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Review

The outcomes of childhood convulsive status epilepticus

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ABSTRACT

Background: Few studies focus specifically on childhood convulsive status epilepticus (CSE). Geographical differences and study design may influence research findings. A comprehensive understanding of the outcomes of childhood CSE needs to bear these factors in mind when examining the published literature. A systematic review of the outcome of childhood CSE was carried out more than a decade ago. Since then, there have been major prospective studies (in the United Kingdom, the United States of America, and in sub-Saharan Africa (SSA)) focused on childhood CSE.

Methods: Six major prospective studies are described, and their results combined through a narrative synthesis with findings of the earlier systematic review. The following CSE outcomes are described: (1) recurrence; (2) short-term mortality; (3) subsequent epilepsy; (4) neurological, cognitive, and behavioral impairments outside of epilepsy; (5) long-term mortality; (6) association with hippocampal injury and mesial temporal sclerosis (MTS); and (7) white matter changes.

Results: One-year recurrence after the first-ever CSE, whether its prolonged febrile seizures (PFS) or non-PFS, is 16% (95% confidence interval [CI]: 10–24). Twenty percent will have a recurrence within 4 years. Case fatality during hospitalization in high income countries is 2.7–5.2%, and 15% in SSA. The cumulative incidence of subsequent epilepsy nine years post-CSE is 25% (95% CI: 16–36). Neurological, cognitive, and behavioral impairments outside of epilepsy are detectable within 6 weeks of CSE. This persists at one year, and by 9 years follow-up, at least at third of subjects will be affected. Long-term mortality ranges from 5 to 17%, with the true estimate at 9 years follow-up to be 8% with standardized mortality ratio of 46. Mesial temporal sclerosis is uncommon, and decreased hippocampal volume is seen in both PFS and non-PFS. Duration is not but etiology/CSE type is, associated with outcome.

Conclusion: Childhood CSE is associated with substantial morbidity and mortality. Etiology but not duration is the main determinant.

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Convulsive status epilepticus (CSE) is the most common medical neurological emergency in childhood. However, there are few studies that focus specifically on childhood CSE with many examining CSE in both adult and child populations with a relatively small number of children within the cohort. Many studies are also hospital-based which may give helpful data but may not reflect the natural history of CSE in the general population. Further, a substantial proportion of studies is retrospective, which may be subjected to recall bias and undercounting. Finally, geographical differences may influence the epidemiology of conditions/diseases. A comprehensive understanding of the outcomes of childhood CSE needs to bear these factors in mind when examining the published literature.

A systematic review of the outcome of childhood CSE [1], aside from geographical differences, considered the other three factors described above. It took the novel approach of assessing the quality of studies using a modified scoring system generated in accordance with the Centre for Reviews and Dissemination guidelines, using items from the checklist for reporting meta-analysis of observational studies proposed by the Meta-analysis of Observational Studies in Epidemiology group, and specific outcomes based on the International League Against Epilepsy (ILAE)'s Guidelines for Epidemiologic Studies on Epilepsy [1–3]. Higher quality studies found lower rates of mortality and morbidity,

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with prospective population-based studies generally being of higher quality compared to other study types. Since that review, there have been major prospective studies (in north London in the United Kingdom (UK), in the United States of America (USA), and in sub-Saharan Africa (SSA) focused on childhood CSE. Details of these studies have been described elsewhere but are summarized below.

1. UK studies

1. The North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) was a 2-year prospective, population-based study that examined the incidence, causes, treatment, and short-term outcome of childhood CSE [4]. The study had high ascertainment and utilized a comprehensive clinical network of pediatric intensive care units and hospitals that covered the target population. Two hundred twenty-six children were enrolled of which 176 had first-ever (incidence) episodes of CSE and patients were followed up until 2 months after the total study period; follow-up range was 2–26 months.
2. Following NLSTEPSS, using the same network, the London group set up a separate childhood CSE cohort in north London to examine the magnetic resonance imaging (MRI) and neurocognitive changes within the first year after CSE, the Status Epilepticus Imaging and Neurocognitive Study (STEPIN) [5]. Children identified to the central research team by members of the clinical network were invited for magnetic resonance (MR) imaging studies within 1 month and repeat MRIs at 6 months and 12 months post-CSE. Of the 225 notified, 80 agreed to participate to have MRI. Participants were similar to nonparticipants by age and socioeconomic status, but there was a greater proportion of females amongst participants. Of these 80, 50 had repeat scan at 6 months and 46 at 12 months (see Table 1) [6].

Magnetic resonance imaging data on 31 controls were available for comparison. Magnetic resonance imaging investigations on subjects with CSE were performed with the child awake, in natural sleep, undersedation, or under general anesthesia as appropriate for the age and developmental stage of the child. All volunteers were scanned either awake or during natural sleep. Magnetic resonance imaging were assessed qualitatively by two experienced pediatric neuroradiologist into normal (normal/normal-variant) or abnormal (minor/major abnormality) and quantitatively by a clinical researcher assessing hippocampal and intracranial volumetry and Tract-based Spatial Statistics (TBSS) analysis of white matter tracts [5–7].

Recruits in STEPIN were also invited to have neurocognitive assessment at 1 month and 12 months post-CSE. Healthy controls were recruited through poster advertising at a tertiary hospital, university and residential school for children with epilepsy, and through parenting groups, cinema screenings for mothers and their babies. Fifty-four (27 with prolonged febrile seizures [PFS] and 27 without PFS) children had neurocognitive assessment, a mean of 38 days post-CSE. Cognitive composites were derived from the Bayley Scales of Infant and Toddler Development (3rd edition) for children aged less than 42 months. Children aged ≥42 months were tested using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)-III UK edition. Twenty-six of the 27 children with PFS also had assessment of recognition memory at baseline using the Visual Paired comparison task; data on 37 controls were available for comparison. At one-year follow-up, 38 subjects with CSE (22 with PFS, 16 without PFS) had neurocognitive assessments [8].

Table 1
Patient numbers according to CSE type at each follow-up in STEPIN [6].

	PFS	Non-PFS	Overall
1st MRI scan	33	47	80
2nd MRI scan	21	29	50
3rd MRI scan	21	25	46

3. To examine the long-term neurological, neuropsychological, and neuropsychiatric outcomes of CSE, the London group carried out the Status Epilepticus Outcomes Study (STEPSOUT), a 9-year follow-up of the original NSLTEPSS cohort. They collected data from structured clinical neurological assessment, neuropsychological and neuropsychiatric assessments, brain MRI, medical records, and structured interviews with participants and their parents [9].

Subjects were enrolled through local collaborators within clinical network. Survival status of each child was determined by examining their hospital records and confirmed by checking their survival status on the National Health Service (NHS) Care Records Service, a national electronic record-keeping service that maintains up-to-date demographic and key health information, including survival status, for all users of the NHS (www.nhscarerecords.nhs.uk). Death certificates of all deceased children were obtained from the UK General Register Office (www.gro.gov.uk), with date of death and cause of death defined as stated on the certificates [10]. Of 203 survivors (90% of inception cohort), 134 (66%) had neurological assessment at a median follow-up of 8·9 year (interquartile range [IQR]: 8·2–9·5). There were no differences between the 134 study participants and the 69 dropouts on CSE-related, clinical, and demographic characteristics [9].

One hundred three (32 with PFS) of the 134 participants had MRI either for the study or had a recent MRI for clinical reasons that were adequate for inclusion in the study. Of the 32 children with PFS, 26 had diffusion tensor imaging (DTI), and TBSS was applied for voxel-wise comparison of white matter microstructure to that of 27 age-matched healthy controls. Age, gender, handedness, and hippocampal volumes (HCVs) were entered as covariates for voxel-wise analysis [11].

To assess behavioral outcomes, the follow-up cohort was grouped into epilepsy- and nonepilepsy-related CSE. Controls were recruited through group emails to employees of a children's hospital (Great Ormond Street Hospital) and Young Epilepsy, a national epilepsy charity, and appealing to the caregivers of subjects with CSE for potential recruitment of healthy patient siblings [12]. Subjects with CSE were compared with population norms and healthy controls using data from the Strengths and Difficulties Questionnaire, the Autism Spectrum Screening Questionnaire, and the Swanson, Nolan, and Pelham questionnaire [13]. Children who scored above recommended clinical cutoffs on any scale were invited for a neuropsychiatric assessment. Families of 83 subjects with CSE completed questionnaires (see Fig. 1) [13]. The 51 who entered into STEPSOUT but did not complete behavioral questionnaires were more likely to be untestable owing to severe cognitive impairments [13].

To assess cognition and memory, the cohort was analyzed as a whole and stratified into a group with PFS and group without PFS. Their performance was compared to population norms and data from 17 neurologically healthy volunteer controls. Cognition of enrolled subjects in STEPSOUT was assessed using the Wechsler Abbreviated Scales of intelligence (WASI) (n = 94; 34 with PFS, 60 without PFS) and global memory (GMS) by using the Children's Memory Scale (CMS) (n = 77; 34 with PFS, 43 without PFS) [14].

Together, data from these studies can be collated to provide information on short-term and long-term morbidity and mortality, and an impression of longitudinal MRI changes within 5 days, to a month, to 6 months, to a year, and up to 9 years post-CSE of different types.

2. USA studies

4. The "Consequences of Prolonged Febrile Seizures in Childhood" (FEBSTAT) study is a prospective, multicenter study. One hundred ninety-nine children, aged 1 month to 6 years, with a febrile seizure lasting 30 min or more were being enrolled. Of the 199 children, 86% had normal development, and 20% had prior febrile seizures.

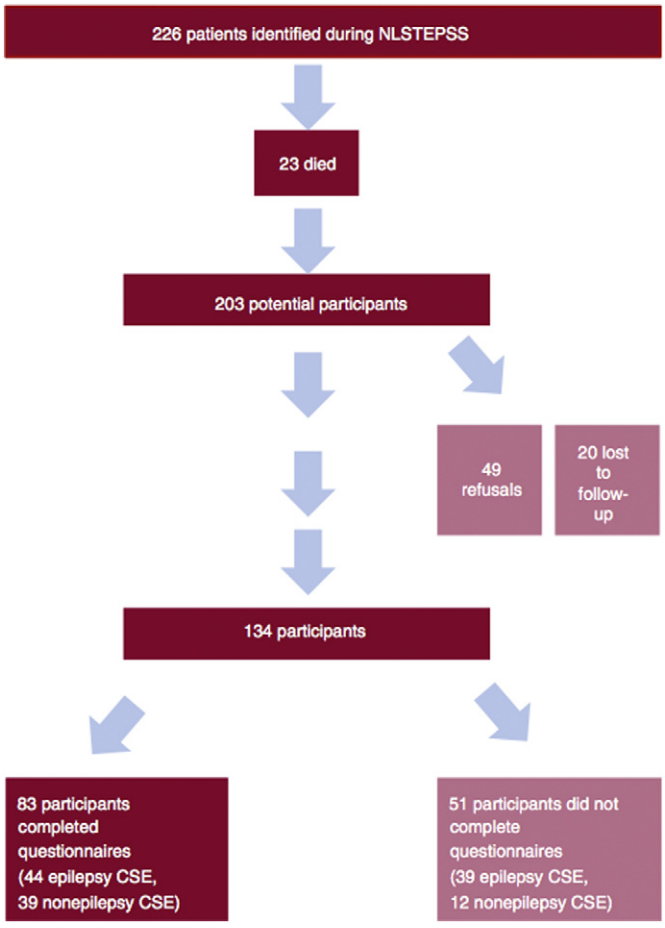

Fig. 1. Flowchart of patients who completed behavioral questionnaires.

Magnetic resonance imaging and a detailed history and neurological examination were done within 72 h of PFS. Development and behavior are assessed at one month and repeated, with age-appropriate developmental testing at one and five years after enrolment. Development of epilepsy is assessed at similar time points. Comparisons are made with a 'control' group of children with a first febrile seizure ascertained at Columbia University with similar baseline and one-year follow-up assessments and a pilot cohort of PFS from Duke University [15]. At the time of writing, data on one-year outcomes have been published [16].

5. The multicenter Pediatric Status Epilepticus Research Group (pSERG) was established in 2010 to prospectively collect observational data on current clinical practice to inform future decisions about care and treatment trials [17]. A network of tertiary hospitals makes up pSERG, and data are collected through a secure web-based interface. By using National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) common data elements and case reports forms for epilepsy (http://www.commondataelements.ninds.nih.gov/epilepsy.aspx#tab=Data_Standards), the network has developed a set of demographic, clinical, neuroimaging, and outcome variables. Their emphasis is on children who failed to respond to first and or second line treatment (refractory CSE). To date, the group has only reported on outcomes during hospitalization for the acute episode [18].

3. Sub-Saharan Africa study

6. In a retrospective cohort study carried out in 2006, Sadarangani et al. reviewed the medical notes of all children aged between one month and 13 years who had been admitted over a one-year period with CSE to a Kenyan rural district hospital in 2002 and 2003 [19]. Confirmed CSE had been observed directly; probable CSE was inferred from convulsions on arrival. Data were linked with demographic surveillance to determine incidence. They identified 388 episodes of CSE, 155 (40%) were confirmed CSE, and 274 (71%) were due to infection. In that study, the researchers had follow-up data up to 3 years post-CSE [19].

Drawing on information from these studies in conjunction with results of the earlier systematic review, this paper seeks to report on the following CSE outcomes: (1) recurrence; (2) short-term mortality; (3) subsequent epilepsy; (4) neurological, cognitive, and behavioral impairments outside of epilepsy; (5) long-term mortality; (6) association with hippocampal injury and mesial temporal sclerosis (MTS); and (7) white matter track changes.

3.1. Recurrence

The median interval for recurrence is 25 days (95% confidence interval [CI]: 0–78) [4]. One-year recurrence after the first-ever CSE, whether its PFS or non-PFS, is 16% (95% CI: 10–24). Twenty percent will have a recurrence within 4 years [1]. Recurrence is almost three times more likely if the child had a previous neurological abnormality (95% CI: 1·01–8·45, p = 0·05) [4].

3.2. Short-term mortality

Case fatality during hospitalization for the acute episode of CSE in high income countries is 2.7–5.2% [1,4,18]. This is much lower than the 13% observed in young adults and 38% CSE in the elderly. However, case fatality during hospitalization in low income SSA is 15% and 21% at 3 years post-CSE [19]. Delayed initial treatment and symptomatic etiology are associated with increased mortality [1,4,18,19].

3.3. Subsequent epilepsy

Previous estimates of the incidence post-CSE were a wide range from 13 to 74% [1]. From more recent work, the cumulative incidence 9 years post-CSE is 25% (95% CI: 16–36), with 89% emerging within 18 months post-CSE [9]. The incidence is much lower in those who were previously neurologically healthy beforehand with an incidence of 14% (95% CI: 6–29) post-PFS, and 13% (4–38) in survivors of acute symptomatic CSE. These contrast to those who had previously neurological problems with an incidence of 46% (21–72·0) in those who had remote symptomatic CSE. Etiology is the main predictor with no effect of duration on the risk of subsequent epilepsy [9].

3.4. Neurological, cognitive, and behavioral impairments outside of epilepsy

Within 6 weeks post-CSE, neurology, cognition, and behavior scores measured by the Bayley Scales of Infant Development (versions II or III) vary according to whether children had PFS or non-PFS [12,16]. Children without PFS will have lower scores in all subscales compared with healthy controls and population normative means [12]. Children with PFS show similar scores to the instrument's population normative means in the cognition, motor, and language scales [12], but lower scores than healthy controls [12]. These findings persist at one-year post-CSE [12]. When children with PFS are compared with controls with simple febrile seizure, their subscale scores are similar at 6 weeks but lower at one-year follow-up [16]. Difference in control groups may explain the observed difference between studies. One may argue that the difference seen in the London study is partly attributable to the high overall cognition scores of healthy controls who were offspring

of "high achievers". Alternatively, lack of difference with the population normative mean scores may be explained by the Flynn effect in which there is a tendency of intelligence quotient (IQ) scores to increase over time and the failure of measuring tools to keep up with this change [20]. Within 6 weeks after CSE, children with PFS have impairment in recognition memory which is still present at one-year post-CSE [8]. In the cohorts of children who had CSE lasting at least 30 min from the onset of seizures, duration is not associated with these short-term neurological, cognitive, and behavioral outcomes [12,16].

At 9 years post-CSE, children have lower Full Scale Intelligence Quotient Full Scale Intelligence Quotient (FSIQ) and Children's memory scores than controls as well as population norms (Martinos et al., Epilepsy and Behavior, in press). This difference is primarily driven by children without PFS. Children who had PFS have lower FSIQs than controls but score in the average range on the WASI. Children who had PFS have similar general memory scores to controls as well as population norms. The latter finding is unexpected given the lower recognition memory scores observed at six weeks and one-year post-CSE described above, albeit in a separate CSE cohort taken from the same geographical region. This discrepancy could be that the incidental recognition memory paradigm adopted for the early outcomes study recruits different brain structures and mental processes than the CMS (Martinos et al., Epilepsy and Behavior, in press). Alternatively, the memory problems seen in the first year are transient. Longer duration is not associated with poor long-term cognition and memory outcomes (Martinos et al., Epilepsy and Behavior, in press).

At 9 years post-CSE, 37% will have behavioral issues, and 28% will have a Diagnostic and Statistical Manual of Mental Disorders (DSM) psychiatric disorder [13]. Children who have impaired intellectual abilities are particularly affected. A history of febrile of afebrile seizures at the time of the initial CSE is also major factors associated with behavioral problems. Children who had epilepsy-related CSE have higher Strengths and Difficulties Questionnaire (SDQ), Autism Spectrum Screening Questionnaire (ASSQ), and Swanson, Nolan and Pelham Teacher and Parent Rating Scale scores than controls and instrument population norms. In comparison, those who had nonepilepsy-related CSE scored higher only on the SDQ/ASSQ. Specific analyses of the group with PFS were not reported but the authors indicated that on individual testing of children with PFS, behavioral issues were evident [13]. It will be interesting to see the longer term follow-up findings from FEBSTAT.

Taken together, the cognition, memory, and behavior data suggest that the estimated 15% morbidity other than epilepsy reported in the previous systematic review of outcomes of CSE is low [1]. Amongst those that are "testable", a third will have memory, cognition, and behavioral problems within 9 years post-CSE. Given that almost 30% are untestable, the overall morbidity could be as high as two-thirds. Memory and cognition problems amongst those "testable" are detectable within the first year and may afford an opportunity for intervention.

3.5. Long-term mortality

The systematic review of childhood CSE outcomes found long-term mortality to be 5.4–17%, with 3% at 10 years' follow-up [1]. More recent data suggest that the true population estimate is higher. After the acute hospitalization, 8% will die over the next 8.5 years, none of which will be in children who had PFS [10]. The standardized mortality rate, a measure of the ratio of deaths compared to the general population, is a staggering 46 times that expected. Amongst children who were neurologically healthy at the time of their CSE, their SMR is 15 but in those who had a known neurological problem, it is 91 [10]. Death was more likely also if there were previous episodes of CSE (see Fig. 2) [10]. Most deaths are not due to status epilepticus/intractable seizures but instead complications of the underlying condition which is consistent with the findings from the systematic review.

3.6. Association of CSE with hippocampal injury and MTS

In the systematic review, a north London study was described. When children with CSE were investigated by MRI within 48 h of PFS, they have large HCVs and prolongation of T_2 relaxation time. Patients investigated more than 48 h after a PFS have large HCVs and normal T_2

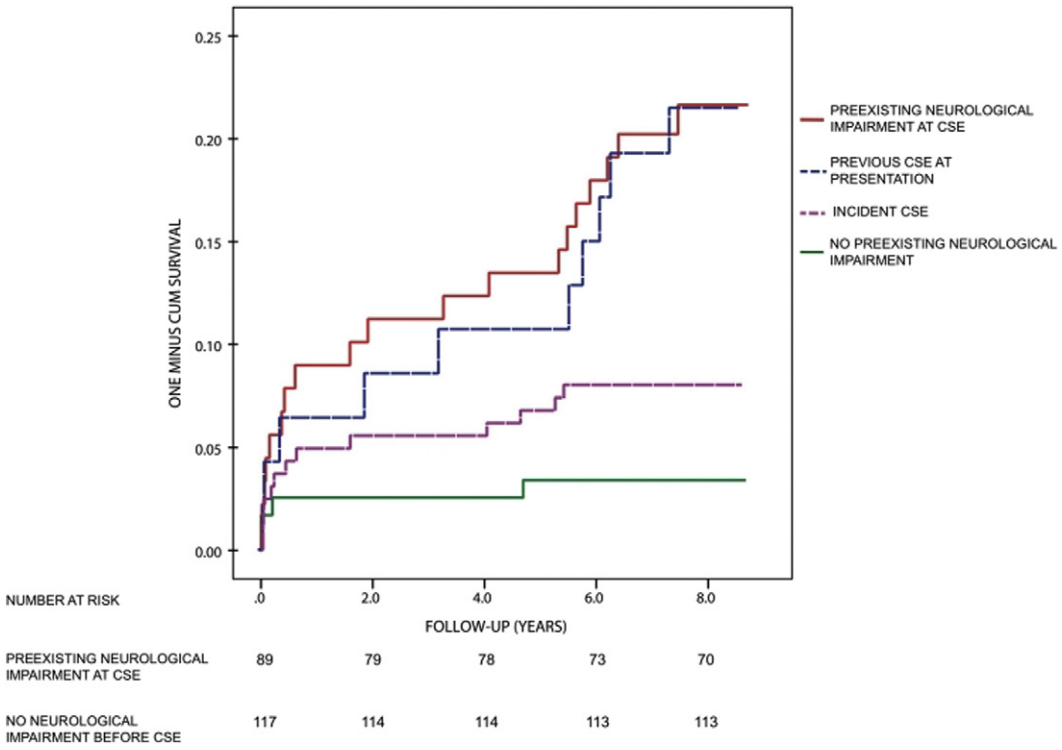

Fig. 2. Survival curve showing the mortality according to incidence or previous CSE, and neurological state prior to CSE.

Table 2
White matter tract changes at 9 years follow-up in children who had CSE compared with controls.

	Early maturing central matter tracts	Late maturing central white matter tracts	Peripheral white matter tracts
Fractional anisotropy (FA)	Increased	=	=
Mean diffusivity (MD)	=	Increased	Increased
Axial diffusivity (AD)	=	Increased	Increased
Radial diffusivity (RD)	=	=	Increased

relaxation time. Non-PFS showed no such changes in T_2 relaxation or HCV [21]. Amongst children with PFS in FESBTAT who were MRI scanned during the acute episode of PFS (68% scanned within 3 days and 86% within a week), 17/199 (9%) increased T_2 in hippocampus [22]. Taken together, these data from two groups are suggestive of acute hippocampal injury after PFS.

Fourteen children with PFS from the north London MRI study had follow-up investigations carried out 4–8 months after the acute investigations [23]. There was a significant reduction in HCV and T_2 relaxation time between the first and second investigations, and there was now no difference in HCV or T_2 relaxation time in patients compared with a control population. Moreover, there was a significant increase in HCV asymmetry in patients at follow-up when compared with initial data. Five out of 14 patients had asymmetry outside the 95th percentile for control subjects and, of these, three had one HCV outside the lower 95% prediction limit for control subjects. A reduction in HCV or T_2 relaxation time, into or below the normal range between the first and second scans, indicates that the earlier findings are temporary and are strongly suggestive of hippocampal edema as the abnormality in the initial investigations [23]. The change in hippocampal symmetry in the patient group is consistent with injury and neuronal loss associated with a PFS, especially in the three individuals who now have a single small hippocampus. However, as there is no T_2 relaxation time abnormality, the hippocampi did not meet the criteria for MTS at 4–8 months post-PFS.

At one-year follow-up, amongst the original 199 children with PFS in FEBSTAT, nine (4.5%; 95% CI: 2–8%) had evidence of hippocampal sclerosis that had not been seen on MRI during the acute episode of PFS; one additional patient had hippocampal sclerosis at one-year follow-up but that was already seen in the acute phase [22]. Twelve (6%; 95% CI: 3–10%) showed decreased HCV [22]. In the north London longitudinal study of imaging and neurocognitive changes over 1-year post-CSE (STEPIN), there were 60 children who had at least two scans amongst at 1 month, 6 month, and one-year post-CSE (ref). No child at follow-up had MTS whether they had PFS (0%; 95% CI: 0–85) or non-PFS (0%; 95% CI: 0–67%) [6]. Five children who had PFS (19%; 95% CI: 9–38%) and ten who had non-PFS (29%; 95% CI: 13–53%) showed longitudinal evidence of HCV loss [6]. None of the changes seen in either FEBSTAT nor STEPIN were related to duration of CSE. Difference between point estimates between FEBSTAT and STEPIN studies is likely to be related to variation in sample size but of note the 95% CI's overlap. A few inferences can be made about MRI changes within a year post-CSE. The first is that at one-year follow-up, MTS is seen in a minority of patients with PFS as well as children who had other types of CSE; hippocampal injury following CSE can be seen in all CSE types and is not a specific PFS phenomenon. If there is a long-lag time needed for the development of MTS following CSE then with longer term follow-up, more children will be found with MTS. In support of this, it is notable that some children at one-year post-CSE are showing volume loss which is seen in both subjects with PFS and without PFS.

At 9 years post-CSE in STEPSOUT, of 32 participants with PFS who had MRIs, one (3%; 95% CI: 0.6–16%) had unilateral MTS. No child who had non-PFS had MTS [9]. In view of the volume losses observed in other cohort studies at one-year follow-up, it was surprising than less than 10% of children who had PFS had volume loss; there was evidence of volume loss in the group without PFS consistent with what was observed in the one-year follow-up studies (Pujar et al. personal communication, unpublished). Attrition may have contributed to this finding but few children who had PFS were lost to follow-up. Other thoughts to be considered/speculated are that there was plateauing or very slow changes of volume loss after one-year or there was neural plasticity. There was no association with CSE duration. Previous seizures were negatively associated with HCV, raising the question of whether multiple hippocampal insults are needed before volume loss is appreciable (Pujar et al. personal communication, unpublished).

3.7. White matter changes in PFS

Longitudinal TBSS in PFS at 1, 6, and 12 months (N = 29) vs controls (N = 18) shows widespread reductions in fractional anisotropy (FA) along several white matter tracts at 1 and 6 months post-PFS, but these resolve by 12 months [6]. The main changes seen at one-month post-PFS were reductions in axial diffusivity (AD) but at 6 months, these predominantly change to increases in radial diffusivity (RD). A potential explanation of these changes is that they represent a transient halting of normal white matter development because of CSE. The subsequent rate of development then compensates so that the white matter tracts appear "normal" but whether that compensatory rate is maintained is unknown. The findings described earlier that there is decreased cognition at one-year post-PFS raise questions about whether the white matter tracts appear structurally "normal" but may have some dysfunction.

At 9 years post-PFS, there is a curious pattern of white matter tract changes compared to controls that is seen using TBSS [11]. These are summarized in Table 2 [11].

In the context of the "normalization" of white matter tracts seen at one year in a separate but similar PFS cohort above, these data suggest that changes in white matter microstructure are evident within 9 years post-PFS, and that this change is accompanied by apparent increases in the coherence of the remaining white matter structure. Findings of FA increase, accompanied by an increase in AD, have also been seen in other forms of brain injury [24,25]. Is it possible that this neuroplasticity and reorganization of the remaining white matter structure is an adaptive change to maintain efficient organization following disruption of the normal trajectory of maturation? The fact that the functional cognitive and memory outcomes 9 years post-PFS are within the average range of population norms lends some support to this speculation but further research is needed.

4. Conclusion

Childhood CSE is associated with substantial morbidity and mortality. Etiology but not duration is the main determinant with those who were previously neurologically healthy prior to CSE having a better outcome. Structural correlates of functional outcomes are being increasingly identified.

Declaration of Competing Interest

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