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Review

Juvenile myoclonic epilepsy — Neuroimaging findings

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ABSTRACT

Juvenile myoclonic epilepsy (JME) has been classified as a syndrome of idiopathic generalized epilepsy and is characterized by specific types of seizures, showing a lack of pathology using magnetic resonance imaging (MRI) and computed tomography scanning. However, JME is associated with a particular personality profile, and behavioral and neuropsychological studies have suggested the possible involvement of frontal lobe dysfunction. The development of highly sensitive neuroimaging techniques has provided a means of elucidating the underlying mechanisms of JME.

Positron emission tomography demonstrated metabolic and neurotransmitter changes in the dorsolateral prefrontal cortex reflecting the particular cognitive and behavioral profile of JME patients. ^{1}H-magnetic resonance spectroscopy has shown evidence of thalamic dysfunction, which appears to be progressive. Such techniques provide evidence of multi-focal disease mechanisms, suggesting that JME is a frontal lobe variant of a multi-regional, thalamocortical 'network' epilepsy, rather than a generalized epilepsy syndrome. Quantitative MRI revealed significant abnormalities of cortical gray matter in medial frontal areas close to the supplementary motor area and diffusion abnormalities with increased functional coupling between the motor and prefrontal cognitive systems. This altered structural connectivity of the supplementary motor area provides an explanatory framework for the particular imaging findings, seizure type, and seizure-provoking mechanisms in JME.

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1. Introduction

Juvenile myoclonic epilepsy (JME) is characterized by myoclonic jerks, generalized tonic-clonic seizures, and, less frequently, absence seizures, with a typical sleep and wake pattern in relationship to seizures. The seizures may be precipitated by a variety of stimuli, including sleep deprivation, fatigue, alcohol intake, menses and stress, but more specifically following complex cognitive tasks, described as praxis-induction. Thalamocortical dysfunction is considered to be the major mechanism of JME, and, as with other IGE syndromes, JME is defined by electrophysiological features that show involvement of both cerebral hemispheres from the beginning of seizures. According to the criteria of the International League Against Epilepsy, structural brain abnormalities using magnetic resonance imaging (MRI) and computed tomography (CT) are not found in JME.

Juvenile myoclonic epilepsy is associated with normal intelligence. However, it has been noted that JME is associated with a particular personality profile, and behavioral and neuropsychological studies have suggested subtle frontal lobe dysfunction. Moreover, neuropathological studies have provided evidence of microdysgenesis in IGE, in the form of cortical and subcortical dystopic neurons and other microscopic structural abnormalities.

The development of highly sensitive neuroimaging techniques has allowed the identification of subtle functional and structural abnormalities, providing a means of elucidating the underlying mechanisms of JME and the relative contribution of focal versus generalized dysfunction.

2. Neuroimaging in JME

2.1. Positron emission tomography

Positron emission tomography (PET) allows the tomographic delineation of cerebral structures and the measurement of tissue concentrations of injected radioactive tracers at the molecular level and may be performed when the subject is at rest or during or following the occurrence of a seizure, the undertaking of a cognitive or motor task, or the administration of a drug. A study using PET and bolus injections of $H_2^{15}O$ was used to measure cerebral blood flow in patients with IGE and a history of absence seizures [1]. It showed that in

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addition to a global increase in cerebral blood flow during absence seizures, there was a significant focal increase in thalamic blood flow, providing evidence that the thalamus plays a key role in the pathogenesis of typical absence seizures.

Swartz and colleagues [2] performed a ^{18}FGD-PET study using a visual working memory paradigm in nine JME patients and 14 controls. Pairs of abstract images were presented and subjects had to indicate by pressing a button whether the images were matching or not. Defined by the delay between the two images, two conditions were created: the immediate match to sample task (IMS), with an image delay of 100 ms, controlled for attention, motivation, motor function, and habituation, whereas the delayed match to sample task (DMS; delay 8000 ms) evaluated the visual working memory. Two categories of mistakes (match-on-mismatch and mismatch-on-match) were recorded as well as reaction times for correct and incorrect answers. The JME patients' performance was comparable to controls on the IMS task but impaired during the working memory condition. Considering possible confounders, groups showed no significant age difference. The authors concluded that dysfunctional thalamo-fronto-cortical networks might account for both ictogenesis and poor working memory performance.

At resting state, ^{18}FDG uptake in patients was decreased in the ventral premotor cortex, caudate, the dorsolateral prefrontal cortex (DLPFC) bilaterally, and the left premotor area, representing widespread frontal impairment. Controls activated areas which are thought to support working memory function, whereas patients presented with a "hypofrontality state" in keeping with poorer performance in the DMS task. Increased metabolism of the lateral orbital and medial temporal regions was interpreted as compensatory mechanisms for prefrontal dysfunction.

In a resting FDG-PET study [3], regional cerebral rates of glucose uptake values (rCMRGlc) were regressed on various executive function test scores in patients with frontal lobe epilepsy (FLE; n = 18), JME (n = 10), and healthy controls (n = 14). The executive function battery included measures of cognitive flexibility, fluency, response inhibition, working memory, and sustained attention. In the JME group, frontal hypometabolic values predicted impairment on measures of figural fluency and cognitive flexibility.

Flumazenil (FMZ), a specific, reversibly bound, high-affinity neutral antagonist of cBZR, can be ^{11}C-labeled and used with PET to provide a marker for the integrity of γ-amino butyric acid (GABA) — the principal inhibitory neurotransmitter in the brain. A study using ^{11}C-FMZ-PET demonstrated that $GABA_A$–cBZR binding is globally increased in the cerebral cortex of patients with JME and other forms of IGE [4]. Frontal lobe $GABA_A$–cBZR binding was particularly elevated in patients with JME but not in patients with other forms of IGE [5].

At a neurotransmission level, evidence exists that serotonergic processes may be involved in the pathophysiology of myoclonus. In human subjects, serotonin 1A receptor binding can be examined in vivo with positron emission tomography (PET) and the radioligand ^{11}C-WAY-100635. Testing the hypothesis that JME may be associated with a disturbance (a hyperreactivity) of serotonergic neurons, leading to altered serotonin 1A receptor binding, Meschaks et al. [6] observed reduced WAY-100635 binding potential in the dorsolateral prefrontal cortex, raphe nuclei, and hippocampus, but not motor cortex (Fig. 1). The observed reductions in serotonin 1A receptor binding suggest that the serotonin system is affected in JME, although provide no definitive information about underlying mechanisms.

Based on previous data showing that the dopamine system is involved in motor as well as cognitive functions, Ciumas et al. [7] investigated the binding potential to the dopamine transporter (DAT) in the midbrain, substantia nigra, caudate, and putamen, and if such changes are linked to dysfunctions in 12 patients with JME compared to 12 healthy controls. Dopamine signaling seemed impaired in the target regions for dopaminergic neurons with reduced

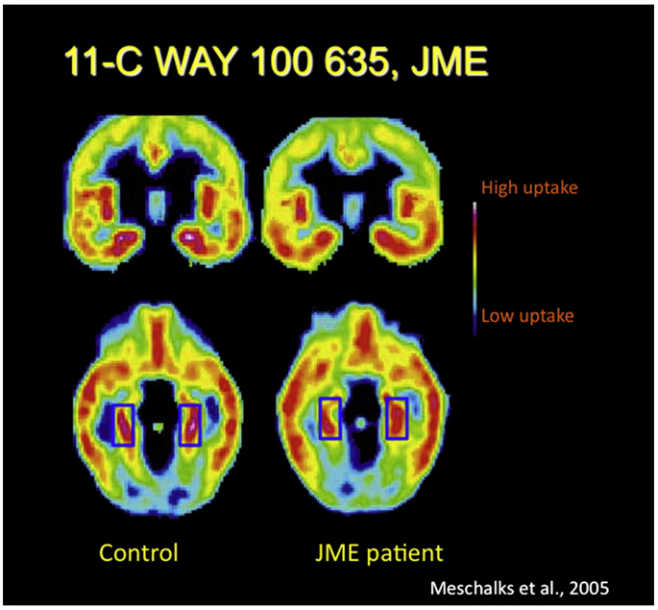

Fig. 1. Late uptake images. ^{11}C-WAY-100635 in a patient with juvenile myoclonic epilepsy (JME) and control. The images illustrate low uptake in the hippocampus and raphe in the patient. The patient's right side is to the left in the image.

binding potential in the substantia nigra and midbrain (p = 0.009 and 0.007), but normal values in the caudate and putamen.

In a second study of Ciumas et al. [8], JME patients were compared with patients with epilepsy with generalized tonic-clonic seizures (GTCS) only. Both patient groups showed a reduced BP compared to controls, albeit in different locations. Juvenile myoclonic epilepsy patients had a lower tracer binding than controls in the midbrain (0.8 +/− 0.1 vs. 1.0 +/− 0.2, p = 0.019), whereas GTCS patients had reduced tracer binding in the putamen (5.9 +/− 1.6 vs. 7.1 +/− 1.2, p = 0.023). While GTCS patients showed impaired performance in motor functions and on one test of executive function, JME patients performed poorly also in tests of working memory and several tests of executive function. Alterations in the DA system seem to exist in both GTCS and JME. However, the regional distribution of these changes differs between the two syndromes, as does their association with psychomotor and working memory performance.

2.2. Proton magnetic resonance spectroscopy

Whereas conventional MRI provides structural information based on signals from water protons, proton magnetic resonance spectroscopy (^{1}H-MRS) provides information on the chemical composition of the brain. Since *N*-acetyl aspartate (NAA) is found exclusively in neurons and neuronal processes, a reduction in the level of NAA can be an indication of neuronal damage or dysfunction [9].

Using this technique, thalamic NAA concentrations were found to be significantly lower in IGE patients than in controls [10]. Volumetric MRI did not identify a significant loss in thalamic volume in these patients, indicating thalamic neuronal dysfunction, rather than loss, in agreement with previous neuropathological studies [11]. Moreover, a negative correlation was found between NAA levels and duration of epilepsy, indicating that thalamic dysfunction in IGE may be progressive.

Proton magnetic resonance spectroscopy has indicated that NAA levels are reduced in the thalami of JME patients, supporting the idea that thalamic dysfunction is part of the underlying mechanism of epileptogenesis in JME [12].

However, ^{1}H-MRS has also demonstrated that patients with JME have significantly reduced prefrontal concentrations of NAA, compared with controls, demonstrating that prefrontal cerebral