly recorded in the drug-resistant group than in the control group **Table (3)**.

The following MRI findings bitemporal, diffuse cortical, right temporal, left temporal, bilateral claustrum hyperintensities and left temporal sclerosis were present more in the drug-resistant group. Bitemporal hyperintensities showed significantly higher percentage of 20.83% compared to control Bilateral fronto-temporal activity, generalized slowing and multifocal activity were significantly more in drug-resistant group than the control group, while generalized activity was exclusively present in the control group **Table (4)**.

Serum neuronal antibodies to GAD were positive in 8.33%. Antibodies to NMDA receptors were positive in 33.3%. Antibodies to VGKC were positive in 25.0% of DRG. Positive cases were about 66.63% of cases in the drug-resistant group compared with none in the control group with a statistically significant difference toward NMDA and VGKC antibodies as demonstrated in figure (1).

Follow up (after 3 months of immunotherapy) seizure diary among drug-resistant group showed that 66.7% of cases improved as shown in figure (2). Percentage of seizures reduction among drug-resistant group reached up to the Mean \pm S.D 41.25 \pm 15.97.

Table (1): Demographic data among group I versus group II

Characteristics	Group I Drug-resistant group (n=24)		Group II Control group (n=24)		χ^2	P	
	Age (in years)						
Less than 5	2	8.3%	1	4.2%	0.659	0.883	
5 <10	6	25.0%	5	20.8%			
10 <15	2	8.3%	3	12.5%			
15 <18	14	58.3%	15	62.5%			
Mean \pm S.D	13.79 \pm 4.75		12.96 \pm 4.76				
T test	-0.607						
P value	0.547						
Gender							
Male	9	37.5%	10	41.7%	0.087	1.000	
Female	15	62.5%	14	58.3%			
Level of education							
Pre-school	1	4.2%	0	0.0%	8.079	0.028*	
Primary	10	41.7%	10	41.7%			
Preparatory	7	29.2%	1	4.2%			
Secondary	6	25.0%	13	54.2%			

t: Independent sample t-test

χ^2 : Chi square test

*: Statistically significant

Table (2): Seizure severity assessment by Chalfont Seizure Severity Scale (CSSS) among group I versus group II.

Chalfont Severity Scale	Seizure	Group	N	Mean \pm S.D			T	P
Focal to GTC		Group I	22	110.82	\pm	38.92	-5.431	0.001*
		Group II	12	47.75	\pm	12.39		
Focal unaware		Group I	16	33.88	\pm	18.60	-2.665	0.019
		Group II	5	16.80	\pm	9.86		
Motor		Group I	12	17.67	\pm	4.52		
		Group II	0	-				
Focal sensory		Group I	3	22.00	\pm	26.96	-1.156	0.367
		Group II	2	4.00	\pm	0.00		
Scale focal Emotional,		Group I	4	43.75	\pm	24.09	-	

cognitive	Group II	0	-				
Myoclonic	Group I	2	29.50	±	13.44	-1.353	0.398
	Group II	4	16.50	±	2.89		
Absence	Group I	3	4.00	±	1.73	-	
	Group II	0	-				
GTC	Group I	2	128.00	±	52.33	-5.390	0.001*
	Group II	10	37.30	±	14.84		
Focal autonomic	Group I	1	6.00	±	0.0	-	
	Group II	0	-				
Total Chalfont	Group I	24	156.91	±	64.37	7.962	0.001*
	Group II	24	46.00	±	22.68		

(-) t cannot be computed because at least one of the groups is empty.

t: Independent sample t-test

*: Statistically significant

Table (3): Neuropsychiatric comorbidities and **psychiatric manifestations** among group I versus group II.

Neuropsychiatric comorbidities	Group I (DRG) (n=24)		Group II (CG) (n=24)		χ²	P
Cognition					40.615	0.001*
Normal	2	8.33%	24	100.0%		
Impaired	22	91.67%	0	0.0%		
Encephalopathy					28.800	0.001*
Absent	6	25.0%	24	100.0%		
Present	18	75.0%	0	0.0%		
Provocation of seizures by fever					17.422	0.001*
Negative	8	33.3%	22	91.67%		
Positive	16	66.7%	2	8.33%		
Hallucination	1	4.16%	0	0.0%	1.021	0.312
Apathy	5	20.83%	0	0.0%	5.581	0.018*
Mood changes	10	41.66%	0	0.0%	12.632	0.001*
Irritability violence	12	50.0%	0	0.0%	16.000	0.001*
OCD	1	4.16%	0	0.0%	1.021	0.312
Bizzare behavior	5	20.83%	0	0.0%	5.581	0.018*

Table (4): Neuroimaging study among group I versus group II.

MRI	Group I (DRG) (n=24)	Group II (CG) (n=24)	χ²	P		
Bilateral claustrum	2	8.33%	0	0.0%	2.087	0.149

hyperintensities							
Diffuse cortical hyperintensities	3	12.5%	0	0.0%	3.200	0.074	
Bitemporal hyperintensities	5	20.83%	0	0.0%	5.581	0.018*	
Right temporal hyperintensities	3	12.5%	1	4.16%	3.200	0.074	
Left temporal hyperintensity	2	8.33%	0	0.0%	2.087	0.149	
Left temporal sclerosis	3	12.5%	0	0.0%	3.200	0.074	

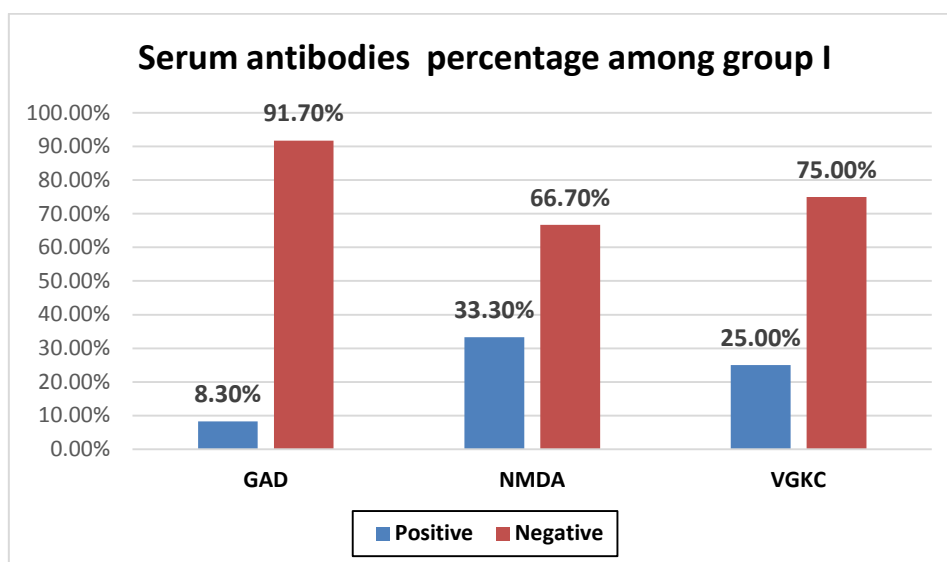


Figure (1): Serum neuronal antibodies percentage among group I.

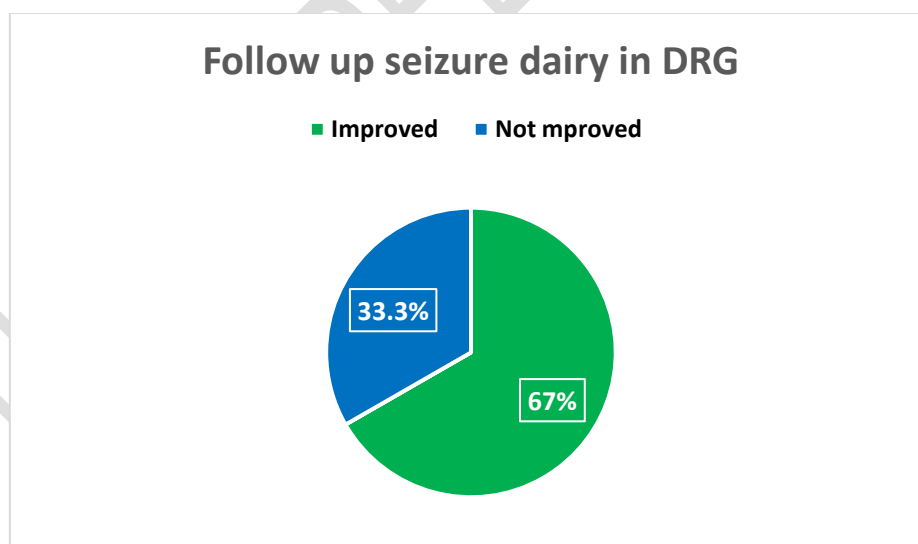


Figure (2): Follow up seizure dairy among drug-resistant group

Discussion:

MRI findings ranging from bitemporal hyperintensities, diffuse cortical hyperintensities, right temporal hyperintensities, left temporal hyperintensities, mesial temporal hyperintensities, and bilateral claustrum

hyperintensities were characteristic finding in DRG with neuronal antibody positivity as a cause of drug-resistance with a preference toward bitemporal hyperintensity in 20% of cases ^[13].

EEG changes in the DRG ranging from bilateral frontotemporal epileptogenic activity (33.3%), generalized slowing (25%), multifocal changes (20.83%), were significantly prevalent in the DRG compared to the control group ^[14].

Chemical and physical analysis of CSF was done in the drug resistant group with suspected autoimmune basis. It was abnormal in 55% of cases with mild pleocytosis and elevated CSF proteins. The median time from seizure onset to initiating immunotherapy was 2.68 ± 2.39 years.

Regarding serum neuronal antibodies in our study, serum positive antibody titre was present in 66.63% of DRG. We found that NMDA antibodies had positive titre in 33.3%, VGKC in 25%, Anti GAD antibodies in 8.33 % of DRG ^[15].

Cerebrospinal fluid neuronal antibodies were positive in 65% of cases, GAD antibodies in 10%, NMDA antibodies in 40%, and VGKC antibodies in 20% of DRG ^[16].

Multiple antibodies were found in two patients (2.6%). 50% of DRG had antibodies in both serum and CSF. This difference might be due to sampling biased which included patients with DRE with suspected autoimmune etiology in our study but their study included all patients presented by epileptic seizures in all age groups. Also, it was noticed that the prevalence of AE among patients with epilepsy of unknown etiology was at least 20.5% ^[17].

NMDA antibodies were positive in several drug-resistant cases. Antibody levels correlate with the clinical severity of the disease in individual patients and showed to substantially reduce NMDAR on hippocampal neurons both in vitro and in vivo, which supporting direct pathogenicity of the NMDAR antibodies in AE ^[18].

Negative test results did not rule out immune-mediated disorders. Steroid use might interfere with the diagnostic test. Hence, test results could be interpreted with caution and put into the context of the clinical presentation. Because antibodies might remain positive despite clinical features, clinicians should focus on patient treatment rather than antibody titers ^[19].

There was one death case, she presented very late, after almost 5 years of duration of illness without receiving any specific treatment and being misdiagnosed with a psychiatric diagnosis. On diagnosis, she received aggressive immunomodulation (steroids and plasmapheresis) but developed drug-induced pancytopenia and died of severe sepsis.

Immunotherapy in the form of corticosteroids and plasmapheresis were given in seropositive and seronegative patients as a therapeutic test. Corticosteroids were given in 83% of DRG and corticosteroids plus plasmapheresis was given in 12.5% of DRG. There was a significant improvement which means that there was a major role of autoimmunity in epileptogenesis ^[20].

Furthermore, **Elisak et al.** ^[21] stated that both seropositive and seronegative patients presented by temporal lobe epilepsy did not differ in their clinical, EEG, or neuroimaging characteristics. Response to immunotherapy (seizure reduction >50%) was observed in three of the six seropositive patients treated.

The use of corticosteroids might have a dual beneficial effect. Based on laboratory data, the use of corticosteroids appeared to be effective in promoting the BBB penetration of Automated external defibrillators rather than targeting a focus and operating by a specific epileptogenic mechanism ^[22]. In addition to plasma exchange led to an interruption of some side effect on different occasions, reducing seizure frequency, and improving cognitive functions.

Based on **Toledano et al.** ^[23] improvement was determined by a decrease in seizure frequency by about 50% and even improvement in cognitive function. Follow up MMSE in drug-resistant cases receiving immunotherapy showed significant improvement. This was documented by a few clinical studies ^[2].

Improved seizures were more in seropositive antibodies for GAD (50.0%), NMDA (75.0%), VGKC (66.6%). The differences were not statistically significant.

Regarding our seronegative patients, the lack of biological confirmation of underlying immune mechanisms might lead to doubt on the underlying etiology. Our center did not have access to further confirmatory techniques including indirect immunohistochemistry or live-cultured neuron techniques. Seronegative patients met diagnostic criteria for autoimmune encephalitis through clinical findings and supportive ancillary testing (MRI, CSF). The lack of clinical distinction between antibody positive and negative groups supported an immune theory as an epilepsy etiology. Furthermore, the absence of neural-specific autoantibodies does not rule out AE.

Cerebrospinal fluid neuronal antibodies were abnormal in about 65%. GAD abs were abnormal in 10%, NMDA in 40%, and VGKC in 20%. The presence of antibodies in CSF confirmed that the antibodies played a major role in autoimmune epilepsy pathogenesis.

Improvement was more in antibodies toward neuronal cell surface to NMDA and VGKC (10/14 cases) (71.4%) than to intracellular antigens GAD (1 from 2 cases) (50%).

Recommendation:

Further large study number is recommended for clarifying each autoimmune epilepsy syndrome. Immunological tests by other method other than ELISA should be offered for further confirmation.

Conclusion:

Pediatric drug-resistant epilepsy with suspected autoimmune etiology should receive immunotherapy early for definite diagnosis and early clinical improvement.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Abbreviations

conduction time; CNS: Central nervous system; EDSS: Expanded Disability

Status Scale; EPs: Evoked potentials; MEPs: Motor EPs; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RL: Radicular latency; TA: Tibialis

anterior; TMS: Transcranial magnetic stimulation

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Settings

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Authors' contributions

Concept—FBH and AKH. Design—ABM and HGK. Supervision—FBH and

AKH. Resources—ABM and HGK. Materials—AMB and AKH. Data collection

and/or processing—FBH and HGK. Analysis and/or interpretation—FBH and ABM. Literature search—ABM and FBH. Writing manuscript—FBH and HGK.

All authors have read and approved the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study design was approved by the Iraqi Council of Medical Specialization (decision No. 1257; date, 20 March 2019).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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