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Clinician views regarding early surgery for paediatric epilepsy

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ABSTRACT

Objective: Many children with lesional epilepsies progress to drug resistance, a criterion required for surgical referral. Expedited surgery may reduce exposure of the developing brain to uncontrolled seizures, improving cognitive outcomes. Designing a trial comparing early surgery with standard care necessitates input from specialist clinicians regarding feasibility and measurable outcomes, which this study investigated.
Methods: Online surveys were disseminated from June-July 2022 via regional paediatric epilepsy networks and professional societies. 51 UK clinicians responded, mostly paediatricians, paediatric neurologists and epilepsy specialist nurses. Candidacy for epilepsy surgery, outcome measures and support for the proposed study were surveyed. Clinician views were compared by speciality, using Pearson's chi-squared tests to explore differences.
Results: 76–98 % of clinicians would refer children for presurgical evaluation at/before drug resistance development across four subgroups (those younger/older than two years, and those with/without a detectable lesion). Earlier referral, at/before epilepsy diagnosis, was considered mostly in those with visible lesions (53 %) and those under two years (31 %). 73 % would consider early surgery before drug resistance is established. Top outcomes to measure were seizure freedom (39 %) and quality of life (22 %). Views of paediatric neurologists and paediatricians did not differ ($p > .05$).
Significance: Clinician opinions generally aligned with published guidance regarding epilepsy surgery referral. Some remain cautious to refer young children with lesions prior to trialling more than one antiseizure medication. Most support early surgery in appropriate patients, with seizure and quality of life outcomes rated highly. Incorporating these perspectives will aid future trial design, recruitment and clinical utility.

1. Introduction

Epilepsy is a major contributing factor to chronic disease burden in the paediatric population, with between 0.5–2 % of children living with the condition globally [1,2]. Of those, approximately one in three have drug-resistant epilepsy (DRE) [3,4], defined as failure to control seizures using two adequate trials of tolerated, suitable antiseizure medications (ASMs) [5]. The majority of patients with MRI detectable epileptogenic lesions, focal cortical dysplasias (FCDs) and long-term epilepsy associated tumours (LEATs), will progress to DRE, with figures of 81 % and 94

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% respectively reported in the literature [6,7]. DRE is generally the point at which referral for surgery is considered, by which time patients have often undergone several failed trials of seizure control using different medications. This can sometimes result in patients living with poorly controlled epilepsy for many years prior to presurgical evaluation [8].

Timely surgery for paediatric DRE has shown better outcomes across several parameters compared to ongoing medical management. Greater seizure freedom following surgery has been demonstrated across several studies [9–11], with early surgical intervention in childhood being shown to produce greater improvements in seizure [12] and developmental [13–15] outcomes compared to patients operated on later. In suitably chosen candidates, epilepsy surgery is safe and displays low complication rates [6,7], and may also be a more cost-effective strategy in DRE patients compared to prolonged treatment with ASMs [16,17]. Regarding the latter, one study has shown that the median time from diagnosis to surgery is five years, and the median number of ASMs trialled before surgery isfive, both values unchanged over an almost 20 year period [18].

Referral for earlier presurgical evaluation prior to the establishment of DRE may reduce the duration that patients live with uncontrolled seizures, which may be associated with improvements in seizure outcome and long-term cognitive development. Establishing this evidence base is challenging and requires support from patients, carers and clinicians in the field of epilepsy. Effective trial design to maximise clinical and scientific utility necessitates understanding and incorporating the perspectives of potential referring clinicians, and to establish support for any prospective studies. According to a recent systematic review, there is marked heterogeneity in the reporting of outcome parameters across paediatric epilepsy surgery studies [19]. Understanding what clinicians regard as the most important outcomes to measure may help to overcome this variability, facilitating standardisation of reporting and more beneficial research [20–22]. The views of patients, parents and carers in this regard will also be explored in a separate study.

The aim of this study was to survey the perceptions of UK clinicians who manage children with epilepsy, with regard to epilepsy surgery, and their willingness to support a proposed clinical trial studying the benefit of expedited surgical management prior to the establishment of drug resistance.

2. Methods

2.1. Participants

An online, cross-sectional survey was disseminated to clinicians managing children with epilepsy via two professional bodies – the Organisation of Paediatric Epilepsy Networks in the UK (OPEN UK) and the British Paediatric Neurology Association (BPNA). Paediatric neurologists, paediatricians and epilepsy specialist nurses working in the UK were eligible for participation in the study. The survey was disseminated via the organisations' mailing lists and open for two months (June and July 2022). Given that we wanted to reach only clinicians who regularly care for children with epilepsy, we did not advertise the survey via social media.

2.2. The survey

The anonymous survey comprised 17 questions spanning three broad categories: (1) demographic information; (2) views regarding who should be evaluated for epilepsy surgery and when; (3) support for the proposed trial on expedited surgery at the time of an FCD/LEAT diagnosis. The majority of questions required participants to select from a provided list of categorical responses. Within the proposed trial section, respondents were asked to indicate how strongly they agreed with three different statements on a Likert scale from 1 to 5 (strongly disagree-strongly agree). They were also asked to choose the primary outcome that should be measured in such a trial from a list of five options. Some questions required a free text response, which was also an option in the categorical questions, should participants wish to provide an alternative answer to the options listed. The complete survey can be found in Supplementary material 1.

2.3. Statistical analysis

Descriptive statistics were utilised to summarise respondent demographic characteristics, views regarding epilepsy surgery and outcome measure preferences. The responses of paediatricians and paediatric neurologists were contrasted, and Pearson's chi-squared tests performed to determine whether there was a relationship between medical speciality and epilepsy surgery views and outcome priorities. A p-value < 0.05 was used to indicate statistical significance. Statistical analyses were conducted in SPSS Statistics version 28 (IBM, Armonk, NY, USA) and Microsoft Excel Version 16 (Microsoft Corp, Redmond, Washington, USA).

3. Results

After excluding one response which was not from a paediatric epilepsy clinician, the final study cohort comprised 51 survey respondents. The BPNA and OPEN UK mailing lists had 175 and 850 users on their mailing lists respectively, although it was not possible to estimate what the overlap was and how many would have been eligible to complete the survey.

3.1. Demographics

31 (61 %) of responses were from paediatricians, 10 (20 %) from paediatric neurologists and eight (16 %) were from epilepsy specialist nurses. Most (61 %) reported having between 1 and 10 children under their care who have undergone epilepsy surgery, with 22 % managing 11–20 children and only 12 % over 20 children. Responses were obtained from across the UK, with North England (33 %), South England (22 %) and London (20 %) having the highest representation (Fig. 1). The full demographic characteristics of the survey respondents are shown in Table 1.

3.2. Referral for presurgical evaluation and epilepsy investigations

In order to assess attitudes of when children with epilepsy should be referred for a presurgical evaluation, we asked when children in four categories should be referred (Fig. 1). Across the categories, 76–98 % would refer at or before the point of drug resistance (failure of two ASMs), with the figure being lowest in children without a visible lesion on magnetic resonance imaging (MRI). Earlier referral, at the time of diagnosis of epilepsy or earlier, was considered most in those with an MRI lesion (53 %) and for children under two years of age (31 %).

A small proportion of survey responses did not fit into the options provided. These were broadly grouped into two categories – referral dependent on the clinical picture (such as seizure types and impacts), and referral via a relevant paediatric neurology link colleague. A few participants also opted for more than one referral criterion (such as at diagnosis of a focal epileptogenic lesion or when two ASMs fail). In these instances, the criteria were added to all relevant categories.

There were no statistically significant differences between the responses of paediatric neurologists ($n = 10$) and paediatricians ($n = 33$) regarding referral of any of these patient subgroups: those aged less than two years old ($p = .430$), children aged two years and above ($p = .052$), those with a visible lesion ($p = .175$) and those with no detectable lesion ($p = .202$).

3.3. Epilepsy surgery and the proposed trial

When considering what types of epilepsy warrant consideration of

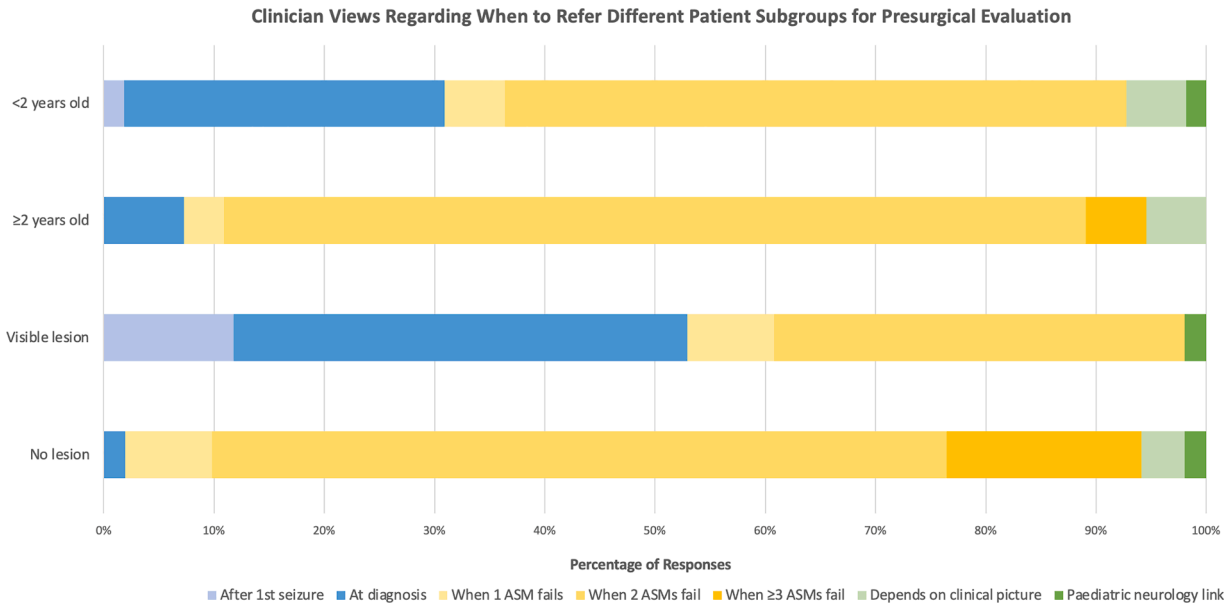

Fig. 1. Clinician views with regard to when different patient groups should be referred for presurgical evaluation. The subgroups comprise children younger than two years old, those aged two years and above, children with a visible radiographic lesion (such as focal cortical dysplasia or a long-term epilepsy-associated tumour) and those with no detectable lesion. The percentage of clinician responses are shown for different categorical timepoints. At diagnosis refers to the time when a diagnosis of epilepsy or a focal epileptogenic lesion is made, the latter involving radiological detection of a lesion following the occurrence of at least one seizure. Although beyond the definition of DRE, the timepoint when ≥3 ASMs fail was utilised to add clarity in depicting when precisely clinicians would refer for presurgical evaluation.

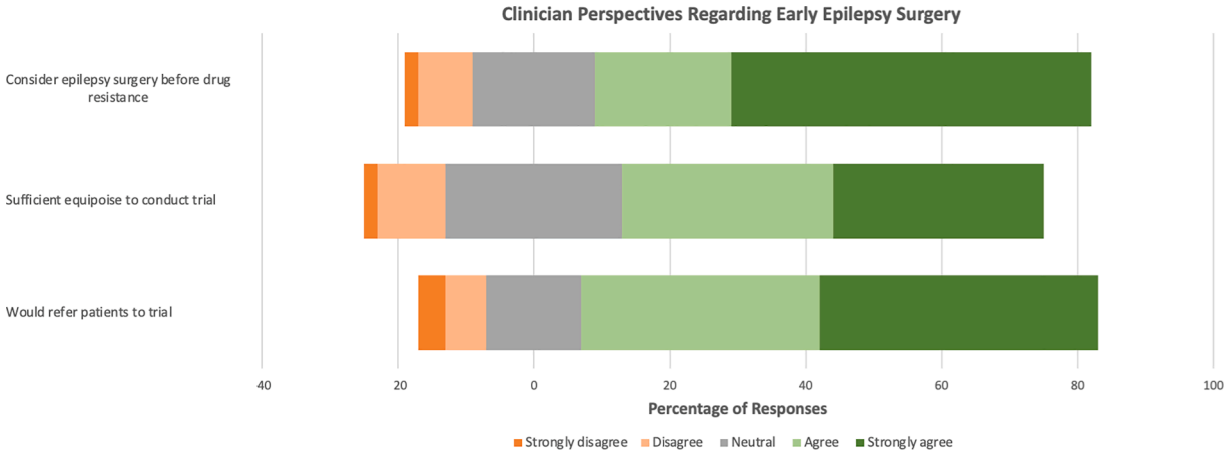

Fig. 2. Clinician perspectives with regard to early epilepsy surgery. Clinicians were asked to rank on a scale from 1 to 5 (strongly disagree-strongly agree), the extent to which they agree with different statements surrounding expedited surgery for epileptic children. The statements were: "Epilepsy surgery should be considered prior to drug resistance in carefully selected candidates."; "I think there is sufficient equipoise to conduct the study."; 'I would refer my patients to the study.". Neutral rankings are centred around zero.

surgery, focal epilepsy was chosen by 94 % of respondents, followed by combined focal and generalised epilepsy (75 %), unknown epilepsy (49 %) and finally generalised epilepsy (37 %).

There was a majority consensus regarding support for expedited surgery and a proposed randomised controlled trial comparing early surgery (within one year of diagnosis of epilepsy) to the current standard of care. When combining agree or strongly agree responses, 73 % of clinicians are in favour of considering epilepsy surgery prior to drug resistance in specific patients, 63 % think there is sufficient equipoise to conduct the proposed trial and 77 % would refer their patients to this trial (Fig. 2). Similarly, 80 % were in support of such a trial being conducted. Paediatric neurologists and paediatricians did not differ significantly in their opinions regarding consideration of surgery before DRE progression ($p = .344$), whether there was sufficient equipoise to carry out the trial ($p = .513$) and whether they would refer their patients to such a trial ($p = .486$).

When asked what the primary outcome measure should be for such a study, the most popular response was seizure freedom (39 %), followed by quality of life (22 %) and seizure frequency/severity (20 %) (Fig. 3). The views of paediatric neurologists and paediatricians showed no statistically significant variation in this regard ($p = .104$).

4. Discussion

In this survey of clinicians working in the UK, we identify discrepancies in thresholds for referral for presurgical evaluation amongst clinicians (paediatricians and paediatric neurologists) caring for children with epilepsy.

Table 1
Demographics of study participants, $N = 51$.

Demographic variable	Response	N (%)
Profession/speciality	Paediatric neurologist working in an epilepsy surgery centre	3 (6 %)
	Paediatric neurologist not working in an epilepsy surgery centre	7 (14 %)
	Paediatrician with special interest in neurology/epilepsy	29 (57 %)
	General paediatrician	1 (2 %)
	Epilepsy specialist nurse	8 (16 %)
	Paediatric trainee	1 (2 %)
	Other	2 (4 %)
Number of children under care who have undergone epilepsy surgery	0	3 (6 %)
	1–10	31 (61 %)
	11–20	11 (22 %)
	20+	6 (12 %)
Region of the UK practicing in	North England	17 (33 %)
	Central England (Midlands)	2 (4 %)
	East England	5 (10 %)
	London	10 (20 %)
	South England	11 (22 %)
	Wales	2 (4 %)
	Scotland	3 (6 %)
	Northern Ireland	1 (2 %)

UK National Institute for Health and Care Excellence (NICE) guidance [23] and International League Against Epilepsy (ILAE) recommendations [24] were used to evaluate clinician views regarding referral for presurgical evaluation. The NICE guidelines on referral to tertiary epilepsy services (inclusive of assessment for surgery) recommend that all children with suspected or diagnosed epilepsy should be referred urgently (within two weeks) to tertiary care if they are younger than three years old, are under four years old and display myoclonic seizures, if they have a diagnosed unilateral epileptogenic lesion or if they are displaying cognitive or behavioural decline. Additionally, the guidelines advise prompt referral within four weeks for children exhibiting seizures resistant to pharmacotherapy, and for cases where there is diagnostic ambiguity. Similarly, Expert Consensus Recommendations put forward by the ILAE Surgical Therapies Commission advise offering all epileptic patients aged up to 70 years old a referral for presurgical evaluation at the point of uncovering DRE. In contrast however, 56 % of survey responses reported that children younger than two years should undergo referral on development of DRE, with a further 29 % opting for referral at diagnosis of epilepsy, or epileptogenic lesion. Participant views were shown to align with regard to lesional epilepsies, with 41 % suggesting they should be referred at diagnosis, and 37 % when two ASMs fail. It is apparent, therefore, that many clinicians are still reluctant to refer young children prior to trialling more than one pharmacological treatment. Additionally, a large proportion would opt to wait until drug resistance develops in patients with MRI lesions, despite published NICE recommendations to refer at radiological diagnosis. Despite not reaching consensus, the ILAE expert recommendations also show strong support for referring children of all ages who have lesions in noneloquent cortex. Nevertheless, with reference to the NICE guidance and ILAE recommendations to promptly refer all those with drug resistant seizures, clinician views were generally aligned regarding those with no detectable radiological lesion (67 % would refer when two ASMs fail) and for children aged two years and above (78 % would refer at development of drug resistance). Across the four patient groups, referral was thus guided largely by DRE diagnosis as opposed to the underlying epilepsy aetiology. This is in keeping with the ILAE recommendations, which suggest referring at establishment of drug resistance, irrespective of seizure/epilepsy duration, type or localisation [24].

The survey also establishes general support for trials of expedited presurgical evaluation and surgery in select children with lesional epilepsy, prior to the establishment of drug resistance. Early surgical intervention for paediatric patients with FCDs and LEATs, prior to the onset of ASM resistance, has the potential to improve outcomes across multiple domains including seizure freedom, cognition, development and quality of life [12–15]. This may be realised through a reduction in ASMs following surgery as well as shortening the length of time that the brain is exposed to uncontrolled seizures during development. Regarding the latter, a recent study reported better health-related quality of life scores for patients undergoing surgery over those treated only with medication, with the improvement largely attributable to greater seizure control [25]. In appropriate patients, surgery offers a safe management option which may also save money on hospital and clinic attendance and ASM treatment [6,7,16,17]. The findings from this survey shed light on a variety of clinician perspectives regarding epilepsy surgery, with important implications for future trial design assessing the efficacy of expedited surgical referral.

Clinicians tended to be in favour of early surgery, with 73 % stating that they would consider expedited surgery referral for patients prior to the traditional criteria of DRE development. Views regarding the proposed trial were also favourable, with 80 % voicing their support for the study and 77 % stating that they would refer their patients to it. The top preference for outcome measures in such a trial was seizure freedom, followed by quality of life, seizure frequency/severity and cognitive or developmental outcomes. These findings align with NICE guidelines, which suggest seizure freedom as the primary parameter to measure, followed by quality of life, seizure frequency and cognition as secondary measures [23]. There were no statistically significant differences observed between paediatricians and paediatric neurologists regarding their perspectives on epilepsy investigations, referral for expedited surgery and outcome measure priorities. This suggests common management practices across medical specialties and adherence to similar criteria when treating people with epilepsy.

This study collated views from clinicians across various specialties and hospitals throughout the UK. An important limitation relates to the low response rate among members of the professional organisations surveyed. The 51 clinician responses comprise a small proportion of the potential reach of the BPNA, who had 651 members according to their most recent annual report [26]. OPEN UK is made up of many different regional epilepsy networks. Whilst there is likely substantial membership overlap between the two organisations, the scope of OPEN UK was not known. Additionally, the study may have been subject to response bias – those completing the survey may be more likely, for example, to have a predilection for early surgical referral. Understanding the perspectives of those opting not to respond may have enabled a more complete appreciation of national practices in epilepsy investigation and management. These non-responding clinicians may be among those who would be approached directly when recruiting tertiary centres for the future clinical trial. Alongside survey dissemination via professional

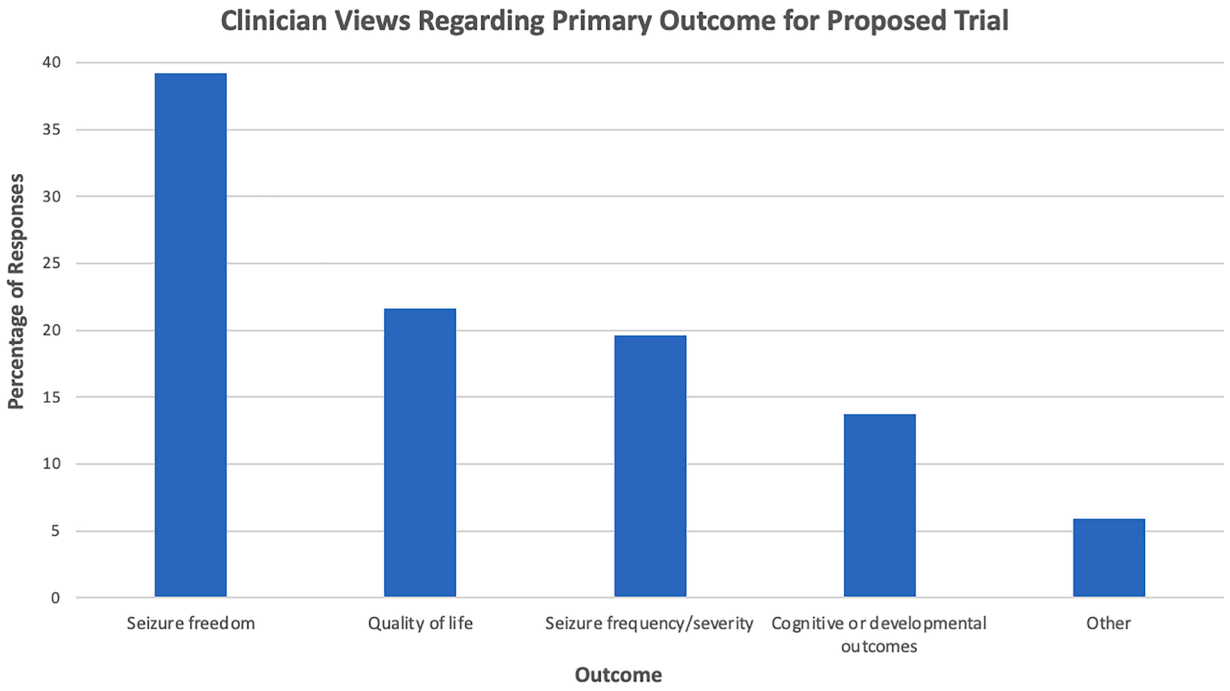

Fig. 3. Primary outcomes of importance that should be measured in an early surgery trial, according to clinicians that responded to the survey.

bodies, such views could have been obtained via targeted correspondence with major UK referral centres. Nevertheless, although information on individuals who declined to take part was not obtained, the primary intention of this study was not to generalise the results to a wider population. Instead, the goal was to collect descriptive findings regarding preferences and perspectives of clinicians, and their level of support for a proposed expedited surgery trial. Accounting for these preferences will aid future trial design and recruitment.

5. Conclusions

This study provides insight into the priorities of clinicians managing epilepsy in children, and the factors they take into account when treating patients under their care. Good agreement was displayed between specialist views and published guidance with regard to the investigation and management of children with epilepsy, with some instances of deviation noted. The majority of respondents also voiced support for considering early epilepsy surgery in suitable patients, and for participation in the proposed future trial comparing expedited surgery with standard care. Going forward, these perspectives can be incorporated into trial design to maximise utility and overall satisfaction amongst both patients and epilepsy specialists.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

Data availability

The dataset supporting the study findings is available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.11.011.

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