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The misdiagnosis of epilepsy: Appraising risks and managing uncertainty

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ABSTRACT

Purpose: To present evidence from the literature on the rates, underlying causes and consequences of the misdiagnosis of epilepsy and place these meaningfully within a practical framework of risk appraisal and managed diagnostic uncertainty towards informing a clinical practice that might make misdiagnosis less likely.
Method: Narrative review.
Results: Misdiagnosis of epilepsy remains common and the consequences for the individual significant. Evidence and critical appraisal are presented as regards the absolute level of risk associated with the false positive diagnosis epilepsy, and reasons as to why those risks need to be appraised against the risks associated to false negative diagnosis.
Conclusions: Diagnostic error is not entirely avoidable and a degree of uncertainty, and perforce risk, is intrinsic to the diagnostic process of epilepsy.
The risks of a false negative diagnosis of epilepsy must be appraised against the also significant risks of a false positive diagnosis.
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1. Introduction

Over the last 20 years there have been significant advances in epilepsy research in terms of the identification of underlying causes and mechanisms and the development of more tolerable and efficacious treatments. However, none of these advances are practically meaningful without an accurate diagnosis. Epilepsy is still overwhelmingly a clinical diagnosis and rates of misdiagnosed epilepsy remain stubbornly high.

Consensus statements and guidelines consistently recommend early availability of and referral to specialist epilepsy services as a way of addressing this issue [1,2]. However the diagnosis of epilepsy can be challenging even for experienced clinicians [3]. The difficulty arises not so much from a greater or lesser ability to recognise epilepsy, but in the particular problems in assessment of risk and management of uncertainty specific to situations where epilepsy may be a possibility but a final diagnosis has to await further confirmation. The perceived risk of not treating, even in a circumstance where the probability of epilepsy is low, mitigates against circumspection and encourages practice that results in misdiagnosis [4]. As such, as well as presenting evidence from the literature on the rates, underlying causes and consequences of the misdiagnosis of epilepsy, the intention of this paper is to place these meaningfully within a practical framework of risk appraisal and managed diagnostic uncertainty towards informing a clinical practice that might make misdiagnosis less likely.

2. Misdiagnosis

2.1. Prevalence of misdiagnosis

Reported misdiagnosis rates vary substantially with estimates ranging between 2% and 71%. This wide variation reflects the heterogeneity across studies in terms of setting, inclusion of patients with refractory epilepsy, diagnostic criteria, diagnostic methods and the experience of the referring clinician [5–15]. With the exception of the studies below, such studies are likely to be confounded, and their populations too highly selected, to derive a ‘base rate’ of misdiagnosis that would inform practitioners addressing the needs of patients presenting following an apparently first seizure, or the majority of those diagnosed with epilepsy who are never deemed ‘treatment refractory’.

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By contrast two purposely designed studies addressed the prevalence of misdiagnosis within the community. In the UK an early study assessing the prevalence of epilepsy within the community, reviewed the diagnosed of 214 patients from seven general practice surgeries. Following review by an epilepsy specialist, alternative causes for the attack disorder were found in 49 (23%) mostly a cardiovascular cause or psychogenic non-epileptic seizures (PNES) [8]. Another UK based study identified 275 patients with epilepsy treated with antiepileptic drugs (AED) from 26 general practices. All patients were reviewed by two experienced epilepsy specialists who concluded that the diagnosis of epilepsy was in doubt in 16.3% of patients [9].

Thus the misdiagnosis rate in unselected patients with a diagnosis of epilepsy may be in the region of 20%.

Higher rates of misdiagnosis are found in adults or children with apparently treatment refractory epilepsy referred to secondary care in and outside the UK [5]. When Smith et al. retrospectively reviewed the diagnosis of relatively unselected patients referred to an epilepsy clinic, the overall misdiagnosis rate amongst the 184 patients with the diagnosis of epilepsy and treated with antiepileptic drugs was 26.1% (46/184). In this study the most common conditions to be mistaken for epilepsy were PNES and syncope and more than half of the patients were on medication [10]. A further study, specifically excluding patients with suspected PNES, still found that of 74 patients referred to an epilepsy clinic, half of whom were deemed to have refractory epilepsy, 41.9% had an alternative, most commonly syncopal or cardiovascular, cause of their symptoms [11]. A retrospective survey of children admitted to a tertiary centre in Denmark found that 30% of the children referred with a definite diagnosis, did not have epilepsy [12].

Even more selected case series from secondary care that would be expected to include more unusual presentations generally confirm syncope followed by PNES as the most common conditions underlying misdiagnosis [5]. The 'typical' scenario of epilepsy misdiagnosis conforms to a relatively prosaic narrative of short lived and in all probability benign 'collapses' whose resolution may be mistaken for a response to AED. The possibility exists that a substantial minority of patients with apparently remitted epilepsy on treatment do not have epilepsy.

Finally it is important to point out that although higher proportions of misdiagnosis have been found amongst non-experts, figures of over 20% have also been reported amongst patients under the care of specialists and referred on to tertiary centres [13,14].

2.2. Consequences of misdiagnosis

In essence, a misdiagnosis of epilepsy carries with it all the secondary handicaps and limitations of a diagnosis of epilepsy in terms of stigma and social marginalisation, lifestyle limitation, employment and driving restrictions, and the side effects and potential teratogenic effects of AEDs [3,5,15]. It seems reasonable to speculate that clinician's insufficient understanding of the profound implications of a diagnosis of epilepsy in and of itself contributes to an over-readiness to make the diagnosis.

Once established, the diagnosis of epilepsy is not readily challenged or reviewed even amongst specialists. Patients eventually correctly diagnosed as having PNES will on average have acquired their misdiagnosis, and its consequences, 7–10 years previously [16].

Some populations court particular risk from misdiagnosis; specifically patients with unrecognised cardiogenic syncope or patients suffering from PNES.

A small minority of patients with apparent syncope will transpire to have an underlying liability to serious arrhythmia, often but not always associated with ECG changes and if untreated associated with a high mortality rate [17,18]. Speculative prescription of AED in this circumstance has potentially disastrous results.

Psychiatric morbidity in PNES populations is substantial and worsens the prognosis. A misdiagnosis of epilepsy not only misattributes the primary psychological nature of the attacks but also prevents appropriate treatment of the substantial associated psychiatric morbidity [16].

Particular risks of iatrogenic harm are incurred by PNES patients presenting with prolonged attacks misattributed to apparent status when this leads to inappropriate use of high doses of intravenous medication or even admission to the Intensive Care Unit and intubation, with all the morbidity that this entails [19].

The economic consequences of misdiagnosis are also significant; figures form NICE guidelines estimated the direct total national medical costs between 164 and 188 million pounds [1]. As well as the costs of an erroneous diagnosis, "undiagnosing" epilepsy is also costly since reversing a diagnosis is at times more complicated and patients may require video EEG monitoring or inpatient admission for a diagnostic withdrawal of medication [10].

2.3. Reasons for the misdiagnosis of epilepsy

As in medicine more generally there are no short cuts to an accurate clinical diagnosis. Epilepsy misdiagnosis however, of all medical missteps, seems to occur within a particular matrix of factors that discourage circumspection and encourage immediate diagnosis on a basis of an inadequate history, traditional but unreliable 'red flags', over-interpretation or misuse of medical investigations (mainly EEG), and the inaccurate perception that the immediate clinical course will be grave if intervention is delayed.

The single most important factor in epilepsy misdiagnosis is the failure to appreciate the importance of a thorough and expert clinical history and its corroboration by a witness description [10]. Rather than diagnostic insight, 'expertise' in this circumstance applies more to perseverance in seeking a history and witness description as well as reservation of judgement when these are unavailable.

To complicate matters, epileptic seizures can manifest in many ways and although there are constellations of features that would alert the clinician to the possibility of the diagnosis one way or another, there is no single pathognomonic semiological feature that would in isolation absolutely endorse a diagnosis of epilepsy or non-epilepsy. Unfortunately many of the often rehearsed 'red flags' of clinical tradition (self-injury, attacks arising from apparent sleep, urinary incontinence) have been shown to have little or no discriminant value, and for the most part are actively misleading if taken in isolation [16].

Laboratory investigations are of limited value in epilepsy diagnosis at the level of the individual patient and in the context of practical decision making. None has sufficient sensitivity or specificity to confirm or rule out a diagnosis.

Interictal EEG is a valuable test in the further investigation of an established diagnosis of epilepsy, however it has little role in diagnosis per se. Overreliance on and misinterpretation of routine EEGs has been found to be a contributory factor in the misdiagnosis of epilepsy [10].

Interpreting EEG reports can be as challenging as interpreting the EEG itself. Non-specific EEG abnormalities are not uncommon in the general population and more frequently observed in populations at higher risk of manifesting non-epileptic attacks, especially those prescribed some types of psychotropic medication. To the inexperienced a subsequent report of 'non-specific focal slowing', might be sufficient to consolidate suspicion into

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