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Title:
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Date:
2021-07-01

Citation:
Alessi, N., Perucca, P. & McIntosh, A. M. (2021). Missed, mistaken, stalled: Identifying components of delay to diagnosis in epilepsy. Epilepsia, 62 (7), pp.1494-1504. https://doi.org/10.1111/epi.16929.

Persistent Link:
https://hdl.handle.net/11343/298571

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Article type : Critical Review – Invited Commentary

Missed, mistaken, stalled: identifying components of delay to diagnosis in epilepsy

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Running title: Delay to epilepsy diagnosis, epilepsy outcomes

Number of text pages: 22
Number of words: 5443
Number of references: 63
Number of figures: 1
Number of tables: 1
Supporting information: 2 tables

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SUMMARY

A substantial proportion of individuals with newly diagnosed epilepsy report prior seizures, suggesting a missed opportunity for early epilepsy care and management. Consideration of the causes and outcomes of diagnostic delay is needed in order to address this issue. We aimed to review the literature pertaining to delay to diagnosis of epilepsy, describing the components, characteristics, and risk factors for delay. We undertook a systematic search of the literature for full-length original research papers with a focus on diagnostic delay or seizures before diagnosis, published 1998-2020. Findings were collated and a narrative review undertaken. Seventeen papers met the inclusion criteria. Studies utilized two measures of diagnostic delay: seizures before diagnosis and/or a study-defined time between first seizure and presentation/diagnosis. The proportion of patients with diagnostic delay ranged from 16% to 77%; 75% of studies reported ≥38% affected. Delays ≥1 year were reported in 13% to 16% of patients. Seizures prior to diagnosis were predominantly non-convulsive and

usually >1 seizure was reported. Prior seizures were often missed or mistaken for symptoms of other conditions. Key delays in the progression to specialist review and diagnosis were: i) 'decision delay' (the patient's decision to seek/not seek medical review), ii) 'referral delay' (delay by primary-care/emergency physician referring to specialist), iii) 'attendance delay' (delay attending specialist review). There was little data available relevant to risk factors and virtually none relevant to outcomes of diagnostic delay. This review found that diagnostic delay consists of several components, and progression to diagnosis can stall at several points. There is limited information relating to most aspects of delay apart from prevalence and seizure types. Risk factors and outcomes may differ according to delay characteristics and for each of the key delays, and recommendations for future research include examining each before consideration of interventions is made.

Key words: diagnostic delay, gap, undiagnosed, clinical decision-making

INTRODUCTION

It has been reported that between 23 and 57% of individuals with a new diagnosis of epilepsy have experienced prior undiagnosed seizures[1-4]. These prior events strongly suggest a delay to obtaining timely diagnosis and management, which is concerning given the implications of seizures and epilepsy for health and well-being. Epilepsy is highly associated with co-morbid chronic health conditions and increased mortality[5-7], and exerts a substantial negative impact on psychosocial and psychological well-being, cognitive functioning, educational achievement and work history[8]. Among neurological diseases, it accounts for the highest disability-adjusted life years (DALY) rates in men and in women[9]. The cost to the health-care system and the community is substantial[9-11].

Interventions aimed at preventing long delays to diagnosis may offer an opportunity for early management with the potential to avert or ameliorate some of the negative impacts and costs associated with epilepsy. Consideration of interventions and early management should be evidence-based, incorporating knowledge of risk factors, circumstances and outcomes of delay to diagnosis. While research in other conditions such as cardiac disease[12], tuberculosis[13] and cancer[14] has aimed to investigate and address diagnostic delay, there has been little equivalent work in epilepsy.

In this review we described the available literature pertaining to diagnostic delay in epilepsy.

We aimed to identify components of delay to specialist review and diagnosis of epilepsy, and to ascertain gaps in current knowledge in order to facilitate future targeted research.

The review addressed a series of research questions:

How common is diagnostic delay?

What are the characteristics of diagnostic delay?

At what point in the progression to a diagnosis does a delay occur?

What are the risk factors for delay?

What are the impacts or outcomes of a delay to epilepsy diagnosis?

Based on the findings, we also discussed potential approaches to future research.

METHODS

Data sources

A systematic MEDLINE search was made for literature published between 1998 and 2020. Boolean search strategy and advanced search techniques were used to encompass all 'like' terms. Three search elements were used: 'Epilepsy', 'Delay' and 'Diagnosis'. Under the search element 'Epilepsy', terms denoting epilepsy types were used. Under 'Delay', search terms included 'delay', variations of 'time/length delay', and 'gap'. Under the search element 'Diagnosis', search terms included 'diagnosis', 'clinical decision-making' and 'delayed diagnosis'. Review papers and reference lists from the final selection of papers were also checked. Abstracts were reviewed, followed by full text review. In addition, we searched our own comprehensive libraries which dated back to papers published in 1989.

Study selection criteria

Included were full-length original studies with relevant data presented in the abstract. In order to adequately scope the literature, we included studies that incorporated diagnostic delay of unprovoked or 'epileptic' seizure/s as well as of epilepsy. Our definition of diagnostic delay included time-related delays; or cases where seizures were reported as having occurred before the diagnosis was made (excluding the index/'presentation' seizure). We used the term 'prior seizure/s' to denote seizures before diagnosis. We accepted the authors' classification of prior seizures. As the circumstances associated with these prior seizures were rarely described, non-epileptic events or previously identified unprovoked seizures may be included in 'prior seizures' in some cases.

Excluded from the review were studies with a sample size <10 patients/participants, in a language other than English, those comprising infants only, and where participant selection was driven by genetic testing as this resulted in highly selected patient samples. Outside the scope of this review were studies that only addressed the period between diagnosis and commencement of treatment, or studies examining accuracy/time to syndrome diagnosis (after an epilepsy diagnosis had already been made).

Analysis

The final selection of papers was reviewed for data relevant to our research questions, and information was collated in tables. As the final yield of suitable papers was relatively small, we undertook a narrative description of the findings. In the reviewed papers, risk factors and outcomes were examined using a variety of methodologies including descriptive and qualitative approaches. Therefore, we summarized these findings rather than detailing effect or making comparisons across studies. Studies were not assessed for quality as the aim was to describe available literature in the area.

RESULTS

There were 4508 papers found in the MEDLINE search and additional searches of our own libraries yielded 809. After the removal of duplicates, a review of abstracts resulted in 54 potentially eligible studies. After assessment of full-text papers we found 15 papers that met the criteria for inclusion, plus an additional two earlier papers from our own library[2-4, 15-28](see supporting information tables S1 and S2). One paper was a registry study that used ICD codes to identify patients and included individuals who obtained anti-epileptic drugs (AEDs) before the epilepsy diagnosis was coded[23]. This study was included as it met our criteria, and the numbers of treated and non-treated patients were noted. Eight of the 17 studies specifically aimed to examine delay to diagnosis or seizures prior to diagnosis (supplementary table S1).

A summary of each study methodology is available in supporting information table S1. Patient samples originated from hospital 'First Seizure' clinics in four of the 17 studies (24%), and in another four studies patients were referred to the study from medical care-providers. One utilized data from a national health-care database[23]. The remaining studies comprised a variety of sources (table S1). Nine studies were of adults, three were of children

and five comprised adults and children. In 60% of studies, delay was assessed for patients with a diagnosis of epilepsy. Definitions of epilepsy utilized as inclusion criteria differed widely between studies (see supplementary table S1). The remaining studies also incorporated patients with a diagnosis of single unprovoked seizure, 'epileptic seizure', 'epileptic event' or unprovoked unspecified convulsion.

Data were obtained from interviews or questionnaires (± chart review) conducted for the study in eight studies[2, 3, 15, 16, 18-20, 25, 26], and eight studies used data from other interviews, investigations and medical records (i.e. emergency department notes, First Seizure clinic assessments, other studies)[3, 4, 17, 21, 22, 24, 27, 28]. One study[23] utilized medical-care claims data.

One study focused on issues described by parents who reported problems with the diagnostic process[18]. The remaining 16 studies employed two measures of delay comprising: i) reports of prior seizures, and ii) length of time between the first seizure and diagnosis. In the latter group, two[23, 28] measured this time-period for comparisons between groups, and six studies[4, 15, 16, 19, 20, 26] utilized a defined period of time between the initial seizure and diagnosis/referral to indicate delay (± prior seizures). This ranged from one week to one year. The remaining studies[2, 3, 17, 21, 22, 24, 25, 27] identified a positive history of seizure/s prior to diagnosis.

The findings relevant to our research questions are summarized in supporting information table S2 and described below.

How common are prior seizures/diagnostic delay?

The proportions of patients who experienced seizures before diagnosis or other study-defined diagnostic delay ranged from 16% to 77%. Seventy-five percent of the studies reported ≥ 38% affected.

What are the characteristics of prior seizures/diagnostic delays?

Seizure type

In one study, the inclusion criteria determined that all prior seizures were non-motor seizures[24]. Of the remaining studies, 13 reported seizure characteristics. All but one[21] noted that seizures prior to diagnosis were predominantly non-convulsive, or conversely that convulsive seizures were associated with lack of delay. Non-convulsive seizures were

predominantly partial/non-motor focal, absence or myoclonic. In one study[4], the concept of disruptive vs non-disruptive seizures was also used, the 'disruptive' category captured non-convulsive seizures that interrupted or disrupted activities in addition to convulsive seizures. Other studies utilized a classification of motor versus non-motor seizures[22, 24, 28]. Delay was significantly more likely with non-disruptive or non-motor seizures. Pellinen et al 2020[28] found median time from first seizure to diagnosis was 10 times longer for those with non-motor seizures compared to those with motor seizures at onset. However, diagnosis of convulsive seizures could also be delayed[2-4, 15, 19, 21]. Firkin et al (2015)[4] found 28% of those with prior events experienced at least one convulsive event before presentation and Jallon et al (2001)[2] found 43% of patients with >1 seizure before diagnosis had a convulsive first seizure.

There was little information relevant to the circumstances of prior seizures (whether they were unprovoked, febrile seizures, acute symptomatic) or whether these events had been adequately assessed previously.

Number of prior seizures

Five studies included data on the number/frequency of prior seizures. A history of at least two events before diagnosis was reported in 64% to 82% of patients with diagnostic delay[3, 4, 22]. Firkin et al (2015)[4] found 50% experienced (>5) prior events. Other studies reported a median of between 2 to 33 seizures before diagnosis, with a wide range[22, 27, 28].

Length of delay to diagnosis.

All but two studies calculated length of delay using the time of diagnosis as the endpoint. The outstanding studies[4, 26] measured time to referral or first medical attention. The length of delay from first event to referral or diagnosis was reported in seven studies. Median delays reported varied from seven months to 25 months[2, 4, 23, 27], with a range up to many decades (i.e. 32 years[4] and 52 years[2, 27]). In studies that examined very long delays, the proportions of patients affected were relatively consistent. Delays ≥1 year were reported for 16% of patients in the two studies by Forsgren et al[15, 16] and 13% in Berg et al (2014)(19). Herath et al (2018) reported a delay >1 year to seek medical attention in 7%, and to specialist consultation it was >1 year for 16% of patients[4, 26]. Firkin et al (2015)[4] found 14% had delays >2 years. Others reported 15% of patients were diagnosed >5 years[2] or >10 years[27] after the initial seizure.

At what point in the progression to a diagnosis does a delay occur?

Of the nine studies that addressed this issue, all identified the same two time-points where the progression to diagnosis could be delayed: i) at the point of the initial event/s where ideally the affected individual, their family or carer decide to seek assessment and ii) at the point of presentation to the primary-care provider/emergency physician or other medical care provider, where ideally a referral to expert assessment is made. Berg et al (2014)[19] and Firkin et al (2015)[4] also examined iii) possible delay to attending the specialist appointment (after referral). We labelled these three potential delays as: i) 'decision delay'[12], ii) 'referral delay' and iii) 'attendance delay'. In two studies[18,20] a delay after specialist/neurologist presentation due to mistaken or post-postponed diagnosis was also noted.

Decision delay

The commonest delay reported was decision delay, primarily attributed to failure to recognise seizures as events that required medical assessment (supplementary Table S2). The data suggest that some events were i) recognised as being of potential concern but were assumed to be a manifestation of another condition or ii) deemed not to require any medical attention[2]. Qualitative data from Miller et al (2014)[20] reported some older people attributed seizure symptoms to 'normal aging', or other conditions (e.g. memory loss), some felt uncomfortable mentioning their symptoms to the doctor. In children, some parents considered the events to be behavioural or due to other reasons (many children in this study had developmental problems)[18] or did not think the events were of concern[19]. Practical problems or lack of opportunity to seek assessment were also reported (i.e. 'lack of time'[20, 26], single parent families[18] or poor access to health care[2]). Concern over potential negative social impact was also noted[26], and some individuals sought traditional/alternative treatment before conventional medical care[26]. Nocturnal seizures may be missed[19, 21]. Triggers to eventually seeking medical assessment included an increase in frequency or severity of seizures, or occurrence of convulsions[4, 15, 17, 19, 24, 28].

Referral delay

The reviewed studies described delays primarily attributed to failure by the initial health-care contact, primary-care or emergency physicians to recognise the events as possible seizures requiring referral (supplementary Table S2). Patients and families described many investigations for non-epileptic conditions, some of which were invasive. Misdiagnoses

included dementia, hormonal issues[20], syncope, transient ischemic attack (TIA), panic attacks, gastrointestinal disturbances[15, 17], ischemic heart disease[17]; and in children – breath-holding[19], family or behavioural issues[18]. Some patients felt that symptoms were dismissed, with older individuals reporting their concerns were not taken seriously by the health-care provider[20]. Convulsive seizures are likely the trigger for eventual referral in many cases.

In three of these studies, information regarding physician-related delay was obtained from patient/parent interviews[18-20]. In other studies, it was unclear if it originated from patient reports, medical records or other sources. None of the reviewed studies indicated that data had been obtained via interviews or feedback from physicians involved in initial assessments.

Attendance delay

Two studies examined the time from referral to appointments[4, 19]. Berg et al (2014) found most delays were minimal, a few weeks to a month. Some patients experienced delays >1 month with scheduling or attending specialist appointments or investigations, often in association with other issues[19]. Firkin et al (2015) found the median time from referral to attendance was 12 days with a range up to 95 days, indicating a minority experienced substantial delays[4]. The cause of these delays was not investigated.

A further potential delay was identified at the **specialist level.** Miller et al noted a situation where the diagnosis was missed[20], and Berg et al(2014)[19] noted cases where neurologists and paediatricians deferred diagnosis in the presence of a normal EGG or waited for additional seizures to occur. There were no studies that assessed the degree to which diagnostic delay was unavoidable due to the need for additional information or seizures.

Other delays

Beulow et al (2006) noted that disorganisation of the diagnostic process associated with multiple health care providers may also result in diagnostic delays[18]. In an illustration of the potential complexity of progression to diagnosis, Bensken et al (2020)[23] described five pathways to diagnosis based on patterns of ICD coding on a Medicaid registry. Three pathways are defined by the presence of >1 seizure episode registered in the time before a diagnosis code is recorded. While half of these patients had commenced AEDs before the diagnosis was recorded (suggesting some may have obtained a diagnosis in the time before

the coding was registered) the delays in this study may illustrate issues relating to physician/referral delay, attendance delay, or access to other medical or health services.

What are the risk factors for delay?

Lower impact seizures (non-convulsive/non-motor/non-disruptive) were most commonly reported in association with prior events. Nine studies examined other potential risk factors or compared baseline characteristics between patients with delay to diagnosis versus those without. Seven studies identified risk factors or noted differences between the patient groups (supplementary Table S2). These included race/ethnicity[23], and socio-economic factors (related to both decision delay and referral delay)[4, 18, 20] with associated issues such as rural location[20], lack of insurance[19] and parental education levels in pediatric samples (in referral delay[18, 19]). Both pediatric-focused papers reported that children with medically complicated conditions[18, 19] featured amongst those who experienced delay. In virtually all studies, the examination of factors associated with diagnostic delay was limited to qualitative, descriptive or summary statistics.

What are the impacts or outcomes of prior seizures/delay to diagnosis?

Pellinen et al(2020)[24] found emergency department management did not differ between those with prior seizures and those without in terms of starting AEDs, hospital admissions or specialist referrals. However, all patients presented with a motor seizure and this may have been the major influence in determining subsequent outcomes in this setting. Berg et al (2014)[19] found developmental scores and IQ scores in children were lower in association with delayed diagnosis, at the time of diagnosis as well as some years later. They postulated that seizure activity in the brain may disrupt the critical period of brain development ('epileptic encephalopathy'), or alternatively, there may be social/family factors that contribute to both the time to diagnosis and developmental levels.

Miller et al (2014)[20] described a patient who did not seek assessment until the events caused a fall with injury. Firkin et al (2015)[4] found that 9% of patients with diagnostic delay described minor injuries (lacerations) associated with prior seizures, and 6% reported either motor vehicle accidents (MVAs) associated with undiagnosed events or that they were in charge of a vehicle at the time of the event; no major injuries were reported. Pellinen et al (2020)[28] reported the majority of MVAs occurred in patients who experienced non-motor undiagnosed seizures, suggesting a higher risk for this group. They also found that the great majority of

injuries amongst those with non-motor seizures were amongst patients who went on to experience motor involvement, although most injuries were minor. Bensken et al (2020)[23] noted a suggestion in their data that longer times to diagnosis in those with >1 seizure were associated with more visits to the emergency department. Although this may be a function of presentation for seizure assessment, it suggests increased costs and use of resources associated with diagnostic delay.

Miller et al (2014)[20] presented patient-reported descriptive data depicting delays as frustrating, and having negative financial and health implications. Some patients in the reviewed studies were described as spending years searching for a diagnosis, undergoing numerous investigations, experiencing misdiagnosis and consequently treatment (and possibly side-effects) for conditions they did not have[17, 18, 20].

In a specialist setting, > one seizure at diagnosis was found to be strongly associated with initiation of treatment[2]. One study[27] noted no significant association between diagnostic delay and treatment response, however a large number of seizures before diagnosis was associated with a poor response to treatment. Apart from this, there were very little or no data relevant to treatment trajectories, AED efficacy, mortality, or financial costs associated with a history of undiagnosed seizures, or their impact on social or other life quality domains. There was no examination of potential interventions to decrease delays.

DISCUSSION

In this review we found 17 full-length studies that met the review criteria, and eight studies where investigation of diagnostic delay was a major aim. Research predominantly addressed prevalence of seizures prior to presentation, with limited work describing delay characteristics, little research identifying risk factors or outcomes, and none addressing interventions.

The proportion of patients who experienced diagnostic delay ranged from 16% to 77% with most studies reporting at least 38% affected, confirming the extent of the issue in these settings. Reports of substantial time periods to diagnosis (≥1 year) were relatively consistent, with 13-16% of patients affected in most studies where this was quantified, and evidence of decades of delay for some individuals. The two measures of delay utilized (>1 seizure before diagnosis and time from seizure onset to presentation/diagnosis) capture independent aspects

of delay to epilepsy diagnosis. As an illustration: potential scenarios include a single seizure with a long delay of many years to assessment; several seizures over a number of years before diagnosis; or multiple seizures over the few days/weeks it may take to get to a medical clinic. One potential focus for future research is the likelihood of different biological, social/economic contributors and outcomes associated with each scenario. Other studies may examine the extent to which the need for more information (including additional seizure/s), contributes to elapsed time between onset and diagnosis. The use of different time-periods between studies as indicators of delay make it difficult to compare studies. The development of standardized measurements and definitions that incorporate time and seizure frequency may facilitate data sharing between sites and future research.

In common with others[1, 29], the reviewed studies found prior seizures were predominantly non-convulsive. This is concordant with the findings that delay often occurs because patients and physicians fail to recognise events as potential seizures. However, convulsive seizures have also been noted[1, 2, 4, 19, 21, 30] confirming factors other than seizure type have a role in delay. Details of seizure frequency were scarce, but data suggests most individuals experienced more than one prior seizure. In future research, consideration may be given to the likelihood that risk factors, outcomes and interventions may be different for failure to present with low-impact seizures versus obvious/convulsive seizures.

Pathways to expert diagnosis can be complex[23] and progression to diagnosis can stall at several points. We categorized the two delays most often identified in reviewed studies as '**decision delay**' (by the patient)[12], and '**referral delay**' (by the practitioner). These are concordant with epilepsy studies outside this review[30], as well as in other medical conditions. Delays to hospital admission for patients with acute coronary syndrome were identified by Ottesen et al 2004[12] as 'decision delay' (time from onset to seeking medical attention) and 'physician delay' (time from seeking attention to the emergency department). For individuals with tuberculosis (TB), 'patient delay' and 'health system delay' to eventual diagnosis has been noted[13].

Potential risk factors for **decision or patient-related delay** noted in this review included developmental problems in children[18] and socio-economic factors[4, 18] including lower socioeconomic status. The latter may be associated with fewer of the resources that facilitate engagement with health-care, such as availability of leave from work, childcare, health

insurance or transport[31]. There are similarities with cardiac infarction, TB and lung cancer, where decision delay has been associated with misinterpretation or failure of the patient to recognise symptoms[12, 13, 32-34]. Atypical[12, 14] or mild symptoms[13] were associated with delay, whereas symptoms widely recognised as typical (hemoptysis in TB)[13] or previous episodes (cardiac)[12] reduced times to presentation. In TB and cardiac events, sociodemographic or lower economic status (including rural location and lack of health insurance) was also associated with increased delay[13, 32, 34]. Other factors associated with delay to presentation with TB were seeking non-medical treatment and perceived stigma[13, 34,] and stigma may also be implicated in avoidance of medical attention by those with mental health disorders[35]. These were also suggested as potential issues amongst those with epilepsy[26]. It may be possible to ascertain strategies to address decision delay in epilepsy from programs aimed at achieving early presentation for conditions such as myocardial infarction and stroke, and attempts to address stigma in mental health care.

Referral delay in the reviewed studies was attributed to failure of medical practitioners to recognise seizures. Studies outside the scope of this review also note difficulties with recognition of subtle epileptic phenomena by general physicians and specialists, including misdiagnosis[30, 36-38], lack of history-taking skills[39, 40] and failure to recognize evidence even when typical presentations had been recorded[41]. In the studies reviewed here, an eloquent illustration of the failure to recognise the importance of event descriptions and symptoms was a report by Hamiwaka et al(2007)[3] that none of the patients who had previous seizures had a referral letter that included a comment on these events.

The few potential risk factors for referral delay noted in this review are patient-related and include socio-economic variables[18, 20], parent education levels[18] and race/ethnicity[23]. More generally, others have noted that education level[18], cultural and linguistic familiarity and health literacy[30, 42, 43] impact on communication with health providers. These factors may influence the ability or confidence of individuals to convey their new experiences and symptoms in a way that makes the events recognisable for primary health-care physicians[18] or otherwise impact on clinicians' interpretations. Additionally, sociodemographic factors have been related to disparities in epilepsy health-care provision, with lower patient income and race/ethnicity factors associated with a pattern of higher generalist and emergency visits but fewer specialist visits[44]. In analyses, this effect may be largely accounted for by site of care[44], raising the possibility of shortage of resources or other barriers to specialist care at

certain sites. Of relevance, in TB[13, 34] and lung cancer[14] physician-related diagnostic delay has been associated with lower literacy and socioeconomic status in patients[13], atypical symptoms, negative tests[13, 14], as well as issues with health-care resources[14, 34]. In mental health care, workforce shortages[35] may contribute to delays, and in dementia care, failing to use standardized criteria for assessment[45] may be associated with diagnostic delay.

Notably, there were no studies in our epilepsy review that included an evaluation of referral delay related to physician or health-care characteristics, or research undertaken with the physicians themselves. Suggestions for future epilepsy research include working with primary-care or emergency practitioners to examine prevalence and cause of misdiagnosis, identify blocks to referral, and develop practical ways of assisting recognition of events that require expert epileptological review.

After referral, there may be **'Attendance delay'** or failure to attend for expert review. Scheduling issues may be due to waiting lists within the host organisation (e.g. hospital clinics), and travel distance may also contribute. Berg et al (2014) suggested that children in need of special care may be particularly at risk of attendance delay[19], and this may also be true for adults and for elders with complex comorbidities. Familiarity, willingness or ability to engage with large formal health-care systems may also be a factor[43]. There are no other data in this review pertaining to risk factors or interventions for attendance delays.

An additional possible delay is at the **point of assessment by a neurologist**. There was little relevant to this issue in the reviewed papers. Diagnostic information may be missed or incorrect diagnoses made, although many delays may be actually be postponements of diagnosis. These may be unavoidable due to the need for more information, including investigations and additional defining seizure symptoms[19]. In many cases, a second seizure will be required in order to diagnose epilepsy. Necessary postponement or the degree to which a delay was unavoidable is an important facet of the issue of diagnostic delay that could be incorporated into future investigations.

It was also noted that patients with medically complicated conditions[18, 19] may be at particular risk of diagnostic delay generally, and episodic care with multiple care providers may also exacerbate the risk[18]. These issues were particularly highlighted in two pediatric studies, suggesting that further examination of details of diagnostic delay in children versus adults

may be informative. Individuals may experience diagnostic delay at more than one time-point; further work is needed to identify risk factors associated with multiple delays.

One important question is that given undiagnosed seizures are more likely to be non-convulsive, non-disruptive/non-motor events, ***does delay to diagnosis warrant further in-depth investigation?*** Outcome data is required to inform this debate.

Of the studies reviewed, Berg et al (2014) found diagnostic delays were associated with decrements in development and IQ in young children[19]. Outside the scope of this review, delay to diagnosis or treatment has also been associated with poorer developmental outcomes in infants with infantile spams[38, 46]. In children, possible unrecognised seizures have been identified as the key risk factor for behavioral problems before the first recognised seizure[47]. There is less data relevant to cognitive outcome in adults, and what is available does not specifically examine the impact of seizures before diagnosis. Cognitive impairment has been noted after diagnosis and before treatment[48, 49] although there was no relationship between cognitive performance and number of seizures before study enrolment[49]. Another study comprising children and adults found the incidence of psychiatric disorders was increased three years before, as well as after epilepsy diagnosis[50]. Possibly also relevant is a reported decline in income and increase in health care costs many years before diagnosis[51]. One hypothesis is that an underlying pathophysiological process may cause both seizure onset and the reported conditions[50]. On the other hand, seizures may have an encephalopathic effect[52] and it follows that undiagnosed epileptic activity is a possible candidate mechanism for seizure induced encephalopathy and consequent disorders[19]. If so, addressing diagnostic delay may prevent some conditions associated with newly-diagnosed epilepsy.

The impact of delay to diagnosis on other outcomes has rarely been investigated. Multiple seizures prior to AED treatment have been associated with poor seizure outcome[27, 53] although this may reflect characteristics of the underlying epilepsy. Others found no difference in long-term seizure outcome between patients with immediate versus delayed treatment after diagnosis[54-56]. However, seizures before diagnosis were not a focus of these studies and the outcomes of managing these events are unknown. Counterintuitively, Bell et al (2016)[57] found those presenting with a single seizure had a higher risk of mortality compared to those presenting with more than one seizure (i.e. epilepsy). This finding flags the need to advance epidemiological knowledge with investigation of very early seizures.

Major injuries may not be a common feature given the non-convulsive nature of most prior seizures[4, 28], although their association with injuries is probably largely missed. Particularly concerning is the risk for activities with little margin for error, such as driving[4, 28, 58], swimming, cooking, work with a ladder or heavy machinery, or child-care. Patients who were not prescribed AEDs after a diagnosis of epilepsy were found to have increased injuries (burns, falls, fractures motor vehicle accidents) and suicidality compared to those prescribed AEDs, suggesting untreated seizures have some risk of injury[59]. However, these patients may have experienced more convulsive seizures than most individuals with diagnostic delay. Other effects may be subtle. Undiagnosed and misunderstood seizure activity may elicit adverse responses from school, family, friends or work-mates. In addition, we do not know the impacts of a long search for diagnosis, numerous investigations, potential misdiagnosis[16-18, 20, 30] or unnecessary 'treatment'.

We have summarized the progression to diagnosis in Figure 1. This schema represents three key delays together with hypothesized contributors and outcomes, and is based on the recommendation that individuals with a suspected recent-onset seizure see an epilepsy specialist urgently[60]. Patients may also be assigned an epilepsy diagnosis and managed in the community or by other specialists without obtaining an epilepsy specialist assessment[61]; further work outside this review is required to assess this aspect of care. Table 1 comprises a summary of components of delay to diagnosis of epilepsy compiled from this review. Most require further research, with research questions and methodology targeted for specific components. As an example; at a very basic level the first three key delays (decision, referral and attendance) are likely to feature delays of recognition and action related to seeking assessment; whereas the delay between specialist assessment and diagnosis is more likely to be related to lack of essential diagnostic information, and will be affected by whether the diagnosis in question is that of an unprovoked seizure or epilepsy.

Knowledge gaps need to be addressed before interventions aimed at decreasing diagnostic delay are considered. If research supports the development of interventions, these may initially aim to improve recognition by the community and primary-care providers of typical symptoms or events that require early medical/specialist review. However, careful research into costs, risks and benefits of proposed interventions will also be required. Given there may be insufficient evidence to formulate a diagnosis until several events have occurred[4, 19],

attempts to raise awareness could provoke unnecessary worry, investigations, and use of health resources[19]. A false positive diagnosis increases the risk of all the issues faced by patients with epilepsy (stigma, limitations, psychosocial and financial impacts) and harm from unnecessary medications[36, 62, 63].

This review was limited by a number of issues. There were a relatively small number of studies available, and study inclusion criteria differed widely with varied definitions of epilepsy. Incorporating standard classification systems into inclusion criteria may assist interpretation of future studies. In some cases the circumstances of prior seizures (whether unprovoked, acute symptomatic, febrile seizures) were not available, probably because these distinctions were not noted in the seizure history data originally. Future researchers or clinicians may consider building standardized and focused seizure history questions into study protocols or routine assessments. Data pertaining to risk factors (other than seizure characteristics) and outcomes were scarce and were predominantly summary or descriptive. These findings may contribute to the generation of hypotheses and subsequent further research, including detailed multivariate assessment of variables. Finally, an important consideration for this review is that only patients that eventually attended for assessment were included in these studies. Individuals who do not present to primary-care providers with symptoms, are not referred, fail to attend for specialist assessment or die as a result of undiagnosed seizures will be missing from these studies.

In this review, we have identified knowledge gaps relevant to early epilepsy diagnosis and management. Future research may be best targeted at specific components of delay, to identify the different research hurdles, methodologies, risk factors, outcomes and interventions for each. While some issues may be able to be addressed using retrospective data already collected, many will require data to be collected with specific aims in mind. This research poses a substantial challenge, as these seizures may be overlooked by the people who are the best source of clinical detail and most of the progression to diagnosis unfolds before the individual presents for expert assessment. As the time-points of interest are within the oversight of family, community and primary health-care workers, research will require substantial collaboration well beyond usual academic research networks.

KEY POINTS

- Most studies reported diagnostic delay in ≥38% of patients
- Several components of diagnostic delay were identified
- Three key delays were 'decision delay', 'referral delay' and 'attendance delay'
- Risk factors and outcomes may differ for each component and delay type
- Research into most aspects of delay is required before interventions are considered

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors thank Ms Jessamae Pieters who assisted with the initial literature search.

Disclosures of conflicts of interest

PP is supported by the National Health and Medical Research Council (APP1163708), the Epilepsy Foundation, the Royal Australasian College of Physicians, Melbourne Health, Monash University, and the University of Melbourne. He has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, Novartis, Sun Pharma, Supernus, and UCB Pharma. NA and AM have no conflicts of interest.

We confirm that we have read the Journal's position on issues involved
in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1 legend

This model is based on the recommendation (National Institute for Health Care Excellence, 2012[60]) that individuals are assessed by a specialist as soon as possible after the first seizure.

**Factors noted in this review of epilepsy literature*

 # Risk factors for diagnostic delay found in non-epilepsy conditions

Table 1:

Components of Diagnostic Delay in Epilepsy

Two dimensions:

- Presence of seizure/s before diagnosis (excluding index seizure) and/or
- Time between first seizure and presentation/diagnosis (delay can occur if there is only one seizure before presentation/diagnosis)

Major characteristics:

- Prevalence in research studies - range 16-77%, most report ≥38% affected
- Predominantly (but not exclusively) non-convulsive/low-impact seizures
- Convulsion or escalation of symptoms triggers presentation and/or referral

Key delays:

- Decision delay (by individual deciding to present for assessment)
- Referral delay (by physician referring to specialist)
- Attendance delay (to specialist appointment)
- Delay between specialist assessment and diagnosis

Risk factors and outcomes: further research required

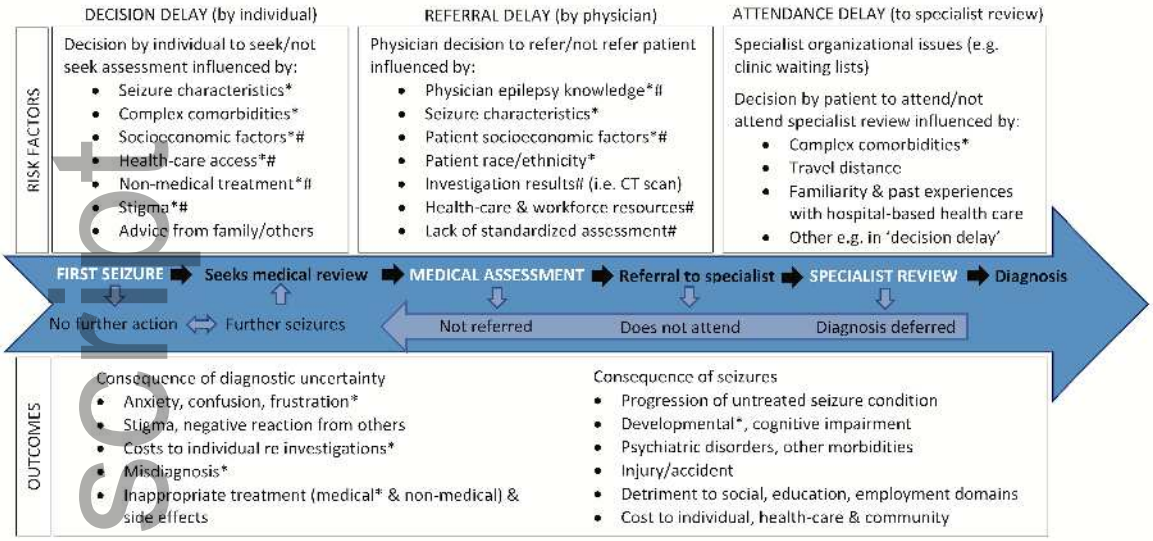

FIGURE 1. Delay to diagnosis of epilepsy: key delays with potential/hypothesized risk factors and outcomes of delay

This model is based on the recommendation (National Institute for Health Care Excellence, 2012[66] that individuals are assessed by a specialist as soon as possible after the first seizure.
**Factors noted in this review of epilepsy literature*
 # Risk factors for diagnostic delay found in non-epilepsy conditions

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