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REVIEW

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Cognitive Disorders in Juvenile Myoclonic Epilepsy

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Abstract

Cognitive disorders are often associated with epilepsy and are a result of a combination of various factors. This review describes scientific advances in the field of cognitive disorders in patients with juvenile myoclonic epilepsy (JME), the most common form of idiopathic generalized epilepsy. Data in this review were collected through an extensive literature search of available full-text publications in PubMed and eLIBRARY.RU databases. We selected four theories of the origin of cognitive impairment in JME patients for discussion, based on the analysis of available studies. Our findings highlight the etiological heterogeneity of cognitive disorders in JME and the importance early screening for them. **(Int J Biomed. 2017; 7(1):9-14.)**

Keywords: juvenile myoclonic epilepsy • cognitive disorders • epileptiform discharges • antiepileptic drugs

Abbreviations

AEDs, antiepileptic drugs; **CBZ**, carbamazepine; **CDs**, cognitive disorders; **EDs**, epileptiform discharges; **EEG**, electroencephalography; **IQ**, intelligence quotient; **IGE**, idiopathic generalized epilepsy; **JME**, juvenile myoclonic epilepsy; **LTG**, lamotrigine; **LVT**, levetiracetam; **PHT**, phenytoin; **TPM**, topiramate; **VPA**, valproate.

Introduction

JME is the most important syndrome of IGE, which is accompanied by frequent myoclonic jerks, generalized tonic-clonic seizures and, less commonly, absences.[1] JME was first described as a syndrome by Janz and Christian in 1957.[2] The peak of disease onset is between ages 14 and 16, with a range of 8–26 years. Under the proposal for revised classification of epilepsies and epileptic syndromes, in 1989 the ILAE Commission on Classification and Terminology defined JME (impulsive petit mal) as follows:[3] "Impulsive petit mal appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. Often, there are GTCS (generalised tonic-clonic seizures) and, less often infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation." A smaller proportion of patients report that seizures may be associated with "thoughts and concentration" (23%) or hand activities (20%).[4,5]

IGE is a socially significant disease with disadvantageous behavioral traits and poor social outcome. Social cognition is the ability to elaborate mental representations of social interactions, to use them correctly in social contexts; it includes the attribution of cognitive and affective mental states to self and others, and presumably relies on complex fronto-temporal interactions.[6]

Recent studies have demonstrated that individuals with JME who were followed over 25 years showed subtle anomalies in brain structure and cognition and poor long-term social outcomes when followed over 25 years, including depression, social isolation, and underemployment.[7,8] Cognitive impairments are frequent consequences of epilepsy.

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Various factors can have a debilitating effect on cognitive function in epilepsy, including underlying structural lesions and disorders that cause epilepsy, seizure type and frequency, presence of interictal epileptic discharges, age at onset, duration of epilepsy, and AED treatment.[9] These impairments cause educational, vocational and management problems for patients. The systematic review of A. Loughman et al.[10] provides a quantitative synthesis of cognitive function outcomes in 26 peer-reviewed, case-controled studies published since 1989. Univariate random-effects meta-analyses were conducted on seven cognitive factor-domains and separately on executive function. Patients with IGE demonstrated significantly lower scores on tests across all cognitive factor-domains except visual-spatial abilities.

The results obtained in the study of J. O'Muircheartaigh et al.[1] provide convincing evidence for abnormalities in a specific thalamo-cortical circuit, with reduced structural and task-induced functional connectivity, which may underlie the functional abnormalities in JME. Neuropsychological studies revealed subtle cognitive deficits in JME patients, mainly implicating the frontal lobes.[11] Dysfunction of these areas results in deficits of concept formation, abstract reasoning, planning and self-regulation of behavior, and control of impulsivity and emotions. These functions have been summarized under the term "executive functions," which refers to processes of elaboration of cognitive and behavioral responses and strategies for the achievement of immediate or future goals.[12,13] However, a strong focus on hypothesis of selective executive deficits may have distracted attention from the pervasive nature of cognitive impairment in patients with IGE and, in particular, JME.[10] Authors highlight, "Since these impairments are likely to have significant educational, vocational and management impact for a proportion of patients, future studies of cognition in IGE and ME should ensure that cognitive abilities are sampled in a broadly representative fashion, so as not to underestimate the potential impact of these seizure syndromes."

Patients with epilepsy tend to have somewhat lower intellectual abilities than in the general population; however, verbal memory and language capacities are usually intact, whereas attention problems often associated with IGE do not depend on the intellectual level of the patients. Therefore, the natural reason for these complications and their connection with the epileptic process are the focus of study by many scientists. The goal of this review was to evaluate scientific literature about cognitive disorders (CDs) in JME and discuss the proposed theories of cognitive dysfunction with this disease.

Data in this review were collected through an extensive literature search of available full-text publications in PubMed and eLIBRARY.RU databases. We considered studies published from 2008 to 2014 and several earlier works (not earlier than 2000), referred by other authors. "Juvenile myoclonic epilepsy" and "cognitive disorders" were used as keywords.

Cognitive functions are defined as an intellectual process by which one becomes aware of, perceives and comprehends ideas. It involves all aspects of the ability to see and to hear, and the ability to think, perceive, reason, and remember.[14]

We considered four theories of CDs in JME:

1. Impact of EDs and disease-related characteristics
2. Adverse side effects of AEDs
3. Genetic predisposition theory
4. Cerebrocortical microdysgenesis

Impact of epileptiform discharges and disease-related characteristics

Human status epilepticus is consistently associated with cognitive problems. Seizures or abnormal EEGs are responsible for the cognitive deterioration. G. Holmes et al.[15] suggest that interictal spikes, particularly if frequent and widespread, can impair cognitive abilities, through interference with waking learning and memory, and memory consolidation during sleep. There are a number of studies using continuous EEG and video EEG monitoring, which indicated that patients without attacks have better results for some cognitive tasks compared to patients with epileptiform EEG activity. Some studies found greater cognitive problems in patients with generalized seizures than in patients with partial seizures;[16] others found it vice versa.[17] Complaints of memory difficulties are common among patients with temporal lobe epilepsy, where memory-related brain structures are directly involved in seizure activity.

In many patients, sensitive methods of observation, notably continuous psychological testing, show brief episodes of impaired cognitive function during EDs. C. Binnie[18] described the phenomenon of transitory cognitive impairment (TCI) in about 50% of patients who show subclinical EDs. These TCIs may be associated with behavioural disorders.

Lavandier et al.,[19] using continuous EEG and video monitoring, found that some frontal tasks were more impaired in patients with epileptiform EEG activity during rest than in those without discharges.

K. Carvalho et al.[20] studied CDs in 61 patients with specific endophenotypes of JME. Patients were divided into 4 groups: no reflex traits (Group 1), praxis induction (Group 2), eye-closure and/or photosensitivity (Group 3), and a combination of different reflex traits (Group 4). All patients underwent Neuropsychological and psychiatric assessment. the clinical variables, e.g. age at epilepsy onset, frequency of myoclonic seizures, total and sedative drug load were also controlled. Praxis induction was more common in groups with reflex traits (2, 3, and 4) presented higher rates of persistent myoclonia, polytherapy, clonazepam use (group 3), and more frequent psychiatric comorbidities. Group 4 patients performed worse in Trail Making Test B than the patients in Group 1. These findings were independent of clinical variables. The authors concluded that the combination of praxis induction and eye-closure/photosensitivity produces greater executive dysfunction, revealing an association between reflex ictogenic mechanisms and cognitive performance.

J.M. Lee et al. [12] showed that JME patients had memory and executive dysfunction and that these cognitive deficits were correlated with age at seizure onset and duration of epilepsy. These results may be consistent with the theory of disease-related characteristics. The authors also noted that

the impaired attention in patients was probably due to a high frequency of interictal EDs.

M. Motamedi et al.[13] investigated possible cognitive dysfunction in the patients with JME and its correlation to factors related to epilepsy and patients' demographic variables. The study showed significant differences between JME patients and healthy controls with respect to scores of mental control (*P=0.015*), forward digit span (*P=0.004*), total digit span (*P=0.008*) and IQ (*P=0.003*). In addition, age, education level, duration of epilepsy and medication showed an impact on several cognitive functions in the patients with JME. The authors concluded that JME is associated with impairment in specific cognitive domains and more specifically in the frontal, prefrontal and memory domains.[13] However, more investigations of JME patients should be performed to understand the associations between cognitive dysfunction and factors related to epilepsy

Adverse side effects of antiepileptic drugs

The deleterious effect of AEDs on cognition is well documented in epileptic patients and volunteer studies.[21,22] The major cognitive effects of AEDs are impaired attention, vigilance, and psychomotor speed, but secondary effects on other cognitive functions can be seen. Even in patients who do not report cognitive changes, neuropsychological tests have shown significant impairments.[21] Almost all AEDs have a negative impact on different aspects of cognition based on the type of therapy (mono or poly), doses, and drug generation.

Differential cognitive effects that are seen with various AEDs. CBZ,[23,24] PHT,[25,26] and VPA[27] can adversely affect cognition to a similar extent, which appears to be less than that of barbiturates and benzodiazepines.[28,29] The limited studies done to detect the effect of new AEDs on cognition revealed that new AEDs such as gabapentin (GBP),[30] lamotrigine (LTG),[31] zonisamide (ZNS),[32] and levetiracetam (LEV) [33] have fewer effects on cognition than do older drugs. Increased doses of AEDs, rapid initiation, and polytherapy entail an increased risk. In general, the cognitive effects of AEDs are less than the sum total of other factors and are usually reversible.[34]

R. Thomas et al.[35] examined 60 patients with drug-refractory JME and concluded that patients were profoundly impaired across the range of tests evaluating intellectual function, memory, language and naming, executive function, the impact of epilepsy, and AED side effects. Eighty-three percent of patients exhibited frank executive dysfunction, which was moderate to severe in 66%. A high prevalence of neurotoxicity symptoms such as fatigue and poorer functioning across intellectual and memory tests were also identified.

JME patients are usually treated with VPA or LTG, more rarely with TPM, and recently also with LVT. Few data exist as to possible cognitive side effects of LVT, but LVT is believed to be well tolerated, showing few cognitive side effects.[36]

In a study by R. Roebling,[37] 10 of 19 patients with JME took VPA either in monotherapy or in combination with another AED. The subgroup of patients treated with VPA scored significantly worse in the verbal memory test (*P=0.043*) and scored worse in most other tests but without reaching significance when compared to the patient subgroup taking either no medication or LTG in monotherapy. Withdrawal of VPA showed a trend toward an improvement of cognitive processing.[38]

It also must be noted that there are reports suggesting that patients with treatment-refractory seizures present a broader impairment related to cognitive deficits and impulsive traits than patients amenable to treatment.[39]

In general, the deleterious effect of AEDs on cognition could be attributed to: (1) Na+ channel blockade, (2) enhanced GABAergic activity, and (3) decrement in glutamate-mediated excitation.[40]

Simultaneously, there are also studies that describe a positive effect of AEDs on cognitive disorders. In general, the beneficial effects of AEDs on cognition could be due to: (1) reduction of seizure activity; (2) modulating effect on neurotransmitters, lowering excitotoxicity associated with a reduction in glutamate release from presynaptic terminals and preventing anoxic depolarization capacities; (3) inhibition of Ca2+-mediated cellular functions (protein phosphorylation and neurotransmitter release) and Ca2+-dependent depolarization; (4) scavenging of free radicals; and (5) their psychotrophic effect. [40,41]

It can be concluded that CDs in JME patients may at least partially be caused by side effects of medication. The basic mechanisms underlying AED-induced cognitive impairments require further investigation.

Genetic predisposition theory

One reason for a variation between results of different research groups may be the genetic and phenotypic heterogeneity of the disease. It is widely accepted that JME is a disease with a high genetic predisposition. JME has both Mendelian inheritance and complex genetic inheritance and accounts for 3% (population-based prevalence) to 12% (hospital/clinic-based prevalence) of all epilepsies.[42,43] Forty-nine percent of our JME families have clinical and EEG traits that are 'vertically' inherited over several generations, suggesting an autosomal dominantly inherited disease. In the other 51%, variants of JME genes, with small to modest effects, contribute to risk/susceptibility and to its complex genetics.[44] It therefore became necessary to carry out neuropsychological family studies to understand the role genes play in the development of cognitive impairment in children with JME.

M. Levav et al.[45] studied 65 families, in which one member had epilepsy. The disorders included childhood absence epilepsy, JME and temporal lobe epilepsy. JME relatives had lower scores than other relatives in tests of visual and auditory sustained attention and attentional flexibility, and showed greater variability in response time.

Iqbal et al.[46] examined expressive language, memory, and higher executive tasks in JME patients as compared with their siblings and a normal control group under video-EEG conditions. Eight sibling pairs, one in each pair with JME, were compared with 16 controls matched for age, sex, ethnicity, and educational level. The JME group differed significantly

from controls on measures of phonemic and semantic verbal fluency. In addition, they more frequently reported behavioral traits associated with executive dysfunction (i.e., impulsivity) on a behavior rating scale. Qualitative inspection of the data suggested a trend for JME patients and their siblings to perform worse than controls on some measures, notably those of expressive language and higher executive function, but on other measures the differences were not statistically significant.

B. Wandschneider[47] studied complex paradigms of the different phases of prospective memory (intention formation, intention retention, intention initiation, intention execution) in 19 JME patients, 21 siblings, and 21 healthy controls. Patients with JME and siblings showed specific deficits during intention formation and intention execution of prospective memory. Patients with JME were more impaired than both siblings and healthy controls.

Currently, five Mendelian JME genes are listed in OMIM or the "Online Mendelian Inheritance in Man" (http://omim.org and http://www.ncbi. nlm.nih.gov/omim/). These cause primarily channelopathies and are comprised as follows: CACNB4 (calciumchannel beta4 subunit),[48] CASR (calcium channel sensor receptor),[49] GABRa1 (GABA receptor alpha one subunit),[50] GABRD (GABA receptor delta subunit),[51] and Myoclonin1/EFHC1 (myoclonin1/ one EF-hand containing gene).[52]. Three SNP susceptibility alleles of putative JME genes in epistasis, namely, BRD2 (bromodomain-containing 2),[53] Cx-36 (connexin 36),[54] and ME2 (malic enzyme2),[55] have been reported to be major susceptibility alleles that contribute to the complex genetics of JME.[42,56] The effect of epistasis is due to influences of multiple genes. This complexity accounts for the obscured inheritance patterns, which must be present in JME.[58]

For example, T. Chachua et al.[59] found a highly significant dominance trait (aggression) in the Brd2+/- haploinsufficient mice compared with the wild type, more pronounced in females. Brd2+/- mice of either sex did not differ from wild-type mice in spatial learning and memory tests. Compared with wild-type littermates, it was found that there were decreased numbers of GABA neurons in the basolateral amygdala, which is consistent with the increase in aggressive behavior. Brd2+/- haploinsufficient mice showed no cognitive impairment but have behavioral traits similar to those found in patients with JME (recklessness, aggression).

It should be noted that Mendelian JME genes and non-Mendelian risk alleles have not been defined in over 90% of affected patients.[56]

Cerebrocortical microdysgenesis

The discovery of the interaction between the motor system and frontoparietal cognitive networks prompted scientists to conduct neuropathological studies of the brain in JME patients. Microdysgenetic lesions were found in the neocortex and subcortical white matter of the frontal lobes and the hippocampus, which suggested a disorder in neuron migration and cortical disorganization. Thus, HJ Mencke and Janz D,[60] in seven of the eight cases of primary generalized epilepsy, found marked microdysgenesis with varying regional distribution.

Woermann et al.,[61] using an interactive anatomical segmentation technique and volume-of-interest measurements of MRI, showed that 40% of JME patients had significant abnormalities of cerebral structure. The voxel-based statistical parametric mapping comparison between the group of JME patients and the control subjects showed an increase in cortical grey matter in the mesial frontal lobes of the patients. The authors concluded that obtained findings indicate a structural cerebral abnormality in JME, with involvement of mesiofrontal cortical structures.

On the other hand, Tae et al.[62] showed that the cortical thicknesses of superior/middle/medial frontal gyri, and superior/middle/inferior temporal gyri were decreased in JME patients. Moreover, cortical thicknesses of precentral gyrus and medial orbital gyrus of right hemispheres were negatively correlated with disease duration. These findings suggest that JME brains have cortical gray matter atrophy in the frontal and temporal lobes.

S. Kim et al.,[63] using the combined structural and diffusion tensor MRI analysis, found that 18 JME patients compared with 22 normal controls exhibited white matter alterations in the antero-superior corona radiata, both centro-parietal regions, and the left temporal lobe. JME patients also had reduced gray matter thickness (right paracentral lobule, precuneus, dorsolateral parietal and inferior temporal cortex; left dorsolateral frontal and anterior temporal areas). Furthermore, manual volumetry analyses revealed a significant volume reduction in the bilateral thalami and hippocampi. Thus, there is some evidence that microdysgenesis could be important in epileptogenesis, but the mechanisms involved remain unknown and difficult to investigate. A consensus on what histopathological criteria to use for the diagnosis of microdysgenesis is needed to explore this further.

In conclusion, the available evidence indicates a distinct cognitive impairment pattern in JME. However, many questions remain to be answered regarding the relationship between cognition and JME. In each case, it is difficult to determine whether cognitive and behavioral impairments in JME are caused by stable, disease-related factors or by the acute effects of paroxysmal epileptic activity, such as epileptiform EEG discharges. The harmful effects of an early onset of seizure and longer duration of disease on cognition have been well demonstrated. These results may be consistent with the theory of disease-related factors. The theory of the acute effects of paroxysmal activity on cognition has also an extensive evidence database. Neuropsychological studies of patients who are seizure free after receiving AEDs medication are needed to answer this question. Described microstructural abnormalities point to the supplementary motor area being a crucial hub in a thalamo-frontocortical network. The pathophysiologic concept of a genetically determined thalamo-frontocortical network dysfunction in JME is supported by family studies.

Thus, cognitive disorders in JME are etiologically heterogeneous.[64] However, all studies were performed in small cohorts of patients, in most cases not exceeding 30

patients. Therefore, this problem requires further and extensive investigation.

Competing interests

The authors declare that they have no competing interests.

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