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REVIEW

Understanding juvenile myoclonic epilepsy: Contributions from neuroimaging

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Summary Advanced neuroimaging techniques have been utilised with ever increasing frequency over the last 10 years. A range of structural and functional imaging modalities have been employed to study the neurobiological mechanisms and anatomical substrates underlying epileptic syndromes. Advanced neuroimaging studies of juvenile myoclonic epilepsy (JME) have utilised PET, SPECT, MRI, DTI and MRS, with all modalities revealing evidence of predominantly frontal lobe and thalamic changes. Abnormalities correlate with clinical features such as seizure frequency and disease duration in some studies. Findings contribute to the ongoing debate surrounding the classification of epileptic syndromes, suggesting JME is a predominantly frontal thalamocortical network epilepsy, challenging the concept of a generalised epilepsy. Existing studies are limited by sample size and methodological considerations, and future studies need to address these as well as pursue underlying mechanisms for phenotypic variation in this heterogenous disorder. The present review aims to outline the existing literature on advanced neuroimaging in JME and highlight future directions for study.

Contents

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Introduction

This systematic review aims to outline the contributions made by advanced neuroimaging techniques for understanding the aetiology and pathophysiology of juvenile myoclonic epilepsy (JME), and the impact this potentially has on revisions to the classification of generalised and focal epilepsy syndromes. JME is a common idiopathic generalised epilepsy, characterised by myoclonic jerks, generalised tonic clonic seizures and less frequent absence seizures, with characteristic electroencephalogram (EEG) findings and normal clinic brain imaging. Related syndromes include juvenile absence epilepsy (JAE) where absence seizures are prominent and myoclonic jerks do not or only rarely occur, and epilepsy with generalised tonic clonic seizures only. An overview of JME is given below followed by a review of the literature of advanced neuroimaging in JME. We performed a series of PubMed searches using the terms JME and/or juvenile myoclonic epilepsy, together with DTI, MRI, MRS, neuroimaging, PET, SPECT, VBM and MEG. Reference lists of relevant studies were manually searched to identify studies not detected by the PubMed search. Relevant review articles on related topics were identified for inclusion as further reading in our reference list. Studies involving patients with JME are covered in detail; in addition to studies of generalised spike wave (GSW), the EEG hallmark of JME. Key features of significant studies are summarised in Table 1

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The earliest description of JME is credited to Théodore Herpin, who in 1867 described a 13 year old boy who developed upper body jerks and then generalised seizures three months later (Herpin, 1867; Pearce, 2005). Descriptions of similar patients by other authors followed but it was not until 1957, 90 years later, that Janz and Christian published a report of 47 JME patients and the clinical features were recognised as a syndrome in their own right (Janz and Christian, 1957). They named the syndrome ''impulsive petit mal'', and over the next 30 years various other names were used, most notably ''Janz Syndrome''. It was not until 1989 that the terminology was unified to juvenile myoclonic epilepsy and the syndrome was admitted to the international classification of epileptic syndromes (ILAE, 1989).

The population prevalence of epilepsy in western populations is 0.7—1% and JME can be expected to account for 5—10% of all adult epilepsy patients, and 26% (the commonest) of all idiopathic generalised epilepsies (IGE) (Panayiotopoulos et al., 1994; Montalenti et al., 2001; Kobayashi et al., 2008). Myoclonic jerks begin in adolescence (age 12—18) with a mean age of onset of 15.4 years. Approximately 90—95% of patients have generalised tonic-clonic seizures (GTCS), mean age of onset 15.5 years, and 30—50% have absence seizures (AS), mean age of onset 11.5 years (Renganathan and Delanty, 2003). Two to three percent may have myoclonus only, and there are descriptions of JME evolving out of childhood absence epilepsy (Martinez-Juarez et al., 2006).

Seizures occur in the first few hours after waking; myoclonic jerks are bilateral, irregular and arrhythmic, affecting predominantly the arms and occurring in single or clustered jerks, sometimes building to a GTCS. Seizures are commonly precipitated by alcohol, sleep deprivation and emotional stress and respond well to Valproate in 80% of cases. Whilst the generally held view is that treatment in most cases needs to be lifelong (Calleja et al., 2001), there is more recent population based data to suggest that almost half of patients may be able to discontinue drug treatment in the long term (Camfield and Camfield, 2009). Photosensitivity is estimated to occur in 30—40% of JME patients, but can be elicited more commonly with more prolonged visual stimulation (Appleton et al., 2000).

Standard EEG in JME typically shows 3—6 Hz GSW or polyspike-wave activity, with a fronto-central predominance, though frequencies outside this range are not unusual (Delgado-Escueta and Enrile-Bacsal, 1984; Pedersen and Petersen, 1998; Montalenti et al., 2001). Focal EEG discharges, have been reported in up to 45% of patients (Aliberti et al., 1994; Jayalakshmi et al., 2010) and are a source of diagnostic errors (Panayiotopoulos et al., 1991). More recently dense array EEG and quantitative analysis has suggested that 'generalised' discharges on standard EEG originate in orbitofrontal, mesiofrontal, and to a lesser extent, temporal lobe regions (Holmes et al., 2010). Visual inspection of standard clinical magnetic resonance imaging (MRI) shows no disease specific structural abnormalities (ILAE, 1989). Genetic studies indicate an interaction of multiple susceptibility genes and the environment. Even in families where a monogenic inheritance pattern does occur, the phenotype often consists of other IGE subsyndromes within the same family, including JME (Kobayashi et al., 2008; Lu and Wang, 2009). Multiple genetic loci have been identified by linkage studies (Zifkin et al., 2005). Important mutations have been identified in the EHFC1 gene (6p12-11), encoding a calcium channel (Suzuki et al., 2004); the GABRA1 gene (5q34-35) encoding the α1 subunit of $GABA_A$ receptors (causing autosomal dominant JME) (Cossette et al., 2002); and the CACNB4 gene (2q22-23) encoding the voltage gated calcium channel β4 sub-unit (and also found in episodic ataxia pedigrees) (Escayg et al., 2000). Potential mechanisms for these mutations causing JME are proposed; their place in the JME population as a whole and their interactions with other genes and the environment are still to be determined.

Personality traits such as impulsivity, poor planning, emotional instability, mental inflexibility and indifference were noted in early descriptions (Janz and Christian, 1957), and have been borne out in systematic studies (Kim et al., 2007b;