Neurol Sci (2017) 38:143–149
DOI 10.1007/s10072-016-2740-5

ORIGINAL ARTICLE

Calgary score and modified Calgary score in the differential diagnosis between neurally mediated syncope and epilepsy in children

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Received: 12 August 2016 / Accepted: 12 October 2016 / Published online: 17 October 2016

Abstract To evaluate the value of Calgary score and modified Calgary score in differential diagnosis between neurally mediated syncope and epilepsy in children. 201 children experienced one or more episodes of loss of consciousness and diagnosed as neurally mediated syncope or epilepsy were enrolled. Calgary score, modified Calgary score and receiver-operating characteristic curve were used to explore the predictive value in differential diagnosis. There were significant differences in median Calgary score between syncope [−4.00 (−6, 1)] and epilepsy [2 (−3, 5)] ($z = -11.63$, $P < 0.01$). When Calgary score ≥1, the sensitivity and specificity of differential diagnosis between syncope and epilepsy were 91.46 and 95.80 %, suggesting a diagnosis of epilepsy. There were significant differences in median modified Calgary score between syncope [−4.00 (−6, 1)] and epilepsy [3 (−3, 6)] ($z = -11.71$, $P < 0.01$). When modified Calgary score ≥1, the sensitivity and specificity were 92.68 and 96.64 %, suggesting a diagnosis of epilepsy. The sensitivity and specificity of modified Calgary score and Calgary score did not show significant differences ($P > 0.05$). Calgary score and modified Calgary score could be used to differential diagnosis between syncope and epilepsy in children.

Keywords Calgary score · Neurally mediated syncope · Seizures · Epilepsy

Introduction

Transient loss of consciousness (T-LOC) is defined as a self-limiting episode of loss of consciousness due to a transient hypoperfusion of the brain [1]. The incidence of T-LOC in the general population is about 25–50 % [2], approximately 40 % of children (females 47 %, males 37 %) experienced at least one episode of T-LOC [3]. In consideration of T-LOC, disorders of central nervous system, cardiovascular system and/or endocrine system should be excluded [4–6]. During childhood, syncope and seizures of epilepsy are the most frequent causes of T-LOC. Syncope is transient cerebral hypoxia-induced periodic and self-limited disorder of consciousness, and accompanied by the loss of spontaneous muscle tension [7, 8]. Epilepsy is characterized by recurrent seizures as a result of excessive electrical discharges in parts of brain cells [9, 10].

Clinical manifestations of syncope and epilepsy are similar; a substantial number of cases with syncope, especially convulsive syncope, are sometimes mistaken for epilepsy [11, 12]. It is reported that 20–30 % of patients diagnosed as epilepsy are actually neurocardiogenic syncope. 25.7 % patients with epilepsy developed profound hypotension or bradycardia during the head-up tilt test (HUTT), finally were diagnosed as vasovagal syncope [13]. These neurocardiogenic syncope with abnormal movements due to cerebral hypovolemia are difficult to differentiate from epilepsy on clinical grounds [14, 15]. When epilepsy is diagnosed, anti-epileptic drugs are often prescribed in these conditions, but anti-epileptic

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drugs have side effects [16, 17]. In children, the common cause of syncope is neurally mediated syncope (NMS), in which cardiovascular effector mechanisms become overactive, resulting in vasodilatation and/or bradycardia [18]. Furthermore, the clinical feature of epilepsy is also different from adults. It is essential to find an effective way to distinguish syncope and epilepsy.

Sheldon and his coworkers started to use Calgary diagnostic scores in adult syncope diagnosis and differential diagnosis since 2002. This evaluation system has a total of three survey score sheets [19–22], and could be used in three areas: (1) differential diagnosis of syncope and epilepsy [19]; (2) differential diagnosis of patients with vasovagal syncope (VVS) or other cause of syncope [20]; (3) identification of patients with known structural heart disease, ventricular tachycardia or VVS [21]. The first sheet was used for questionnaire of epileptic seizures and syncope in adults; it could accurately distinguish 94 % of epilepsy from syncope. Here is our first report for Calgary score and modification of Calgary score used to distinguish epilepsy from NMS in children.

Participants and methods

Participants

Participants with one or more episodes of T-LOC diagnosed as NMS or epilepsy at Children's Medical Center, the Second Xiangya Hospital, Central South University, from October 2013 to April 2014, were enrolled. The Medical Ethical Committee of the Second Xiangya Hospital approved the research protocol. All included patients or their parents signed informed consent.

Inclusion and exclusion criteria

Patients aged from 5 to 18 years, with one or more episodes of T-LOC and diagnosed as NMS or epilepsy according to the current criteria were included in this study. Subjects with structural heart diseases were excluded by a standard basic evaluation consisting of careful history, full physical examination, baseline laboratory testing, 12-lead ECG, dynamic ECG, and echocardiogram. Children with mental retardation who could not make themselves clear, or those with both positive responses of HUTT and epileptic discharge of electroencephalogram were excluded. For those subjects who presented with at least one episode of T-LOC, but could not recall episodes situation, additional information were collected from their parents or guardians.

HUTT

Subjects were asked to rest in supine position for 10 min, and random fasting blood glucose, baseline heart rate (HR), respiratory rate (RR), blood pressure (BP), oxygen saturation and electrocardiogram were subsequently recorded. In the following 15 s, subjects were tilted from supine to 60° position, with head upwards and feet secured. This position would last for pre-determined 45 min or stopped until positive responses appeared. HR, RR, BP, oxygen saturation and electrocardiograph were recorded every 5 min or whenever subjects felt discomfort during this test. Subjects with negative responses of baseline HUTT maintained the same position, and were sublingually administrated nitroglycerin in a dosage of 5 μg/kg (maximum 300 μg), then underwent sublingual nitroglycerin HUTT. HR, RR, BP, oxygen saturation and electrocardiograph were recorded every 2 min until positive responses appeared or the test lasted for 20 min [23, 24].

Diagnosis of NMS

Clinical diagnostic criteria of NMS: (1) postural orthostatic tachycardia syndrome (POTS) was diagnosed when the change of HR $\geq$30 beats per minute from supine position to tilted position or HR reached up to 120 beats per minute during the first 10 min of HUTT, accompanied by symptoms such as dizziness, syncope, shortness of breath, headache, palpitations, paleness, blurred vision and fatigue [25]. (2) Orthostatic hypotension (OH) was diagnosed when the decrease of diastolic BP $\geq$10 mmHg and systolic BP $\geq$20 mmHg during the first 3 min of HUTT, whereas HR showed no obvious changes. (3) Vasovagal syncope (VVS) and its different responses were diagnosed as described previously, accompanied by the onset of syncope or presyncope [3].

Diagnosis of epilepsy

Epilepsy was diagnosed based on medical history and positive electroencephalograms. The inclusion criteria for epilepsy: (1) age ranged from 5 to 18 years; (2) no liver dysfunction at presentation of epilepsy, and (3) investigation according to the prevailing practice within the department of Pediatric Neurology [26].

Calgary score and modified Calgary score

The Calgary score consisted of nine diagnostic questions related to medical history, triggers, circumstances, and symptoms of transient loss of consciousness. All questions were answered as 'yes' or 'no'. If a question was answered as 'yes', points were added or subtracted depending on

Table 1 Individual items of the Calgary score

	Question	Score (if yes)
Q1	Waking with cut tongue?	2
Q2	Prodromal deja vu or jamais vu?	1
Q3	Loss of consciousness with emotional stress?	1
Q4	Head turning to one side during loss of consciousness?	1
Q5	Abnormal behavior noted by bystanders, including witnessed unresponsive, unusual posturing or limb jerking? (score as yes for any positive response)	1
Q6	Postictal confusion?	1
Q7	Any presyncope, such as dizziness, palpitation or nausea?	−2
Q8	Diaphoresis before a spell?	−2
Q9	Loss of consciousness with prolonged sitting or standing?	−2

Table 2 Individual items of the modified Calgary score

	Question	Score (if yes)
Q1	Waking with cut tongue?	2
Q2	Prodromal deja vu or jamais vu?	1
Q3′	Loss of consciousness during sleeping?	1
Q4	Head turning to one side during loss of consciousness?	1
Q5	Abnormal behavior noted by bystanders, including witnessed unresponsive, unusual posturing or limb jerking? (score as yes for any positive response)	1
Q6	Postictal confusion?	1
Q7	Any presyncope, such as dizziness, palpitation or nausea?	−2
Q8	Diaphoresis before a spell?	−2
Q9	Loss of consciousness with prolonged sitting or standing?	−2

whether the answer increased the likelihood of epilepsy. The total score ranged from −6 to 7. The modified version also consisted of nine questions, with an alternative for the third question. In Calgary score, the question was "Loss of consciousness with emotional stress?" (Table 1), and in modified version, the alternative one was "Loss of consciousness during sleeping?" (Table 2) [19].

Statistical analysis

The continuous variables were expressed as mean ± SD. *t* test statistics, or the Mann–Whitney test statistic was used when appropriate. The dichotomous variables were expressed as cases (percentage), and Chi-square test was used to compare confidence intervals (CIs) between groups. The receiver-operating characteristic (ROC) curve was used to analyze the predictive values of the Calgary score and modified Calgary score in distinguishing between syncope and epilepsy. The area under the curve (AUC) represented the predictive values. AUC between 0.5 and 0.7 had low diagnostic values, between 0.7 and 0.9 had moderate diagnostic values, and over 0.9 had high diagnostic values. The 95 % CI not including 0.5 or P value <0.05 showed significantly predictive value.

Results

Study group

A total of 201 patients (95 male, 106 female) aged from 5 to 18 years were included. 119 cases were diagnosed as NMS, among which 106 patients were VVS, and 13 patients were POTS-triggered syncope. 82 cases were epilepsy. Both the age and onset age of patients with epilepsy were younger, but there were no significant differences in gender distribution and family history between the two groups (Table 3).

Predictive value of the Calgary score

The median of Calgary score for NMS was −4 (−6, 1), for epilepsy was 2 (−3, 5), and there was significant difference ($z = 11.63$, $P < 0.01$). ROC was used to evaluate the sensitivity and specificity of Calgary score for epilepsy predictive diagnosis (Fig. 1a). The AUC was 0.98, with standard error of 0.008, 95 % CI (0.965–0.995) (Fig. 1b). It did not include 0.5, suggesting Calgary score was valuable for predicting epilepsy. Different Calgary scores were selected to analyze the sensitivity and specificity (Table 4). A score of 0.5 had a sensitivity of 91.50 % and a specificity of 95.80 % for differentiating epilepsy from syncope. Since the score was an integer, a Calgary score ≥1.0 could be considered as epilepsy, with the sensitivity of 91.46 % and specificity of 95.80 %.

Predictive value of the modified Calgary score

The median modified Calgary score for NMS was −4 (−6, 1), and for epilepsy was 3 (−3, 6). There was significant difference ($z = 11.71$, $P < 0.01$). ROC of the modified Calgary score is shown as Fig. 2a. AUC was 0.984, with standard error of 0.007, 95 % CI (0.970–0.998) (Fig. 2b). The area did not include 0.5, suggesting modified Calgary scores had high predictive value of epilepsy. Different cutoff scores of diagnostic sensitivity and specificity are shown as Table 5, the results indicated that score of 0.5 had sensitivity of 92.70 % and specificity of 96.60 % for distinguishing epilepsy and syncope. Since the score was an

Table 3 Basic characteristics of subjects included in the study

Group	*N*	Male (*n*)	Age (years)	Onset age (years)	Family history (*n*)
NMS	119	50	12.91 ± 2.67	11.13 ± 3.17	20
Epilepsy	82	45	10.10 ± 2.74	6.96 ± 3.45	10
Chi-square/*t* value		3.22	7.24	8.85	0.73
P value		0.07	0.00	0.00	0.40

NMS neurally mediated syncope

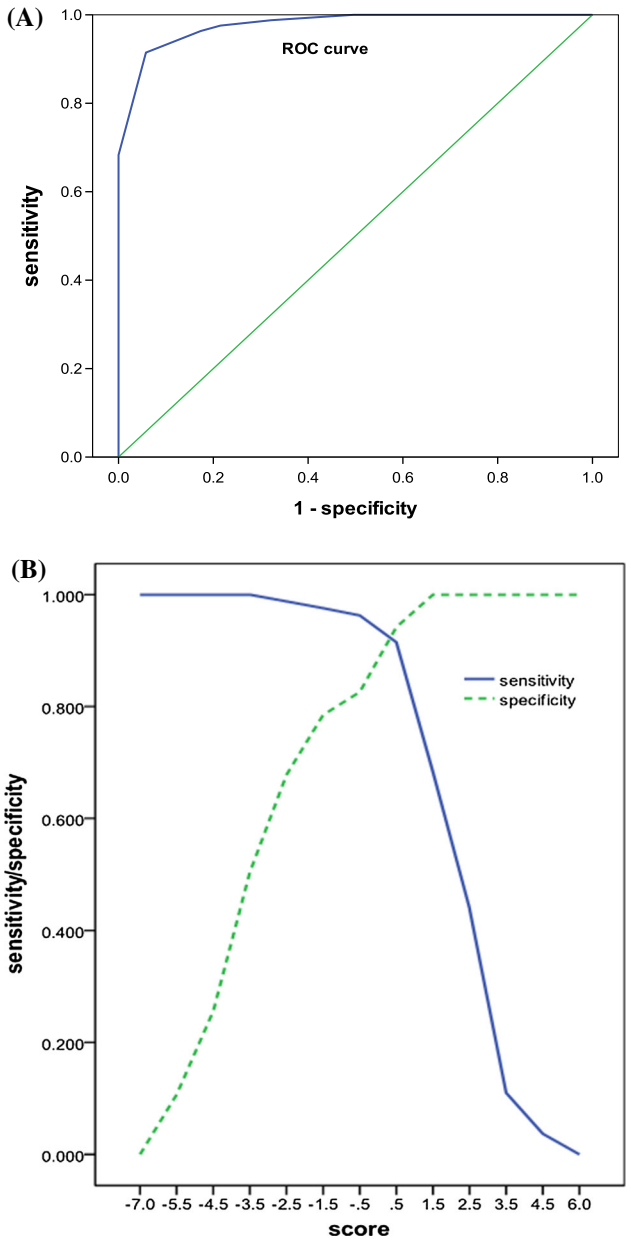

Fig. 1 Receiver-operating characteristic analysis (**a**) and area under the receiver-operating characteristic analysis curve (**b**) of Calgary score in the differential diagnosis between neurally mediated syncope and epilepsy

integer, modified Calgary score ≥1, with the sensitivity of 92.68 % and specificity of 96.64 % was considered to have high predictive value of epilepsy.

Comparison of Calgary and modified Calgary score

With the cutoff score of 1, the sensitivity and specificity of modified Calgary score and Calgary score were no significant differences (Chi-square = 0, $P > 0.05$).

The third question (Q3) of Calgary score was "Loss of consciousness with emotional stress?". As shown in Table 6, the positive rate of Q3 was 11.0 % (9/82) in epilepsy group, and 16.8 % (20/119) in NMS group, there was no significant difference between the two groups (Chi-square = 1.337, $P > 0.05$). The third question (Q3') of modified Calgary score was "Loss of consciousness during sleeping?", positive rates in epilepsy and NMS group were 47.6 % (39/82) and 0 % (0/119), respectively, and there was significant difference (Chi-square = 70.22, $P < 0.01$).

There were nine questions in Calgary score, Q1–Q6 increased the likelihood of seizures, and Q7–Q9 increased the likelihood of syncope. In this study, Q1, Q4, Q5, Q6 and Q3′ increased the likelihood of epilepsy ($P < 0.05$), while Q7, Q8 and Q9 increased the likelihood of syncope ($P < 0.05$). Q2 and Q3 showed no significant differences between NMS and epilepsy group ($P > 0.05$) (Table 6).

Discussion

Necessity of Calgary score in syncope and epilepsy differential diagnosis

T-LOC is a transient symptom due to many underlying causes. The most common causes in children are syncope and epilepsy. In clinical evaluation, loss of consciousness accompanied with featured symptoms such as seizure-like activity, tongue-biting and physical trauma, are used for epilepsy diagnosis. Prolonged standing or sitting, specific situations (such as urination, defecation, blood sight and so on), prodromal symptoms (such as nausea, vomiting, sweating, palpitations and so on) before the loss of

Table 4 The predictive value of different scores in diagnosis of epilepsy using Calgary score

Bound value	Sensitivity	Specificity	1-specificity
−7	1.000	0.000	1.000
−5.5	1.000	0.109	0.891
−4.5	1.000	0.261	0.739
−3.5	1.000	0.513	0.487
−2.5	0.988	0.689	0.311
−1.5	0.976	0.798	0.202
−0.5	0.963	0.840	0.160
0.5	0.915	0.958	0.042
1.5	0.683	1.000	0.000
2.5	0.439	1.000	0.000
3.5	0.110	1.000	0.000
4.5	0.037	1.000	0.000
6.0	0.000	1.000	0.000

consciousness usually predict syncope. However, it is difficult to differentiate convulsive syncope from epileptic atonic seizure. Syncope is a common acute disease in children, among which about 70 % cases are due to NMS, including VVS, POTS, OH and autonomic dysfunction orthostatic intolerance [27]. At present, diagnosis of NMS mainly depends on history and HUTT. Nevertheless, HUTT has risks of arrhythmia in reproducing syncope, and has a complex mix of significant methodological variables and has not been validated against a gold standard population [28]. The diagnosis of epilepsy depends on clinical history and electroencephalogram. Video EEG, ambulatory EEG and sleep evoked EEG could increase the positive rate of epileptic discharges of EEG [29], but some epilepsy patients have normal EEG results. Calgary score was established from Sheldon and his coworkers' findings [19]. The Calgary score was developed from a 118-item historical questionnaire [30]. The data set were randomly divided into two groups for the separate development and testing of the clinical decision rule. The likelihood ratio of each variable (the prevalence in the seizure group divided by the prevalence in the syncope group) was used to predictive diagnosis of syncope and epilepsy. Likelihood ratio >1 was predictive of epilepsy, and ratio <1 was predictive of syncope.

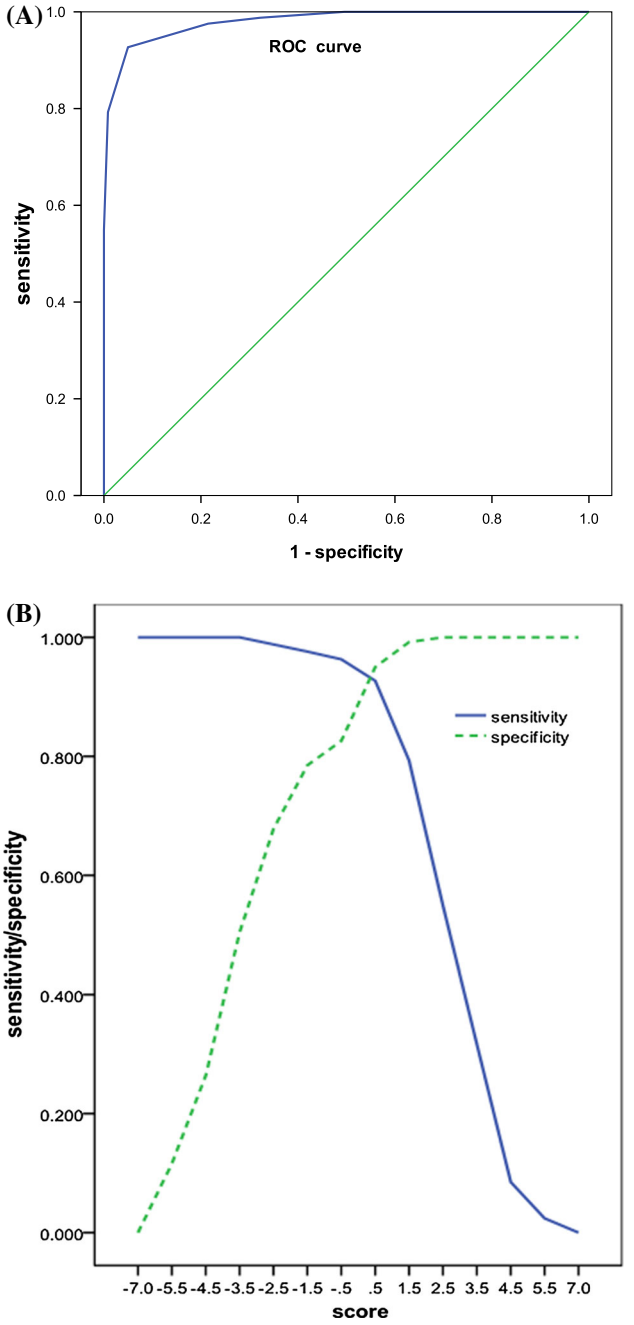

Fig. 2 Receiver-operating characteristic analysis (**a**) and area under the receiver-operating characteristic analysis curve (**b**) of modified Calgary score in the differential diagnosis between neurally mediated syncope and epilepsy

Modification of Calgary score in syncope and epilepsy diagnosis

Calgary score contains nine questions, Q1–Q6 are predictive of epilepsy, and Q7–Q9 are predictive of syncope. In present study, modification of Calgary score was made according to clinical features and characteristics of children, that was modified Q3 "Loss of consciousness with emotional stress?" to Q3′ "Loss of consciousness during sleeping?". The modification was based on following reasons: (1) mental stimulation and stress were commonly seen in syncope and hysteria [31]. Studies showed that occurrence and recurrence of seizures were less associated with mental factors [32, 33]. In the present study, positive response of Q3 has no significant difference between epilepsy and NMS, suggesting less significance of the query in

Table 5 The predictive value of different scores in diagnosis of epilepsy using modified Calgary score

Bound value	Sensitivity	Specificity	1-specificity
−7	1.000	0.000	1.000
−5.5	1.000	0.118	0.882
−4.5	1.000	0.269	0.731
−3.5	1.000	0.513	0.487
−2.5	0.988	0.689	0.311
−1.5	0.976	0.798	0.202
−0.5	0.963	0.840	0.160
0.5	0.927	0.966	0.034
1.5	0.793	1.000	0.000
2.5	0.549	1.000	0.000
3.5	0.317	1.000	0.000
4.5	0.085	1.000	0.000
5.5	0.024	1.000	0.000
7.0	0.000	1.000	0.000

Table 6 Comparisons of positive rates for questions in Calgary score and modified Calgary score between epilepsy group and neurally mediated syncope group

Question	Epilepsy (%)	Syncope (%)	Chi-square	*P* value
Q1	11.0	0.8	8.514	0.004
Q2	40.2	34.5	0.700	0.403
Q3	11.0	16.8	1.337	0.248
Q4	46.3	0.8	64.272	0.000
Q5	100.0	24.4	112.301	0.000
Q6	24.4	2.5	22.913	0.000
Q7	12.2	89.1	117.574	0.000
Q8	3.7	43.7	39.157	0.000
Q9	1.2	63.9	80.618	0.000
Q3′	47.6	0.0	70.223	0.000

Q3′ was the 3rd question of modified Calgary score

differentiating epilepsy from syncope. (2) Mental stimulation and mental stress is indistinct, especially for younger individuals. It is very difficult for children to evaluate the strength of mental stress. (3) Occurrence during sleep was a strong predictor for epilepsy [29], whereas NMS occurred during standing or posture changes. In the present study, positive rate of Q3′ was higher in seizures group than NMS group, indicating high predictive value of Q3′ in distinguishing epilepsy and syncope.

Cutoff score of modified Calgary score

ROC curve was used to evaluate the sensitivity and specificity of Calgary score and modified Calgary score in predictive diagnosis of epilepsy and syncope. AUC of Calgary score was 0.980 (95 % CI 0.965–0.995). AUC of modified Calgary score was 0.984 (95 % CI 0.97–0.998). Both areas were higher than 0.9, and did not include 0.5, suggesting high predictive values. Both cutoff scores of Calgary score and modified Calgary score were 1, which were consistent with previous study in adults [19]. The sensitivity and specificity of Calgary score were 91.46 and 95.8 %, modified Calgary score were 92.68 and 96.64 %. Both questionnaires had high sensitivity and specificity, indicating good value of Calgary score and modified Calgary score in syncope and epilepsy differential diagnosis. When Q3 was modified to Q3′, there were no significances in sensitivity and specificity of modified Calgary score compared to Calgary score. However, considering its better performance in clinical practice and understandability for children and their parents, modified Calgary score would be recommended for differential diagnosis of syncope and epilepsy in children.

In conclusion, The Calgary score and modified Calgary score have high sensitivity and specificity in distinguishing NMS and epilepsy, and could be used to initial differential diagnosis between syncope and epilepsy in children.

Acknowledgments Supported by grants from Project of Development and Reform Commission of Hunan Province, PR China (2015-83) and the Natural Science Foundation of Hunan Province, PR China (2016JJ2167).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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