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Cognitive Impairment in Patients with Temporal Lobe Epilepsy

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Abstract

Objectives: To evaluate the frequency and the type of cognitive impairment (CI) in patients with temporal lobe epilepsy and to determine eventual risk factors for its occurrence.

Methods: We have conducted cross-sectional study in TLE patients and healthy controls (HC). All of them underwent neuropsychological assessment by using a large battery of tests to detect CI. EEG and Cerebral MRI were performed for all patients.

Results: Thirty-two TLE patients and thirty matched HC were enrolled. The mean age of our patients was 35 ± 8.3 yrs. The rate duration of evolution epilepsy until the appearance of CI was 14 ± 10 yrs. In our study, comparative neuropsychological assessment between TLE patients and controls demonstrates that epileptic patients have an impairment of many cognitive processes. The most common CI are: alteration of reaction and processing speed (100% of cases), attention deficit (93.6% of cases), deterioration in verbal episodic memory (87.5% of cases) and visual episodic memory (78.1% of cases). Verbal fluency and working memory are impaired in respectively 3/4 and about half (53.1%) of our patients. At the opposite, executive and visual-spatial functions are rarely affected. Neuropsychological scores worsen with advanced age, long duration of epilepsy, high seizure frequency, clonazepam intake and presence of temporal lesion at cerebral MRI. However, high level of education seems to be protective. TLE patients with lesion evolving the temporal lobe of the dominant hemisphere have had lower scores, especially in tests for verbal memory. At the opposite, when the other side is affected, only the episodic visual memory is impaired.

Conclusion: CI is frequent in TLE and alters the quality of patient's life. We emphasize the importance of periodical neuropsychological assessment to detect early CI and undertake the adequate measures to prevent patient to get worse.

Keywords: Temporal lobe epilepsy; Psychology; Cognitive symptoms; Risk factors

Introduction

Temporal lobe epilepsy (TLE) is the most common symptomatic partial epilepsy in adolescents and adults. It's well known that this form of epilepsy is very resistant to pharmacologic treatment in many cases [1]. If the ictal manifestations of TLE are stereotyped and quite similar in patients, the cognitive impairments (CI) observed in the inter-ictal period will be heterogeneous and variable from one case to another. In fact these patients have a high risk for CI and behavioral abnormalities (20-50%) [2]. The latter are often considered more detrimental to quality of life than seizures, and they may even persist with sufficient control of seizures. The mechanism of CI remains unclear. It's well known that during TLE we observe severe neuronal loss and gliosis in the hippocampus, but the relationship between this pathological pattern and CI is not established [3,4].

Cognitive morbidity of TLE may extend to many cognitive domains including memory, executive function, language, processing speed, intelligence, motor dexterity, and other abilities. A wide variety of neuropsychological tests and batteries are available for the assessment of high brain functions during TLE.

To clarify the spectrum of CI in our population, we have conducted cross-sectional study of a series of TLE patients who were treated in our department. We have used a large battery of neuropsychological tests and we tried to find a correlation between the demographic profile of patients, clinical, electrophysiological and radiological characteristics of the epilepsy and the neuropsychological dysfunction.

Methods

A series of 32 patients with TLE followed in our department underwent neuropsychological assessments between Mai and November 2016. A control group composed by 30 matched

individuals (age, gender, education) was also evaluated. This study has been approved by our institutional review board (IRB). We confirm that we have read the journal's position on issues involved in ethical publication and we affirm that this report is consistent to those guidelines. All patients were receiving antiepileptic drugs (AED) at the time of their evaluation. Each participant had to fulfill the following criteria to be included into the study:

- Diagnosis of TLE was established according to the International League Against Epilepsy (ILAE) criteria [5].
- Each participant had to sign an informed consent.
- Age between 18 and 65 years.
- Absence of MRI abnormalities a part of an eventual temporal lesion.
- Absence of other neurological or psychiatric disorder that can induce CI. To exclude epileptic patient with depression, we have used the Beck Depression Inventory (Second Edition). If the score is greater than 4, the patient will be not considered.

We have collected the clinical characteristics of each patient: age, sex, age at onset of epilepsy, educational level, family history of epilepsy, the semiology of the temporal seizures, the eventual presence of residual seizures and their frequency, etiologic factors, and number of AED. We have administered a comprehensive neuropsychological test battery to all subjects. Verbal Episodic Memory (VEM) has been assessed by the Selective Reminding Test (SRT) and Grober Buschke Test. The visual memory has been measured by the Brief Visio-spatial Memory Test–Revised (BVRT-R). The Empan Test (direct and inverse) has been designed to evaluate working memory. Go/no-go and Trail Making Tests (TMT A and B) have explored executive functions. To determine Visio-Spatial capacity we have used Rey complex figure. The attention was measured by the Bell test. We have used the Controlled Oral Word Association Test (COWAT) and the test of denomination (DO80 test) to analyze the verbal language's naming and fluency. EEG and cerebral MRI were done in all patients.

Statistical analysis

Continuous variables are presented as mean \pm SD. Categorical variables are presented as frequencies. Based upon the control group data, standardized scores were computed to evaluate the performance of the epileptic groups. The chi-square test (categorical variables), the T-test (quantitative variables) and Pearson's test (dichotomous variables) were used to evaluate associations between epilepsy and CI. The level of statistical significance was set at $P < 0.05$. SPSS statistical software, version 20.0 was used for all analyses.

Results

A series of 32 patients and a group of 30 healthy controls have been selected for our study.

Demographic characteristics

Participants with TLE: The average age of our patients was 35 ± 8.3 yrs (range: 19-62 yrs). They started to have epileptic seizures at the main age of onset 18 ± 5.1 yrs (range: 4-60 years). We have observed a male predominance and the ratio woman/man was 0.6. All patients were educated, 76% of them from the primary, 18% from the secondary school and the remaining (6%) were from higher education level.

Consanguineous parents were noted in 5 cases and a family history of epilepsy in 4 cases (12.5%). Eight patients reported a personal history of febrile seizures at infancy (25% of cases).

Healthy controls: The healthy controls (HC) did not differ from the TLE group regarding age, sex distribution and educational level. The main age of healthy control group was 31.1 years ± 8.6 (19-60 years). Men were more represented in this group than women. All these healthy subjects were educated; the majority of them had only a primary grade education (76%).

Characteristics of epilepsy

Thirty percent of patients had only focal seizures and in 70% of cases; the temporal seizure evolves to be bilateral tonic-clonic one. The average duration of epilepsy was 18.37 ± 2.4 yrs (range: 15-32 yrs). Epilepsy was resistant to AED in 25 patients (frequency > 1 seizure/day). Seven patients were on carbamazepine monotherapy. The remaining were either on bi-therapy (12 patients) or polytherapy (13 patients). Carbamazepine was associated with valproic acid, clonazepam or levetiracetam in respectively 10, 3 and 3 cases. Only 9 patients were not on carbamazepine (combination between valproic acid and clonazepam). Demographic data of our patients and disease characteristics are summarized in **Table 1**.

Table 1 Patients' demographic and disease characteristics. Yrs: years; AED: antiepileptic drugs.

| Parameter | Value |
|--|---------|
| Sex (female/male) | 0.6 |
| Mean age (yrs) | 35 |
| (range) | (19-62) |
| Education level | |
| Primary school (number) | 24 |
| Secondary school | 6 |
| University | 2 |
| Mean age at onset of epilepsy (yrs) | 18 |
| (range) | (4-60) |
| Mean seizure frequency per day | 1 |
| Mean duration of epilepsy (yrs) | 18.35 |
| (range) | (15-32) |
| Focal-to-bilateral tonic-clonic (number) | 24 |

| Number of AEDs | |
|----------------|----|
| one | 7 |
| Two | 12 |
| > 3 | 13 |

Neuroimaging results

MRI has shown structural abnormalities in 26/32 patients. These patients were divided into 2 subgroups: patients with mesiotemporal abnormalities (mesiotemporal sclerosis 7 cases and hippocampic atrophy 1 case) and patients with temporolateral abnormalities (18 patients). The latter includes a variety of temporal structure abnormalities: Tumor (4 cases), cavernous hemangioma (4 cases), cortical dysplasia: (5 cases), arachnoid cyst (2 cases) and stroke sequelae (3 cases).

Patients were divided into 3 groups according to the lateralization of the temporal lobe abnormalities: left (13 cases), right (12 cases) or bilateral (1 case). EEG study has shown focal sharp/wave discharges in 10 cases and a global slowing in 6 cases. Interictal EEG was normal in the remaining 16 cases.

Cognitive impairment (CI)

Despite of the great variety in the severity and the affected neuropsychological domain, all patients with TLE have CI. The main age of CI onset was 28.61 ± 7 yrs. There was a significant negative correlation between the age of onset of epilepsy and the severity of CI, especially verbal episodic memory ($p=0.001$).

Before the appearance of CI; the mean duration of evolution of epilepsy was 14 ± 10 yrs. The principal revealing symptoms (90% of cases) were memory complaints and attention deficit. In our series, neuropsychological assessment has demonstrated that the most common CI are: alteration of reaction and processing speed (100% of cases), attention deficit (93.6% of cases), deterioration in verbal episodic memory (87.5% of cases) and visual episodic memory (78.1% of cases). The Verbal fluency and working memory are impaired in respectively $\frac{3}{4}$ and about a half (53.1%) of our patients. At the opposite, executive and visual-spatial functions are rarely affected (**Figure 1**).

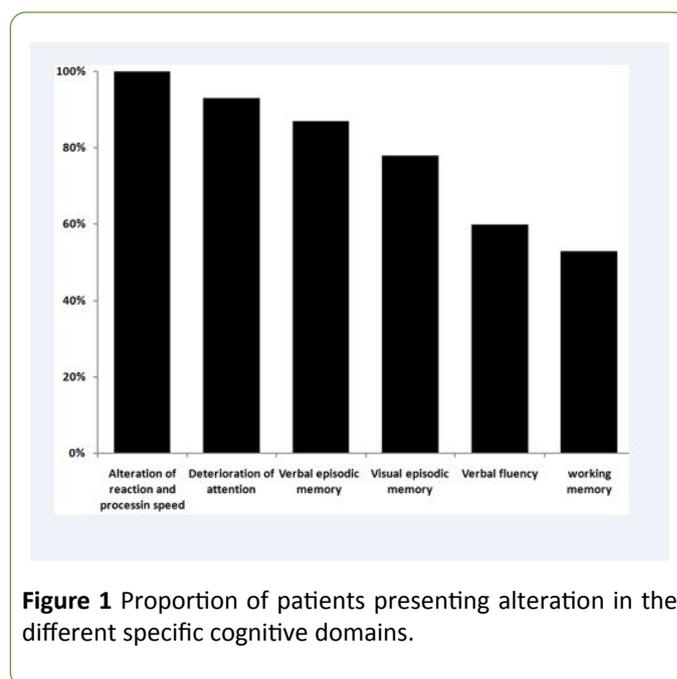


Figure 1 Proportion of patients presenting alteration in the different specific cognitive domains.

Regarding to the episodic verbal memory, Grober-Buschke test has shown that TLE patients have significantly lower scores than HC in both immediate and delayed recalls, either for free or cued recalls (total score was respectively 27/48 and 40/48). We didn't observe any improvement in 72% of TLE patients after cuing. It led to say that memory dysfunction is related to encoding problem. SRT has showed that episodic verbal memory was affected in more than 4/5 of cases (81.5%). Even though the difference was insignificant; women obtained lower scores than men.

Patients with TLE performed significantly worse in visual memory compared with healthy subjects. The immediate recall was poor in 53.2% of cases, concerning delayed recall (7 min), only 7 patients had scores comparable with controls. Working memory was affected in TLE patients. Verbal fluency has been analyzed using the naming tasks; patients exhibited deficits comparing with HC.

In addition to CI detailed before, neuropsychological studies have shown an impairment of other cognitive processes such as attention deficits. However, visual-spatial and executive functions were unaffected.

Results of neuropsychological assessment are summarized in **Table 2**.

Table 2 Results of the neuropsychological tests in temporal lobe epilepsy group and healthy controls. TLE, temporal lobe epilepsy; HC, healthy controls; the BVMT-R test, the Brief Visio-spatial Memory Test-Revised; TMT, Trail Making Test.

| Neuropsychological test | TLE | HC | P value |
|--------------------------------|-----------|-------------|---------|
| The Grober Buschke test | | | |
| • Immediate free recall/16 | 9 ± 4.16 | 15.55 ± 0.6 | 0.001 |
| • Total free recall /48 | 27.08 ± 8 | 40.4 ± 3.7 | <0.002 |

| | | | |
|-------------------------------------|-------------|--------------|--------|
| • Total recall /48 | 30.76 ± 7.1 | 45.7 ± 1.8 | 0.002 |
| • Delayed free recall/16 | 3.9 ± 3.8 | 14 ± 1.8 | <0.05 |
| • Delayed cued recall/16 | 5 ± 3 | 15.76 ± 0.5 | <0.001 |
| The selective reminding test | | | |
| • Immediate free recall | 2.38 ± 3.7 | 8.61 ± 0.2 | 0.017 |
| • Sum of recall | 68.1 ± 3.9 | 96.7 ± 12.23 | 0.007 |
| • Mean number of words recalled | 6.1 ± 0.59 | 12 ± 1.9 | 0.006 |
| • Learning index | 60 ± 3.7% | 80 ± 12.9% | 0.012 |
| • Delayed free recall/15 | 1.37 ± 5.14 | 9.95 ± 2.7 | 0.009 |
| • Delayed cued recall/15 | 1.43 ± 0.8 | 15 | <0.001 |
| The BVMT-R test | | | |
| • Total recall /36 | 23.13 ± 2.8 | 34.47 ± 3.6 | 0.001 |
| • Delayed recall/12 | 5.9 ± 3.27 | 11.9 ± 0.3 | 0.04 |
| Recognition Trial | | | |
| - Correct Answer | 5.44 ± 0.7 | 5.66 ± 0.48 | 0.2 |
| - False Answers | 0.48 ± 0.7 | 0.33 ± 0.44 | 0.1 |
| Empan test | | | |
| • Empan direct/16 | 5 | 10 | 0.02 |
| • Empan inverse/14 | 4.52 | 9 | 0.01 |
| Verbal fluency | | | |
| • Semantic Fluency | 15 ± 3.6 | 32.14 ± 4.9 | 0.04 |
| • Literal Fluency | 7 ± 3.8 | 24 ± 4 | 0.01 |
| Bell's test(120 sec) | 24.1 ± 12 | 51 ± 7 | 0.02 |
| GO no GO test: Correct answers | 39.3 ± 1.4 | 40 | 0.3 |
| TMT test | | | |
| • TMT A test (score) | 0.42 | 0.49 | 0.9 |
| • TMT A test (time) | 3 | 0.59 | 0.01 |
| • TMT B test (score) | 0.92 | 0.99 | 0.95 |
| • TMT B test (time) | 4 | 0.88 | 0.02 |

Correlations between the occurrence of CI and clinical characteristics, treatment, and investigation findings

In the TLE group, we observed a worsening of CI with age. In fact, we found a significant negative correlation between the different cognitive scores (attention, verbal and visual memory) and the age (p value was respectively 0.01, 0.001 and 0.002). Gender was not a factor influencing the degree of

impairment while educational level played a significant role and we have found that the educated subjects had better cognitive scores than the illiterate ($P < 0.05$ for all scores).

We have divided our patients into two subgroups according to the type of seizures: patients with focal seizures and others with focal-to bilateral tonic-clonic seizures (10 vs 22). Taking in account the overall neuropsychological assessment, we have found no significant difference between the two subgroups or between those with mesio-temporal seizures versus lateral temporal seizures. However, regarding verbal episodic memory tests (Grober-Buschke and SRT tests), we have found a negative correlation between age at onset of TLE and the occurrence of verbal episodic memory impairment. In fact; earliest age at onset of seizures is associated with a higher risk of encoding capacity loss and alteration of mechanisms of consolidation and recovery.

Our study demonstrates that high seizure frequency and long duration of epilepsy have a negative impact on the different domains of cognition (**Table 3**).

Table 3 Correlations between cognitive impairment and clinico-radiological aspects. AAOE, age at onset of TLE; SF, seizures frequency; DE, duration of epilepsy; FR, free recall; CR, cued recall; SRT, the Selective Reminding Test; the BVMT-R test, the Brief Visio-spatial Memory Test–Revised, NS: not significant.

| Neuropsychological disorders | AA OE | SF | DE | Lateralisation |
|--|-----------|-----------|-----------|----------------|
| Alterations in verbal episodic memory | | | | |
| FR/CR | 0.0 46 | 0.0 05 | 0.0 02 | 0.002 |
| Alterations in visual episodic memory | | | | |
| BVMT-R | 0.0 2 | 0.0 05 | 0.0 09 | 0.04 |
| Disruptions in working memory | | | | |
| Empan inverse | 0.0 1 | 0.0 2 | 0.0 15 | NS |
| Deterioration of attention (Bell's test) | 0.0 59 | 0.2 | 0.0 07 | NS |
| Processing speed | 0.0 05 | 0.0 1 | 0.0 65 | 0.01 |

Regarding cognitive performance and therapy, we have noticed that patients treated with clonazepam performed badly in verbal and visual episodic memory and they had lower mental flexibility compared with patients free from this drug. We haven't found any correlation between the number of AED and the alteration of the different cognitive domains.

The presence of a temporal lesion on cerebral MRI, especially hippocampal sclerosis, is a significant risk factor for CI. These CI vary according to lateralization, when the lesion affects the dominant hemisphere, mental flexibility and verbal memory are more altered, but when the other side is involved, visual memory dysfunction is more prominent.

Discussion

CI in TLE

Cognitive impairment, a classic complication of TLE, is largely debated in the medical literature [2-4,6,7]. However, the majority of articles reported a small series or studied only a single cognitive domain [8,9].

Memory impairment constitutes the most common cognitive deficit in TLE; around 70% of patients have episodic memory failure [6,10]. In addition, recent publications draw attention to the involvement of semantic memory [8,9].

In fact, during TLE the pathological process usually involves the hippocampus or the lateral temporal lobe; and via the network many structures are functionally connected to these areas including: anterior temporal lobe, insula, thalamus, cingulate gyrus, and prefrontal cortex [11]. These structures are the anatomical support of memory.

All steps of long-term memory processing are affected with a decline in the three main stages: initial learning (encoding), storage (consolidation) and recovery. This memory deficit profile which is called "hippocampal pattern" is similar to what we observe during Alzheimer's disease (AD). In our series, 22 patients had amnesia with hippocampal profile (78%).

Relying on the similarity of the amnesic syndrome found in TLE and AD, some authors measured CSF biomarkers and performed cerebral functional imaging in TLE patients with memory deficit. They detected pathological changes reminiscent of AD, and they concluded that the progressive memory deterioration in TLE may be due to an underlying degenerative process quite similar to AD [12]. Similarly, to AD; some genetic profiles are considered as risk factors to the occurrence of CI in TLE patients. In fact, the allele APOE 4 is more prevalent in TLE patients with memory deficit [13].

After the memory failure, the most frequent CI during TLE are alteration of reaction and mental flexibility as observed in our series and reported in the literature [14]. These alterations are usually associated with other cognitive dysfunctions such as failure of episodic memory and attention deficit [14,15]. The latter is a complex neuropsychological process involving several cortical and sub-cortical networks. It's frequently affected in TLE but also in many other types of focal epilepsy [15]. Attention and reaction tests are influenced by the number of AED. Patients taking one or two AED have a higher performance than those taking three or more [15].

When the epileptic process affects the dominant lobe, involving the anterior temporal lobe and/or the fronto-temporal linguistic circuits, the verbal fluency is frequently disturbed [16].

The disruptions in working memory in TLE patients remain controversial. It is largely admitted that working memory is completely dependent on the fronto-parietal network [16]. Several studies supported this view and demonstrate that working memory is more affected in frontal epilepsy. Other authors reported an alteration of this function in TLE

particularly in patients with a long-standing course of the disease [15]. In our study, working memory was affected in about half of cases (53%). The executive functions were always normal; this may be explained by the fact that this function is controlled by the frontal lobes. Visuo-constructive functions were rarely studied in the literature. They were normal in our patients, but some authors reported a significant decline [7].

Cognitive impairment correlations with epidemiological, clinical and paraclinical factors

In our study, we have found a positive correlation between cognitive decline and patients' age. This is concordant with the results of a multivariate analysis published by Valton et al. [17]. Some authors suggested that this correlation could be explained by a neurodegenerative mechanism similar to what was observed in AD. In fact; in patient who underwent surgical treatment; pathological examination of resection materials showed amyloid plaques and accumulation of Tau proteins. This pathological pattern reminiscent of AD, was more pronounced in older patients [18].

The age of the disease's onset is also a determinant risk factor: the earlier the epilepsy occurs; the more severe CI is. In fact, the age at which the lesion is sustained can modify the normal functional organization of the brain [19]. In concordance with the literature; we have found a negative correlation between the degree of cognitive decline and the age of onset of the epilepsy [19,20]. Gender of the patients doesn't influence the risk of occurrence and severity of CI in our series and in the literature [21].

The most educated subjects have a lower risk to develop CI, this can be explained by great cognitive reserves in highly educated patients [22]. In our study, we have found that subjects with a secondary school level have cognitive scores better than those with a primary school level.

In literature, some studies have shown that cognitive performance is worse in patients with focal-to bilateral tonic-clonic seizures [21]. In our study, we haven't found this correlation.

In our patients, as reported in the literature, degree of CI is significantly correlated with the duration of epilepsy [23].

The effect of the frequency of the epileptic seizures remains controversial. Some authors revealed that it does not impact the appearance of CI. At the opposite; others demonstrated an association between the frequency of seizures and memory dysfunction [24]. These findings have been confirmed in our study.

The long-term effects of AED on cognition have been widely discussed in the literature. The majority of the studies have shown that CI are linked to AED [25]. Based on the fact that CI may occur in untreated patients, some authors refuted this correlation [26]. Polymedication increases the risk and severity of CI [27], this fact is not demonstrated in our series. Serum level of AED has also a negative impact on the cognitive

capacities especially attention [27]. Memory may be affected by lorazepam intake [28]. Meador et al. show that phenytoin, carbamazepine and valproate are less harmful than Benzodiazepines and barbiturate [29]. The new generation AED seems to be safer than older [30]. We have found low cognitive scores in all domains in patients receiving clonazepam.

Dinkelacker et al. demonstrated that the presence of interictal electrical discharges (ED) increases the risk of cognitive decline [31]. It can interfere with the specific hippocampal functions: weakening of the word recovery networks. Other studies attempted to find specific cognitive domain impairment according to the topography of ED. The alteration of the phonemic and semantic fluency was correlated with the presence of ED in the anterior temporal cortex [32]. More recently, Kleen et al. have reported that hippocampal intercritical discharges may disrupt storage and retrieval, but not encoding [33]. In our series, we found only slow waves that were not correlated with cognitive deterioration. Cognitive decline is more important if ED are located in the dominant hemisphere [34]. In addition, it is classically admitted that the memory deficit predominates on verbal memory in the case of left ED, whereas right sided ED affect more visual memory [35].

During TLE, we have noticed that the occurrence and the severity of CI are also related to its underlying pathological process [31]. A significant correlation has been found between the presence of a lesion at MRI especially HS and the degree of CI [23]. The extent of cognitive decline is related to the degree of neuronal loss in the hippocampus and the adjacent temporal structures. The memory is strongly affected if the loss of granular cells exceeds 60% within the hippocampus [36,37]. We have also found that the presence of symptomatic epilepsy is a predisposing factor for the appearance of CI. In our study, as in the literature, HS is the most harmful lesion on the cognitive functions.

Conclusion

TLE is the most frequent form of focal epilepsy in adult (about 80%). Mesial seizures related to HS constitute an epileptic syndrome which is very resistant to pharmacologic treatment. In fact, approximately half of the patients are drug resistant. Persistence of seizures is considered both a medical and a social problem and can induce CI.

It is well known that TLE patients have a high risk for CI and behavioral abnormalities (more than 50% of cases). In our study, comparative neuropsychological assessment between TLE patients and controls demonstrates that epileptic patients had an impairment of many cognitive processes. Neuropsychological scores worsen with advanced age, long duration of epilepsy, high seizure frequency, clonazepam intake and presence of temporal lesion on cerebral MRI. However, high level of education seems to be protective.

TLE Patients with lesion evolving the temporal lobe of the dominant hemisphere have lower scores in almost neuropsychological tests, especially tests for verbal memory.

At the opposite, when the other side is affected, only the episodic visual memory is impaired.

Declaration

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of Interest

The authors have no conflict of interest to declare.

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