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RESEARCH

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Re-appraisal of callosotomy: rates and predictors of short-term seizure outcome in pediatric epileptic encephalopathy

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Abstract

Background Epilepsy is a chronic debilitating disease especially in pediatric population. Most of reported studies for corpus callosotomy as a palliative surgery in drug-resistant cases are on limited number of cases and there is scarcity in literature for outcomes reported from developing countries. Here, we present our study on a large series of cases with analysis of potential predicators outcomes in the era of more expensive devices like vagal nerve stimulation to give a litany on a universal epilepsy surgery procedure which had been missed in the literature through the last decade.

Results An observational retrospective study was done reviewing 129 patients with PEE underwent open microscopic corpus callosotomy. Total and drop attack seizure outcomes were studied after surgery. Potential outcomes predictors studied are: preoperative EEG and MRI. Preoperative IQ impairment epilepsy duration, age at diagnosis, MRI finding, IQ score, EEG findings, history of infantile spasm and extent of callosotomy done. All the recorded outcomes were substantially improved after callosotomy in our study population of 129 pediatric patients. The median (IQR) preoperative drop attack frequency was 70 (21–140) which decreased to 3 (0–14) postoperatively. Similarly, the number of anti-epileptics used by patients had a median of 3 (2–4) which decreased to 2 (2–3) after the surgery. All patients were experiencing status epilepticus which disappeared in 72% of the patients after callosotomy. Preoperative normal MRI was a predictor for drop attack favorable outcome and mild preoperative impairment of IQ was a predictor of favorable total seizure and drop attack outcome.

Conclusions Corpus callosotomy is a well-tolerated palliative procedure for drug-resistant generalized epilepsy notably, drop attacks which had its notorious effect on quality of life of pediatric patients and their families, no appreciable prognostic factors for favorable outcome were clearly observed except for normal preoperative MRI, mild preoperative IQ affection, and complete callosotomy.

Keywords Callosotomy, Epilepsy, Surgical technique

Background

Epilepsy is a chronic, debilitating disease affecting approximately between 4 and 10 out of 1000 people world-wide [1, 2]; most of the patients are treated medically and seizure freedom could be achieved, however, in about one-third of patients, fits might not be adequately controlled by medical treatment and those patients would eventually suffer from drug-resistant

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epilepsy (DRE) [3]. Consequently, an early surgical option could be advocated for DRE to decrease seizure burden, improve quality of life and increase life expectancy [4, 5].

Pediatric epileptic encephalopathies represent a clinically challenging and often devastating group of disorders that might disturb children at different stages of infancy and childhood affecting normal brain development and carry high possibility of being drug resistant [6].

Callosotomy is considered a well-tolerated palliative option for those patients who have multifocal epilepsy, generalized epilepsy, and diffuse non resectable unilateral epileptogenic lesion; and it is well established in precluding injurious drop attacks via preventing the seizure spread through the corpus callosum (generalization), and it also has variable effects upon other types of seizures [7].

Surgical and neurological complications do occur, but there are typically no enduring complications in children [8, 9], namely disconnection syndrome, cerebrospinal fluid (CSF) leakage and hydrocephalus which are all successfully managed either conservatively or via shunting procedures.

The study of the rates and the predictors of seizure outcome for different surgical options is always demanding, but the abundancy of the well-formed studies reviewing resective option, makes us eager to study those of callosotomy option. Here we present our study on a large series of pediatric cases from a developing country, with analysis of potential predicators outcomes in the era of more expensive devices like vagal nerve stimulation to give a litany on a universal epilepsy surgery procedure which had been missed in the literature through the last decade.

Methods

An observational retrospective study was done reviewing 129 patients with pediatric epileptic encephalopathy (PEE) underwent open microscopic corpus callosotomy, they were selected after fulfilling the criteria of being drug resistant and offered at least phase 1 battery of preoperative investigations according to the recommendations of international league against epilepsy (ILAE) for referral and evaluation [10].

A multi-disciplinary team involving neurosurgeons, neurologists and neuropsychiatrist were involved in the management plan of our epilepsy board.

Inclusion criteria involved drug-resistant epilepsy pediatric patients, non-concordant preoperative data (clinical, EEG and MRI), patients who had the drop attacks causing frequent falls as the main seizure burden, and patients with intelligence quotient (IQ) < 70.

While the exclusion criteria included patients with benign childhood epilepsy, and patients who underwent additional resection at the time of resection.

Etiology of epilepsy was categorized into symptomatic if the presumed cause of epilepsy was known or cryptogenic if the cause was potentially unknown and/or presumed genetic predisposition.

All seizure types were registered for all the patients with special focusing on drop attacks either atonic or tonic in nature as they are one of the most disabling seizures.

All seizures burden per week was calculated preoperatively and postoperatively.

All patients had a magnetic resonance imaging (MRI) epilepsy protocol [11], and they were subdivided according to MRI findings into normal MRI which include no appreciable epileptogenic lesion, global brain atrophy and/or hydrocephalic changes and lesional MRI which include bilateral or unilateral non resectable epileptogenic lesions.

All patients had a preoperative long-term electroencephalogram (EEG) at least 6 h to catch both inter-ictal and ictal activity and categorized according to EEG findings into group of patients with a non-lateralized epileptic activity in the form of either synchronous generalized activity or multifocal epileptogenic activity, while the other group of patients had a lateralized epileptic activity in the form of either focal activity or a bilateral activity with unilateral predominance, the epileptic activity usually in the form of spike or poly spikes-slow waves complexes with variable frequency and interpreted independently by two well-trained epileptologists.

Corpus callosotomy was done through a standardized microsurgical right parasagittal corridor dissecting medial to the right hemisphere traversing the pericallosal cistern till reaching the corpus callosum with the overlying pericallosal arteries and begins to divide the traversing callosal fibers till reaching the ependyma of the lateral ventricles trying not to puncture it to minimize complications.

The extent of callosotomy was subdivided into anterior (sparing the splenium) or complete. Postoperative CSF leak, hydrocephalus and disconnection syndrome was reviewed for analysis in the study.

Seizure outcome was studied for drop attacks outcome and other seizure's types (total seizure) outcome. For statistical analysis, post-operative drop attacks and total seizure outcomes was categorized according to the severity of seizure burden into favorable (seizures improvement > 50%) and unfavorable (seizures improvements < 50%). Follow-up point for assessment of total and drop attack seizure outcome was 3 months post-operative.

Post-operative status epilepticus with hospital admission was another measure for assessment of seizure outcome.

Neurophysiological assessment in the form of IQ testing (Wechsler intelligence scale for children version 5) grades were plotted pre- and post-operatively, post-operative IQ was assigned at last follow-up.

Grades of mental retardation (MR) were subdivided according to IQ scores into low average > 79, borderline MR (70–79), mild MR (50–69), moderate (35–49), severe (< 35).

Potential predictors of patients' seizure outcomes were reviewed for analysis, these prediction included: epilepsy duration, age at diagnosis, MRI finding, IQ score, EEG findings, history of infantile spasm and extent of callosotomy done.

For descriptive statistical analysis, continuous and normally distributed variables were expressed as mean ± standard deviation. Scores and non-normally distributed variables were expressed as median with inter-quartile range (IQR). Categorical variables were summarized as count and percentages. Clinical outcomes including drop attack frequency, number of anti-epileptics, status epileptics, and preoperative IQ were compared for all patients before and after surgery. Analysis was done using Wilcoxon signed rank test for non-normally distributed variables and McNemar's test for categorical variables. Patient groups with favorable and unfavorable outcomes (with respect to drop attack and total seizure outcomes) were compared for differences in the measured parameters. These associations were tested for statistical significance using Mann–Whitney test for non-normally distributed variables, Chi-square, or Fisher's exact test for categorical variables and linear by linear association test for ordered categories (preoperative IQ). Statistical significance was set at $p < 0.05$. For clinical parameters that had a statistically significant association with the outcomes, odds ratio for having a favorable outcome with 95% confidence intervals were calculated using simple logistic regression. All calculations were performed using R 4.1.2 through R studio.

Results

The study included analysis of 129 pediatric patients with a mean age of 8 years (± 3.6). Ninety-three patients (72%) were males and 36 (28%) were females. The most common diagnosis was symptomatic Lennox–Gastaut syndrome (LGS) found in 67.4% of the cases followed by cryptogenic epilepsy in 25.6% of the cases while few patients were diagnosed as symptomatic LGS TS, symptomatic SW or symptomatic west. Patients had a mean epilepsy duration of 6.4 (± 3.4) years (Table 1).

Table 1 Main baseline characteristics and callosotomy outcomes of the patients

Characteristic	Descriptive statistics
Age in years (mean ± SD)	8 (± 3.6)
Gender	
Male	93 (72%)
Female	36 (28%)
Diagnosis	
Cryptogenic	33 (25.6%)
Symptomatic LGS	87 (67.4%)
Symptomatic LGS TS	3 (2.3%)
Symptomatic SW	3 (2.3%)
Symptomatic west	3 (2.3%)
Epilepsy duration in years (mean ± SD)	6.4 (± 3.4)
Drop attack outcome	
Favorable	105 (81%)
Unfavorable	24 (19%)
Total seizure outcome	
Favorable	57 (44%)
Unfavorable	72 (56%)
Complications	
Hydrocephalus	9 (7%)
Disconnection syndrome	33 (26%)

SD standard deviation, *LGS* Lennox–Gastaut syndrome, *LGS TS* Lennox–Gastaut syndrome tuberous sclerosis, *SW* Sturge–Weber

Patients in the study had callosotomy as a palliative epilepsy either partial (ACC) or complete corpus callosotomy (CCC). Only 9/129 patients of our study had CCC. All the recorded outcomes were substantially improved after callosotomy compared to the preoperative measurements. The median (IQR) preoperative drop attack frequency was 70 (21–140) which decreased to 3 (0–14) postoperatively. Similarly, the number of anti-epileptics used by patients had a median of 3 (2–4) which decreased to 2 (2–3) after the surgery. All patients were experiencing status epilepticus which disappeared in 72% of the patients after callosotomy. Patients' IQ impairment were also improved, 40% of patients had post-operative mild IQ impairment compared to 26% of patients with preoperative mild impairment (p-value < 0.001) (Table 2).

We reviewed patient who needed surgical intervention for post-operative CSF leakage or hydrocephalus. CSF leakage or hydrocephalus was recorded in 6/12 (50%) cases of CCC and in 3/117 (2.6%) cases of ACC patients, this higher rate in CCC was statistically significant; p-value < 0.001. Also, disconnection syndrome was frequently reported in CCC cases (9/12) compared to (24/117) in ACC, this difference in rate of development of disconnection syndrome was found to be statistically significant with p-value < 0.001.

Table 2 Comparison of the main outcomes before and after surgery

	Preoperative	Postoperative	*p*-value
Drop attacks frequency as median (IQR)	70 (21–140)	3 (0–14)	< 0.001
Number of anti-epileptics as median (IQR)	3 (2–4)	2 (2–3)	< 0.001
Status epilepticus			
No	0 (0%)	93 (72%)	< 0.001
Yes	129 (100%)	36 (28%)	
IQ degree of impairment			
Mild	33 (26%)	51 (40%)	**< 0.001**
Moderate	54 (42%)	39 (30%)	
Severe	42 (32%)	39 (30%)	

IQR inter-quartile range, *IQ* intelligence quotient

Most of the patients (81%) were classified as having a favorable drop attack outcome. However, less than half of the patients (44%) achieved a favorable outcome with regard to the total seizure's improvement (Table 1). The group of patients who achieved a favorable drop attack or total seizure outcome was compared to patients with unfavorable outcomes regarding their baseline potential predictors. It was found that patients with a favorable outcomes tend to have longer duration of epilepsy, older ages at surgery and lower percentage of patients with history of infantile spasm. Higher percentage of patients with favorable outcome was found to have normal preoperative MRI and milder impairment in preoperative IQ scores compared to patients with unfavorable outcomes. It was found that preoperative impairment of IQ and MRI statistically significant different among the favorable and unfavorable groups and are potential predictors for drop attack and total seizure outcomes, respectively (Table 3).

Univariate logistic regression analysis showed statistically significant higher odds for patients with normal preoperative MRI to have favorable drop attack outcome compared to patient with lesional preoperative MRI, OR 2.68 (95% CI 1.2–6.08) and higher odds for patients with mild impairment in preoperative IQ compared to patients with severe impairment in preoperative IQ to have favorable total seizure outcome OR 5.6 (95% CI 1.6–25.9). Also, patients with moderate impairment in preoperative IQ compared to patients with severe impairment in preoperative IQ had higher odds of having favorable total seizure outcome OR 4.4 (95% CI 1.6–13.7). All the other studied predictors have no statistically significant odds of favorable outcomes neither for drop attack outcome nor total seizure outcome.

Preoperative lateralized EEG was found in 15/129 patients of our study, 9/15 of them had favorable drop attack outcome and only 6/15 patients had favorable total seizure outcome. Regarding the extent of resection, 9/12 (75%) patients who had CCC in our study had favorable drop attack and total seizure outcome, compared to 96/117 (82%) and 49/117 (42%) favorable outcome for drop attack and total seizure outcomes, respectively, in patients who received ACC. Both EEG and extent of resection was not studied in univariate analysis due to low number of cases in our study only 15/129 (12%) and 12/129 (9%) cases who had preoperative lateralized EEG or received CCC, respectively.

Discussion

Our study is reporting one of the largest series of pediatric patients who received corpus callosotomy as a palliative surgery in the literature. We present our

Table 3 Comparison of baseline characteristics between the group of patients with favorable versus unfavorable drop attack and total seizure outcomes

	Unfavorable drop attack outcome	Favorable drop attack outcome	*p*-value	Unfavorable total seizure outcome	Favorable total seizure outcome	*p*-value
Epilepsy duration in years Median (IQR)	3.5 (3–7.75)	6 (3.5–8.5)	0.17	6 (3–7.62)	6 (3.5–10)	0.336
Age at surgery in years Median (IQR)	4.85 (3.95–13.2)	7.5 (5.3–10)	0.1	7.15 (4.72–9.25)	7.5 (5.3–12)	0.13
Preoperative IQ						
Mild	3 (12.5%)	30 (28.6%)	**0.002***	15 (20.8%)	18 (31.6%)	0.1
Moderate	6 (25%)	48 (45.7%)		30 (41.7%)	24 (42.1%)	
Severe	15 (62.5%)	27 (25.7%)		27 (37.5%)	15 (26.3%)	
MRI						
Normal	12 (50%)	75 (71.4%)	0.075	42 (58.3%)	45 (78.9%)	**0.0219***
Lesional	12 (50%)	30 (28.6%)		30 (41.7%)	12 (21.1%)	

IQR inter-quartile range, *IQ* intelligence quotient, *MRI* magnetic resonance imaging

short-term seizure outcomes from a tertiary referral epilepsy surgery center in a developing country with limited resources and a population of around 100,000,000. In this study, we reported predicted outcomes in our 129 patients who were operated in our Institute through the last 2 decades since we started our pediatric epilepsy surgery program at our institute. We had higher odds for patients with normal preoperative MRI to have favorable post-callosotomy drop attack outcome compared to patient with lesional preoperative MRI, OR 2.68 (95% CI 1.2–6.08). In our study population, patients with mild and moderate impairment in preoperative IQ had favorable total seizure outcome post-callosotomy compared to patients with severe impairment in preoperative IQ OR 5.6 (95% CI 1.6–25.9) and OR 4.4 (95% CI 1.6–13.7), respectively. Also, we found 9/12 (75%) patients who had CCC in our study had favorable drop attack and total seizure outcome, compared to 96/117 (82%) and 49/117 (42%) favorable outcome for drop attack and total seizure outcomes, respectively. In patients who received ACC, however, we could not find significant for this predictor due to small number of cases who had CCC in our patients.

Callosotomy is believed to have a palliative anti-epileptic effect through preventing generalization of the seizure via sectioning the callosal commissural fibers, implementing this concept, callosotomy can be presented as a palliative option for all types of seizure [12].

In the sense of being palliative procedure, different scales are proposed to assess seizure outcome after callosotomy to define favorable and unfavorable outcome, some authors stuck to Engel classification as it has good interrater reliability, some authors like Cendes and colleagues [12] adopt Spencer & Spencer's classification system [12], but most of authors define their own classification system according to the percentage of decrease of total seizure burden per seizure type [12].

In our study, we had a favorable outcome when seizure burden decreased 50% or more than preoperative, and unfavorable outcome when seizure burden decreased less than 50%. So our favorable outcome is aligned with Engel I, II, III, while unfavorable outcome is aligned with Engel IV. [13].

Comparing our results to Graham and colleagues [9], a favorable seizure outcome was recorded (50% seizure reduction or more) in pediatric patients, 81% for drop attacks, and 44% other seizure types versus 84% for total seizure types, respectively.

In other studies, [14–16] that distinguished drop attacks outcome from other types of seizures, there were significantly more patients with more favorable outcome (50% reduction or more) in drop attacks than other generalized (90% versus 45.4%, $p=0.014$).

Most of authors [14, 17] advocate complete callosotomy versus partial callosotomy in the control of drop attacks (Engel I, II) (77.8% versus 45.4% $p=0.00036$) while no significant difference between complete and partial callosotomy for other seizure outcome (50% reduction 89.6% versus 77.8%, $p=0.22$), while Cendes and colleagues [12] found no significant difference between complete and partial callosotomy outcomes using spencer and spencer's classification (76.9% versus 61.5%, $p=0.44$), while in our study there was a tendency for higher favorable outcome with complete callosotomy in total seizure outcome 9/12 (75%) compared to 49/117 (42%) in partial callosotomy cases, this tendency was inverted in the case of drop attack outcome, in which 9/12 (75%) of complete callosotomy cases had favorable drop attack outcome compared to 96/117 (82%) cases had favorable drop attack outcome in partial callosotomy. This paradox in our results can be explained by the limited number of patients underwent complete callosotomy (12/129) 9.3% of the study population, furthermore, using wide range of favorable seizure outcome definition (50% or more reduction of seizure burden) could affect the results. Also, the number of anti-epileptic drugs AED is significantly decreased postoperatively from median 3 (2–4) to 2 (2–3) agreed with Graham and colleagues [18] contradicting with pediatric literature [9]. This may reflect a strategy for optimizing AED usage to reduce the number of side effects.

Regarding the adverse effects of procedure, we observed a lower rate of surgical complication (CSF leakage, hydrocephalus) in anterior callosotomy versus complete callosotomy [3/117 2.6% versus (6/12) 50%] that agreed with Graham and colleagues [9] (2.7% versus 5.9%, $p=0.39$). we believed that relatively higher surgical complication rate after complete callosotomy related to the limited number of cases only 12 and the classic intraventricular technique for callosotomy before the adoption of extra-ventricular technique preserving the ependymal lining of both ventricles significantly decreases the incidence of CSF leakage and hydrocephalus postoperatively [18, 19], also disconnection syndrome was found to be significantly higher following complete callosotomy rather anterior callosotomy (9/12 compared to 24/117 with p value <0.001), that agreed with one recent systematic review applied on pediatric age group only and found that disconnection syndrome associated with 12.5% of complete callosotomy compared to 0% with anterior Callosotomy [9]; on the contrary, chan and colleagues [21] did not observe a higher rate of disconnection syndrome among patients with complete (8.0%) compared with anterior (12.4%) callosotomy, as little

advantage to be added from sparing the posterior callosal interhemispheric tracts in anterior callosotomy because interhemispheric tracts related to motor and many important neurocognitive functions cross anteriorly [22].

Predictors of seizure outcome

Favorable drop attacks and other seizure types outcome are significantly linked with the presence of preoperative normal MRI OR 2.5 CI (1–6.25) for drop attacks and OR 2.68 CI (1.2–6.08) which is advocated by many authors [20] as MRI lesion most probably suggests a focal epileptogenic zone, which will respond well to resection unless those lesion are multiple or located in challenging areas that cannot be resected safely.

A disagreement over the prognostic value of a preoperative IQ is observed [7], In our study we found that mild IQ significantly predict favorable outcome in drop attacks, because profound IQ affection usually reflect the severity of disease, furthermore Turanlı and colleagues [13] found that patients with IQ < 50 had a poorer outcome and on the contrary Cendes and colleagues [12] found no correlation between intelligence and outcome which may be to heterogenous IQ assessment tests.

Age of patient at surgery, duration of epilepsy and history of infantile spasm were not found to be predictors of outcome in both drop attacks and other seizure types which is coherent with the literature unlike the resective surgery in children [23], thus giving more time for examination of the indication. Nevertheless, some authors suggest that early surgery could offer a better quality of life regardless of the results on drop attacks [24–26].

Although some authors reported better seizure outcomes for patients with preoperative lateralized EEG [25], in our series preoperative EEG was not found of prognostic value regarding the degree of lateralization of generalized epilepsy in agreement with other authors [27]. Of note, we had a limited number of cases with lateralized EEG 15/129 in our study which would have affected our results.

Our study is considered the first organized series reporting the efficacy of callosotomy in pediatric patients suffering from all forms of generalized epilepsy notably drop attacks, totally based in Egypt. All patients were assessed by a single multi-disciplinary team and all surgeries were done by 2 authors of nearly same experience. The study is also useful through adding new information about the durability of seizure outcomes within the hypothesis that corpus callosotomy is a safe and effective palliative treatment for pediatric patients. Moreover, this paper is a reflection of actual practice in Egypt, and prospective data collection was not possible.

Our limitations are inherited for all observational retrospective study designs that lack blinding, control, or randomization, another limitation is the heterogenicity of sample available for a study in etiology of generalized epilepsy and EEG diagnostic standard. Our follow-up point was only 3 months post-operative. This is attributed to the lack of long-term follow-up in our health care system database, also we tried to include maximum significant number of cases from our database to analyze the potential predictors.

As discussed elsewhere in the literature [9, 28], there is a clear need for a randomized control trial of corpus callosotomy outcomes compared with optimal medical management. The design of such a trial was outlined by Graham and colleagues [9] in their systematic review based on the landmark randomized controlled trial of Wiebe and colleagues [29] of temporal lobectomy, such a trial could randomize patients selected for corpus callosotomy to either corpus callosotomy or 12 months of continued optimal medical therapy.

Epilepsy surgery practice in Egypt is challenging and still lacking fundamentals like patient doctor awareness, the scarce of well-trained multi-disciplinary team and financial issues providing adequate diagnostic and therapeutic facilities. Thus, those studies would draw attention to build up a well-developed epilepsy surgery centers with international standards to develop the capabilities of local neurosurgeons in the field of epilepsy surgery.

Conclusions

Corpus callosotomy is a well-tolerated palliative procedure for drug-resistant generalized epilepsy, notably, drop attacks which had notorious effect on quality of life of pediatric patients and their families. No appreciable prognostic factors for favorable outcome were clearly observed except for normal preoperative MRI, mild preoperative IQ affection, and complete callosotomy. It is of a great importance to note that an inclusion of a control group of other palliative procedures like vagal nerve stimulation is a great limitation in our study which hinders it a descriptive rather than a comparative one, and that would be strongly considered in our future studies.

Abbreviations

ACC	Anterior corpus callosotomy
AED	Antiepileptic drug
PCC	Posterior corpus callosotomy
CCC	Complete corpus callosotomy
CC	Corpus callosum
CSF	Cerebrospinal fluid
SSS	Superior sagittal sinus
DRE	Drug-resistant epilepsy
IQ	Intelligence quotient
PEE	Pediatric epileptic encephalopathy
ILAE	International League Against Epilepsy
MRI	Magnetic resonance imaging
EEG	Electroencephalogram
IQR	Inter-quartile range

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Author contributions
The study design, execution and follow up of the clinical cases, data analysis and results formulation, and writing of the manuscript, were all the joint work of all the authors. All authors have approved the manuscript for submission. The manuscript has not been published, or submitted for publication elsewhere. All authors read and approved the final manuscript.

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Availability of data and materials
All the raw data and results of the statistical analysis are available with the authors and ready to be shared with authorized personnel upon request, however, for reasons of patency protection it was not submitted with the manuscript.

Declarations

Ethics approval and consent to participate
This research was conducted upon obtaining the approval of the ethical committee of the Faculty of Medicine—Ain Shams University, in March 2020. Since this study involved human subjects, an informed written consent was signed and acquired from all the participants or their legal guardians in accordance with the ethical committee recommendations.

Consent for publication
Not applicable

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

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