Cerebellar Degeneration in Epilepsy

Subjects: Others
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Cerebellar degeneration has been associated in patients with epilepsy, though the exact pathogenic mechanisms are not understood. The aim of this study was to identify the prevalence of cerebellar degeneration in patients with epilepsy and identify any pathogenic mechanisms. Methodology: A systematic computer-based literature search was conducted using the PubMed database. Data extracted included prevalence, clinical, neuroradiological, and neuropathological characteristics of patients with epilepsy and cerebellar degeneration. Results: We identified three consistent predictors of cerebellar degeneration in the context of epilepsy in our review: temporal lobe epilepsy, poor seizure control, and phenytoin as the treatment modality. Whole brain and hippocampal atrophy were also identified in patients with epilepsy. Conclusions: Cerebellar degeneration is prevalent in patients with epilepsy. Further prospective studies are required to confirm if the predictors identified in this review are indeed linked to cerebellar degeneration and to establish the pathogenic mechanisms that result in cerebellar insult.

Keywords: epilepsy ; cerebellar degeneration ; ataxia

1. Introduction

Epilepsy affects approximately 50 million people worldwide [1] and an estimated 362,000 to 415,000 people in England [2]. Epilepsy is characterised by recurrent and unprovoked seizures [3]. Based on the International League Against Epilepsy (ILAE) Guidelines, epilepsy can be classified by seizure type, epilepsy type, and epilepsy syndrome. Causes of epilepsy include structural, genetic, infectious, metabolic, immune, and unknown factors [4].

Much of what is known about the cerebellum stems from examining the consequences of damage to it [5]. The classical symptoms of cerebellar dysfunction include a broad array of clinical signs, with the most commonly noted being ataxia (a combination of slurred speech, limb incoordination, and gait instability) [6].

The past three decades have witnessed a shift in our understanding of the cerebellum, its function and significance in various neurological conditions [7]. This new understanding, challenges traditional views, suggesting that the cerebellum is associated with the modulation of a variety of cognitive functions including perception, language, memory, and emotion [8][9][10][11].

Cerebellar degeneration refers to the chronic and irreversible loss of neuronal structure and function within the cerebellum [12]; the Purkinje cells are most susceptible. The causes of cerebellar degeneration can be broadly divided into two categories; acquired and genetic [13]. Acquired cerebellar degeneration has been attributed to endogenous or exogenous non-genetic causes [14], such as alcohol abuse and vitamin deficiencies [15], infections of the central nervous system (CNS) [16], autoimmune disorders [17], and primary or metastatic tumours [17], among others. Neuroimaging studies including magnetic resonance (MR) and nuclear medicine techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) provide structural and functional assessments of cerebellar atrophy [18].

Cerebellar degeneration has been associated with epilepsy [19]. Marcian et al., (2016) [19] postulated a triad of questions; is cerebellar dysfunction a coincidence, consequence, or cause of epilepsy. The authors suggested that cerebellar degeneration can be attributed to cellular damage from seizure activity, the effects of anti-epileptic drugs (AEDs), anoxic-ischaemic injury from seizures, or cerebral hemiatrophy of the cerebellum [20][21][22]. Some patients with epilepsy display variable severity of ataxia as a result of structural cerebellar damage. Sometimes this is merely part of a syndrome where both epilepsy and cerebellar degeneration are features (e.g., mitochondrial diseases), but in many cases, ataxia may be a direct result of seizure mediated cell loss or an adverse effect of certain anti-epileptic medication. Cerebellar damage is also said to result in disinhibition of cerebral epileptic activity. Animal studies have evidenced that cerebellar stimulation induces inhibition of paroxysmal epileptic waves in the cerebrum. Complete ablation of the cerebellum exhibited continuous hypersynchronous activity, in Sprague Dawley rats [23]. Studies linking radiological evidence of cerebellar

dysfunction with clinical cerebellar ataxia in patients with epilepsy is also limited. However, the question still remains as to whether atrophy of the cerebellum, causing it to lose its inhibitory effect on cerebral epileptic activity, is the cause or effect of worsening disease progression.

2. Discussion

2.1. TLE and Cerebellar Degeneration

Although cerebellar degeneration was evident in patients with epilepsy regardless of epilepsy classification, it was most prevalent in patients with TLE. Temporal lobe epilepsy is the most common pharmaco-resistant epilepsy in adults [24] and frequently requires resective surgery of the affected temporal lobe [25]. It is characterised by seizures that arise anywhere within the temporal lobe. In TLE, the seizure originates in the limbic structures within the temporal lobe, more specifically, the hippocampus [26][27]. Hippocampal sclerosis is a hallmark feature of drug-resistant TLE and characterised by neuronal death, gliosis, and atrophy [28].

Additionally, Bonilha et al., (2010) [29] using DTI and VBM techniques, identified a relationship between hippocampal deafferentation and regional brain atrophy in TLE patients; this hippocampal fibre disconnection may be partially responsible for grey matter atrophy in temporal, basal nuclei, and cerebellar areas. The presence of HS, however, does not necessarily imply cerebellar atrophy. In other words, cerebellar volume loss was identified, even in the absence of HS [30][31] and prolonged seizure freedom did not prevent cerebellar atrophy [32]. These findings are supportive of the growing evidence that the distribution of atrophy within the brain of TLE patients, preferentially affects brain structures that are anatomically and functionally connected to the hippocampus and cerebellum [29]. However, the high prevalence of pharmaco-resistant TLE patients with cerebellar degeneration may reflect the lack of routine neuroimaging in drug-responsive patients, patients with generalised epilepsy, and those with no clinical deficits [33].

2.2. Pharmaco-Resistance and Cerebellar Degeneration

Epilepsy treatment has evolved significantly, from the traditional use of bromides, to the modern era in which we now utilise various treatment modalities. These include medications, implantable devices, non-pharmacological therapies, and surgery [34]. AEDs remain the mainstay treatment options for epilepsy, with approximately 50% of patients becoming seizure free with monotherapy [35]. However, only 11% of patients who fail to achieve seizure freedom with monotherapy, due to inefficacy, experience a reduction with a second treatment option [36]. These findings suggest that the probability of treatment response reduces with each treatment failure [37][38]. Although, the terms “refractory”, “intractable”, and “pharmaco-resistant” epilepsy are used interchangeably. The ILAE defines “drug-resistant epilepsy” as a failure to achieve and maintain seizure freedom despite trialling two AEDs that are well tolerated, in terms of side effects, whether as a monotherapy or polytherapy [39].

Approximately 30 to 40% of patients with epilepsy fail to achieve adequate control of seizures, despite the use of multiple AEDs and different treatment therapies [40]. Our review identified an exceedingly high prevalence of drug-resistant patients that demonstrated cerebellar degeneration (87.2%). This is consistent with the general consensus that drug-resistant epilepsy has more profound brain damage than drug-responsive epilepsy [26][41]. Factors that induce cerebellar degeneration in pharmaco-resistant patients remain to be determined, whether this is related to seizure mediated cell loss or from direct effects of status epilepticus or from the use of multiple AEDs at high serum concentrations.

Patients responsive to AED treatment were also observed to have cerebellar degeneration, indicating that multiple factors may contribute to the development of cerebellar degeneration in epilepsy [42]. However Bilevicius et al., (2010) [42] found that cerebellar degeneration in patients with drug-resistant and relapsing-remitting seizures was more profound and widespread than drug-responsive epilepsy. Despite this, there is a paucity of studies evaluating the influence of seizure control on cerebellar degeneration. There may be bias in performing neuroimaging only in patients with pharmaco-resistant epilepsy. Studies evaluating cerebellar degeneration should include both patients with uncontrolled epilepsy as well as stable epilepsy.

2.3. Phenytoin and Cerebellar Degeneration

The correct choice of an AED is crucial to therapeutic success. Our review identified an increased number of patients using phenytoin. Since its introduction to epilepsy treatment in 1938, phenytoin had become the most extensively prescribed and studied anticonvulsant [43]. It acts by blocking voltage-dependent sodium channels, suppressing the propagation of discharges from seizures. However, due to the narrow therapeutic index of phenytoin; its risks of acute

over-dosage and the toxicity effects of its chronic use [44], phenytoin is now gradually becoming less popular. Long-term use of phenytoin has already been associated with significant risk of cerebellar degeneration and ataxia, which can persist long after discontinuation [7].

The chronic effects of phenytoin are often difficult to discriminate from that of the seizures [45]; as the analyses are complicated by the fact that patients with severe epilepsy are also on higher doses of medication [46]. Despite this, our findings lend confidence to the notion that chronic phenytoin use, whether in the therapeutic range or not, is an important factor of cerebellar degeneration. As we are now in an era whereby there is a variety of viable AED options, it would be interesting to compare phenytoin-exposed patients with those that have not been exposed [20]. Phenytoin use in epilepsy may be much higher than any other AED; thus, the connection with cerebellar degeneration may simply be because it is used frequently. Proportionally more patients on phenytoin develop ataxia than patients on other AED. Further studies should focus in comparing phenytoin as monotherapy and/or combination therapy with other AED and treatment duration in determining its link with cerebellar degeneration.

2.4. Clinical Characteristics of Cerebellar Degeneration

Previous research has demonstrated a weak relationship between the clinical manifestations of cerebellar dysfunction and neuroimaging characteristics of cerebellar atrophy [47]. In our review, cerebellar degeneration by assessment of cerebellar atrophy was evidenced in 86.7% of patients with epilepsy. Whether this was related to the toxic effects of AEDs or drug-resistant epilepsy or the use of polytherapy as a treatment mechanism; or the combination of all three, remains unclear. Although, studies evaluated on their own merits did not find a link between cerebellar atrophy in neuroimaging and the clinical evidence of ataxia, Shanmugarajah et al., (2018) [48] identified significantly smaller cerebellar volumes in patients with phenytoin related ataxia, compared with patients taking phenytoin without ataxia. These findings suggest a possible threshold by which cerebellar atrophy may manifest clinically with cerebellar signs.

Although studies have postulated that ataxia is a direct result of cerebellar atrophy [49][50], others have found no association between the presence or absence of cerebellar atrophy on the clinical manifestation of ataxia [51][52], or of the severity of symptoms [53].

Ataxia, in all available studies, was associated with the cerebellar atrophy. Reports on peripheral neuropathy were limited, therefore no conclusions could be derived in this regard. Although we aimed to examine neuropathological studies in our review, these were limited in our search.

3. Conclusions

In summary, cerebellar degeneration is prevalent in patients with epilepsy. This review identified a trio of predictors of cerebellar degeneration. Patients with temporal lobe epilepsy, patients with drug-resistant epilepsy and those treated with chronic use of phenytoin were most susceptible to cerebellar degeneration. Whether cerebellar atrophy is a predisposing factor for cerebellar ataxia in patients with epilepsy is inconclusive, due to the lack of clinical symptom reporting. Further prospective studies are required to confirm if the predictors identified in this review are indeed linked to cerebellar degeneration and to establish the pathogenic mechanisms that result in cerebellar insult.

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