

EDITORIAL

Foreword for inaugural issue of *Acta Epilepsy*

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As the editor-in-chief, it is a great honor for me to announce the birth of *Acta Epilepsy*, a new open access, peer-reviewed journal of the China Association Against Epilepsy (CAAE).

Acta Epilepsy is published by BioMed Central. All articles published in *Acta Epilepsy* will be listed in Biomed Central immediately upon publication, and freely and permanently accessible online.

The primary goal of *Acta Epilepsy* is to publish rapidly robust and high-quality results that provide insights into all aspects of epilepsy research, covering basic, translational and clinical research in epilepsy. Submissions of high-quality research on the mechanisms of epileptogenesis, broader comorbidities of epilepsy, new treatments and their measures are especially welcome. *Acta Epilepsy* also publishes communications and guidelines from the CAAE. This new journal is creating a unique forum for the reputable and speedy open-access publication of epilepsy research. It is committed to facilitating basic and clinical epilepsy research.

Many people would ask why we need a new journal. We have thought about it thoroughly during the planning and preparation of this journal. The following reasons have brought us to establish this new journal.

First, the population explosion is becoming a most serious problem in society, in addition to the resource shortage and environmental degradation. The World Health Organization (WHO) has reported that the global population will reach about 8 billion by the year 2025, a time when the average life expectancy will reach 73. In fact, we have already been facing an aging society with various public health problems, among which epilepsy is one of the most common risks for human health. The WHO has estimated that epilepsy affects more than 50 million people worldwide, so it is imperative to reduce the time and cost for diagnosis and treatment of epilepsy.

With this regard, the *Acta Epilepsy* can serve as a platform offering freely-accessible practical and cutting-edge research and guidelines.

Second, while experts are calling for individualized treatment of epilepsy in most developed countries, doctors in rural areas and less developed countries are still lacking the knowledge on basic principles of epilepsy treatment. The *Acta Epilepsy* is therefore motivated to disseminate the evidence-based knowledge on epilepsy diagnosis and treatment worldwide, especially among the Belt and Road countries. This would be an efficient educational approach to standardizing the treatment of epilepsy and finally reducing the epilepsy treatment gap.

Third, epilepsy research has entered an exciting phase as advances in molecular analysis on a faster and larger scale have supplemented *in vitro* and *in vivo* electrophysiological and phenotypic characterization. However, it is challenging to effectively translate basic research to clinical practice to benefit the patients. Effective translational research integrates the basic sciences and clinical medicine with the aim of optimizing preventive measures and patient care. Translational medicine, in short, is the process of translating biological discoveries into drugs and medical devices that can be used in the treatment of patients. Accordingly, the *Acta Epilepsy* aims to promote knowledge sharing by providing a platform where knowledge and experience of the latest research on the epidemiology, etiology, pathogenesis, diagnosis, management and prevention of epilepsy are shared among researchers and doctors.

Acta Epilepsy addresses the needs of both understanding the mechanisms of epilepsy, and clinical prevention, diagnosis and treatment of epilepsy. Join us in this new Journal! Publication is prompt and reader access is worldwide and free!

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GUIDELINE

Grading standards of epilepsy centers in China

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Introduction

An epilepsy center is a medical facility and a comprehensive service platform that adapts to the modern mode of epilepsy diagnosis and treatment. It could be a specialized hospital, an independent section of a hospital, a collaborative entity of related departments, or a primary epilepsy service unit.

An epilepsy center usually involves the following medical specialities: neurology, neurosurgery, pediatric neurology, pediatric neurosurgery, psychiatry (or psychology), and other auxiliary technical departments, such as neurophysiology, neuroimaging, neuropharmacology, and neuropathology, etc. In many countries, epilepsy centers are graded according to their scale, service scope and professional level.

To promote the standardized development of epilepsy centers in China, in reference to the experience of other countries and the practical situation in China, the China Association Against Epilepsy (CAAE) developed the Grading Standards of Epilepsy Centers as a trial version recommended for use in the assessment, management and operation of epilepsy centers in China.

In China, hospitals are graded in three tiers by the health authority, i.e., Third-Level (Tertiary) Referral Hospital (sub-graded in A,B,C), Second-Level (Secondary) Referral Hospital (sub-graded in A, B, C) and First-Level (Primary) Referral Hospital. Epilepsy centers are also classified into three levels, namely, Tertiary Comprehensive Epilepsy Center (TCEC), Secondary Epilepsy Center (SEC), and Primary Epilepsy Service Facility (PESF).

The grading standards of epilepsy centers are as follows.

Tertiary Comprehensive Epilepsy Center

A TCEC can be set up in a tertiary referral hospital, a well-equipped secondary referral hospital, and a specialized epilepsy hospital. The TCEC will be able to:

- Provide integrated and high-level care for patients with epilepsy.
- Have the ability to perform class 1–3 epilepsy surgeries according to the Standard Management and Technical Regulations for Epilepsy Surgery promulgated by CAAE.

Epilepsy diagnosis and treatment services can be provided by an independent TCEC department or by multiple departments with specific regulations to ensure close and regular cooperation among the relevant departments.

TCECs meet the standards for a tertiary level providing the following are met:

General conditions

- Have an independent Outpatient Department for epilepsy with at least three consulting rooms, a treatment room, and several emergency observation rooms.
- Electrophysiological examination rooms have sufficient space for an electroencephalogram (EEG) room, an evoked potential room, and an electromyography room.
- Have a separate epilepsy ward with at least 20 beds. At least five of the beds are equipped with video EEG (VEEG) monitoring instrument.

Personnel

Physicians:

Bed-to-physician ratio should be 3:1. At least three physicians have a professional title of Associate Chief Physician or above (referring to specialists of neurology, neurosurgery, and pediatrics with experience in epilepsy). Other physicians have a master's or doctoral degree in epileptology and/or have a certificate for more than one-year special training on epilepsy diagnosis & treatment by a domestic tertiary (A) hospital or an overseas qualified epilepsy center. The ability requirements of physicians who work in epilepsy centers are listed in Appendix 1.

Nurses:

Bed-to-nurse ratio should be 2:1. One nurse serves for one to two beds.

EEG technicians:

Electrophysiological technicians are staffed according to the number of VEEG equipment. At least one technician handles two to three monitoring beds.

Facilities

Conventional facilities for diagnosis and treatment, emergency equipment, and information system are in place according to the provisions of hospitals graded in the three-tier grading system.

Specialized equipment for epilepsy includes:

- a. Electrophysiological examination equipment, inclu-

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ding conventional EEG, multichannel VEEG (more than 128 channels), evoked potential instrument, electrical stimulator, transcranial magnetic stimulator, and magnetoencephalography (MEG) apparatus if conditions permit.

b. Neuroimaging apparatus, including computed tomography (CT), magnetic resonance imaging (MRI, above 1.5 T), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) if conditions permit.

c. Equipment for measuring blood concentrations of antiepileptic drugs (AEDs).

d. Essential equipment for (functional) neurosurgery.

e. Essential equipment for the neurointensive care unit (NICU).

Services

Service contents and capacity requirements of specialized staff in TCEC are listed in Appendix 1. A qualified TCEC is not a simple combination of personnel and facilities. Reliable data in the last two years of the center are used for assessment and grading, and the corresponding medical records are provided for future reference.

Rules and regulations

The administrative rules, regulations, and official duties of staff should be developed and documented according to practical situation. Those documents also include diagnosis and treatment guidelines with nationwide approval, management standards, and operation procedures for clinical, nursing, and surgical technology, in the form of manuals.

Secondary Epilepsy Center

A SEC can be set up in a tertiary referral hospital, a secondary referral hospital, and a specialized epilepsy hospital. The SEC will be able to:

- Provide proper neurological and/or pediatric neurological services for epilepsy diagnosis and treatment.
- Perform Class 1 and Class 2 epilepsy surgeries if the technical level and equipment facilities meet the surgical treatment requirements according to the Standard Management and Technical Regulations for Epilepsy Surgery promulgated by the CAAE.

Based on the actual situation of the hospital, epilepsy services can be provided by an independent SEC department or by multiple departments with specific regulations to ensure close and regular cooperation among the relevant departments.

SECs meet the standards for a secondary level providing the following are met:

General conditions

- Have an independent Outpatient Department for epilepsy with at least one consulting room.

- Electrophysiological examination rooms have sufficient space for an EEG room and other necessary examination rooms.

- Have a separate epilepsy ward with at least 10 beds. At least two beds are equipped with VEEG monitoring instrument.

Personnel

Physicians:

Bed-to-physician ratio is 3:1. At least one physician has a professional title of Associate Chief Physician or above (referring to specialists of neurology, neurosurgery, and pediatrics with experience in epilepsy). Other physicians have a master's or doctoral degree in epileptology and/or have a certificate for more than one-year special training on epilepsy diagnosis & treatment by a domestic tertiary(A) hospital or an overseas qualified epilepsy center. The ability requirements of physicians who work in SEC are listed in Appendix 2.

Nurses:

Bed-to-nurse ratio is 2:1. One nurse serves for one to two beds.

EEG technicians:

Electrophysiological technicians are staffed according to the number of VEEG equipment. At least one technician handles two to three monitoring beds.

Facilities

Conventional facilities for diagnosis and treatment, emergency equipment, and information facilities are in place according to the provisions of the hospital graded in the three-tier grading system.

Specialized equipment for epilepsy includes:

a. Electrophysiological examination equipment, including conventional EEG instrument and multichannel VEEG (more than 64 channels).

b. Neuroimaging apparatus, including CT and MRI (above 1.5 T).

c. Equipment for measuring AED blood concentrations.

d. Essential equipment for (functional) neurosurgery (optional).

e. Essential equipment for NICU.

Services

Service contents and capacity requirements of specialized staff in SEC are listed in Appendix 2. A qualified SEC is not a simple combination of personnel and facilities. Reliable data in the last two years of the center are used for assessment and grading, and the corresponding medical records are provided for future reference.

Rules and regulations

The administrative rules, regulations, and official duties of staff should be developed and documented according to practical situation. Those documents also include diagnosis and treatment guidelines with nation-

wide approval, management standards, and operation procedures for clinical, nursing, and surgical technology, in the form of manuals.

Primary Epilepsy Service Facility

A PESF is an epilepsy clinic (outpatient department, OPD) set up in a primary referral hospital or a higher graded hospital. The PESF will be able to:

Provide fundamental medical services, including diagnosis, consultation, and treatment, for patients with epilepsy.

Set up of PESF can rely on the department of internal medicine, neurology, or pediatrics. It can also be an independent clinical entity. The PESF should have a better epilepsy diagnosis and treatment capability than the OPDs of general internal medicine, neurology and pediatrics. Epilepsy surgery is not permitted in PESF.

PESFs meet the standards for a primary level providing the following are met:

Clinic layout

The layout and working process of PESF should meet the practical needs. Corresponding working areas are required and should include the waiting zone, reception zone, neurophysiological examination zone, storage room, pollutant disposal area, and other basic functional areas. The waiting area, storage room, and pollutant disposal area can be shared with other outpatient departments.

Personnel

Physicians:

Have at least two licensed physicians of neurology, internal medicine, or pediatrics with clinical experience in epileptology. At least one of the physicians is an attending doctor or at a higher professional rank, and has a certificate for special training on epilepsy diagnosis & treatment for over half a year by a domestic tertiary(A) hospital or an overseas qualified epilepsy center.

The physicians will be able to:

- a. Classify epileptic seizure types accurately.
- b. Read and assess EEG, especially the epileptic EEG.
- c. Be familiar with common epilepsy syndromes.
- d. Select AEDs properly, and avoid and deal with adverse events of AEDs.
- e. Make differential diagnosis on childhood paroxysmal disorders.

Nurses:

Have at least two registered nurses with appropriate medical knowledge and nursing experience in epilepsy, with a junior or higher professional title.

EEG technicians:

Have at least one electrophysiological physician or technician who has mastered the skills of routine EEG examination and analysis, with an ability to write an EEG report after receiving formal training in EEG (defined

as training in a domestic tertiary(A) hospital for more than three months). EEG technicians are proficient in operating EEG instruments and capable of storing and keeping confidential daily EEG data.

The number of licensed doctors, registered nurses, and technicians can be increased appropriately in accordance with the business conditions.

Physicians in other related specialities, such as neuropsychology, neuroimaging, and neuropharmacology, can be recruited in an appropriate proportion if conditions permit.

Housings

- Have at least one consulting room.
- Have at least one electrophysiological examination room.

Facilities

- Have regular equipment for diagnosis, treatment, and testing corresponding to the hospital grade and function.
- Emergency facilities are in place, including a cardiac defibrillator, simple breathing apparatus, and resuscitation cart, which can be shared with other outpatient departments.
- Information facilities can be shared with other outpatient departments.
- Specialized equipment for epilepsy includes:
 - a. A qualified EEG or VEEG monitor.
 - b. CT and MRI (above 1.5 T) are optional.

Services

- Diagnosis and differential diagnosis of epilepsy.
- Routine EEG examination.
- Neuroimaging test.
- AED treatment of epilepsy.

Rules and regulations

The administrative rules, regulations, official duties of staff should be developed and documented according to practical situation. A quality management system should be established and the related technical specifications and operation procedures be formulated. The rules involve the contents of medical quality control, drug management, emergency plan, doctor-patient communication, consultation, confidential psychological service, hospital infection control, disinfection and isolation, equipment management, patient registration and medical record writing and management, and medical personnel occupation safety.

Appendix 1

Capacity and service content requirements of specialized staff in Tertiary Comprehensive Epilepsy Center (TCEC)

I. Capacity requirements of epileptologists and staff

The head of the TCEC has a senior professional title and

an accumulation of relevant achievements in epilepsy. The chief professional(s) should possess long-term experience of engagement in clinical epileptology and proof materials of epilepsy-related research papers and research subjects. Furthermore, the qualification level of the personnel in the TCEC should be continuously improved.

1. Roles of neurologists

- (1) Classify epileptic seizure types accurately.
- (2) Master the characteristics of clinical EEG, especially epileptic EEG.
- (3) Master common epileptic syndromes.
- (4) Choose AEDs correctly and meanwhile avoid and deal with adverse events of AEDs.
- (5) Make diagnosis and differential diagnosis of paroxysmal diseases.
- (6) Be familiar with indications of epilepsy surgery and the localization principles for epileptic foci.
- (7) Provide consultations for patients with epilepsy in the aspects of learning, working, marriage, pregnancy, and motor vehicle driving.
- (8) Understand epilepsy-related systemic diseases.

2. Roles of pediatric neurologists

- (1) Master seizure classification and epileptic syndromes of childhood epilepsy and characteristics of child EEG.
- (2) Choose AEDs correctly and meanwhile avoid and deal with adverse events of AEDs for children with epilepsy.
- (3) Implement the ketogenic diet therapy properly.
- (4) Make differential diagnosis of paroxysmal diseases in children.

3. Roles of neurosurgeons

- (1) Accomplish class 1–3 epilepsy surgeries independently according to the Standard Management and Technical Regulations for Epilepsy Surgery promulgated by the CAAE. The surgical operations include: resection of epilepsy-related lesion, temporal lobe resection of non-lesional epilepsy, surgery for MR-negative extra-temporal lobe epilepsy, corpus callosotomy, hemispherectomy, vagus nerve stimulator implantation, and deep brain stimulator implantation.
- (2) Cope with all sorts of perioperative complications.

4. Other relevant specialists

- (1) Psychiatrists and psychologists are responsible for psychological consulting and mental disorder treatment of patients with epilepsy. They have mastered the application and interpretation of evaluation scales of cognitive function, mental function, and life quality, such as the life quality, IQ, depression, and anxiety scales.
- (2) Electrophysiologists with working experience in routine EEG for at least five years should have received

formal training, passed the national EEG level tests (intermediate level or higher), and hold corresponding certificate documents. They are capable of properly conducting long-term or VEEG monitoring and explaining the results. They also have the capability of analyzing and interpreting the MEG examination results. Electrophysiologists are responsible for the interpretation of intracranial EEG monitoring results and participate in localizing epileptogenesis.

- (3) Neuroradiologists have the ability to interpret and issue reports for the imaging results of CT, MRI, functional MRI (fMRI), SPECT, and PET.

5. Other specialists and technicians

(1) Electrophysiological technicians

Qualification requirements:

Formal training experience (more than half a year in a domestic tertiary(A) referral hospital or an overseas qualified epilepsy center) in electrophysiology with corresponding training qualifications or other certificate documents.

Capacity requirements:

- a. Conduct routine EEG examination, operation, and analysis, and perform long-term or VEEG monitoring.
- b. Perform long-term intracranial EEG monitoring.
- c. Inspect evoked potentials in patients with epilepsy, intracranial evoked potentials to localize the cerebral function zone, transcranial magnetic stimulation, and cortical electrical stimulation.
- d. Restore EEG instrument from common failures.
- e. Be skilled in applying and interpreting the results of cortical electrical stimulation to localize cerebral function zone and deal with complications that may occur at any time.
- f. Participate in localizing epileptogenesis.

(2) Pharmacologists: Test serum concentrations of AEDs, explain the results, assist in rational drug use, and provide patient consulting.

(3) Rehabilitation physiatrists: Responsible for mental and psychological rehabilitation, and cognitive ability training. Supervise the lifestyle, learning, working, marriage, and fertility of patients with epilepsy.

(4) Neuropathologists and molecular biologists: Provide pathological diagnosis based on a biopsy and molecular biological diagnosis for special patients with epilepsy (optional).

(5) Basic-research personnel: Conduct provincial-level or higher scientific research projects (optional).

II. Services

1. Diagnosis and differential diagnosis of epilepsy

- (1) Routine, long-term, VEEG monitoring (more than 2000 person-times per year for EEG monitoring; more than 500 person-times per year for long-term EEG monitoring). Intracranial EEG monitoring (more than

20 person-times per year). Intracranial evoked potential, cortical electrical stimulation, and transcranial magnetic stimulation treatment.

(2) Neuroradiological examinations (CT, MRI, SPECT, PET, and fMRI).

(3) Monitoring of AED serum concentrations.

(4) Outpatient epilepsy evaluation (more than 4000 person-times per year).

(5) Inpatient epilepsy evaluation (more than 200 person-times per year).

(6) Epilepsy surgery (more than 80 person-times per year).

2. AED treatment of epilepsy

3. Surgical treatment of epilepsy: Perform class 1–3 epilepsy surgeries according to the Standard Management and Technical Regulations for Epilepsy Surgery promulgated by the CAAE.

4. Ketogenic diet treatment.

5. Psychological assessment, consultation with patients with epilepsy, consultation on or treatment of psychiatric comorbidities in epilepsy, mental rehabilitation, and cognitive training.

6. Pathological diagnosis based on biopsy and molecular biological diagnosis.

7. Be authorized to award master's and doctoral degree and offer corresponding teaching and training programmes.

Appendix 2

Capacity and service content requirements of specialized personnel in Secondary Epilepsy Center (SEC)

I. Capacity requirements of epileptologists and staff

The head of the SEC has a senior professional title and an accumulation of relevant achievements in epilepsy. The chief professional(s) should possess long-term experience of engagement in clinical epileptology and proof materials of epilepsy-related research papers and research subjects. Furthermore, the qualification level of the personnel in the SEC should be continuously improved.

1. Roles of neurologists

(1) Classify epileptic seizure types accurately.

(2) Master the characteristics of clinical EEG, especially epileptic EEG.

(3) Master common epileptic syndromes.

(4) Choose AEDs correctly and meanwhile avoid and deal with adverse events of AEDs.

(5) Make diagnosis and differential diagnosis of paroxysmal diseases.

(6) Be familiar with the indications of epilepsy surgery and the localization principles of epileptic foci.

(7) Provide consultation services for patients with epilepsy in the aspects of studying, working, marriage, pregnancy, and motor vehicle driving.

(8) Understand epilepsy-related systemic diseases.

(9) In SEC without pediatricians, neurologists should master the seizure classification and epileptic syndromes of childhood epilepsy and characteristics of child EEG. They will be able to choose AEDs correctly, avoid and deal with adverse events of AEDs in children with epilepsy, implement the ketogenic diet therapy properly, and make differential diagnosis of paroxysmal diseases in children.

2. Roles of pediatricians (pediatric neurologists)

(1) Master the seizure classification and epileptic syndromes of childhood epilepsy and characteristics of child EEG.

(2) Choose AEDs correctly and meanwhile avoid and deal with adverse events of AEDs in children with epilepsy.

(3) Make differential diagnosis of paroxysmal diseases in children.

3. Roles of neurosurgeons

Neurosurgeons (optional) will be able to perform independently resection of epilepsy-related lesions and temporal lobe resection of nonlesional epilepsy. They should be able to cope with all sorts of perioperative complications and have mastered the principle and approach of localization of epileptogenesis.

4. Other relevant specialists

Other relevant specialists include: in-service personnel, specially invited part-time personnel, and collaborative doctors.

(1) Electrophysiological physicians: one or two physicians who have at least five years of working experience in routine EEG, have received formal training and passed the national EEG level tests (junior level or above) with the corresponding qualification documents, and have the ability to conduct long-term or VEEG monitoring properly and explain the results.

(2) Electrophysiological technicians should have formal training experience (more than three months in a domestic tertiary hospital) in electrophysiology and have mastered the skills of routine EEG examination, operation, and analysis. They will be able to perform long-term or VEEG monitoring, conduct intracranial EEG monitoring (according to the Technical Regulations for Epilepsy Surgery), interpret the results, and participate in localizing epileptogenesis.

(3) Pharmacologists monitor the serum concentrations of AEDs, explain the results, assist in rational drug use, and provide patient consulting.

(4) Neuroradiologists (optional) will be able to interpret and issue reports for the imaging results of CT and MRI.

II. Services

1. Diagnosis and differential diagnosis of epilepsy

(1) Routine, long-term, video-EEG monitoring (more

than 1000 person-times per year for EEG monitoring; more than 100 person-times per year for long-term EEG monitoring).

- (2) Neuroradiological examinations (CT, MRI).
- (3) Monitoring of AED serum concentrations.
- (4) Outpatient epilepsy evaluation (more than 2000 person-times per year).
- (5) Inpatient epilepsy evaluation (more than 100 person-times per year).

(6) Surgery (optional, more than 30 person-times per year).

- 2. AED treatment of epilepsy.
- 3. Surgical treatment of epilepsy: perform class 1 and class 2 epilepsy surgeries according to the Standard Management and Technical Regulations for Epilepsy Surgery promulgated by the CAAE if conditions permit (optional).
- 4. Ketogenic diet treatment (optional).

REVIEW

Toward social neuropsychology of epilepsy: a review on social cognition in epilepsy

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Abstract

Social cognition is the ability to identify, perceive, and interpret social information. It is an important skill for successful interpersonal functioning. Although social cognition is known to be impaired in several neurological and psychiatric conditions, its functional integrity in epilepsy is less well established. The aim of this review was to characterize the impairment of social cognition in domains of emotion recognition (ER) and theory of mind (ToM) in patients with epilepsy. An electronic search was conducted to identify clinical studies investigating social cognition in epilepsy populations, yielding 42 studies to be included in this review. Meta-analysis of the literature demonstrated that (1) ER and ToM are impaired in both patients with temporal lobe epilepsy and patients with epilepsy not originating within the temporal lobe; (2) in patients with temporal lobe epilepsy and extratemporal lobe epilepsy, there are no significant differences in the median effect size between ER and ToM. The social interaction difficulties observed in some patients with epilepsy may, at least in part, be due to an impaired ability to correctly process and interpret emotional expression and mental states of others. Establishing a clear understanding of the mechanisms underlying impaired social cognition in patients with epilepsy will help improve their clinical management and characterize the phenotypes of epilepsy, and at a broader level, reduce the disease burden in society.

Keywords: Social cognition, Epilepsy, Temporal lobe epilepsy, Emotion recognition, Theory of mind.

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Introduction

Epidemiological studies have revealed that the major determinants of quality of life (QoL), including employment, social interactions, family relationships, and experiential activities, are at a considerable risk of impairment in patients with epilepsy [1]. While a significant proportion of epilepsy patients have impaired social cognitive skills and suffer from communication problems and interpersonal difficulties [2], empirical evidence on social abilities in this population is limited compared to that on cognitive functions like memory, language and executive functions.

Correct interpretation of social signals and behaviour is a prerequisite for successful interpersonal interaction [2-4]. Difficulties in social competence in patients with epilepsy may arise from a number of interrelated factors. From the psychological perspective, the stigma, role and experience restrictions, parental overprotectiveness and fear of seizures, can all impact on social engagement and the ability to learn and practice social knowledge and rules [5]. From the traditional neuropsychological

perspective of the 20th century, social difficulties may result from cognitive impairment, such as impaired speed and capacity of information processing, attention deficits and memory impairments, which are common in this population [5]. Particularly, such deficits may cause difficulties in remembering details of previous interactions, names and faces, or sustaining attention in, e.g., long conversations. Furthermore, deficits in cognitive functioning can impact on nonverbal and verbal communications in social interactions. The psychiatric perspective concerns the higher prevalence of affective disorders in patients with epilepsy than in the general population [6] and the higher rate of fatigue and ADHD [7]. These alterations may have an impact on social engagement and functioning and result in an impaired coping ability and a poor perceived QoL [1]. A complementary perspective comes from neuroscience and the relatively new area of social cognition. In this discipline, social cognition is defined as a form of information processing that contributes to the correct perception of dispositions and intentions of others [8] and encompasses a wide range of sub-processes, including the theory of mind (ToM), empathy, emotion regulation, emotion recognition (ER), and prosody perception. The effective social cognition relies on the exchange of signals, which can be processed on an automatic and

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controlled level and influenced by motivational aspects [9]. These processes act rapidly in different sensory modalities in parallel and provide social information from others such as speech, facial expression, prosody, lexical information, gaze direction, gestures and posture, and draw on implicit as well as explicit memories [9,10].

Recent imaging and lesion studies have revealed that the cerebral networks employed in social cognition are those frequently affected in patients with temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) [3,11-16], namely, the medial frontal cortex including the anterior cingulate cortex, the superior temporal sulcus at the temporal parietal junction, the temporal lobes and the amygdala [3].

Although there is a paucity of experimental research on social cognition in epilepsy, preliminary evidence has suggested ER and ToM difficulties in patients with TLE [12-14,17-21]. A focus on these particular sub-processes, however, may have occurred due to longstanding research traditions and well-established test materials [3].

Facial ER is a commonly used target in studies on social cognition in epilepsy. In a recent meta-analysis, Bora & Meletti [22] analysed facial ER in adult TLE patients before or after surgical intervention. They found that in both pre- and post-surgery patients, the recognition of facial expressions was diminished for all six basic emotions (anger, disgust, fear, happiness, sadness, and surprise). The effect was most significant for the recognition of fear, whereas the effects for happiness and surprise were rather small. In cross-sectional studies, no significant difference was found in facial ER performance before and after resection of the mesial temporal lobe. With regard to laterality, poorer facial ER abilities were found in the right-sided TLE compared to the left TLE for the recognition of fear, disgust, and sadness, whereas no difference was found for anger, surprise and happiness [22].

ToM is the ability to infer mental states of others and to predict their behaviour based on their intentions, beliefs and emotions. This construct is considered to be most closely related to real-life social functioning [23], self-appraisal, coping and overall perception of QoL [13], and is therefore of clinical importance. In neuropsychological tests of ToM, patients are usually presented with situations that closely resemble daily social interactions. Impaired ToM functions have been reported in TLE patients, with effect sizes occasionally exceeding that for facial ER [22]. Hennion et al. [24] have reported that the TLE patients have difficulties in deducing beliefs and emotions in stories in which protagonists unintentionally commit social blunders (faux-pas) or understand sarcastic comments. Giovagnoli et al. [13] have found poor ToM abilities in TLE patients and FLE patients compared to healthy controls, but the former two groups did not differ from each other in the abilities to detect and understand faux-pas. Moreover, patients

with better performance in this task use more efficient coping strategies in response to stressful events and perceive a higher QoL. The importance of ToM in daily life was further demonstrated in a study by Wang et al. [25], which examined ToM in a large sample of therapy-refractory TLE patients. The results showed that the TLE patients performed worse in understanding false belief, implied meaning, faux-pas and cartoon ToM stories. ToM deficits in the faux-pas test also predict poor social functioning such as social engagement, leisure activities and instrumental living skills in patients. Impairments in ToM, together with the severity of psychiatric symptoms, would further predict poor interpersonal relationship, difficulties in communication and poor employment status [25].

In this review, we set out to (1) explore the social functioning in patients with extratemporal lobe epilepsy, and (2) compare the effect sizes of the most frequently used tests of ER and ToM, by searching for literature on social cognition in epilepsy.

Methods

Literature search strategy

Electronic searches were conducted on Medline, Embase, PsycINFO and PsycARTICLES to identify empirical research on the behavioral relationship between ER and ToM in patients with epilepsy. No date limits were placed on any of the database searches. The following search strings were used:

For ER: (((face OR facial OR prosody OR prosodic OR nonverbal) AND (affect* OR emotion* OR expression*) AND (perce* OR identif* OR recogni* OR process*)) AND (epilepsy OR epilep* OR seizure* OR convulsion));

For ToM: ((tom OR ttom OR (theory AND mind) OR mentalizing OR mentalising OR empath* OR mindreading OR (mind AND reading) OR (social AND inference) OR (pragmatic AND ability) OR pragmati* OR (social AND predictive AND coding) OR (interpersonal AND predictive AND coding) OR (social AND perception)) AND (epilepsy OR epilep* OR seizure* OR convulsion*));

For social cognition: ((social AND cognition) AND (epilepsy OR epilep* OR seizure* OR convulsion*)).

Relevant reviews were consulted to refine the literature search by adopting (slightly adjusting) their search strings to detect subsequent articles and/or sourcing their reference lists [22,26-28].

The search was finished on January 14, 2018.

Study selection

The titles and abstracts of research papers were screened to exclude irrelevant articles. The full-texts were downloaded and the methods inspected in detail to determine the eligibility. Studies included in the analysis were required to meet the following criteria: (1) diagnosis

of an epileptic disorder was formerly made according to the ILAE criteria [29]; (2) patients were aged 18 or above; (3) behavioral data relating to a social cognitive task in one or more of the following domains were reported: facial affect recognition, ToM, prosody, or body language interpretation; (4) a control group with no neurological or psychiatric disorders was included; and (5) at least ten participants were employed in both control and epilepsy groups. Functional MRI studies with no reported behavioral results were excluded. Once selected, their reference lists were scanned for further relevant articles to be included by the initial database searches. If sufficient data were available, the pooled effect size was calculated and information on sample characteristics, paradigms and P values were extracted from each study. If the data were insufficient for effect size calculation, the effect sizes were retrieved from published meta-analyses [22,26,28].

Analysis

The effect size was calculated for ER and ToM tests separately. If more than one effect size was extracted per study and function, the median effect size was retrieved for further statistical analysis. The collected effect sizes were then descriptively reviewed as well as inferentially tested for deviations from normal distribution and for homogeneity of variance between ToM and ER. Since tests for independent measures are more robust regarding type-one errors, a two-tailed Mann-Whitney U -test was applied to compare the median effect sizes of ER and ToM, treating all data as independent measures, although some studies contained both effect sizes from ER and ToM from the same samples.

Results

Over the past decade, a considerable number of studies have been published to characterize the relationship between social cognition and epilepsy. Following a thorough search in the databases, we obtained 42 studies for further analysis, of which 39 studies used clinical samples of TLE patients (Table 1) [12-14,17,18,21,24,25,30-60] and 14 studies used clinical samples of other types of epilepsy (Table 2) [12-14,17,20,34,38,39,41,47,53,54,61,62].

Five out of the 39 studies focusing on TLE patients contained effect sizes for both ER and ToM. The effect sizes concerning random and goal-directed animations in the moving triangles task as well as the faux-pas recognition and faux-pas rejection measures, were not used to calculate the median effect sizes as they do not represent validated measures of ToM.

Median effect sizes in TLE

The overall medians of the median effect sizes for ER and ToM in patients with TLE were 0.80 (SEM, 0.08) and 0.98 (SEM, 0.08), respectively. The median effect sizes were approximately normally distributed (Fig. 1).

ER versus ToM in TLE

The median effect size was numerically higher for ToM (mean, 0.90; SD, 0.32) than for ER (mean, 0.81, SD, 0.40). With the exclusion of dependent measures (studies measuring both ER and ToM, $n = 5$), Levene's F -test did not confirm the assumption of homogeneity of variances [$F(30) = 9.08$, $P = 0.005$], therefore a non-parametric test was applied. The two-tailed Mann-Whitney U test revealed no statistically significant difference between the median effect sizes of ER (mean rank = 20.23, $n = 26$) and ToM (mean rank = 23.56, $n = 16$) with $U = 175.00$ ($z = -0.855$, $P = 0.393$).

Median effect sizes in extratemporal lobe epilepsy

The overall medians of the median effect sizes for ER and ToM in patients with extratemporal lobe epilepsy were 1.10 (SEM, 0.17) and 0.85 (SEM, 0.13), respectively.

ER and ToM: TLE versus extratemporal lobe epilepsy

The median effect size for ER was numerically higher in patients with extratemporal lobe epilepsy (mean, 1.06, SD, 0.46) than in patients with TLE, but those for ToM were numerically comparable between extratemporal lobe epilepsy (mean, 0.83, SD, 0.40) and TLE. The two-tailed Mann-Whitney U -test revealed no statistically significant differences in the median effect sizes of social cognition between TLE (ER, mean rank = 15.73, $n = 26$; ToM, mean rank = 14.31, $n = 16$) and extra-temporal lobe epilepsy groups (ER, mean rank = 21.71, $n = 7$; ToM, mean rank = 12.20, $n = 10$) with $U = 58.00$ ($z = -1.453$, $P = 0.146$) for ER and $U = 67.00$ ($z = -0.685$, $P = 0.493$) for ToM.

Discussion

In this review, we demonstrate that (1) ER and ToM are impaired in both TLE and epilepsy not originating within the temporal lobe, and (2) in patients with TLE and extratemporal lobe epilepsy, there are no significant differences in the median effect size between ER and ToM. These results are not only consistent with previous reports of social cognition impairment in TLE patients, but further suggest that this impairment is not restricted in TLE.

Hermann et al. [63] have shown that patients with idiopathic and focal epilepsies have very similar cognitive profiles on average. However, few studies have addressed the general cognitive impairment in the context of social cognition [64]. Several cognitive domains such as attention, memory, and executive functioning have been found to be impaired in epilepsy. These cognitive deficits may play a role in the associated impairments of social cognition, which is an important area for future research.

In this review, we observed an overall large median effect size between 0.8 and 1.1 for both ER and ToM. We also found comparably large effect sizes for tests of social cognition in individual studies that also justify

Table 1 Studies comparing temporal lobe epilepsy patients versus control groups.

References	Sample characteristics N (mean age ± SD; M:F)	Social cognition tasks	Results
Åhs et al. (2014)[30]	IMTLE, 9 (44.8 ± 12.5; 2:7) rMTLE, 8 (47.7 ± 9.4; 4:4) HC, 19 (46.1 ± 14; 9:10)	ER: PFA	MTLE patients performed significantly worse than HC ($P = 0.04$, $d = 0.724$).
Amlerova et al. (2014)[31]	lpreTLE, 24 (33 ± 10; 12:12) lpostTLE, 13 (33 ± 7; 6:7) rpreTLE, 22 (41 ± 11; 14:8) rpostTLE, 15 (35 ± 8; 13:2) HC, 20 (33 ± 13; 6:14)	ER: PFA ToM: FPT	ER: Patients performed significantly worse than HC ($P = 0.0001$; pre-surgical, $d_{\Delta} = 0.580$; post-surgical, $d_{\Delta} = 0.830$). ToM: Patients performed significantly more poorly than HC ($P = 0.007$; pre-surgical, $d_{\Delta} = 0.450$; post-surgical, $d_{\Delta} = 0.710$).
Anderson et al. (2000)[32]	LTL, 11 (32 ± 8; 3:8) RTL, 12 (38 ± 8; 4:8) HC, 23 (38 ± 8; 7:16)	ER: PFA	RTL but not LTL performed significantly more poorly than HC ($P < 0.05$; $d_{\Delta} = 0.810$).
Benuzzi et al. (2004)[18]	IMTLE, 5 (30.4 ± 7.2; 3:2) rMTLE, 8 (35.7 ± 7.2; 4:4) HC, 14 (21-27***; 7:7)	ER: PFA (FAN, FAS, FAM)	No overall comparisons between patients and HC (HC vs MTLE) were reported. Performance of rMTLE patients was significantly impaired compared to HC in the FAN ($P = 0.006$, $d = 1.438$). No further significant group differences have been found (FAS, $P = 0.218$; FAM, $P = 0.328$).
Bonora et al. (2011)[33]	MTLE, 41 (48.05 ± 11.50; 17:24) HC, 50 (34.9 ± 9.18; 20/30)	ER: PFA, PAN	MTLE patients performed worse than HC in the PFA ($P = 0.007$, $d = 1.372$) and the PAN ($p = .002$, $d = 1.334$) tasks.
Boucher et al. (2015)[34]	ATL, 15 (38.7 ± 10.3; 7:8) IR, 15 (37.6 ± 8.6; 6:9) HC, 20 (36.1 ± 10.2; 10:10)	ER: DEF ToM: RMET	No significant differences were found between ATL and HC in the DEF task ($d = 0.820$) and the RMET ($d = 0.553$).
Brierley et al. (2004)[35]	ATL, 28 (37.4 ± n.a.; 12:16) HC, 32 (n.a.)	ER: PFA, PAN	ATL patients performed significantly worse than HC ($P < 0.05$) with regard to fear ($d = 0.523$) disgust ($d = 0.505$) and anger ($d = 1.095$), but not sadness ($d = 0.417$) and happiness ($d = 0.382$) in the PFA, and with regards to happiness ($d = 1.028$), but not fear ($d = 0.755$), disgust ($d = 0.159$), anger ($d = 0.640$) and sadness ($d = -0.174$) in the PAN.
Broicher et al. (2012)[17]	MTLE, 28 (34.43 ± 13.25; 12:16) -MTLE, 14 (33.36 ± 11.74; 10:4) HC, 29 (33.69 ± 10.94; 13:16)	ER: CATS ToM: MT, RMET, FPT	ER: MTLE patients performed significantly worse compared to HC in all CATS quotient scales (ARQ, $P = .006$, $d = 0.933$; PRQ, $P < 0.001$, $d = 1.290$; ERQ, $P < 0.001$, $d = 1.294$) and two of five composite scales (CFS, $P = 0.01$, $d = 0.801$; PS, $P = .003$, $d = 1.016$; SFS, $P > 0.05$, $d = 0.621$; LS, $P > 0.05$, $d = 0.341$; CMS, $P > 0.05$, $d = 0.456$). ToM: MTLE patients attributed significantly less intentionality in MT task in ToM animations ($P = .003$, $d = 0.752$) and goal-directed animations ($P = 0.003$, $d = 0.990$) than HC, but not in random animations ($d = -0.074$). MTLE patients gave significantly less appropriate explanations than HC in goal-directed animations ($P = 0.04$, $d = 0.790$), but not in ToM ($d = 0.350$) or random animations ($d = 0.459$). MTLE patients performed significantly worse compared to HC in the FPT ($P = 0.02$, $d = 0.958$), but not in the RMET ($d = 0.379$).
Carvajal et al. (2009)[36]	LTL, 20 (35.4 ± 9.6; 10:10) RTL, 23 (35 ± 12.1; 10:13) HC, 43 (53.7 ± 14.9; 20:23)	ER: FAB (FAD, FAN, FAS)	In the FAD task, LTL performed significantly worse than HC ($P < 0.05$, $d = 0.809$), with no significant difference between HC and RTL ($d = 0.457$). LTL performed significantly worse than HC in the FAN ($d = 1.141$), with no significant difference between HC and RTL ($d = 0.233$). No significant differences were found between patients and HC in the FAS (LTL, $d = 0.414$; RTL, $d = 0.341$).
Cohn et al. (2015)[37]	Left-TLE, 24 (38.9 ± 11.9; 13:11) Right-TLE, 26 (38 ± 13.7; 14:12) IATL, 18 (42.5 ± 12.9; 11:7) rATL, 19 (38.9 ± 9.6; 7:12) HC, 15 (38.3 ± 8.6; 5:10)	ER: TASIT ToM: TASIT	ER: All patient groups performed significantly more poorly than HC (IATL, $P < 0.001$; rATL, $P = 0.03$; left-TLE, $P = .002$; right-TLE, $P < 0.001$). ToM: There were no group differences between patients and HC in the comprehension of sincere exchanges ($P = 0.76$). The performance of every patient group was weaker than that of the HC (IATL, $P < 0.001$; rATL, $P < 0.001$; left-TLE, $P = 0.003$; right-TLE, $P < 0.001$) in the comprehension of deceitful exchanges. All patient groups performed worse than HC in the comprehension of sarcastic exchanges (IATL, $P < 0.001$; rATL, $P = 0.003$; left-TLE, $P = 0.009$; right-TLE, $P < 0.001$). Effect sizes: pre-surgical, $d_{\Delta} = 1.130$; post-surgical, $d_{\Delta} = 1.200$.
Fowler et al. (2006)[21]	rAAD, 13 (33*, 31-42**; n.a.) lAAD, 15 (41*, 31-46**; n.a.) HC, 18 (n.a.)	ER: PFA, NVS, PAN	No significant differences between groups were found (PFA, $P > 0.10$; PAN, $P > 0.10$; NVS, $P > 0.10$).
Giovagnoli et al. (2009)[38]	ULD, 21 (39.29 ± 15.69; 8:13) TLE, 21 (39.67 ± 14.41, 11:10) HC, 21 (41.81 ± 16.7; 8:13)	ToM: FPT	No significant differences between TLE patients and HC were reported (FP recognition, $d = 0.639$; FP rejection, $d = -0.758$).
Giovagnoli et al. (2011)[39]	Left-TLE, 62 (35.96 ± 11.64; 24:38)	ToM: FPT	Left-TLE patients had significantly lower scores than HC in the

Table 1 continued

References	Sample characteristics N (mean age ± SD; M:F)	Social cognition tasks	Results
	Right-TLE, 47 (38.33 ± 10.64; 20:27) FLE, 29 (35.77 ± 12.53; 11:18) HC, 69 (52.03 ± 17.04; 29:40)		FP recognition ($P = 0.004$, $d = 0.725$) and the comprehension responses (Q1, $P = 0.002$, $d = 0.764$; Q2, $P < 0.001$, $d = 0.943$; Q3, $P < 0.001$, $d = 0.892$; Q4, $P < 0.001$, $d = 0.834$). Right TLE patients performed significantly worse than HC in the second (Q2, $P = .001$, $d = 1.030$), third (Q3, $P < 0.001$, $d = 0.918$) and fourth (Q4, $P = 0.001$, $d = 0.817$) comprehension question, but not in the first one (Q1, $d = 0.544$) or the FP recognition score ($d = 0.412$). Effect sizes for TLE (combined) vs HC: FP recognition, $d = 0.517$; FP rejection, $d = 0.234$; Q1, $d = 0.577$; Q2, $d = 0.711$; Q3, $d = 0.833$; Q4, $d = 0.730$.
Giovagnoli et al. (2013)[13]	TLE, 54 (37.80 ± 9.20; 26:28) FLE, 12 (37.17 ± 13.41; 6:6) HC, 42 (40-64*** ± 12.61; 18:24)	ToM: FPT	Grouped together, patients performed significantly worse than HC ($P < 0.001$). Effect sizes of group differences between TLE patients and HC: FP recognition, $d = 0.448$; FP rejection, $d = 0.468$; Q1, $d = 0.565$; Q2, $d = 0.820$; Q3, $d = 1.137$; Q4, $d = 1.080$.
Giovagnoli et al. (2016)[40]	eTLE, 31 (31.87 ± 9.4; 19:12) ITLE, 54 (34.91 ± 10.23; 33:21) HC, 40 (36.05 ± 9.64; 29:11)	ToM: FPT	Patients were assessed before and after ATL. Preoperatively, patient groups were impaired in comparison with HC (no P -values reported) in the FPT (eTLE: FP recognition, $d = 0.634$; FP rejection, $d = 0.610$; FP comprehension, $d = 1.256$; ITLE: FP recognition, $d = 0.508$; FP rejection, $d = 0.032$; FP comprehension, $d = 0.780$). Postoperatively, no p -values of the comparison of patients and HCs in the FPT were reported (eTLE: FP recognition, $d = 0.646$; FP rejection, $d = 0.220$; FP comprehension, $d = 1.242$; ITLE: FP recognition, $d = 0.432$; FP rejection, $d = -0.076$; FP comprehension, $d = 0.721$).
Gomez-Ibañez et al. (2014)[41]	MTLE, 19 (41.9 ± 10.6; 8:11) IGE, 20 (32.7 ± 9.4; 10:10) HC, 23 (37.3 ± 10.7; 7:16)	ER: PFA	MTLE patients performed significantly worse than HC ($P = 0.002$, $d_{\Delta} = 0.320$).
Gosselin et al. (2011)[42]	TL, 14 (42.1, 30-60***; 8:8) + 2 HC, 16 (n.a.)	ER: PFA	TL patients recognized fear significantly less well than HC ($P = 0.025$, $d = 0.720$). Performance of patients and HC did not significantly differ for any other emotion (happiness, $P = 0.06$, $d = 0.570$; anger, $P = 0.60$, $d = 0.890$; sadness, $P = 1$, $d = 0.020$; disgust, $P = 1$, $d = -0.090$; surprise, $P = 1$, $d = -0.200$).
Hennion, et al. (2015)[43]	TLE, 50 (42.4 ± 11.82; 23:27) HC, 50 (42.81 ± 12.46; 23:27)	ToM: FPT, CoS, CoA	FPT: TLE patients performed significantly worse than HC ($P < 0.0001$, $d = 1.998$). CoS: TLE patients performed significantly worse than HC regarding open questions for direct ($P < 0.0001$, $d = 1.185$) and indirect sarcastic remarks ($P < 0.0001$, $d = 1.320$), as well as direct ($P < 0.0001$, $d = 0.920$) and indirect sarcastic remarks ($P = 0.0014$, $d = 0.641$) in multiple choice questions. CoA: TLE patients performed significantly worse than HC in open questions ($P < 0.0001$, $d = 1.125$) and multiple choice question ($P = 0.0023$, $d = 0.723$) on mental actions.
Hennion et al. (2015)[44]	TLE, 50 (42.4 ± 11.82; 23:27) HC, 50 (42.81 ± 12.46; 23:27)	ER: NimStim, MAV	TLE patients performed significantly worse than HC in the NimStim task ($P = 0.0002$, $d = 1.182$) and the MAV task ($P = 0.0317$, $d = 1.034$).
Hennion et al. (2016)[24]	Right-MTLE, 12 (42.09 ± 12.62; 8:4) Left-MTLE, 13 (42.54 ± 9.6; 6:7) HC, 25 (42.5 ± 12.3; 14:11)	ToM: MT	Patients performed significantly more poorly than HC (right-MTLE: $P = 0.0016$; ToM interactions, $d = 1.178$; goal-directed interactions, $d = 0.62$; random interactions, $d = 0.771$; left-MTLE: $P = 0.0434$; ToM interactions, $d = 0.664$; goal-directed interactions, $d = 0.278$; random interactions, $d = 0.432$).
Hlobil et al. (2008)[45]	r/preAMTL, 24 (28.8 ± 11.4; 10:14) l/preAMTL, 12 (29.5 ± 7.4; 3:9) r/postAMTL, 21 (33.4 ± 10.5; 10:11) l/postAMTL, 19 (30.1 ± 11.7; 9:10) HC, 28 (31.1 ± 12.3; 17:11)	ER: PFA, JFFE, PICS	No p -values of overall comparisons (happiness, fear, anger) between AMTL and HC were reported (tendency towards poorer performance of patients compared to HC, $d_{\Delta} = 0.659$).
Li et al. (2013)[46]	Left-TLE, 11 (37.55 ± 14.7; 5:6) Right-TLE, 13 (43.31 ± 11.83; 8:5) Bilateral-TLE, 7 (46.14 ± 13.07; 5:2) HC, 24 (37.75 ± 16.77; 13:11)	ToM: FB, FPT, IS, VC	TLE patients performed significantly more poorly than HC in all ToM tasks (FB, $P = 0.003$, $d = 0.774$; FPT, $P < 0.001$, $d = 1.684$; IS, $P = 0.001$, $d = 0.975$; iVC, $P < .001$, $d = 1.519$; eVC, $P < 0.001$, $d = 1.044$).
McCagh (2009)[47]	Left-TLE, 15 (35.5 ± 10.7; 8:7) Right-TLE, 12 (34.2 ± 10.7; 3:9) Left-FLE, 13 (37 ± 11.9; 7:6) Right-FLE, 14 (29.9 ± 11.5; 6:8) IGE, 11 (36 ± 13.4; 5:6) FHI, 12 (28.8 ± 11.9; 11:1) HC, 18 (29.72 ± 13.7; 8:10)	ToM: ToM-Stories (FB, deception), HT	No significant differences were found between TLE patients and HC in the first-order ToM FB task (identical mean and SD). In the second-order ToM deception task, in contrast to right-TLE, left-TLE patients performed significantly more poorly than HC (left-TLE, $P < 0.05$, $d = 1.101$; right-TLE, $P > 0.05$, $d = 0.524$). Left-TLE patients performed significantly worse than HC in the HT ($P < 0.05$, $d = 1.376$), while there were no significant differences between right-TLE patients and HC ($d = 1.024$).
McClelland et al. (2006)[48]	(l/e)ATL, 12 (30.3 ± n.a.; n.a.)	ER: PFA	No p -values of overall comparisons between ATL patients and

Table 1 continued

References	Sample characteristics N (mean age ± SD; M:F)	Social cognition tasks	Results
	HC, 10 (30.4 ± n.a.; 5:5)		HC reported (tendency towards poorer performance in ATL patients, $d = 0.586$).
Meletti et al. (2003)[12]	MTLE, 33 (36.1 ± 10.6; 13:20) TLE, 30 (35.8 ± 10.7; 12:18) Extra-TLE, 33 (33.5 ± 10.7; 15:18) HC, 50 (34, 18-65***; 18:32)	ER: PFA	MTLE and TLE patients performed significantly worse than HC ($P < 0.001$, $d_{\Delta} = 0.680$).
Meletti et al. (2009)[49]	MTLE, 140 (38.6 ± 9.9; 63:77) TLE, 36 (37.1 ± 11.6; 16:20) HC, 50 (34.9 ± 9.1; 20:30)	ER: PFA	Patients performed significantly worse than HC (MTLE, $P < 0.0001$, $d = 0.932$; TLE, $P < 0.01$, $d = 0.668$).
Meletti et al. (2014)[50]	ATL, 42 (45.3 ± 11.3; 25:17) HC, 39 (44 ± 11.5; 22:17)	ER: PFA	ATL performed significantly worse than HC ($P < 0.001$, $d = 1.662$).
Okruszek et al. (2017)[51]	MTLE, 31 (30.9 ± 7.7; 14:17) SCZ, 48 (35.8 ± 8.6; 26:22) HC, 47 (32.3 ± 9.1; 25:22)	ToM: RMET	MTLE patients performed significantly more poorly than HC ($P < 0.001$, $d = 1.138$).
Palermo et al. (2010)[52]	Left-TL, 7 (46 ± 10; 1:6) Right-TL, 8 (44.6 ± 6; 3:5) HC, 13 (43 ± 13; 7:6)	ER: PFA, FD	Left-TLE ($P < 0.009$) but not right-TLE patients ($P = 0.75$) were impaired in detecting fearful faces in comparison to HC (tendency towards poorer fear detection in TL patients, $d = 0.667$).
Realmuto et al. (2015)[53]	TLE, 21 (37 ± 12.5; 8:13) IGE, 18 (26.3 ± 7.2; 6:12) HC, 21 (31.95 ± 11.54; 12:9)	ER: PFA ToM: SET	TLE patients performed significantly worse than HC in the PFA ($P = 0.04$, $d = 0.824$) and SET ($P = 0.03$, $d = 0.793$)
Reynders et al. (2005)[54]	IF-TLE, 13 (39.23 ± 9.72; 8:5) TLE, 14 (39.57 ± 12.36; 7:7) IGE, 10 (32.9 ± 19.31; 4:6) HC, 12 (39.92 ± 12.87; 6:6)	ER: PFA	Patients performed significantly worse than HC ($P = 0.004$; IF-TLE, $d = 1.440$; TLE, $d = 1.458$).
Schacher et al. (2006)[14]	MTLE, 27 (36.5 ± 10.7; 13:14) Extra-MTLE, 27 (35.9 ± 12.8; 13:14) HC, 12 (33.8 ± 12.4; 7:5)	ToM: FPT	MTLE patients performed significantly worse than HC ($P < 0.001$, $d_{\Delta} = 1.160$).
Sedda et al. (2013)[55]	Right-TLE, 24 (35.33 ± 11.06; 14:10) Left-TLE, 32 (38.31 ± 12.11; 18:14) HC, 54 (35.7 ± 11.35; 23:31)	ER: AFFECT-R	Right-TLE but not left-TLE patients performed significantly worse than HC ($d_{\Delta} = 1.234$) at 35% ($P = 0.014$), 50% ($P = 0.003$) and 75% ($P < 0.001$) emotional intensity of displayed emotional expressions. No significant group differences were found at 100% intensity.
Shaw et al. (2007)[56]	RATL, 10 (41 ± 9; 5:5) LATL, 9 (33 ± 11; 3:6) HC, 19 (33 ± 11; 6:13)	ER: PFA ToM: FPT, HSS	ER: No information on overall significant differences between pre-operative patients and HC available ($d_{\Delta} = 0.080$). ToM: Patients and HC did not significantly differ pre-operatively ($d_{\Delta} = 0.150$; FPT, $P = 0.81$; HSS $P = .12$) and post-operatively (FPT, $P = 0.24$; HSS, $P = 0.21$).
Szaflarski et al. (2014)[57]	Left-TLE, 34 (41 ± 12; 7:27) HC, 30 (39 ± 11; 8:22)	ER: NimStim	No significant differences have been found between patients and HC (happy, $P = .19$, $d = 0.337$; fearful, $P = 0.63$, $d = 0.113$; sad, $P = 0.081$, $d = 0.438$; neutral, $P = 0.46$, $d = 0.188$).
Tanaka et al. (2013)[58]	MTLE, 63 (41.5*, 33-60**, 32:31) PTL, 25 (43*, 28.8-58**, 9:16) HC, 32 (33*, 26-47.5**, 7:25)	ER: DFE	Patients performed significantly worse than HC (MTLE, $P < 0.001$, $d = 1.027$; PTL, $P < 0.001$, $d = 1.244$).
Walpole et al. (2008)[59]	TLE, 16 (45.31 ± 11.81; 9:7) HC, 14 (43.86 ± 10.92; 6:8)	ER: PFA	TLE patients performed significantly worse than HC ($P = 0.039$, $d = 0.794$).
Wang et al. (2015)[25]	TLE, 67 (32.19 ± 10.22; 36:31) HC, 30 (33.4 ± 9.57; 16:14)	ToM: FB, FPT, IS, VC	TLE patients performed significantly worse than HC in all ToM tasks ($P < .001$; FB, $d = 1.166$; FPT, $d = 1.103$; IS, $d = 1.687$; iVC, $d = 1.394$; eVC, $d = 1.609$).
Wendling et al. (2015)[60]	SAH, 27 (41.38 ± 8.3; 10:17) ATL, 33 (40.12 ± 9.12; 17:16) HC, 30 (40.58 ± 4.78; 15:15)	ER: PFA	Patients performed significantly worse than HC ($d = 0.960$; SAH, $P = 0.0001$; ATL, $P = 0.006$)

(r/l)AAD (right/left)asymmetrical amygdala damage; AFFECT-R Animated Full Facial Expression Test – Revised; (l/e/pre/post)A(M)TL (early onset; late onset epilepsy / pre-surgery; post-surgery) anterior (mesial) temporal lobectomy; (R/L)ATL (right/left) anterior temporal lobectomy; CATS comprehensive affect testing system; ARQ affect recognition quotient; PRQ prosody recognition quotient; ERQ emotion recognition quotient; CFS complex facial scale; PS prosody scale; SFS simple facial scale; LS lexical scale; CMS, cross modal scale; CoA comprehension of action task; CoS comprehension of sarcasm task; DEF Goeleven's and Lundqvist's directed emotional faces database; DFE dynamic facial expressions; ER emotion recognition; FAB Florida affect battery; FAD facial affect discrimination; FAM facial affect matching; FAN facial affect naming; FAS facial affect selection; FD fear detection task; FHI frontal head injury; FB false belief test; FLE frontal lobe epilepsy; FPE non-faux pas exclusion; FPR faux pas recognition; FPT faux pas test; HC healthy controls; HSS Happé's strange stories; HT Hinting Task; IF ictal fear; IGE idiopathic generalized epilepsy; IS implication stories test; IR insula resection; JFFE Japanese Female Facial Expression Database; M:F ratio male to female; MAV Montreal Affective Voices MT moving triangles; (r/l)MTLE (right/left) mesial temporal lobe epilepsy; N sample size; NimStim Tottenham's NimStim set of facial expressions; NVS non-verbal sounds; n.a. not available; PAN prosodic affect-naming; PFA Ekman and Friesen's pictures of facial affect; PTL posttemporal lobectomy MTLE; PICS University of Sterling PICS Image Data Base; Q1-4 question 1-4; RMET reading the mind in the eyes test; SAH selective amygdalohippocampectomy; SCZ schizophrenia patients; SET story-based empathy task; (R/L)TL (right/left) temporal lobectomy; (r/l/pre/post)(e/l)TLE (right/ left/ pre-/ postsurgical) (early onset/ late onset) temporal lobe epilepsy; ToM theory of mind; ULD Uverricht-Lundborg disease; (i/e)VC (implicit/explicit) visual cartoon test.

*median age; **interquartile range; ***range;

d_{Δ} , pooled effect sizes retrieved from Bora and Meletti (2016)[22]; d_{Δ} , pooled effect sizes retrieved from Edwards, Stewart, Palermo, and Lah (2017)[26]

Table 2 Studies comparing extratemporal lobe epilepsy patients *versus* control groups.

References	Sample characteristics <i>N</i> (mean age \pm SD; M:F)	Social cognition tasks	Results
Boucher et al. (2015)[34]	ATL, 15 (38.7 \pm 10.3; 7:8) IR, 15 (37.6 \pm 8.6; 6:9) HC, 20 (36.1 \pm 10.2; 10:10)	ER: DEF ToM: RMET	IR patients performed significantly worse than HC (DEF, $d = 1.203$; RMET, $d = 0.923$).
Broicher et al. (2012)[17]	MTLE, 28 (34.43 \pm 13.25; 12:16) Extra-MTLE, 14 (33.36 \pm 11.74; 10:4) HC, 29 (33.69 \pm 10.94; 13:16)	ER: CATS ToM: MT, RMET, FPT	ER: Extra-MTLE and HC did not differ in the CATS quotient scales (all $P > 0.05$, ARQ, $d = 0.337$; ERQ, $d = 0.481$; PRQ, $d = 0.661$) and composite scales (all $P > 0.05$, SFS, $d = 0.363$; CFS, $d = 0.252$; PS, $d = 0.448$; LS, $d = 0.057$; CMS, $d = -0.074$). ToM: Extra-MTLE and HC did not differ in the MT regarding attribution of intentionality (ToM animations, $d = 0.222$; goal-directed animations, $d = 0.178$; random animations, $d = 0.584$) and appropriateness of explanations (ToM animations, $d = -0.320$; goal-directed animations, $d = 0.175$; random animations, $d = -0.217$). There were no significant differences between Extra-MTLE and HC in the RMET ($d = 0.302$) and FPT ($d = 0.284$).
Bujarski et al. (2016)[61]	PWE, 42 (33.3 \pm 10; 22:20) CM, 22 (41.1 \pm 10.4; 8:14)	ER: TASIT (part 1) ToM: TASIT (part 2/3)	ER: PWE performed significantly more poorly than CM in the TASIT part 1 ($P < 0.001$; $d = 1.104$). ToM: PWE performed significantly worse than CM (part 2, $P < 0.0001$, $d = 1.333$; part 3, $P < .0001$, $d = 1.440$).
Farrant et al. (2005)[20]	FLE, 14 (34.36 \pm 12.05; 6:8) HC, 14 (35.79 \pm 9.91; 6:8)	ER: PFA ToM: HS, FPT, CHT, RMET	ER: FLE patients performed significantly worse than HC ($P = 0.0001$, $d = 1.831$). ToM: FLE and HC did not significantly differ in the HS (ToM stories, $P = 0.549$; $d = 0.444$; non-ToM stories, $P = 0.729$, $d = 0$) and FPT (correct detection, $P = 0.734$, $d = 0.299$; correct rejection, $P = 0.571$, $d = 0.085$; correct attribution, $P = 0.178$, $d = 0.723$; composite score, $P = 0.056$, $d = 0.949$). FLE patients performed significantly more poorly in the CHT (ToM, $P = .014$, $d = 0.925$; non-ToM, $P = 0.014$, $d = 0.912$) and RMET ($P = 0.014$, $d = 1.009$).
Giorgi et al. (2016)[62]	JME, 20 (26.7 \pm 6.6; 2:18) HC, 20 (26.2 \pm 5.8; 2:18)	ToM: EAT, HSS, FPT, RMET	JME performed significantly worse than HC in the HSS ($P = 0.022$, $d = 0.628$) as well as in the FPT regarding the faux pas cumulative score ($P = 0.022$, $d = 0.889$), faux pas intentionality (Q4, $P = 0.033$, $d = 0.642$; Q5, $P = .0495$, $d = 0.541$) and affective state attribution (Q6, $P = 0.017$, $d = 0.862$), but not in the faux pas recognition (Q1, $P = 0.076$, $d = 0.347$), faux pas attribution (Q2, $P = 0.076$, $d = 0.347$), comprehension (Q3, $P = 0.076$, $d = 0.347$) and rejection ($P = 0.251$, $d = 0.172$). No significant group differences were found in the EAT ($P = 0.108$, $d = 0.522$) and RMET ($P = 0.62$, $d = 0.392$).
Giovagnoli et al. (2009)[38]	ULD, 21 (39.29 \pm 15.69; 8:13) TLE, 21 (39.67 \pm 14.41; 11:10) HC, 21 (41.81 \pm 16.7; 8:13)	ToM: FPT	No P -values of the comparison of ULD patients and HC were reported (FP recognition, $d = 0.614$; FP rejection, $d = 0.291$).
Giovagnoli et al. (2011)[39]	Left-TLE, 62 (35.96 \pm 11.64; 24:38) Right-TLE, 47 (38.33 \pm 10.64; 20:27) FLE, 29 (35.77 \pm 12.53; 11:18) HC, 69 (52.03 \pm 17.04; 29:40)	ToM: FPT	Compared to HC, FLE patients were significantly impaired in all FPT sub-scales (all $P < 0.001$, FP recognition, $d = 1.35$; FP rejection, $d = 0.452$; Q1, $d = 1.520$; Q2, $d = 1.460$; Q3, $d = 1.156$; Q4, $d = 1.425$).
Giovagnoli et al. (2013)[13]	TLE, 54 (37.80 \pm 9.20; 26:28) FLE, 12 (37.17 \pm 13.41; 6:6) HC, 42 (40-64* \pm 12.61; 18:24)	ToM: FPT	Grouped together, patients performed significantly more poorly than HC ($P < 0.001$). Effect sizes of the group differences between FLE and HC: FP recognition, $d = 0.401$; FP rejection, $d = -0.032$; Q1, $d = 1.057$; Q2, $d = 1.125$; Q3, $d = 1.383$; Q4, $d = 1.042$.
Gomez-Ibañez et al. (2014)[41]	MTLE, 19 (41.9 \pm 10.6; 8:11) IGE, 20 (32.7 \pm 9.4; 10:10) HC, 23 (37.3 \pm 10.7; 7:16)	ER: PFA	IGE patients performed significantly worse than HC ($P = 0.006$, $d_a = 0.870$).
McCagh (2009)[47]	Left-TLE, 15 (35.5 \pm 10.7; 8:7) Right-TLE, 12 (34.2 \pm 10.7; 3:9) Left-FLE, 13 (37 \pm 11.9; 7:6) Right-FLE, 14 (29.9 \pm 11.5; 6:8) IGE, 11 (36 \pm 13.4; 5:6) FHI, 12 (28.8 \pm 11.9; 11:1) HC, 18 (29.72 \pm 13.7; 8:10)	ToM: ToM-stories (FB, deception), HT	Left- and right-FLE as well as IGE patients did not differ significantly from HC in the FB task (right-FLE, $d = 1.013$; left-FLE, $d = 0.777$; IGE, $d = 0$). HC performed significantly better than all patient groups in the second order ToM deception task ($P < 0.05$; left-FLE, $d = 0.357$; right-FLE, $d = 0.775$; IGE, $d = 0.354$), no further contrasts were significant. HC performed significantly better than all patient groups in the HT ($P < 0.001$; right-FLE, $d = 1.191$; left-FLE, $d = 0.879$; IGE, $d = 1.417$), no further contrasts were significant.
Meletti et al. (2003)[12]	MTLE, 33 (36.1 \pm 10.6; 13:20)	ER: PFA	The extra-TLE patients and HC did not significantly differ in

Table 2 continued

References	Sample characteristics N (mean age ± SD; M:F)	Social cognition tasks	Results
	TLE, 30 (35.8 ± 10.7; 12:18) Extra-TLE, 33 (33.5 ± 10.7; 15:18) HC, 50 (34, 18-65*; 18:32)		emotion recognition performance.
Realmuto et al. (2015)[53]	TLE, 21 (37 ± 12.5; 8:13) IGE, 18 (26.3 ± 7.2; 6:12) HC, 21 (31.95 ± 11.54; 12:9)	ER: PFA ToM: SET	IGE patients did not significantly differ from HC in the PFA task ($d = 0.809$) and the SET ($d = 0.466$).
Reynders et al. (2005)[54]	IF-TLE, 13 (39.23 ± 9.72; 8:5) TLE, 14 (39.57 ± 12.36; 7:7) IGE, 10 (32.9 ± 19.31; 4:6) HC, 12 (39.92 ± 12.87; 6:6)	ER: PFA	Patients performed significantly worse than HC ($P = 0.004$; IGE, $d = 1.235$).
Schacher et al. (2006)[14]	MTLE, 27 (36.5 ± 10.7; 13:14) Extra-MTLE, 27 (35.9 ± 12.8; 13:14) HC, 12 (33.8 ± 12.4; 7:5)	ToM: FPT	Test performance of extra-MTLE patients did not differ from that of controls ($P = 0.20$; $d = 0.443$).

ARQ affect recognition quotient; CATS comprehensive affect testing system; CFS complex facial scale; CHT cartoon humour task; CM controls with migraine; CMS cross-modal scale; DEF Goeleven's and Lundqvist's directed emotional faces database; EAT emotion attribution task; ER emotion recognition; ERQ emotion recognition quotient; F female; FB false belief; FHI frontal head injury; FIED frontal interictal epileptiform discharges; FLE frontal lobe epilepsy; FPT faux pas test; HC healthy controls; H(S)S Happé's (strange) stories; HT hinting task; IF ictal fear; IGE idiopathic generalized epilepsy; IR insula resection; JME juvenile myoclonic epilepsy; LS lexical scale; M male; MA mean age; MT moving triangles test; MTLE mesial temporal lobe epilepsy; N sample size; PRQ prosody recognition quotient; PS prosody scale; PWE patients with epilepsy; Q1-4 question 1-4; RMET reading the mind in the eyes test; SET story-based empathy task; SD standard deviation; SFS simple facial scale; TASIT The Awareness of Social Inference Test; ULD Unverricht-Lundborg disease; YTYoni task.

*range

d_p , pooled effect sizes retrieved from Edwards, Stewart, Palermo, and Lah (2017)[26]

d_r , pooled effect sizes retrieved from Stewart, Catroppa, and Lah (2016)[28]

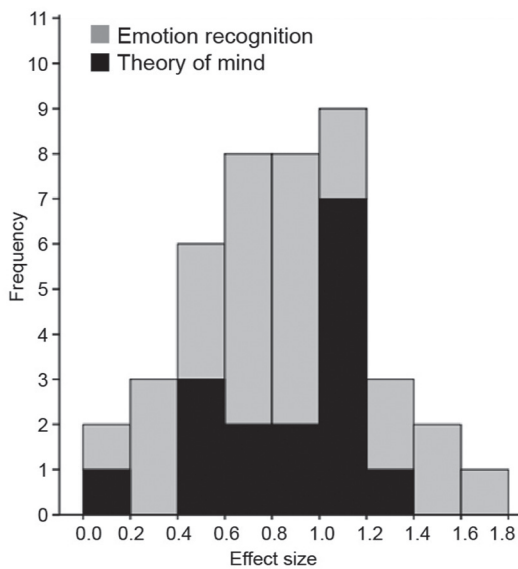


Fig. 1. A stacked histogram showing distributions of the pooled median effect sizes regarding social cognition in the 42 studies that compared healthy controls versus temporal lobe epilepsy patients.

neuropsychological investigations in the domains of memory, speed, attention and executive functions.

Discrepant results among some studies may be due to the variety of tests to measure social cognition. Multiple measures exist for ER and ToM. This prevents accurate comparison between results, and limits the reproducibility. Additionally, the majority of studies on social cognition used a unimodal design that exclusively focuses on one domain of social cognition, most com-

monly ER. Future studies that test ER, ToM, general cognition, speed, attention, memory, and executive functions in the same population would be informative.

In addition, other domains of social cognition such as prosody and body language interpretation as well as expression have not been well-described in epilepsy populations and thus need further investigations. In general, larger longitudinal studies would help advance our understanding of the effects of epilepsy duration, seizure frequency, age at epilepsy onset, effect of seizure freedom, and antiepileptic drugs, on social cognition. The standardization of terminology and testing in the field of applied social cognition would enhance the reproducibility and comparability of results. It should be noted that the process of successful and enjoyable social interactions is characterized by reciprocity, smooth social encounters, mutual adjustment, temporal and emotional synchronisation, and entrainment. Therefore, the presentation of photographs and sheets of paper with faux-pas stories, only represents an initial effort to establish social cognition within neuropsychology [2].

The difficulties with social interaction and functioning observed in some epilepsy patients may, at least in part, be due to an altered ability to correctly interpret emotions or mental states. It appears that epilepsy patients may struggle more with subtle or nuanced expressions of emotion. Currently, it is unknown how the socio-cognitive deficits seen in some patients significantly affect diverse areas of life as employment, romantic and family relationships, or friendships. It is therefore important to quantify the functional burden of impaired social cognition in epilepsy to determine its specific clinical relevance.

Conclusion

Considering the importance of social skills in personal and economic success and in improving QoL, it can no longer be justified to exclude the domain of social cognition from the canon of relevant functions investigated in epilepsy. A better understanding of the nature of social cognition in epilepsy may help further characterize certain epilepsy syndromes, and facilitate development of therapeutic interventions to improve social abilities in these patients.

Abbreviations

ER, emotion recognition; FLE, frontal lobe epilepsy; QoL, quality of life; TLE, temporal lobe epilepsy; ToM, theory of mind.

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW

Managing reproductive problems in women with epilepsy of childbearing age

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Abstract

Girls and women constitute nearly 50% of all epilepsy cases. Apart from the disease symptoms, epilepsy and antiepileptic drugs (AEDs) may also affect their reproductive function and pregnancy, and even the health of their offspring. Therefore, it is very important to identify and summarize the problems and risks for women with epilepsy (WWE) of childbearing age, and offer internationally recognized methods through multidisciplinary collaboration. In this review, we summarize the reproduction-related problems with WWE and propose multidisciplinary management by epileptologists, gynecologists and obstetricians, as well as other experts, from preconception to delivery. Large, multicenter registries are needed to advance our knowledge on new AEDs and their effects on WWE and their offspring.

Keywords: Women with epilepsy, Reproduction, Antiepileptic drugs, Teratogenicity, Offspring.

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Introduction

Epilepsy is a serious neurological disorder characterized by recurring seizures and accompanied by many comorbidities [1]. The estimated worldwide prevalence of epilepsy is 7.6 per 1000 persons [2]. In females the prevalence of epilepsy was estimated to be 3.45 per 1000 women in China, while that within childbearing age (20-40) in particular was 2.83-3.14 per 1000 women [3], which means that more than 3 million women with epilepsy (WWE) in China are facing reproductive problems. Two reasons can account for this problem. First, epilepsy and antiepileptic drugs (AEDs) have been verified to interact with regulations of sex hormones, leading to unsatisfactory seizure control and impaired reproductive function, particularly causing a polycystic ovarian syndrome (PCOS) that may lead to infertility in WWE [4]. Second, nearly one third of patients taking AEDs are women of childbearing age, and almost half of them have unplanned pregnancy [5], thus putting themselves at risks of seizure attack during pregnancy and AED-induced fetal malformation [6]. It has been reported that in UK the case fatality rate in WWE is much higher in the pregnant period than in the non-pregnant period [7], and the mortality rate in pregnant WWE is ten times higher than that in normal pregnant women [8]. Recent research on WWE further showed that some new AEDs such as the topiramate also have teratogenicity on fetus. In this review, we summarize

the reproduction-related problems with WWE, update studies in WWE, and propose multidisciplinary management strategies for WWE from preconception to delivery.

Preconception period

Epilepsy and decreased fertility

According to a previous report, the infertility rate in WWE is 38.4%, which is two-fold higher than that in normal women [9]. The infertility rate in WWE is positively correlated to the number of AEDs used (7.1% in those with no AED use, 31.8% with 1 AED, 40.7% with 2 AEDs, and 60.3% with 3 or more AEDs) [9]. The most important factor causing infertility in WWE is reproductive endocrine disorders such as the PCOS, which occur more frequently in WWE than in women without epilepsy [10, 11], probably because of the interactions among epilepsy, AEDs and reproductive hormones [4] though the exact mechanism is unclear. There has been sufficient evidence for an impact of valproate (VPA) on the reproductive function of women with epilepsy, which would even cause PCOS through hyperandrogenemia and insulin resistance [12]. Thus, VPA exposure should be avoided in women of childbearing potential whenever possible [13]. Women with menstrual disorder, hirsutism and VPA therapy usually have a high probability of PCOS [14]. Another study has also shown a higher rate of PCOS in women with left temporolimbic epileptiform discharges compared with those with a right laterality and possibly with right-sided nontemporal discharges [15]. For women of reproductive age, PCOS screening as well as

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giving treatment on it is as important as seizure control, as PCOS has been reported to be closely associated with type 2 diabetes mellitus [16] and endometrial cancer [17]. However, during screening of PCOS, the circulating hormone level test and transvaginal b-mode ultrasonography need to be performed in WWE at early follicular phase (days 3-5 of the menstrual cycle)[11], which compromises the compliance of the patients. Therefore, every WWE should be informed that screening of PCOS is necessary and beneficial for their long-term prognosis. Once diagnosed, gynecologists should communicate with epileptologists and start treatments on PCOS. At the same time, epileptologists should modulate the therapy if necessary (e.g., reduce the dosage of VPA or replace VPA with other AEDs). So far the reproductive impact of other AEDs has not been sufficiently evidenced.

However, epilepsy itself and AEDs are not the only factors that lead to reproductive dysfunction in WWE. Psychiatry, family and society may also affect their reproductive health. Stigma, depressive disorder and anxiety appear to be more common in patients with epilepsy than in normal persons [18, 19]. WWE would even have an increase in births after epilepsy surgery [20]. These social psychological factors can affect the reproductive endocrine of WWE, and could be a prominent cause for reproductive dysfunction [21]. Thus, WWE should be recommended to psychologists and psychiatrists when needed. By this multidisciplinary management mode, WWE can be treated appropriately and have babies successfully.

Planning pregnancy

It is recommended that WWE become pregnant after seizure freedom and withdrawal of AEDs for 6-9 months, mainly because the best predictor of seizure control during pregnancy is the seizure control prior to pregnancy [22]. However, almost half of WWE had unplanned pregnancy [5], mainly resulting from the low contraceptive rate or contraceptive failure. Pharmacokinetic interactions between some AEDs and oral contraceptives (OCs) may result in not only decreased seizure control but also contraceptive failure. AEDs that can impair the contraceptive efficacy of hormonal contraceptives by increased clearance of the synthetic steroids include strong enzyme inducers like carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB) and primidone (PRM), and mild enzyme inducers like topiramate (TPM), oxcarbazepine (OXC), and felbamate [23]. On the other hand, OCs containing estrogen could decrease the concentrations of some AEDs such as lamotrigine (LTG), through enhancing their metabolism by UGT1A4 (an enzyme responsible for the glucuronidation of some AEDs by ethinylestradiol) [23]. The LTG plasma levels could be reduced by >50% during OC co-medication [24] and increased by 84%

after cessation of OCs [25]. Thus, epileptologists should ask their female patients if they are already using AEDs and the type of AEDs if any, before prescribing an AED therapy. For women who must take enzyme-inducing AEDs or LTG to control seizures, continuous use of the hormonal contraceptive without a free interval may increase the contraceptive efficacy [26]. However, for women taking strong enzyme-inducing OCs, additional protection such as barrier methods like condoms can be useful. In China, although the predominant contraceptive methods are intrauterine devices, sterilization and condom [27-29], the use of OCs is increasing [27], to which epileptologists should pay more attention.

Folic acid

Generally, folate deficiency is associated with spontaneous abortion and developmental abnormalities in the offspring. Folic acid supplementation is associated with a lower risk of spontaneous abortion[30], better verbal outcomes[31] and a reduced risk of major congenital malformations[32] in women with epilepsy. In addition, women taking AEDs are at a higher risk of low serum folate compared to the general population, probably because that AEDs which could induce the cytochrome P-450 enzyme such as CBZ and PHT, could interfere with folate metabolism [33]. Thus, many guidelines have recommended folic acid supplementation from pre-conception to period during pregnancy, albeit with variations of the dosage and duration among different guidelines (Table 1).

A recent retrospective study of 153 pregnant WWE found that only 24% of them had folic acid supplementation before conception, among whom only 13% began the supplementation three months prior to conception. More than one third of the WWE were never supplemented with folic acid throughout pregnancy. The lack of knowledge on folic acid may account for this supplementation failure, since over one third of them did not know that folic acid can decrease the risk of birth defect and 83.7% did not know the necessity of higher doses of folic acid supplementation in pregnant WWE [39]. Some patients even thought that folic acid could induce seizures and aggravate epilepsy. This fear is most likely from the Chinese drug instruction of folic acid, which states that "high doses of folate can antagonize the anti-epileptic effect of phenobarbital, phenytoin and PRM, leading to an obvious decrease in the seizure threshold and an increase of seizure frequency in sensitive patients". The instruction may be derived from the report of decreased plasma concentrations of those AEDs and increased seizure occurrence after high-dose (1-5 mg/day) supplementation of folic acid [40, 41], mainly because that high levels of folate could increase the affinity of metabolizing enzymes, thus greatly enhancing the metabolism of the AEDs [42].

Recently, it has been reported that the offspring of rats receiving a high dose of folic acid before and during

Table 1 Recommendations for folic acid supplementation by different guidelines

Guideline	Recommendation for dosage	Recommendation for adding time
SIGN 2015[34]	400 µg/day: not on AEDs 5 mg/day: on AEDs or not on AEDs, but high risk (with a family history of neural tube defects or a BMI >30 kg/m ²)	From preconception and throughout the first trimester of pregnancy
RCOG 2016[35]	5 mg	Prior to conception and continue the intake until at least the end of the first trimester
AAN/AES 2009[36]	At least 0.4 mg/day	Prior to conception and during pregnancy
ETDP-EFA 2007[37]	0.4 mg/day for nonpregnant women, 0.6 mg/day for pregnant women and those contemplating pregnancy, and 0.5 mg/day for lactating women. Many epileptologists recommend higher doses (0.8–4 mg/day) for women with epilepsy. However, for women with a family history of a neural tube defect, 4 mg/day is the recommended dosage.	Before conception and throughout pregnancy
NICE 2012 (update 2016)[38]	5 mg/day	Before any possibility of pregnancy

AED antiepileptic drug; AAN American Academy of Neurology; AES American Epilepsy Society; ETPD – EFA Epilepsy Therapy Development Project – Epilepsy Foundation of America; NICE National Institute for Health and Care Excellence; RCOG Royal College of Obstetricians and Gynaecologists; SIGN Scottish Intercollegiate Guidelines Network

gestation have a 42% lower seizure threshold than the offspring of rats without folic acid supplementation, and *in vitro* acute application of folic acid or its metabolite 4H-folate to neurons induces hyper-excitability and bursting [43]. Another study found that a 20-fold higher intake of folic acid than recommendation was associated with embryonic delay and growth retardation, thinner ventricular walls in embryonic hearts, and susceptibility to embryonic defects [44]. However, the interactions between folic acid and new AEDs have been rarely reported. Therefore, as “of two evils, choose the less”, folic acid supplementation is highly recommended for WWE (4-5 mg/day) from three months prior to conception till the end of the first pregnancy trimester.

During pregnancy

Detrimental effect of AEDs on the offspring

As almost half of the WWE have unplanned pregnancy [5], a major task during pregnancy is to deal with the contradictory relationship between the teratogenicity of AEDs on fetus and the seizure control on mothers. Many AEDs have been verified to have teratogenicity in animal models [45-47]. The mechanisms may be that the active metabolites of AEDs can induce neuronal apoptosis or functional and physiological alterations in fetus [48-51]. Generally, polytherapy is associated with a higher teratogenic risk than monotherapy and VPA has the highest teratogenic risk among all the monotherapies [52-54]. Recently, a meta-analysis has also suggested that VPA or TPM exposure in uterus is highly associated with major congenital malformations (MCMs) in infants and children, while the odds ratio of MCMs is low in the offspring of women with uterus exposure to LTG or levetiracetam (LEV) [54]. The odds ratios of overall MCMs, separate MCMs, and common adverse obstetric outcomes of frequently-used AEDs, as obtained by meta-analysis, are shown in Table 2.

A large retrospective study with 5374 births recently

found that infants of mothers with epilepsy are at increased risks of stillbirth, having both medically indicated and spontaneous preterm birth, being small for gestational age at birth, as well as having neonatal infections, any congenital malformation, major malformations, asphyxia-related complications, lower Apgar score, neonatal hypoglycemia, and respiratory distress syndrome, compared with infants of unaffected women [55]. However, in this study, AEDs use during pregnancy is not associated with adverse maternal and fetal or neonatal outcomes. And similarly, another study also found that AEDs are not associated with malformations in offspring [56]. Combined together, there are two reasons for the different conclusions concerning AED's effect on offspring: first, LTG and CBZ account for approximately 77% of the therapies, whereas the more harmful AEDs VPA and TPM are used in only 19.2% and 4.0% of the pregnancies in the first study; second, both of the two studies analyzed the MCMs rate of all AEDs together rather than analyzing the MCMs rate of each monotherapy.

On the other hand, some studies have suggested dose-dependent teratogenicity of some AEDs [57-59]. Tomson *et al.* found that LTG at <300 mg/day correlates with the lowest rate of malformation (2%), while VPA doses ≥1500 mg/day are associated with a very high malformation rate (around 24%) [52, 58]. Thomas *et al.* also observed a dose-dependent teratogenicity of VPA (33.3% had MCMs at >800 mg/day) [59]. Results of another large registry suggested that LTG at >400 mg/day causes lower rate of MCMs than any VPA dose, although the result is not significant [53]. Nevertheless, the results may not be the same in Chinese WWE and their offspring since Asians have a lower body weight than Europeans on average. In a recent Chinese pregnancy registry of WWE, 5 of 155 pregnancies had MCMs (three congenital heart disease, one hydrocephalus and one meningocele) and four of the five mothers were taking AEDs during pregnancy. Also in this study, the newborns to women who received epilepsy surgery were more likely to get an Apgar score ≤7 [60].

Table 2 Odds ratios of different AEDs on major congenital malformations and other adverse prenatal outcomes (OR, [95% CI], n) [54]

	MCMs										Prenatal growth retardation	Preterm birth
	Overall	Cardiac disease	Cleftlip/palate	Club foot	Hypospadias	Inguinal hernia	Undescended testes	Combined fetal losses				
LTG	0.96 [0.72, 1.25] 6290	0.55 [0.32, 0.95] 4788	1.21 [0.45, 3.20] 4664	0.70 [0.12, 2.89] 1621	0.66 [0.23, 2.26] 95	0.86 ^d [0.17, 15.92] 8	0.31 [0.05, 1.66] 1660	1.38 [0.70, 2.88] 2540	0.90 [0.56, 1.42] 2882	1.05 [0.70, 1.48] 3015		
VPA	2.93* [2.36, 3.69] 4455	1.54* [0.98, 2.37] 3194	3.26 [1.38, 7.57] 2721	3.26* [1.43, 8.25] 802	2.58 [1.24, 5.76] 1437	1.64 [0.39, 10.02] 1845	1.10 [0.33, 3.78] 542	1.83* [1.04, 3.45] 2612	1.28 [0.86, 1.95] 1622	0.96 [0.65, 1.37] 1694		
OXC	1.32 [0.72, 2.29] 372	0.69 [0.20, 2.18] 346	3.33 [0.66, 11.80] 304	2.40 [0.24, 13.37] 198	5.19* [0.95, 20.58] 200	1.17 [0.02, 17.89] 189	0.25 [0.00, 5.19] 182	1.66 [0.50, 4.50] 567	0.99 [0.56, 1.76] 1002	0.80 ^d [0.51, 1.26] 1045		
TPM	1.90 ^f [1.17, 2.97] 599	0.66 [0.16, 2.11] 429	6.12* [1.89, 19.05] 429	1.77 [0.16, 11.44] 359	3.52 [0.77, 15.72] 429	1.52 [0.13, 14.90] 429	0.14 ^d [0.00, 2.72] 359	23.58 [1.18, 549.60] 2	2.64* [1.41, 4.63] 472	1.38 [0.73, 2.35] 408		
LEV	0.72 ^f [0.43, 1.16] 1015	0.25 ^f [0.03, 0.96] 754	0.48 ^f [0.07, 2.18] 872	0.26 ^f [0.00, 3.80] 450	0.29 ^f [0.00, 2.56] 754	1.75* [0.22, 14.87] 1845	2.07* [0.38, 12.21] 450	2.47 [0.50, 10.15] 28	1.27 [0.34, 3.54] 81	0.87 [0.31, 2.04] 93		
CBZ	1.37 [1.10, 1.71] 8437	0.93 [0.62, 1.43] 1436	1.39 [0.56, 3.15] 5577	1.64 [0.68, 3.62] 99	1.09 [0.53, 2.61] 3540	1.54 [0.40, 8.78] 3307	0.53 [0.14, 1.96] 1386	1.25 [0.73, 2.36] 3911	1.15 [0.77, 1.67] 2897	1.10 [0.77, 1.56] 2141		
PHT	1.69 [1.30, 2.17] 2237	0.99 [0.60, 1.57] 1697	3.11 [1.30, 7.72] 1172	2.73 [1.13, 6.18] 932	1.12 [0.51, 2.26] 1350	1.54 [0.38, 9.12] 878	1.27 ^f [0.40, 4.38] 629	1.50 [0.85, 2.91] 618	0.68 ^f [0.37, 1.21] 519	1.03 [0.55, 1.82] 283		
PB	1.83 [1.35, 2.47] 1709	1.54 ^f [0.96, 2.57] 1255	5.74 ^f [2.41, 24.08] 894	1.38 [0.51, 3.42] 1057	1.53 [0.60, 3.84] 3824	1.21 [0.26, 7.54] 484	0.94 [0.27, 3.32] 526	0.90 ^f [0.44, 1.93] 407	1.88 ^f [1.07, 3.32] 400	1.59* [0.87, 2.75] 206		

Notes: each cell consists of three parts, odds ratio, [95% credible intervals], and number of cases; ^fthe highest OR, ^dthe second highest OR, ^hthe lowest OR. CBZ carbamazepine; LTG lamotrigine; LEV levetiracetam; MCMs major congenital malformations OXC oxcarbazepine; PB phenobarbitone; PHT phenytoin; TPM topiramate; VPA valproate

Apart from fetus and infants, uterus exposure to some AEDs may also affect the long-term neurodevelopment of the offspring [61]. VPA exposure has been widely reported to be associated with a dose-dependent decline of intelligence quotient (IQ), impaired verbal or nonverbal ability, impaired comprehensive or expressive language ability, impaired gross motor skills and autistic spectrum disorders in the offspring at the age of 2–14 years [62–69]. CBZ-exposed children have been reported to have impaired fine motor skills and social skills at age 1.5, increased aggressive symptoms at age 3 and reduced verbal ability at age 6 [63, 66]. LEV-exposed children have impaired sentence skills and increased autistic traits at age 3 [66]. However, none of these studies were from Asia and commonly used AEDs for pregnant WWE, such as LEV and LTG, were rarely studied. Recently, a registration system about AEDs among pregnant WWE in West China has been established [70], whereas more large multicenter prospective pregnancy registration of WWE and their offspring in Asia is still needed.

Maternal seizure control

Uncontrolled seizures can affect both fetal and maternal health [66, 71, 72]. As is indicated by previous studies, seizures still occur in 21.2%-67.1% of WWE during pregnancy (Table 3) although the seizure frequency remains unchanged in 28%-80% of the women (Table 4). As we can see, the percentage varies widely. On the one hand, different studies used different standards to define the word “unchanged” and different periods as reference, and patients in each study had various kinds of AEDs. On the other hand, the changes of seizure frequency during pregnancy are related to many factors, such as the seizure type, the type and number of AEDs, as well as the dose change of AEDs. Thus, it is necessary to establish an international standard on evaluating the seizure control and study the control effect of each AED. From the existing evidence, LTG seems to perform worse in seizure control compared to both old and new AEDs during pregnancy, while LEV may perform best in controlling maternal seizures among new AEDs [72–75]. However, the most reliable predictor for seizure frequency during pregnancy is the seizure frequency before pregnancy, that is, women who had seizures before pregnancy are more likely to have seizures during pregnancy [60, 76, 77].

The increasing seizure frequency during pregnancy may be a result from the decrease of plasma AEDs [80, 83, 90], which may be attributed to the increased volume of distribution, declined plasma protein concentrations, increased renal clearance, and enhanced metabolism (e.g. glucuronidation and hydrolysis) during pregnancy [91, 92]. AED clearance increases and plasma concentration decreases as pregnancy advances. This occurs especially for LTG, LEV and OXC [83, 91], which may be because of the strong enhancement of maternal glucuronidation and hydrolysis during pregnancy, through which the three

Table 3 Seizure occurrence rate in different studies

Study	Number of pregnancies	Study method	Center	Seizure rate			SDD	SE
				Total	AED use			
EURAP 2006[78]	1956	Prospective registry	Multi (>30)	41.60%	LTG (43.30%) VPA (23.80%) CBZ (34.30%) PB (29.00%) PHT (31.80%) OXC (58.50%)	3.50%	1.80%	
EURAP 2013[72]	3784	Prospective registry	Multi (>30)	33.40%	LTG (41.80%) VPA (25.00%) CBZ (32.70%) PB (26.60%)	2.60%	0.56%	
Thomas 2009[79]	643	Prospective registry	Single	53.00%	LTG (44.40%) VPA (49.00%) CBZ (56.70%) PB (60.00%) PHT (66.70%)	1.59%	0.47%	
Vajda 2014[73]	1111	Prospective registry	Multi (3)	-	LTG (51.30%) VPA (27.00%) CBZ (37.80%) LEV (31.70%)	-	-	
Sabers 2009[80]	42	Prospective registry	Single	46.00%	LTG (46.00%)	-	-	
Thomas 2012[77]	1297	Prospective registry	Single	52.20%	CBZ PB PHT VPA CLB CLZ LTG LEV OXC PRM TPM	-	-	
Cagnetti 2014[81]	274	Prospective registry	Single	65.30%	CBZ LEV LTG OXC PB VPA	-	-	
He 2017[60]	155	Prospective registry	Single	67.10%	LEV VPA LTG CBZ OXC PHT TPM	9.68%	5.16%	
Abe 2014[82]	132	Retrospective	Multi (2)	27.30%	PB CBZ VPA CLZ CLB PRM DZP,ZNS	-	-	
Reisinger 2013[83]	115	Retrospective	Single	21.20%	LTG LEV CBZ TPM OXC PHT VPA ZNS ESM	-	-	
Tomson 1994[84]	89	Prospective registry	Single	45.00%	CBZ PHT CLZ PB PRM VPA ESM	-	-	

AED antiepileptic drug; CBZ carbamazepine; CLB clobazam; CLZ clonazepam; DZP diazepam; ESM ethosuximide; LTG lamotrigine; LEV levetiracetam; OXC oxcarbazepine; PB phenobarbitone; PHT phenytoin; PRM primidone; SDD seizure during delivery; SE status epilepsy; TPM topiramate; VPA valproate; ZNS zonisamide

Table 4 Seizure frequency changes in different studies

Study	Study method	Center	Number of pregnancies	SF increased	SF decreased	SF unchanged	AED use	Reference
EURAP 2006[78]	Prospective	Multi (>30)	1956	17.30%	15.90%	63.60%	CBZ OXC LTG VPA PHT PB	First pregnancy trimester
Cagnetti 2014[81]	Prospective	Single	274	23.40%	17.50%	59.10%	CBZ LEV LTG OXC PB VPA	Nine months before pregnancy
Bardy 1987[85]	Prospective	Single	154	32.00%	14.00%	54.00%	PHT CBZ CZP PRM ESM SLT PB VPA	Prepregnancy
Reisinger 2013[83]	Retrospective	Single	115	38.30%	17.40%	44.30%	LTG LEV CBZ TPM OXC	Twelve months before pregnancy
Otani 1985[86]	Prospective	Single	110	16.00%	4.00%	80.00%	PHT PB PRM CBZ VPA	Ten months before pregnancy
Tomson 1994[84]	Prospective	Single	89	15.00%	24.00%	61.00%	CBZ PHT CLZ ESM PB PRM VPA	One month before pregnancy
Gjerde 1988[87]	Prospective	Single	78	17.00%	17.00%	67.00%	CBZ PHT PB VPA PRM CLZ CLB	Prepregnancy
Sabers 2009[80]	Prospective	Single	42	19.00%	10.00%	71.00%	LTG	Prepregnancy
Hoeritzauer 2012[88]	Prospective	Single	39	30.80%	17.90%	51.30%	LEV	Prepregnancy
Pennell 2008[89]	Prospective	Single	36	39.00%	33.00%	28.00%	LTG	Prepregnancy
La Neve 2015[75]	Prospective	Single	36	19%	8%	72%	CBZ VPA	Prepregnancy

AED antiepileptic drug; CBZ carbamazepine; CLB clobazam; CLZ clonazepam; ESM ethosuximide; LTG lamotrigine; LEV levetiracetam; OXC oxcarbazepine; PB phenobarbitone; PHT phenytoin; PRM primidone; SF seizure frequency; SLT sulthiame; TPM topiramate; VPA valproate.

AEDs are metabolized [91]. Different guidelines have different recommendations on monitoring the plasma concentrations of AEDs during pregnancy (Table 5). As in China, WVE are mostly treated with AEDs which have obvious plasma level alterations, and thus have increased seizure frequency during pregnancy [60]. Therefore, we suggest routine monitoring of AED concentration in women with a high risk of seizure occurrence.

A recent study found that withdrawal of or switch from VPA in the first trimester during pregnancy may result in

a loss of seizure control [93]. Thus, epileptologists should always be cautious when adjusting the type or dose of AEDs during pregnancy, and try best to control seizures with the minimum dosages of AEDs.

Perinatal period

The risk of pregnancy-related complications was once considered with no significant difference between pregnant WVE and pregnant women without epilepsy [76].

Table 5 Recommendations from guidelines on monitoring plasma concentration of AEDs during pregnancy

Guidelines	Recommendation
AAN/AES 2009[36]	Monitoring should be considered routinely for LTG (seizure frequency is probably increased when 65% of target level is reached), CBZ, and PHT. Monitoring may be considered routinely for OXC and LVT.
NICE 2012 (update 2016)[38]	Monitoring is not recommended otherwise in routine. Monitoring is recommended if seizures increase or are likely to increase. Monitoring is recommended if dose needs to be adjusted (Lamotrigine and phenytoin are at risk of low serum levels).
ETDP-EFA 2007[37]	Monitoring of AED levels is needed throughout pregnancy. AED levels should be monitored closely in the weeks following delivery since they may increase gradually. LVT, OXC, and LTG showed elevated levels with days of delivery.
RCOG 2016[35]	Routine monitoring is not recommended although individual circumstances may be taken into account.
SIGN 2015[34]	Routine monitoring of AED concentrations is not indicated. Monitoring can be useful in the following circumstances: for adjustment of phenytoin dose, assessment of AED adherence and suspected AED toxicity.

AED antiepileptic drug; AAN American Academy of Neurology; AES American Epilepsy Society; ETPD-EFA Epilepsy Therapy Development Project- Epilepsy Foundation of America; NICE National Institute for Health and Care Excellence; RCOG Royal College of Obstetricians and Gynaecologists; SIGN Scottish Intercollegiate Guidelines Network

However, a retrospective study with 205 deliveries has suggested that WWE using AEDs during pregnancy have an increased risk of severe preeclampsia (odds ratio, 5.0), bleeding in early pregnancy (6.4), induction (2.3) and caesarean section (2.5) than women with no epilepsy, while women without AEDs use only had increased risks of forceps delivery and preterm birth[94]. Recently, the EURAP group has reported that WWE have higher risks of preeclampsia (adjusted relative risk, 1.24), infection (1.85), placental abruption (1.68), induction (1.31), elective cesarean section (1.58), and emergency cesarean section (1.09) than women without epilepsy. Nevertheless, they did not find a relatively higher risk of pregnancy and perinatal complications in women with exposure to AEDs during pregnancy, except for induction of labor (1.30) [55]. So far, whether AEDs play a role in pregnancy and obstetric complications remains uncertain, but a recent meta-analysis has suggested higher risks of spontaneous miscarriage (odds ratio, 1.54), antepartum hemorrhage (1.49), post-partum hemorrhage (1.29), hypertensive disorders (1.37), induction of labor (1.67), caesarean section (1.40), any preterm birth (1.16), and fetal growth restriction (1.26) in pregnant WWE [95]. Hence, WWE are likely to have a higher risk of pregnancy-related complications and cesarean section, and the high cesarean rate is often related to obstetric complications [56]. Therefore, epileptologists and obstetricians should pay attention to prevent those complications in pregnant WWE.

Additionally, women who were not taking AEDs often have a higher percentage of peripartum seizures (4.6%) compared to those on monotherapy (0.5%) or polytherapy (2.3%) [79]. In the case of a seizure, venous access should be prepared for timely administration of clonazepam or midazolam. In the case of generalized tonic-clonic seizures, continuous cardiotocography should be performed. The fetus should be monitored to prevent respiratory complications [96]. Thus, it is suggested that WWE deliver their babies at a hospital if

they have the above conditions.

At birth, all infants of WWE taking enzyme-inducing AEDs should be provided with vitamin K1 (1 mg, intramuscularly) to prevent hemorrhagic diseases unless there are contraindications [97, 98]. If there are additional risk factors for hemorrhagic disease of the newborn (e.g., maternal liver disease, anticipated premature delivery), maternal administration of oral vitamin K1 (phytomenadione, 10 mg daily) in the third trimester of pregnancy should be considered [34].

It is recommended that WWE breastfeed their babies just like normal women, because the plasma concentration of AEDs in babies is low and causes no harm according to previous reports [99, 100], and breastfed children may even have higher IQ and enhanced verbal abilities [101].

Conclusion

While a girl or a woman is diagnosed with epilepsy, epileptologists should select the best therapy for her, and avoid AEDs that would affect the reproductive function (especially VPA), unless there is no better choice. Screening and treatment for reproductive disorders (such as PCOS) by a gynecologist are needed when a woman has typical symptoms or high risks. Epileptologists should inform the patient that becoming pregnant after the seizure is controlled for 9 months is safer for both maternal and fetus health. They should also enquire the patient whether and what OCs she is taking, and then prescribe AEDs without interactions with OCs (such as LEV). Barrier method like condom is recommended if the patient must take enzyme-inducing AEDs or lamotrigine to control seizures. When considering pregnancy, AEDs with high fetal teratogenicity (such as VPA or TPM) should be replaced with other AEDs like LEV and LTG. Patients should also be informed of folic acid intake at 4-5 mg/day from three months prior to conception till the end of the first pregnancy trimester, in order to

prevent fetus malformation and spontaneous abortion. During pregnancy, monitoring the serum concentration of AEDs (especially LTG) is important for the control of maternal seizures with a minimum dose of AED. At 18-20 weeks of gestation, obstetricians should offer the patient an ultrasound examination to assess the fetal anatomy and detect MCMs. One milligram of Vitamin K1 should be administered intramuscularly to newborns of women taking enzyme-inducing AEDs (such as CBZ, OXC and TPM), in order to prevent bleeding diseases.

Although there are many reproductive problems and risks among WWE, over 95% of them have experienced a normal process of pregnancy and have healthy offspring. The above-mentioned risks can be even lower after multidisciplinary management of WWE. However, the new-generation AEDs (such as LEV) have many unknown effects on pregnancy. The pregnancy registry is still the direction of future studies on the interaction between epilepsy and pregnancy. There have already been several large multicenter pregnancy registries in the North America, Australia, the United Kingdom, as well as the International Registry of AED and Pregnancy [22]. It is very important to start such registry as soon as possible in China, or at least in Asia, in order to provide evidence of different ethnicities and help WWE have healthy offspring.

Abbreviations

AAN, American Academy of Neurology; AEDs: antiepileptic drugs; AES, American Epilepsy Society; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; DZP, diazepam; ETPD-EFA, Epilepsy Therapy Development Project-Epilepsy Foundation of America; ESM, ethosuximide; IQ, intelligence quotient; LEV, levetiracetam; LTG, lamotrigine; MCMs, major congenital malformations; NICE: National Institute for Health and Care Excellence; OCB, oxcarbazepine; OCS, oral contraceptives; OXC, oxcarbazepine; PB, phenobarbitone; PCO, polycystic ovaries; PCOS, polycystic ovarian syndrome; PHT, phenytoin; PRM, primidone; RCOG, Royal College of Obstetricians and Gynaecologists; SIGN; Scottish Intercollegiate Guidelines Network, odds ratio (OR); SDD, seizure during delivery; SE, status epilepsy; TPM, topiramate; VPA, valproate; WWE, women with epilepsy; ZNS, zonisamide

Authors' contributions

Wanlin Lai reviewed the relative articles online and was a major contributor in writing the manuscript. Shixu He reviewed the articles online and participated in writing the manuscript. Professor Dong Zhou revised the manuscript for intellectual content. Professor Lei Chen revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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ARTICLE

Cognitive deficits in patients with newly diagnosed and chronic epilepsy and the predictive factors

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Abstract

Objective: To characterize and compare the cognitive deficits in patients with newly diagnosed and chronic epilepsy, and analyze their predictive factors.

Methods: A comprehensive neuropsychological test battery was used to assess neuropsychological functioning in 65 patients with newly diagnosed epilepsy and 101 patients with chronic epilepsy, including Rey Auditory Verbal Learning Test, the Stroop color word test, the Trail Making Test, the Rey-Osterrieth Complex Figure Test, the Verbal Fluency test, the Logical Memory from the Wechsler Memory Scale-revised, the Symbol Digit Modalities Test, and the Boston Naming Test.

Results: The newly diagnosed patients exhibited the most obvious cognitive deficits in delayed verbal memory, while the visual spatial memory and attention function were preserved. Patients with chronic epilepsy exhibited broad cognitive deficits, particularly in attention function and psychomotor speed. Our results revealed that the seizure onset age was positively correlated with cognitive impairment. The number of antiepileptic drugs was inversely related to verbal and episodic memory, visual memory, attention, and psychomotor speed.

Conclusion: Evaluating the nature of cognitive deficit in patients with epilepsy and its related factors may help predict functional recovery and determine the optimal treatment.

Keywords: Epilepsy, Cognitive function, Newly diagnosed epilepsy, Predictive factor, Neuropsychological assessment.

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Introduction

Patients with epilepsy are prone to cognitive and behavioral deficits [1]. The deficits in both global mental functions such as consciousness, energy, and drive, and specific cognitive functions such as attention, memory, and language, may be more debilitating than seizures themselves [2]. Epilepsy *per se* may induce or exacerbate cognitive impairment. A variety of factors may contribute to such deficits, such as the underlying neuropathology, the seizure type, age of onset, psychosocial problems, and treatment-associated side effects [3]. While treating epilepsy is necessary and by itself may resolve or alleviate the cognitive and behavioral deficits associated with the disease, it may also be associated with side effects. The major therapeutic modalities, i.e., antiepileptic drugs (AEDs) and epilepsy surgery, are associated with cognitive and behavioral risks [4]. While the majority of such dysfunctions are reversible, some are not remediable or even avoidable. Currently, no effective treatments are available for epilepsy-related cognitive deficits. Therefore, the treatment of epilepsy must be tailored to individuals while keeping the potential risks in mind.

It is currently unclear whether the cognitive function impairments arise at the beginning of seizure attacks, and the specific types of neuropsychological deficits in patients with newly diagnosed epilepsy and in those with chronic epilepsy. In addition, it is unknown whether certain types of epilepsies, the seizure onset age and AED therapy are characterized by a specific profile of cognitive strengths and weaknesses. Resolving these questions may provide valuable information for the diagnosis and treatment of epilepsy.

In this study, we set out to evaluate the characteristics of cognitive deficits in patients with newly diagnosed epilepsy and patients with chronic epilepsy, and identify the difference (if any) between them. As such, we employed an extensive neuropsychological battery including tests of memory, language, psychomotor and executive function. Using multivariate analysis, we attempt to identify and evaluate a range of factors that might predict neuropsychological deficits in patients with epilepsy, including demographic variables, epilepsy features and treatment with AEDs.

Methods

Participants

In this cross-sectional study, 166 patients with newly

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diagnosed epilepsy ($n = 65$; mean age, 25.3 ± 9.9) and chronic epilepsy ($n = 101$; mean age, 28.6 ± 6.5) who had received AEDs treatment for more than 6 months were recruited when attending an outpatient epilepsy clinic at Huashan Hospital. Another group of neurologically normal participants ($n = 68$; mean age, 28.2 ± 5.8) was employed from the community as the control group. All patients were aged >16 . Based on medical records and neurological examinations, participants with a history of serious medical disorders, progressive neurological diseases, significant psychiatric disturbance, or substance abuse were excluded from the study. The controls were healthy and were not treated with psychoactive medications during neuropsychological testing.

Evaluation

Clinical information of age at seizure onset, type of epilepsy, presence of primary/secondary generalized tonic-clonic seizures, epilepsy duration, seizure frequency in a one-year period and number of AEDs, was verified by chart review in all patients. The participants underwent extensive examination and record review to determine the seizure subtype, based on the International Classification of the Epilepsies [5].

Neuropsychological assessment

Cognitive tests were performed in a sound-attenuated, temperature-controlled room, by an examiner trained in administration of the battery through individual instruction and videotaped examples of test administration. The test battery covered four major areas of neuropsychological functioning that are reported to be impaired in patients with epilepsy: memory, attention and concentration, executive functions, and language function. The specific tests included in the test battery were the Rey Auditory Verbal Learning Test (RAVLT) which measures verbal memory and learning ability [6]; the Stroop color word test (SCWT) which taps attention, freedom from distractibility, and mental flexibility [7]; the Trail Making Test (TMT), a test of speed of visual search, attention, mental flexibility, and visuomotor skill [8]; the Rey-Osterrieth Complex Figure Test (ROCF), a test of visuospatial constructional ability [9]; the Verbal Fluency (VF) test which measures verbal fluency for abstract information, short-term memory and retrieval from semantic memory [10]; the Logical Memory (LM) from the Wechsler Memory Scale-revised (WMS-R), a test that measures verbal and episodic memory [11]; the Symbol Digit Modalities Test (SDMT) that assesses attention, scanning abilities, and motor skills [12]; and the Boston Naming Test (BNT) which reflects the visual confrontation naming capacity [13]. No patient was tested within 12 h of a primarily/secondarily generalized seizure, or within 4 h of a complex partial seizure.

For all neuropsychological tests except the TMT (parts A and B) and SCWT, a higher score indicates better

performance, while for the latter two tests, a higher score is associated with poorer performance.

Ethics

All procedures at every point in the study were approved by the Institutional Review Boards of Huashan Hospital. Written informed consent was obtained from all participants or their parents/ legal guardians on behalf of the minors/children participants.

Statistical analysis

Continuous variables are presented as mean \pm SD. Categorical data are presented as frequencies and were analyzed using the chi-square test with Fisher's exact test. Differences in cognitive scores between two groups were analyzed using Student's *t*-test. In the epilepsy groups, factors that may significantly influence cognitive function were analyzed *via* multiple regression analysis. By using the stepwise multiple regression analysis, all variables were analyzed to screen for those related to the neuropsychological tests. All statistical analyses were conducted with SPSS12.0 for Windows (SPSS Inc., Chicago, IL), and a *P*-value < 0.05 was considered as statistically significant.

Results

The demographics of all participants, and the clinical variables of patients with newly diagnosed epilepsy and chronic epilepsy are presented in Table 1. The three groups were matched in gender, age, and educational level. The patients with newly diagnosed epilepsy did not differ significantly from those with chronic epilepsy in any demographic or clinical background feature, except that the former had an earlier seizure onset and a longer epilepsy duration (Table 1).

The patients with newly diagnosed epilepsy performed poorer than normal controls in immediate and delayed recall of RAVLT, delayed recall of LM, SDMT, SCWT, TMT, VF and BNT (Table 2), but performed better than the patients with chronic epilepsy in immediate and delayed recall of RAVLT, delayed recall of LM, TMT, SDMT, SCWT and copy score of ROCF (Table 3).

Predictive factors for cognitive deficits

Multiple regression analysis revealed that the demographic factor educational level, and clinical factors of seizure onset age, epilepsy duration, and number of AEDs were important factors affecting the cognitive function in patients with epilepsy (Table 4). The seizure onset age was inversely related to the delayed recall of RAVLT, delayed recall of LM, and TMT. The number of AEDs was inversely related to the immediate and delayed recall of RAVLT, copy and recall of ROCF, VF, SDMT, TMT and SCWT. Primarily or secondarily generalized tonic clonic seizure was found to be associated with poor performance in VF and BNT.

Table 1 Demographics and clinical characteristics in each group

	New epilepsy (n = 65)	Chronic epilepsy (n = 101)	Control (n = 68)	New versus chronic epilepsy P value	New epilepsy versus control P value	Chronic epilepsy versus control P value
Gender						
Male (%)	41 (63.1)	64 (63.4)	39 (57.4)	>0.05	>0.05	>0.05
Female (%)	24 (36.9)	37 (36.6)	29 (42.6)			
Age (years)	25.3 ± 9.9	28.6 ± 6.5	28.2 ± 5.8	>0.05	>0.05	>0.05
Educational level (%)						
Elementary school	4 (6.2)	6 (5.9)	3 (4.4)	>0.05	>0.05	>0.05
Middle school	17 (26.2)	32 (31.7)	25 (36.8)			
High school	34 (52.3)	48 (47.5)	29 (42.6)			
College or above	10 (15.4)	15 (14.9)	11 (16.2)			
Seizure onset age (years)	23.77±13.8	18.37±12.2		<0.05		
Duration of epilepsy (range)	6 months–12 years	2–26 years		<0.01		
Seizure frequency, n (%)						
≤1 week	10 (15.4)	13 (12.9)		>0.05		
>1 week, ≤1 month	20 (30.8)	23 (28.8)				
> 1 month, ≤3 months	18 (27.7)	22 (27.5)				
>3 months, ≤6 months	6 (9.2)	13 (16.3)				
>6 months, ≤1 year	8 (12.3)	9(8.9)				
>1 year	50 (76.9)	64 (63.4)				
Seizure type (%)						
Generalized seizure	32 (49.2)	48 (47.5)		>0.05		
Partial seizure	33 (50.8)	53 (52.5)				
Single type	46 (70.8)	65 (64.4)				
Multiple types	19 (29.2)	36 (35.6)				
AEDs therapy (%)						
Monotherapy	-	55 (54.5)				
Combined therapy	-	46 (45.5)				

AEDs anti-epileptic drugs.

Table 2 Comparisons of main scores of neuropsychological tests between patients with newly diagnosed epilepsy and normal controls

Items	New epilepsy	Control	t-value
RAVLT3	7.43±2.31 [§]	9.47±1.71	5.61**
RAVLT5	5.80±2.54 [§]	8.03±2.04	5.43**
LM	10.38±4.60	13.02±3.73	3.52**
TMTB (s)	108.38±46.03	87.48±34.58	2.88**
SDMT	53.00±14.98	62.02±13.73	3.53**
SCWT C	44.37±6.18 [§]	47.06±2.38	3.20**
VF	14.31±5.12 [§]	18.42±3.89	5.07**
BNT	22.37±4.80	25.03±3.00	3.73**

BNT Boston naming test; LM logical memory; RAVLT auditory verbal learning test; SCWT stroop color word test; SDMT symbol digit modalities test; TMT trail making test; **P < 0.01; [§]Differences between means in the newly diagnosed group and the control group are larger than 1 SD.

Discussion

Most patients with epilepsy exhibit a normal range of intelligence, albeit with inter-subject variability. Nevertheless, patients with epilepsy have been found to exhibit impaired cognitive performance compared to healthy subjects matched for age and education [14]. Multiple adverse factors for cognition have been found in epilepsy, including the etiology of seizures, cerebral lesions acquired before onset of seizures, seizure type, age at onset of epilepsy, seizure frequency, duration

Table 3 Comparisons of main scores of neuropsychological tests between patients with newly diagnosed epilepsy and those with chronic epilepsy

Items	New epilepsy	Chronic epilepsy	t-value
RAVLT3	6.35±2.16	7.17±2.37	2.12*
RAVLT5	4.43±2.68	5.65±2.55	2.67**
LM	8.16±5.32	10.04±4.91	2.08*
TMTB (s)	166.69±108.46	116.35±53.71	3.13**
SDMT	39.07±16.13	50.50±15.55	4.12**
SCWT C (s)	100.41±48.79	75.00±28.62	3.43**
ROCF	30.60±7.46	33.91±4.66	2.38*

LM logical memory; RAVLT auditory verbal learning test; ROCF rey-osterrieth complex figure test; SCWT stroop color word test; SDMT symbol digit modalities test; TMT trail making test; VF verbal fluency *P < 0.05, **P < 0.01.

and severity, intractable and interictal physiological dysfunction, structural cerebral damage caused by repetitive or prolonged seizures, hereditary factors, psychosocial factors, and sequelae of treatments for epilepsy, including AEDs and epilepsy surgery [15].

To our knowledge, the occurrence and the types of cognitive impairment associated with epilepsy remain largely unknown, especially in adult epilepsy. One study examining a community-based cohort of children reported that, when first diagnosed with epilepsy, approximately one out of four individuals (26.4%) exhibited evidence of subnormal global cognitive

Table 4 Multivariate progressive regression analysis of related factors for main neuropsychological tests ($n = 166$)

Multivariate progressive regression equation	
RAVLT3=	$3.496+0.996$ educational level ^{**} -0.402 number of AEDs [*]
RAVLT5=	$2.507+1.078$ educational level ^{**} -0.797 CPS-0.041 seizure onset age [*] -0.0466 number of AEDs ^{**}
LM2=	$4.046+2.215$ educational level ^{**} -1.457 number of AEDs ^{**} -0.093 seizure onset age ^{**}
DS=	$34.300-6.751$ number of AEDs ^{**} +7.301 educational level ^{**} -0.371 age ^{**}
TMTB (s)=	$170.614+30.999^{**}-22.938$ educational level ^{**} +1.398 seizure onset age [*]
SCWTC (s)=	$135.279-16.483$ educational level ^{**} +15.525 number of AEDs ^{**}
VFT=	$7.797+2.170$ educational level ^{**} -2.712GTCS ^{**} -1.940 number of AEDs ^{**} -0.008 epilepsy duration [*]
ROCF=	$7.690+2.271$ educational level ^{**} -1.883 number of AEDs [*]
BNT=	$13.004+3.073$ educational level ^{**} -2.050 CPS ^{**} -1.922 GTCS [*]

AEDs antiepileptic drugs; BNT Boston naming test; CPS complex partial seizure; GTCS generalized tonic-clonic seizure; LM logical memory; RAVLT auditory verbal learning test; ROCF rey-osterrieth complex figure test; SCWT stroop color word test; TMT trail making test; VF verbal fluency * $P < 0.05$, ** $P < 0.01$.

function [16]. A study on newly diagnosed adult epilepsy in China reported that 59.3% of patients had mildly declined cognitive function [17]. Adult patients with newly diagnosed epilepsy exhibit cognitive deficits in verbal learning, verbal memory, episodic memory, attention, naming ability and psychomotor function. Among these deficits, the delayed verbal memory is the most pronounced, while visual spatial memory and attention function are preserved. The results of this study were consistent with the findings of a previous study in Nigeria, which reported cognitive impairments in memory psychomotor speed and sustained attention in patients with newly diagnosed epilepsy [18].

Here, we found that compared with the newly diagnosed cases of epilepsy, patients with chronic epilepsy exhibited broad cognitive deficits, especially in terms of attention function and psychomotor speed. Importantly, they had a longer epilepsy duration, earlier seizure onset age, and longer-term exposure to AED therapy, suggesting that these factors may be related to the attention and psychomotor impairments.

Further, multivariate analysis revealed that, apart from demographic characteristics such as sex, age and educational level, the seizure onset age, epilepsy duration, seizure type and the number of AEDs were also related to cognitive functions in patients with epilepsy. In particular, the age of seizure onset was positively correlated with cognitive impairment, especially in verbal memory, attention and visual motor skills. This finding indicates that an earlier seizure onset is associated with better cognitive function outcomes among patients. It has been reported that children with a seizure onset under 5 performed significantly worse in IQ tests than those with a late seizure onset, regardless of the partial or generalized seizures [19]. Children with a seizure onset >5 years typically display behavioral problems more often than cognitive deficits [20]. It has also been reported that the early-onset left temporal lobe epilepsy confers a less pre- to postoperative decline in confrontation naming ability, suggesting intrahemispheric reorganization of language function among these patients [21]. The current

results suggest that early onset may be protective, presumably due to the functional plasticity at the time of early cerebral injury and the increased potential for reorganization of function.

There is convincing evidence supporting that the generalized tonic-clonic seizures with a risk of intra-ictal cerebral hypoxia are more likely to impair cognitive functions than simple or complex partial seizures. Histologically, a condition of prolonged brain anoxia is usually characterized by neuronal loss, most prominent in the hippocampus. It has been demonstrated that memory deficits in patients with epilepsy might be secondary to anoxia [22, 23]. Our results showed that generalized tonic clonic seizure was related to cognitive deficits in naming capacity, short-term memory and retrieval from semantic memory, suggesting a potential temporal lobe impairment, which is possibly related to prolonged seizure attacks and increased seizure severity.

In this study, we also found that the complex partial seizure was related to delayed verbal memory and naming capacity impairment, which adds to the limited data on cognitive characteristics in patients with complex partial seizure. The temporal lobe epilepsy, which is usually accompanied by memory deficits due to damage to the hippocampal system, is the most frequent cause of complex partial seizures. The classic model of material-specific memory proposes that lesioning or resection of the hippocampus of the left temporal lobe produces deficits in verbal memory, while that of the right temporal lobe produces deficits in visual memory. Temporal lobe epilepsy, particularly the bilateral type, is commonly associated with language difficulties, verbal and visual memory problems, and features of post-ictal psychosis [4, 24].

AEDs produce global changes in the excitation levels in the central nervous system, and commonly lead to cognitive and behavioral deficits. AEDs affect cognition by suppressing neuronal excitability or enhancing inhibitory neurotransmission. Polypharmacy and high blood levels of an AED may increase the risk of cognitive side effects [4]. We found that the use of more AEDs was associated with poorer performances in verbal and

episodic memory, constructional ability, visual memory, attention, and psychomotor speed.

There is convincing evidence that seizures with a higher frequency and a longer duration are associated with more severe cognitive deficits [25]. In addition, generalized cognitive impairment with a global decline in attention, memory, and general intelligence is more likely to occur with increasing seizure frequency and epilepsy duration [26]. Here we found an inverse relationship between epilepsy duration and verbal memory impairment. However, the seizure frequency was not included in multiple regression analysis in the current study. We consider seizure frequency not to be a consistent variant, since it typically changes throughout the epilepsy. The seizure frequency analyzed here was the average value in the previous year before cognitive assessment, and it cannot represent the general seizure severity. As such, we did not reveal a relationship between seizure frequency and cognitive function. This finding does not conflict with previous studies [25, 26].

The present study may have been limited by sampling bias. Because our samples were recruited from a general tertiary hospital in China, patients with well-controlled epilepsy were likely to have been under-represented. Besides, a follow-up longitudinal study on the newly diagnosed group would be critical to confirm or disprove the differences observed in this study.

In conclusion, cognitive impairment of verbal learning, verbal memory, episodic memory, attention, naming ability and psychomotor function is present in patients with newly diagnosed epilepsy. Patients with chronic epilepsy exhibit broad cognitive deficits, especially in attention function and psychomotor speed. The educational level, seizure onset age, epilepsy duration and number of AEDs are factors associated with cognitive function in patients with epilepsy. Evaluating the nature of cognitive deficit in patients with epilepsy and its related factors may help predict functional recovery, make rehabilitation recommendations, and determine the optimal treatment.

Abbreviations

AED, antiepileptic drug; BNT, Boston naming test; LM, logical memory; RAVLT, auditory verbal learning test; ROCF, rey-osterrieth complex figure test; SCWT stroop color word test; SDMT, symbol digit modalities test; TMT, trail making test; VF, verbal fluency; WMS-R, Wechsler memory scale-revised

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Competing interests

None of the authors have any conflict of interest to disclose.

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ARTICLE

Analysis of electroclinical features of nonconvulsive status epilepticus: a study of four cases

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Abstract

Objective: To advance the recognition of nonconvulsive status epilepticus (NCSE).

Methods: We reported 4 cases of NCSE and reviewed the semiology, electroencephalogram features, etiology, treatment, and prognosis of NCSE.

Results: The 4 patients manifested with typical symptoms and EEG patterns of NCSE. With a favorable response to antiepileptic drugs, they all had a good outcome without any sequela.

Conclusion: NCSE is characterized by vague or no obvious symptoms, thus being often underrecognized, underdiagnosed or even undetected by clinicians. NCSE may have a favorable outcome in most patients.

Keywords: Nonconvulsive status epilepticus, Electroencephalogram, Treatment, Prognosis.

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Introduction

The nonconvulsive status epilepticus (NCSE) is an epileptic condition characterized by continuous or recurrent seizure activity, and diverse clinical symptoms such as alterations of mental state, abnormal behavior, perception disturbances or consciousness impairment, accompanied by generalized or focal epileptiform activity on the electroencephalogram (EEG), usually lasting more than 30 min [1,2]. On the other hand, there is also proposition that the duration be greater than 1 hour [3].

The NCSE is much more common than was considered in the past. NCSE constitutes about 25%–50% of all status epilepticus (SE) cases, with an incidence of 2-8/100,000 per year [4,5]. According to the previous studies, NCSE is traditionally divided into two subtypes: the generalized NCSE and the focal NCSE. The generalized NCSE includes the absence status epilepticus (ASE) which was first described by Lennox in 1945 [6] and atypical absence SE. The focal NCSE, also referred to as complex partial status epilepticus (CPSE), was initially described by Gastaut in 1956 [7], and is characterized by prolonged

or recurrent complex partial seizures. In recent years, some experts put forward a more detailed classification as discussed below.

The diagnosis criteria for NCSE include a period of behavioral change from baseline, EEG evidence of epileptic activity, and a response to antiepileptic drugs (AEDs) [2,8]. In comparison to clinical signs (if any) which are often subtle and nonspecific, the EEG criterion is indispensable for the diagnosis of NCSE. In most cases, diagnosis of NCSE relies largely on EEG symptoms, especially in comatose patients [9]. In addition, debates still remain on whether a response to AEDs can be used as the diagnostic criterion. Some clinicians believe that although a response to benzodiazepine confirms the diagnosis, an absence of response cannot simply exclude the diagnosis.

In comparison to generalized tonic-clonic status epilepticus (GCSE) which exhibits a state of ongoing convulsions and may cause a significant morbidity and mortality, the NCSE is featured by little or no evidence of movement or other symptoms, and thus is often underrecognized, underdiagnosed or even neglected by clinicians. In this article, we report 4 cases of NCSE and further review the semiology, EEG features, etiology, treatment and prognosis of this disease, with the aim of helping clinicians better recognize and diagnose this subtype of SE.

Case reports

Case 1

A 47-year-old woman had experienced epileptic seizures for 4 years. During initial seizures, she manifested with

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complex partial seizures as follows: she first became motionless suddenly, then her eyes and head deviated to the right, with hands fumbling. The event usually lasted no more than 1 min, and there were no signs to predict it. The above seizure type occurred twice a year. The patient did not pay any attention to these events or seek any medical advice until she experienced two generalized tonic-clonic seizures (GTCS) 2 years later. Magnetic resonance imaging (MRI) of the brain showed increased signals on T2-weighted images suggestive of the left mesial temporal sclerosis, and the interictal-EEG showed left frontal and left temporal intermittent sharp waves. Then she began an oxcarbazepine regimen (600 mg/day), and did not experience seizures in the next two years.

One day at the age of 46, the patient suddenly became confused, upset, slow in reacting to the outside world and gave irrelevant answers to other's questions. This episode lasted through the day and gradually resolved. The patient did not go to the hospital for any treatment. One month later, she followed the doctor's advice to increase the oxcarbazepine dose to 750 mg/day during a routine visit to outpatient service.

At the age of 47, the patient suddenly became confused again, slow to react, and kept doing meaningless movements like washing her hands repeatedly, as noticed by her family. To simple questions, she either failed to respond or gave delayed, often inappropriate responses. She could not execute instructions properly, either. The episode lasted about 20 h without remission, so she was transferred to our hospital. The physical examination showed that the patient was confused, slow in speech and disoriented. She was scored 13 points for MMSE. Video-EEG was applied and demonstrated persistent 2.5- to 3.5-Hz generalized spike-and-wave discharges, with frontal and central predominance (Fig. 1a). The patient was given an intravenous administration of 10 mg of diazepam, and almost immediately, the EEG started to recover (Fig. 1b) and the discharge resolved within 2 min (Fig. 1c), but the symptoms still existed. About 30 min later, the video-EEG showed re-occurrence of 2.5- to 3-Hz spike-and-wave, slow waves and spike discharge (Fig. 1d), so the patient was further given an intravenous 10 mg of diazepam. After 3 min, normal background EEG rhythms returned (Fig. 1e), but they only lasted 20 min and again evolved into a spike-and-wave complex (Fig. 1f). However, almost all of the clinical symptoms had disappeared by this time. The patient recovered to have clear consciousness, was fluent in speech and capable of responding correctly, and was scored 23 points for MMSE. Given the clinical remission, the patient was given an oral administration of 1000 mg of levetiracetam instead of another diazepam dose. Two hours later, her EEG patterns returned to normal, eventually with a total clinical remission (Fig. 1g). When the patient left hospital, her regimen was adjusted as levetiracetam 1000 mg/day and oxcarbazepine 600 mg/day. In the following

one month, she never experienced any seizure again, and was scored 29 points for MMSE one month after the event.

Case 2

A 62-year-old woman was admitted to Xuanwu Hospital for experiencing episodes of being slow to react, speechless, and answering incorrectly to questions in the past 2 years. Each attack lasted 1 to 2 days. Despite treatment with lamotrigine and carbamazepine (switched to oxcarbazepine later), the seizure still occurred every 3 to 4 days. It is worth mentioning that she never had any GTCS during the disease course. Her previous MRI showed increased signals in the right hippocampus and abnormal signals in the boundary region of the right temporal lobe and insula.

During her stay in our hospital, a seizure occurred. The clinical symptoms were almost the same as before: slow reaction, reduced speech and clouding of consciousness. Physical examination revealed normal orientation, decreased calculation, and a slightly lower MMSE (26 points) score than normal. This episode lasted more than 20 h. During the attack, video-EEG monitoring showed 4- to 7-Hz generalized spike-and-wave complex and spikes (Fig. 2a). At first, the patient was given an intravenous diazepam (10 mg) and an intramuscular injection of phenobarbitone (100 mg), but no improvement was seen. She did not recover from the seizure and the EEG was basically unchanged. Thirty minutes later, she was given a further intravenous injection of 10 mg of diazepam, then the symptoms disappeared and EEG resolved as well within 5 min (Fig. 2b).

Case 3

A 48-year-old man was sent to our emergency room of Shunyi District Hospital by his family because they noted that he was a little confused, restless, upset and not fluent in answering questions through the day with no improvement at all. He had been diagnosed as "epilepsy" and "low intelligence" for more than 10 years. With intermittent oral administrations of phenytoin and phenobarbital, the seizures were well controlled. In our emergency room, the video-EEG showed generalized, continuous 2.5- to 4-Hz spike-and-wave patterns (Fig. 3). He was given an intravenous injection of diazepam (10 mg) and an infusion of diazepam (30 mg), and several minutes later, he came back to normal with almost all symptoms gone. But as the postictal EEG was not recorded at that time, whether the spike-and-wave pattern resolved or not after the treatment was unknown.

Case 4

A 59-year-old woman was transferred to Xuanwu Hospital. She was complaining about episodes of being confused for one day, but could respond to others,

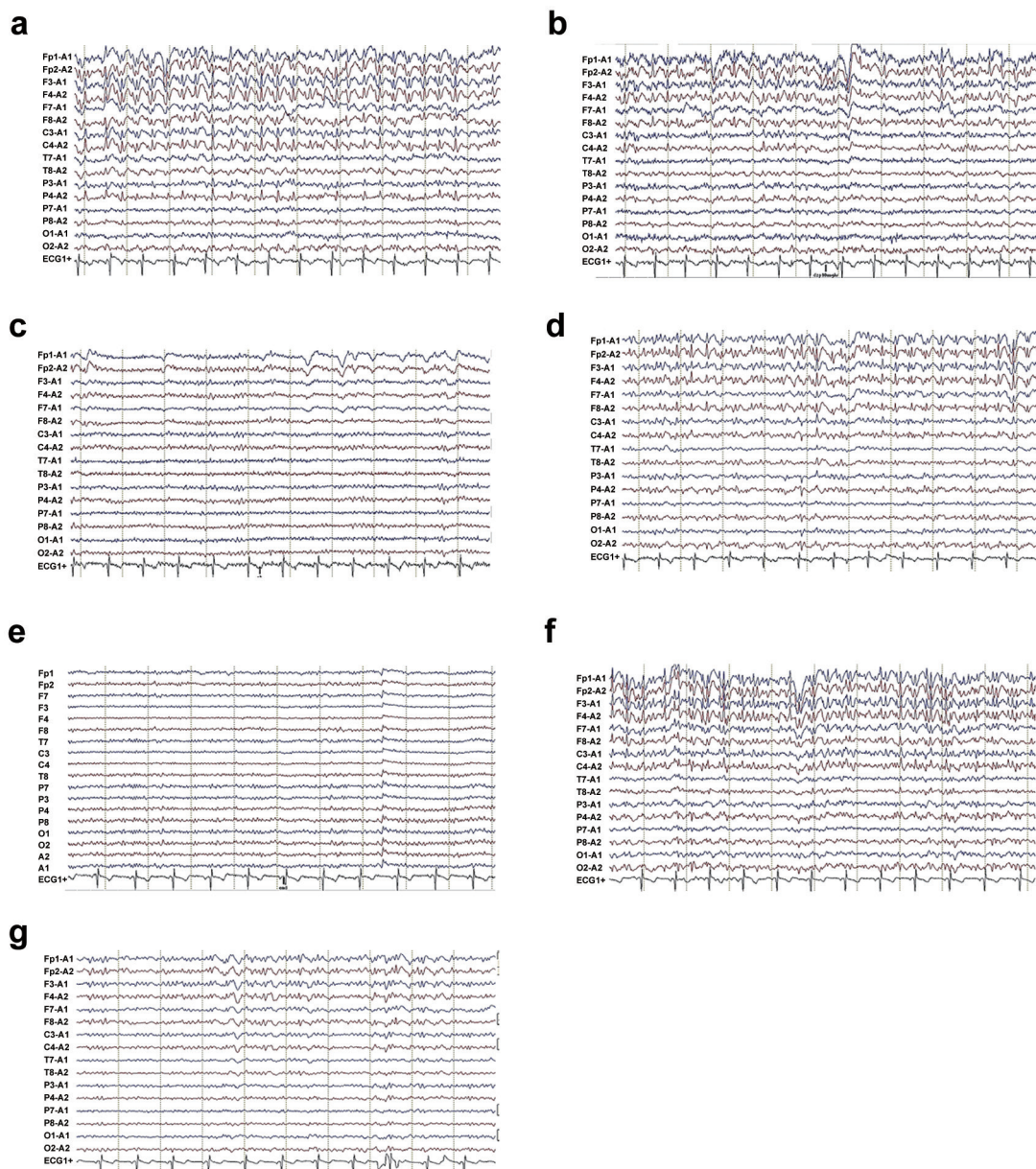


Fig.1 EEG recordings of case 1. a. 2.5- to 3.5-Hz generalized spike-and-wave discharges associated with symptoms of being confused, slow in speech and disoriented. b. The EEG started to return to normal once the patient was given intravenous administration of 10 mg of diazepam. c. Resolution of generalized spike-and-wave pattern within 2 min after intravenous administration of 10 mg of diazepam. d. Thirty minutes later, EEG showed 2.5- to 3-Hz spike-and-wave, spikes and slow waves with frontal and central predominance again. e. Within 3 min after another 10 mg of diazepam, normal background EEG rhythms reappeared. f. Although the EEG evolved into spike-and-wave pattern again, the patient became free from symptoms: being clear in consciousness, fluent in speech and capable of responding correctly. g. The EEG eventually returned to normal with a total clinical remission.

though very slowly. She could also handle dressing, eat meals and do some housework by herself. It seemed that there was nothing wrong with the patient but a little confused to strangers. She did not have a pre-existing history of epilepsy. Her past history included diabetes mellitus (DM) for several years, but the blood sugar level was well controlled with two kinds of hypoglycemic drugs. Once hospitalized, she received

the video-EEG monitoring, which showed sharp-and-wave and sharp waves at the bilateral frontal, central, parietal and sphenoid electrodes (Fig. 4). Given the mild symptoms, she was not given an intravenous therapy, but an oral administration of levetiracetam (500 mg/day). Her clinical signs disappeared gradually and were totally gone on the next day. The postictal EEG was also not recorded.

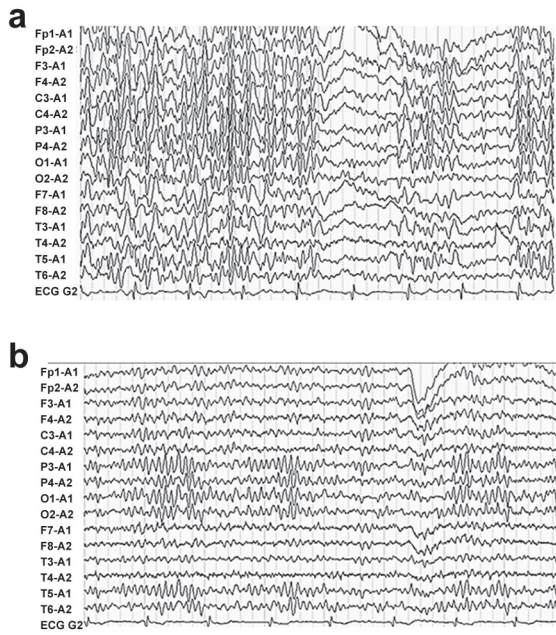


Fig.2 EEG recordings of case 2. a. Generalized 4- to 7-Hz spike-and-wave complex and spikes during behaviors associated with slow reaction, reduced speech and clouding of consciousness. b. The symptoms disappeared and EEG pattern resolved after treatment.

Discussion

In recent years, there have been increasing attempts by physicians to better define and classify NCSE, in order to establish treatment paradigms for different subtypes. Instead of the traditional dichotomy, some clinicians suggested that classification should be more elaborated. First, NCSE can be divided into two categories: the

generalized and the focal NCSEs. The generalized NCSE comprises typical absence SE, atypical absence SE and late-onset absence SE. The focal NCSE consists of simple partial SE (SPSE), complex partial SE (CPSE) and subtle SE [10]. Regardless of the type, the classification scheme is mainly based on clinical symptoms and EEG features. However, in fact, it is sometimes quite difficult to distinguish between generalized and focal NCSEs, especially when there is no EEG available. Even with the availability of EEG data, it is still hard to differentiate these subtypes because the EEG pattern can be a transient phenomenon. For example, it can be focal initially and transform to be generalized later, or the opposite[11]. Therefore, clinicians should take advantage of all information available to determine the subtypes, with at least diagnosis of NCSE in extreme difficulties.

Unlike convulsive status epilepticus which is easy to diagnose from the clinical manifestations, NCSE is often misdiagnosed, sometimes even undetected because of its protean symptoms. Therefore, NCSE was used to be considered as a rare condition. In this report, most of the 4 cases presented with impaired consciousness (confused, slow reaction and lags in response) and some strange behaviors (being upset and restless or washing hands repeatedly). None of them had any obvious motor symptom like tonic or clonic movements. Notably, the clinical signs of case 4 were so mild that spectators may overlook these abnormalities and come to a conclusion of “Nothing wrong with her. Maybe she is just a little tired”. Indeed, the semiology of NCSE is diverse and daedal. Some patients present with typical absence or complex partial SE, whereas some may display other unusual alterations of consciousness (varying from mildly inattentive, confused, somnolent to unresponsive), affect (euphoric, anxious, amused, etc.),

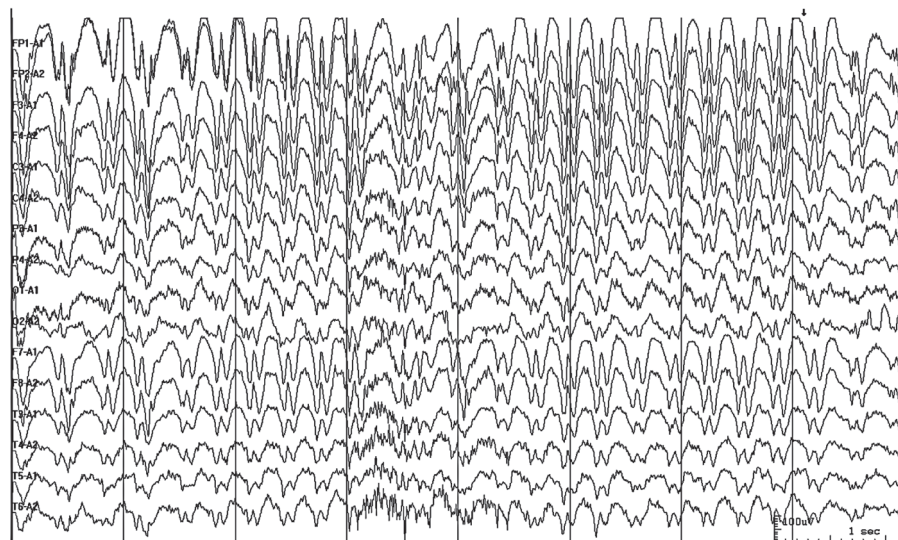


Fig.3 EEG recordings of case 3. The EEG showed generalized 3.5- to 4.5-Hz spike-and-wave pattern associated with symptoms of being confused, restless, upset and not fluent in answering questions.

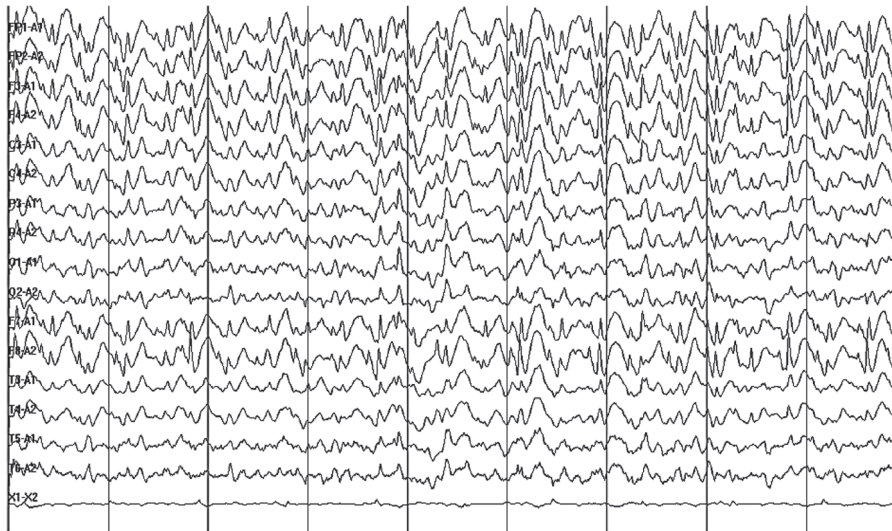


Fig.4 EEG recordings of case 4. Generalized 3- to 5-Hz spike-and-wave with frontal and temporal predominance.

behavior (agitated, bizarre and inappropriate; Fugue states), speech and language (slow or decreased speech and volume; dysarthria, speech arrest), motor (staring, blinking, bradykinesia; automatisms like chewing, grimacing, licking, kissing, picking, and ambulation; subtle facial, perioral, and limb myoclonus, tremor, apraxia, clumsiness; head deviation) and autonomic/vegetative symptoms [2,8]. Even comatose patients without overt seizure activity may meet the diagnosis criteria of NCSE [9,12]. Thus most symptoms of NCSE are so inconspicuous that they can be easily neglected by others, even the family members. Moreover, it is not uncommon for some clinicians to mistake NCSE for postictal confusion after a generalized tonic-clonic seizure [13], transient global amnesia, hysterical fugue states, acute psychosis, migraine aura, posttraumatic amnesia, and severe depression, which may result in the underrecognition and underdiagnosis of NCSE[10,14].

Apart from the above clinical manifestations, EEG also plays an important role in the diagnosis of NCSE. Under some circumstances where clinical signs are subtle or even absent, EEG is becoming especially valuable. However, we have to note that EEG interpretation is a subjective “art”, and diagnosis of NCSE based on it may not come to consistency among interpreters. Furthermore, EEG of NCSE can have various forms, which makes it more difficult to interpret. Some clinicians suggest that the typical EEG features of NCSE are typical spike-and-wave, atypical spike and wave, multiple spike-and-wave, and rhythmic delta with intermittent spikes. These discharges may be continuous or persistent with brief pauses of a few seconds, or intermittent [15]. Some have also mentioned that different subtypes may show different EEG patterns. ASE usually manifests with continuous or frequently recurring generalized spike and wave discharges during

the ictal period, and the number of spikes per wave is >1 [16]. CPSE manifests with continuous or persistent sharp wave and spike-and-wave discharges, which can have a generalized onset or a focal onset that frequently progresses into the generalized pattern [17]. In this report, EEG of the 4 cases initially manifested with either a focal or a generalized onset, then evolved into spike-and-wave pattern gradually. Three cases, except for case 2, all presented with focal predominance. To facilitate clinicians to recognize and diagnose NCSE, the following EEG diagnostic criteria have been suggested: frequent or continuous focal electrographic seizures; the amplitude, frequency and spatial distribution change with time; patients without a pre-existing epilepsy history manifest with frequent or continuous generalized spike wave discharges; in patients with an epileptic encephalopathy/syndrome, EEG presents with frequent or continuous generalized spike wave discharges which are significantly different in intensity or frequency (usually a higher frequency) from baseline EEG; patients who are in coma after a generalized tonic-clonic SE show periodic lateralized epileptiform discharges or bilateral periodic epileptiform discharges [18].

According to the previous studies, the underlying causes and medical conditions of NCSE may include pre-existing epilepsy, metabolic disorders, alcohol withdrawal, the use of some neuroleptic/psychotropic drugs, cerebral infarction or hemorrhage, infection like meningitis and encephalitis, sepsis, carbon monoxide exposure and toxicity [10,19]. There are even some case reports of NCSE associated with AEDs, like tiagabine [20]. Among the 4 cases, three had a history of complex partial epilepsy except for case 4 with an unknown cause.

As far as is concerned, the most challenging work for clinicians is to diagnose NCSE rather than to treat it. Nevertheless, there is still debate over how aggressive the

treatment should be. The most widely-accepted opinion is that the treatment should be individualized, due to the diverse causes and types. Typical ASE is usually treated by intravenous administration of 10 mg of diazepam or 4 mg of lorazepam, which can be repeated if the seizures continue 10 min after the treatment [10]. Atypical ASE may not have a favorable response to benzodiazepines. Valproic acid and phenobarbital are reasonable alternatives. In patients with pre-existing epilepsy, SPSE and CPSE may respond to benzodiazepines rapidly, sometimes even spontaneously terminate without any medical therapy. In this report, the first three patients with pre-existing partial epilepsy all responded well to benzodiazepines (diazepam) in both clinical and EEG aspects. As for those without a history of epilepsy but with other underlying causes and medical conditions, SPSE and CPSE are usually refractory to the first-line treatments. In that case, subsequent intravenous phenobarbital or valproic acid should be added [21]. However, here we found that in the case 4 patient who did not have a previous history of epilepsy, the clinical signs gradually disappeared after an oral administration of levetiracetam, without an intravenous medicine like benzodiazepines, phenobarbital or valproic acid. Therefore, it remains unknown whether the NCSE terminated spontaneously or because of the medicine, though levetiracetam has also been proved to be an effective treatment in recent years [22,23]. Although medical treatment has been proved to be helpful, in some occasions aggressive treatment can have a greater risk for morbidity and mortality [24,25]. For example, comatose NCSE patients treated with benzodiazepines may worsen [26]. So caution should be taken with drug administration.

The outcome assessment of NCSE is challenging for clinicians because it is difficult to separate the effects of ongoing seizure activity from those of an underlying course and complications which occur in the clinical course. The prognosis of NCSE remains controversial. Some case series have reported high mortality and morbidity rates. Shneker et al. found that 18 NCSE patients in their series died (18%), and suggested that the mortality is significantly associated with the underlying etiology, severe mental status impairment, and development of acute complications [27]. Kjersti and his colleagues reported a poor outcome in 48 NCSE patients: 3 died (6.3%), 4 had severe sequelae (8.5%) and 7 had cognitive sequelae (14.9%). They concluded that the absence of previous seizures is a predictor for a worse outcome than the patients having epilepsy before NCSE [28]. Also, some clinicians have emphasized that NCSE, especially CPSE, can lead to a poor outcome: death, persistent or permanent cognitive or memory loss, and motor and sensory dysfunction [29]. Qiu et al. found that children suffering from ASE showed a significant increase of apparent diffusion coefficient value in the left medial

prefrontal cortex, which was positively associated with duration of epilepsy [30]. Furthermore, some researchers have confirmed that serum neuron-specific enolase (s-NSE), a marker for acute neuronal injury, is increased significantly in NCSE patients, indicating that NCSE can cause brain injury [31-33]. So these authors insist that the aggressive therapy is indeed necessary and worthy. On the contrary, some clinicians have suggested that NCSE is a kind of "benign" condition and the outcome is quite good. They suggest that even inadequate treatment can lead to favorable prognosis [34]. Some researchers believe that NCSE would not cause damage to the brain, and the high morbidity in some case series of NCSE may be due to the underlying disease of the patients rather than the NCSE *per se* [35]. In this report, all the 4 patients had a good prognosis without any cognitive and severe sequela. The favorable prognosis may be associated with the pre-existing epilepsy, satisfactory response to medication (the first 3 cases), and the extremely mild clinical signs (case 4).

Conclusion

NCSE is a great burden both for families and in economic concerns. Despite a favorable outcome in most patients, it still can be fatal in some cases. The risk of death will be increased if patients are untreated or receive insufficient treatment. Yet there are no widely accepted definition and criteria of NCSE, which makes it difficult to diagnose this disease and administer corresponding treatment. What is more, it remains unclear how aggressive the treatment should be. Further work should be focused on these aspects, with the aim for establishing and improving the diagnosis of and treatment patterns for NCSE.

Abbreviations

ASE, absence status epilepticus; ASW, atypical spike-and-wave; biPEDs, bilateral periodic epileptiform discharges; CPSE, Complex partial status epilepticus; EEG, electroencephalogram; GCSE, generalized tonic-clonic status epilepticus; GTCS, generalized tonic-clonic seizures; MSW, multiple spike-and-wave; NCSE, nonconvulsive status epilepticus; RDIS, rhythmic delta with intermittent spikes; SPSE, simple partial status epilepticus; SE, status epilepticus; TSW, typical spike-and-wave

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Competing interests

None of the authors have any conflict of interest to disclose.

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