

Psychiatric outcome of epilepsy surgery in patients with psychosis and temporal lobe drug-resistant epilepsy: A prospective case series



Luciana D'Alessio^{a,b,*}, Laura Scévola^a, Mónica Fernandez Lima^{a,b}, Silvia Oddo^{a,b}, Patricia Solís^a, Eduardo Seoane^c, Silvia Kochen^{a,b}

^a Epilepsy Center, Ramos Mejía Hospital, Buenos Aires, Argentina

^b E de Robertis Neuroscience Institute, Epilepsy Research Laboratory, CONICET, Buenos Aires, Argentina

^c Neurosurgery Center, Ramos Mejía Hospital, Buenos Aires, Argentina

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ABSTRACT

Objectives: Temporal lobe resistant epilepsy has been associated with a high incidence of psychotic disorders; however, there are many controversies; while some patients get better after surgery from their psychiatric condition, others develop psychosis or de novo depression. The aim of this study was to determine the psychiatric and seizure outcome after epilepsy surgery in patients with a previous history of psychoses.

Methods: Surgical candidates with temporal lobe drug-resistant epilepsy and a positive history of psychosis diagnosed during the presurgical psychiatric assessment were included. A two-year prospective follow-up was determined after surgery. The DSM-IV Structural Interview, GAF (global assessment of functionality, DSM-IV), Ictal Classification for psychoses, and Engel's classification were used. The Student *t* test and chi-square–Fisher tests were used.

Results: During 2000–2010, 89 patients were admitted to the epilepsy surgery program, 14 patients (15.7%) presented psychoses and were included in this series. After surgery, six patients (43%) did not develop any psychiatric complications, three patients (21%) with chronic interictal psychosis continued with no exacerbation, three patients (21%) developed acute and transient psychotic symptoms, and two patients (14%) developed de novo depression. Seizure outcome was Engel class I–II in 10 patients (71%). Total GAF scores were higher after surgery in patients found to be in Engel class I–II ($p < 0.05$).

Conclusions: Patients with comorbid psychosis and temporal lobe drug-resistant epilepsy may benefit from epilepsy surgery under close psychiatric supervision.

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1. Introduction

A wide range of psychosis prevalence from 4% to 18% has been described in epilepsy surgical candidates with temporal lobe drug-resistant epilepsy (TLRE¹) [1–5]. In general terms, psychiatric contraindications for epilepsy surgery are not clearly defined, and there are controversies found in the literature. Many patients with psychosis had a good psychiatric and seizure outcome after surgery [6–11], but others developed depression, de novo psychosis, or an exacerbation of their previous psychiatric condition [11–17].

Psychotic disorders are conditions characterized by delusions, hallucinations, and disorganized behaviors, and different chronic and transient psychotic disorders are codified in the DSM-IV according to the persistence of psychotic symptoms, the presence of negative

symptoms, and/or affective symptoms (DSM-IV 2000) [18]. Additionally, the Ictal Classification for psychoses in people with epilepsy (PWE²) described three subtypes: postictal psychoses (PIP³) (temporally related to epileptic seizures), interictal psychoses (IIP⁴) (not temporally related to seizures), and bimodal psychoses (both kinds of episodes – PIP and IIP) [2,5,19–23].

While PIP are more clearly not a contraindication to epilepsy surgery [15,20], patients with IIP are often excluded from epilepsy surgical programs [4,15,24]. Nevertheless, some studies found no exacerbation of psychosis after epilepsy surgery in patients with chronic IIP who had good post-operative seizure control [8–10].

Our research group has studied psychiatric aspects of PWE during the last 10 years, with special reference to psychosis [16,23,25]. In the present study, we prospectively analyzed the psychiatric and seizure outcome during the first two years after epilepsy surgery in patients

* Corresponding author at: B. Mitre 3419 9° A, 1201 Buenos Aires, Argentina. Tel./fax: +54 1148636438.

E-mail addresses: ldAlessio@intramed.net, luladalessio@gmail.com (L. D'Alessio).

¹ TLRE: temporal lobe drug-resistant epilepsy.

² PWE: people with epilepsy.

³ PIP: postictal psychoses.

⁴ IIP: interictal psychoses.

with a positive history of psychosis diagnosed during the standardized psychiatric presurgical assessment.

2. Methods

2.1. Population

This investigation was performed at the Epilepsy Center of Ramos Mejía Hospital – Cellular Biology and Neuroscience Institute – CONICET (ECRMH-IBCN). The ECRMH is an epilepsy referral center in Buenos Aires City, Argentina, which serves a population with high rates (70%–80%) of RE⁵ (resistant epilepsy) [26,27].

2.2. Study design and patient selection

Surgical candidates with TLRE and a positive history of psychosis, determined during the standardized psychiatric assessment, were included in this study. A prospective follow-up during the first two years after surgery was obtained by the same trained psychiatrist.

Patients with an extratemporal epileptic focus or another neurological disease associated with epilepsy and/or a history of mental retardation (attending a special school and/or having an IQ < 70 according to the Wechsler Adult Intelligence Scale) were excluded from this study.

2.3. Diagnosis of resistant epilepsy (RE)

All patients included in this study presented temporal lobe drug-resistant epilepsy (TLRE) and received different types of antiepileptic drugs as per international protocols (the major antiepileptic drugs are freely available in the country at the Public Hospital Epilepsy Program) [26]. All patients were evaluated according to the diagnosis protocol of the ECRMH, including a complete clinical and neurological assessment. Clinical history data were gathered retrospectively by anamnesis. Complementary studies confirmed the epileptogenic zone by using interictal EEG, video-EEG monitoring, and MRI⁶ (magnetic resonance imaging) with a temporal lobe epilepsy protocol [27].

2.4. Psychiatric diagnosis: diagnoses of psychoses

The psychiatric semiology was supplemented with structural interviews for present and past history of psychiatric disorders codified in the DSM-IV (Structured Clinical Interview for DSM Disorders [SCID]-I and -II) [28]. Presurgical and postsurgical psychiatric assessments were performed by the same specialist trained in psychiatry. All patients with psychotic symptoms (Module B of SCID-I) were grouped according to the DSM-IV diagnostic criteria. Brief psychotic disorder and schizophreniform disorder were considered transient psychosis (psychosis duration between one month and six months), with total inter-episode resolution according to the DSM-IV criteria. On the contrary, schizoaffective, schizophrenic, and delusion disorders were considered chronic psychosis with more than 6-month evolution and without total inter-episode resolution [18,28].

Patients with psychotic episodes according to the DSM-IV criteria were also analyzed and grouped depending on the Ictal Classification, which takes into account the temporal relationship between the ictal episode and the onset of psychosis. The three main subtypes of psychoses were diagnosed according to the Ictal Classification: postictal psychoses (PIP), psychotic episodes preceded at least 24 h by one or more seizures with or without a lucid interval; interictal psychoses (IP); and psychotic disorders in the absence of a clear temporal relationship between onset of psychotic symptoms and epileptic seizures. Patients who met the criteria for both types of psychoses occurring in

different episodes were considered a third subgroup, that is, those having bimodal psychoses (BP) [2,5,19–22].

Patients who had mild psychotic symptoms and met criteria for Cluster A personality disorder (schizoid, paranoid, and schizotypal), but did not meet criteria for Axis I acute psychotic disorder, were excluded.

Global assessment of functionality (GAF⁷), Axis V of DSM-IV, was determined in all patients after surgery. The GAF is a numeric scale (0 through 100) used to rate subjectively (by the psychiatrist) the social, occupational, and psychological functioning of adults. The GAF was administered after resolution of acute psychiatric episodes, as well as during the stable phase of chronic disorders [18].

2.5. Postsurgical evaluation

After epilepsy surgery (anterior temporal lobectomy in all cases), neurological and psychiatric follow-ups were performed periodically according to clinical and psychiatric requirements in patients with psychiatric complications. All patients included in this series were reexamined with the DSM-IV Structural Interview, and GAF scores were determined one and two years after surgery. Engel's classification was used to determine the seizure outcome [29].

2.6. Ethics committee

Approval of the Ethics Committee of Ramos Mejía Hospital was obtained for the study, and it was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the patients submitted informed consent for their voluntary participation in this study.

2.7. Statistical analysis

Student's *t* test (*t*) was used to analyze quantitative variables compared before and after surgery (GAF scores). The chi-square test and/or Fisher test were used for qualitative data. Statistical significance was fixed at $p \leq 0.05$. SPSS for Windows was used for statistical analysis.

3. Results

During 2000–2010, 89 patients with resistant epilepsy (RE) were admitted to the ECRMH program and underwent epilepsy surgery. During this period, 81 patients (91%) completed the psychiatric assessment before surgery. From this population, 15 patients (16.8%) (14 patients (15.7%) with temporal lobe epilepsy and one patient (1.1%) with frontal lobe epilepsy) had a positive history of psychosis according to Axis I of DSM-IV. In the current series, 14 patients (15.7%) with psychosis and TLRE completed the psychiatric follow-up during the first two years after surgery and were included in this study.

Demographic and epilepsy-related variables are shown in Table 1. Nine patients (64%) had a right epileptic focus, and five patients (36%) had a left epileptic focus. In relation to the psychiatric diagnosis, psychotic symptoms appeared after epilepsy onset in all cases, and the mean time duration of epilepsy before psychosis was 17.8 ± 6.3 years. The median age at psychosis onset was 27.4 ± 7 years (Table 1).

Before surgery, 11 patients (78%) had transient psychotic episodes, and three patients (21%) had chronic psychosis (DSM-IV criteria). According to the Ictal Classification, PIP were present in six patients (43%), IIP in 7 patients (50%), and BP in one patient (7%). Topiramate exacerbated psychotic symptoms in two patients (14%) (Table 2, Figs. 1, 2).

During the first two years after surgery, six patients (43%) did not develop any psychiatric complication. Three patients (21%) developed acute psychotic symptoms requiring ambulatory antipsychotic therapy, and

⁵ RE: resistant epilepsy.

⁶ MRI: magnetic resonance imaging.

⁷ GAF: global assessment of functionality.

Table 1
Sociodemographic and clinical features.

Case number	Gender	Age	Age at epilepsy onset (years)	Age at psychosis onset (years)	Frequency of seizures	Localization and laterality of epileptic foci	Type of lesion (MRI)	Highest school grade achieved (years)	Employment
1	M	30	14	23	1–4/month	RTL	FCD	7	No
2	F	44	10	41	1–4/month	LTL	HS	>12	Yes
3	F	65	1	40	1–4/month	RTL	HS	>12	No
4	F	36	9	25	>4/month	LTL	HS	8–11	No
5	M	35	12	28	1–4/month	RTL	HS	>12	No
6	M	49	19	20	>4/month	RTL	HS	7	No
7	F	45	9	32	1–4/month	RTL	HS	8–11	No
8	M	30	16	34	>4/month	LTL	HS	8–11	No
9	F	25	2	20	>4/month	RTL	HS	8–11	No
10	F	22	8	20	>4/month	LTL	HS	>12	No
11	M	26	2	24	1–4/month	LTL	HS	7	No
12	M	42	17	30	1–4/month	RTL	HS	8–11	Yes
13	M	20	3	18	>4/month	RTL	HS	7	No
14	M	40	11	35	1–4/month	RTL	HS	>12	Yes

M: male, F: female, RTL: right temporal lobe, LTL: left temporal lobe, HS: hippocampal sclerosis, MRI: magnetic resonance imaging, FCD: focal cortical dysplasia.

three patients (21%) with presurgical chronic psychosis continued having mild psychiatric symptoms after surgery but did not require more anti-psychotic medication. Two patients (14%) developed other psychiatric episodes (de novo depression) (Table 2, Figs. 1, 2). Ambulatory psychiatric treatment was indicated in all patients with psychiatric complications.

Seizure outcome was determined (Engel I–II) in 10 patients (71%) (Fig. 1). Total GAF scores were significantly higher after surgery ($p < 0.05$) in patients found to be in Engel class I–II (Fig. 3).

4. Discussion

The prevalence of psychiatric conditions in TLRE ranges from 19% to 80% for psychiatric disorders and from 4% to 18% for psychosis. About 3% of patients undergoing epilepsy surgery have psychiatric complications

[2–5,30]. Furthermore, many centers do not include psychiatric assessment in presurgical protocols, and more prospective and controlled studies are required to better delineate the prevalence and severity of psychiatric conditions occurring in the context of epilepsy surgery [24, 30,31].

In relation to psychosis, the literature is sparse, and patients with preexisting psychosis are often unlikely to be considered for surgical intervention [4,15,24]. This attitude seems to be based on the ineffectiveness of surgery as treatment for psychosis in most patients or on the possibility of a postoperative psychiatric deterioration related or not to the seizure cessation (forced normalization) [24,32–34]. Nevertheless, this picture is changing in the last 15 years since a routine psychiatric assessment has been incorporated by many centers, and epilepsy surgery is recommended under close psychiatric supervision arguing

Table 2
Presurgical and postsurgical psychiatric assessments.

Case	Presurgical psychosis (DSM-IV criteria)	Presurgical psychosis (Ictal Classification)	Comorbid psychiatric disorder (Axis I and II DSM-IV)	Postsurgical psychosis (two-year follow-up)	Other postsurgical psychiatric disorders (two-year follow-up)	Engel class (two-year follow-up)
1	BPE	IIP	Cluster A	No	No	II
2	BPE	PIP	No	No	Depression (de novo)	I
3	BPE	IIP	Depression Anxiety Cluster B	Yes BPE/IIP	Conversion disorder Exacerbation Cluster B	II
4	BPE	IIP	Depression Anxiety Cluster B	No	No	III–V
5	BPE	PIP	Anxiety Cluster C	No	No	I
6	Schizoaffective disorder	BP	No	No	No	I
7	BPE	PIP	No	No	No	I
8	Schizophreniform disorder ^a	IIP	Cluster A	Yes Schizophreniform 2 episodes/IIP	No	II
9	BPE	PIP	Depression Impulsivity Cluster A	No	Depression Impulsivity Cluster A Exacerbation ^a	III–IV
10	BPE ^a	IIP	No	No	No	I
11	Delusion disorder	IIP	No	Yes Delusion disorder/IIP	No	I
12	BPE	PIP	Depression Anxiety Cluster C	Yes BPE/PIP 3 episodes	Depression	III–IV
13	Schizoaffective disorder	IIP	No	Yes Schizoaffective disorder/IIP	No	III
14	BPE	PIP	Cluster A	Yes BPE/IIP	No	I

Psychosis classification and postsurgical evolution. BPE: brief psychotic episode, PIP: postictal psychoses, IIP: interictal psychoses, BP: bimodal psychoses, personality disorders – Cluster A: paranoid, schizoid, and schizotypal; Cluster C: avoidant, dependant, and obsessive–compulsive; and Cluster B: antisocial, borderline, histrionic, and narcissistic.

^a Induced by topiramate.

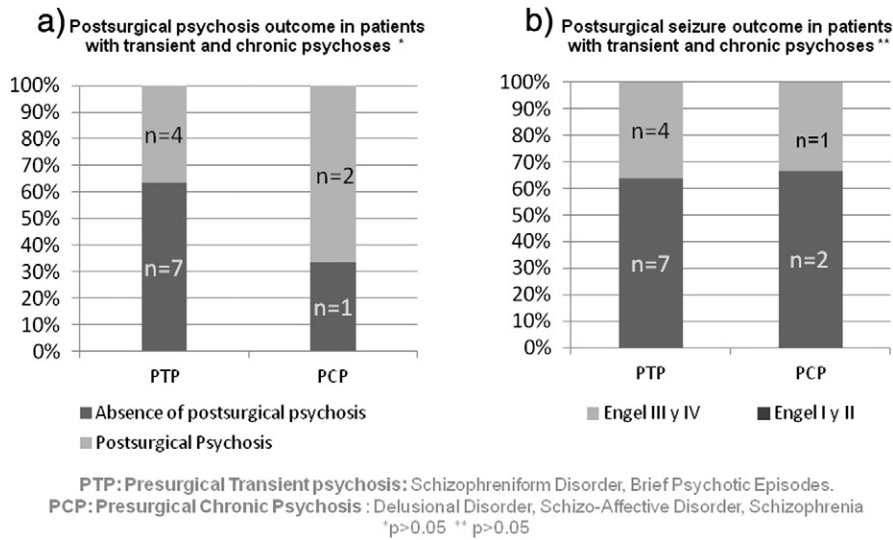


Fig. 1. Psychiatric and seizure outcome in patients with transient and chronic psychosis (DSM-IV).

that epilepsy surgery may also benefit patients with psychiatric comorbidity [4,8–10,20,31,30].

In our study of epilepsy surgery over a 10-year period, 16.8% of operated patients had a positive history of psychosis pre-operatively. A similar prevalence was reported by the Taylor and Marsh series in 1972, who found that 12–15% of patients with presurgical psychosis had a good seizure outcome after epilepsy surgery. In line with these findings, the Jensen and Larsen series in 1979 found a low incidence of worsening of psychosis after surgery. More recently, a lower prevalence of psychoses among surgical candidates was reported, ranging from 4% to 6% [1,11,30,34]. Nevertheless, many studies described the psychiatric profile before and after epilepsy surgery but did not include patients with presurgical psychosis [4,31,35–38].

The implementation of both the DSM-IV and the Ictal Classification revealed that the major part of both PIP and IIP have transient outcome with *ad integrum restitution*, coinciding with acute interictal psychosis previously described [39,40]. A history of transitory PIP episodes has not been considered a contraindication to epilepsy surgery, and many authors have recommended surgery in these patients, arguing

that the first goal of management of patients who have only transient episodes of psychosis following seizures should be attaining seizure control [17,20]. Nevertheless, more recently, it has been found that a history of PIP (or PIP episodes during video-EEG) is associated with the presence of bilateral independent ictal foci and diffuse brain damage, both of which have been associated with a poor postsurgical seizure outcome [19,32,33,40,41]. However, these authors also considered that this observation should not be interpreted as a categorical reason to exclude these patients from consideration of epilepsy surgery [33].

There are a few studies of the prospective psychiatric follow-up of patients with preoperative PIP [31]. Kanemoto et al. in 1998 found that affective disorders after epilepsy surgery were more common in subjects with PIP [15]. Other authors reported a few cases of PIP or IIP with a good psychiatric outcome after surgery [11,30,34]. Cleary et al. in 2013 found a great incidence of de novo psychiatric disorders among patients with epilepsy with PIP who underwent epilepsy surgery in a retrospective analysis [17]. With regard to interictal chronic psychosis, three series with a total of 24 patients and some case reports about chronic IIP and epilepsy surgery have been reported. Overall, these

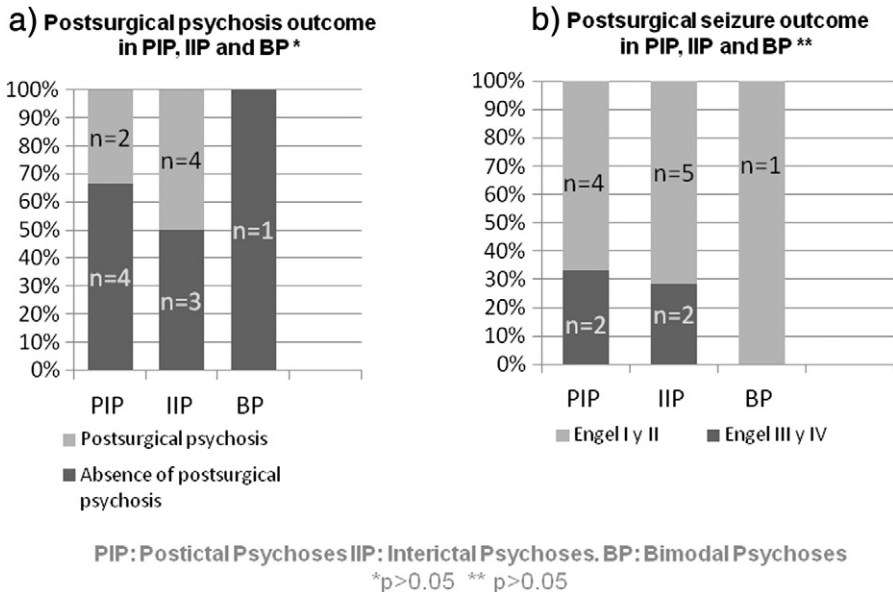
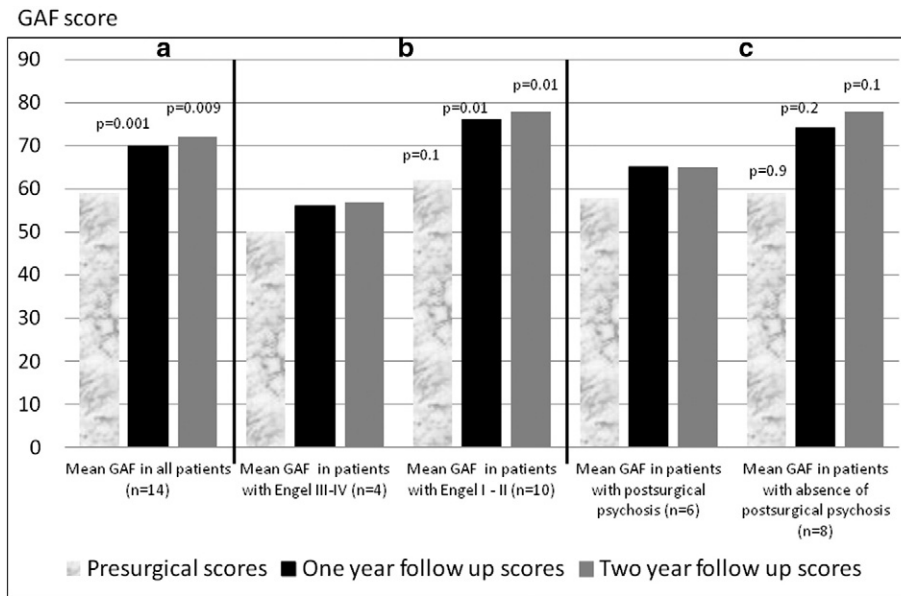


Fig. 2. Psychiatric and seizure outcome in patients with PIP, IIP, and BP (Ictal Classification).



GAF: Global Assessment of Functionality

Fig. 3. Presurgical and postsurgical global assessments of functionality scores.

authors found a good psychiatric outcome, with no exacerbation of psychosis after surgery with the correct psychiatric treatment [8–10]. Moreover, the Ictal Classification considered PIP and IIP as separated syndromes although several similarities have been found, and a progression from postictal to interictal psychosis has been described [21–23]. Furthermore, a unifying hypothesis suggesting that the same pathomechanisms are involved in the pathogenesis has been proposed [42,43]. The pathomechanisms are still unknown but have been connected to epileptic syndromes [42,43]. Nevertheless, epileptic psychosis differs from idiopathic schizophrenia and has been considered a different syndrome with a better outcome and a low incidence of negative symptoms [23,42,23]. In this series, we found patients with chronic psychoses without criteria for schizophrenia and that negative symptoms were infrequent.

In the present series, we prospectively found that almost half of patients with transient psychotic episodes before surgery had a good psychiatric outcome during the first two years after surgery (no psychiatric complication). Nevertheless, the other group of patients developed transient psychotic episodes, or another psychiatric complication (de novo depression), or continued having mild psychiatric symptoms related to a chronic psychosis. These patients required antipsychotic medication (low doses of risperidone), antidepressants (citalopram), or a topiramate reduction, or continued receiving the same presurgical antipsychotic treatment (low doses of risperidone or quetiapine), respectively. Transient psychosis (both PIP and IIP) was more frequently found before and after surgery, with a good response to antipsychotic medication.

In this study, a good seizure outcome (Engel I–II) was found in 71% of the patients, and, overall, these patients presented a higher GAF score. No differences were found between patients with and without postsurgical psychosis probably because of the small sample. Nevertheless, in this study, epilepsy surgery and being seizure-free improved global functioning in patients found to be in Engel I–II. Since global functionality scale was determined by the psychiatrist, it does not necessarily reflect the “subjective state of quality of life” of the patients; therefore, it is important to include, in the future, quality-of-life scales in the presurgical protocols.

Some limitations of this study must be mentioned; in this partial analysis, we put the focus on psychotic illness, a severe psychiatric syndrome affecting people with TLRE. Indeed, the results are limited only to

this small sample, and more research is needed to confirm these preliminary findings. The future studies will concentrate on the analysis and comparison of patients with other psychiatric comorbidities and patients without psychiatric comorbidity to prospectively determine risk factors for developing postsurgical psychiatric complications.

5. Conclusions

Patients with comorbid psychosis and TLRE may benefit from epilepsy surgery under close psychiatric supervision.

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Conflict of interest

The authors have no conflicts of interest. The work described is consistent with the Journal's guidelines for ethical publication.

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