Prognosis of patients with bilateral fixed dilated pupils secondary to traumatic extradural or subdural haematoma who undergo surgery: a systematic review and meta-analysis

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ABSTRACT

Primary objective To review the prognosis of patients with bilateral fixed and dilated pupils secondary to traumatic extradural (epidural) or subdural haematoma who undergo surgery.

Methods A systematic review and meta-analysis was performed using random effects models. The Cochrane Central Register of Controlled Trials and PubMed databases were searched to identify relevant publications. Eligible studies were publications that featured patients with bilateral fixed and dilated pupils who underwent surgical evacuation of traumatic extra-axial haematoma, and reported on the rate of favourable outcome (Glasgow Outcome Score 4 or 5).

Results Five cohort studies met the inclusion criteria, collectively reporting the outcome of 82 patients. In patients with extradural haematoma, the mortality rate was 29.7% (95% CI 14.7% to 47.2%) with a favourable outcome seen in 54.3% (95% CI 36.3% to 71.8%). In patients with acute subdural haematoma, the mortality rate was 66.4% (95% CI 50.5% to 81.9%) with a favourable outcome seen in 6.6% (95% CI 1.8% to 14.1%).

Conclusions and implications of key findings Despite the poor overall prognosis of patients with closed head injury and bilateral fixed and dilated pupils, our findings suggest that a good recovery is possible if an aggressive surgical approach is taken in selected cases, particularly those with extradural haematoma.

Trial registration number CRD42013005198.

INTRODUCTION

Bilateral fixed and dilated pupils (BFDPs) in the severely head injured patient are an ominous sign suggestive of a significant brainstem herniation and injury. Studies reporting the outcomes of such patients have generally concluded that there is no appreciable chance of meaningful survival, and that further interventions such as surgery and admission to an intensive care unit may not be warranted.[1–3] An aggressive surgical approach may reduce mortality in this patient subgroup, but comes at the risk of producing severely disabled survivors. Profoundly brain injured survivors may be both a burden on their friends and family and a significant financial burden to the state.[4] A routinely encountered argument in healthcare resource provision is that intensive, costly interventions (and subsequent ongoing care) should be directed at those who have the greatest chance of making a meaningful recovery. Some commentators have therefore argued that trauma patients with closed head injury and BFDPs should be managed conservatively with resuscitative efforts concentrating on salvaging the patient for organ donation, if appropriate.[1–3]

While the benefits of surgery for diffuse or intraparenchymal brain injury remains contentious,[5–8] surgical evacuation of traumatic extradural (epidural) or subdural haematomas is accepted as the gold standard treatment for symptomatic patients. To this end, several groups have made the case that, in spite of the overall poor prognosis of patients with BFDPs, selected patients with extradural or subdural haematomas may still benefit from urgent surgery and go on to make a good recovery.[9–14]

To determine whether surgery is justified in the subset of patients whose injury pattern is known to be amenable to intervention, we conducted a systematic review and meta-analysis of the prognosis of patients with BFDPs and traumatic extradural or subdural haematoma who undergo surgery.

METHODS

Search strategy and selection and criteria

The protocol for this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] The review protocol was registered on the PROSPERO international prospective register of systematic reviews (CRD42013005198).[16]

A systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed databases was undertaken. The search period was between January 1993 and July 2013 inclusively, and the date of the last search was 22 July 2013. The search terms used were: pupil* AND (fixed or unreactive) AND (trauma* or TBI). We also reviewed reference lists of all selected reports as well as seeking expert opinion to identify additional eligible manuscripts. Two investigators (JS and HJM) independently identified articles derived from the above search criteria.

Titles and abstracts were screened to identify studies that met the following criteria: (1) patients had BFDPs (≥4 mm in size and unreactive to light, despite medical resuscitation); (2) patients underwent surgical evacuation of a traumatic extradural or subdural haematoma; and (3) the rate of favourable clinical outcome (Glasgow Outcome Score (GOS) 4 or 5) was reported. Full articles were obtained and assessed for eligibility, with discrepancies resolved by discussion with the senior author (MHW).

Data extraction and quality assessment

For each study, the following data were extracted from eligible full articles: (1) study design; (2) study group characteristics; and (3) patient outcome (GOS). In the event of insufficient information being reported in studies, corresponding authors were contacted to determine if supplementary data could be provided.

Studies were quality assessed independently by two reviewers (HJM and JS) based on standard criteria as described in the Methodological Index for Non-Randomised Studies (MINORS) scoring systems, with discrepancies resolved through discussion with the senior author (MHW).[17]

Statistical analysis was carried out using MedCalc V.12.7.5.0 using a random effects model. Functional outcome was reported as the proportion of postoperative patients who demonstrated GOS of ≥4 (low–moderate disability) at follow-up review compared with unfavourable outcome defined as a GOS ≤3 (severe disability–death).

RESULTS

Our initial database searches yielded 86 articles, 15 of which had relevant titles and abstracts and were retrieved for further analysis (figure 1). A further published abstract summarising our own group's findings was included.[18] After the full texts had been reviewed, four articles met our inclusion criteria. One additional paper was included in the meta-analysis after supplementary data on the subset of patients who underwent surgery for extradural haematoma were provided by the corresponding author.[19] In all, five articles were included in the meta-analysis (table 1).[12 14 18–20]

All five articles reported retrospective cohort studies (level 3 evidence), although the Sakas *et al*[14] study did include some prospectively collected data. The quality of the studies was comparable using the MINORS system, with the report by Sakas *et al*[14] scoring 12/16 and the remaining four studies scoring 10/16 (table 2).

A total of 82 patients with BFDPs who underwent surgical evacuation of either subdural or extradural haematoma were identified (table 1). Fifty-seven patients had subdural haematomas, and the remaining 25 had extradural haematomas.

A wide age range was observed. Hendrickson *et al* reported the findings of adult patients only, but in all other studies it was not possible to retrieve primary data for the adult and paediatric subpopulations with acute extradural or subdural haematoma.

Delay to surgery was formally addressed in three of the studies. Kalayci *et al*[20] reported that the mean delay from injury to surgery was 4.8 and 5.5 h for patients with favourable and unfavourable outcomes, respectively, with no significant difference between the groups (p=0.168). Cheung *et al*[19] reported that the median delay from the emergency department to theatre was 3.3 h, and also failed to demonstrate a significant difference between survivors and non-survivors. Sakas *et al*[14] found that the majority of patients undergoing surgery within 3 h of pupils becoming fixed and dilated survived, while the majority undergoing delayed surgery died. Although Hendrickson *et al*[18] did not systematically address the delay from injury to surgery, they did note that the sole patient who

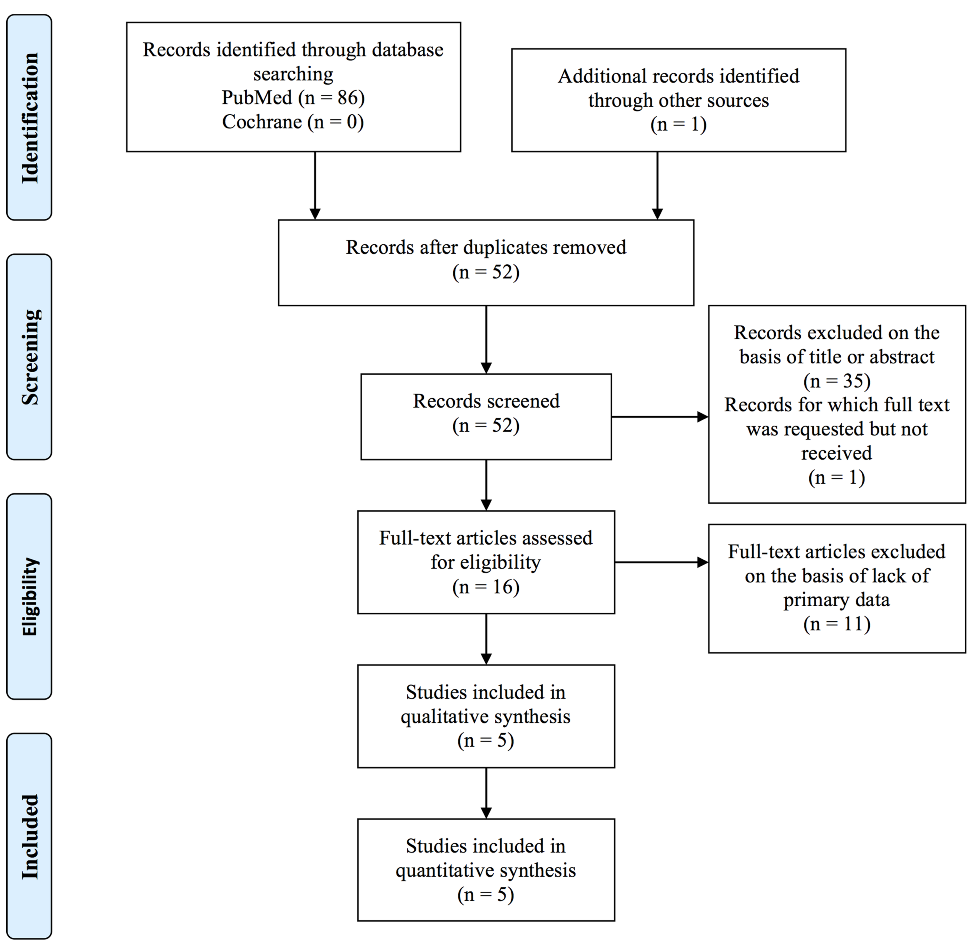

Figure 1 Flow chart of search and selection process.

Table 1 Summary of included studies

Citation	Level of evidence	Study cohort (time frame)	Mean (range) age, years Gender ratio	Total cohort initial GCS (range)	Subgroup meeting inclusion criteria	Outcomes recorded	Key results
Hendrickson *et al*[18]	3	n=20 (2011–2013) Adult pts with EDH/ASDH who presented with post-resuscitation BFDP	50 (17–86) M:F 3.2:1	Mean=3 (3–6)	n=14 (1 EDH, 13 ASDH)	▶ Mortality ▶ GOS at 6–26 months (mean 16 months)	EDH ▶ Mortality: 0/1 (0%) ▶ GOS 4–5: 0/1 (0%) ASDH ▶ Mortality: 6/13 (46.2%) ▶ GOS 4–5: 1/13 (7.7%)
Kalayci *et al*[20]	3	n=34 (2001–2009) Pts with ASDH who underwent decompressive craniectomy	37.2 (2–81) M:F 3.3:1	Median=7 (3–13)	n=12 (0 EDH, 12 ASDH)	▶ Mortality ▶ GOS at 6 months	ASDH ▶ Mortality: 9/12 (75%) ▶ GOS 4–5: 0/12 (0%)
Cheung *et al*[19]	3	n=89 (2001–2004) Pts with EDH	37.7 (0–87) M:F 3.7:1	Mean=12 (3–13)	n=4 (4 EDH, 0 ASDH)	▶ Mortality ▶ GOS at 6 months	EDH ▶ Mortality: 2/4 (50%) ▶ GOS 4–5: 2/4 (50%)
Sousa *et al*[12]	3	n=166 (1996–2000) Pts with severe head injury and post-resuscitation BFDP	Detailed age data not available* M:F 10.6:1	Mean=5 (3–8)	n=19 (9 EDH, 10 ASDH)	▶ Mortality ▶ GOS at 6–40 months (mean 24 months)	EDH ▶ Mortality: 3/9 (33.3%) ▶ GOS 4–5: 6/9 (66.7%) ASDH ▶ Mortality: 9/10 (90.0%) ▶ GOS 4–5: 0/10 (0.0%)
Sakas *et al*[14]	3	n=40 (1985–1988) Pts with traumatic haematoma who presented with BFDP and underwent decompressive surgery	36 (6–75) M:F 5.7:1	Motor response only recorded†	n=33 (11 EDH, 22 ASDH)	▶ Mortality ▶ GOS at 6 months and 1 year	EDH ▶ Mortality: 2/11 (18.1%) ▶ GOS 4–5: 6/11 (54.5%) ASDH ▶ Mortality: 14/22 (63.6%) ▶ GOS 4–5: 2/22 (9.1%)

*Cohort includes adult and paediatric patients.
†Motor scores ranged from 'No response' to 'Obeying–localising'.
ASDH, acute subdural haematoma; BFDP, bilateral fixed dilated pupils; EDH, extradural haematoma; F, female; GCS, Glasgow Coma Score; GOS, Glasgow Outcome Score; M, male; pts, patients.

Table 2 Appraisal of quality of evidence using MINORS scoring system

	Hendrickson *et al*	Kalayci *et al*	Cheung *et al*	Sousa *et al*	Sakas *et al*
A stated aim of the study	2	2	2	2	2
Inclusion of consecutive patients	2	1	2	2	2
Prospective collection of data	0	0	0	0	1
End point appropriate to study aim	2	2	2	2	2
Unbiased evaluation of end points	1	1	1	1	1
Follow-up period appropriate to the major end point	1	2	1	2	2
Loss to follow up not exceeding 5%	2	2	2	1	2
Prospective calculation of study size	0	0	0	0	0
Total/16	10	10	10	10	12

Each question on the MINORS scoring system is scored out of two possible points.
MINORS. Methodological Index for Non-Randomised Studies.

made a good recovery underwent surgical evacuation within 30 min of their pupils becoming dilated and unreactive.

Functional outcome was determined by recording GOS at 6 months after injury for three papers, with Sousa *et al*[12] recording GOS at a mean time of 24 months after injury and Hendrickson *et al*[18] recording GOS at a mean time of 16 months after injury.

Outcome in extradural haematomas

Four papers reported mortality as well as functional outcome in a total of 25 patients with BFDPs and extradural haematomas (figure 2). The overall mortality rate was 29.7% (95% CI 14.7% to 47.2%). The proportion of patients who had a favourable outcome was 54.3% (95% CI 36.3% to 71.8%).

Outcome in subdural haematomas

Four papers measured outcome in a total of 57 patients with BFDPs and subdural haematomas (figure 3). Mortality rates ranged from 46.2%[18] to 90%[12] with an overall mortality rate of 66.4% (95% CI 50.5% to 81.9%). The collective proportion of patients who went on to have a good functional outcome was 6.6% (95% CI 1.8% to 14.1%). Two of the studies (which comprised 22 of the total of 57 patients with subdural haematoma) demonstrated 100% poor outcome,[12 20] while Sakas *et al*[14] reported that 9.1% of their patient cohort had a GOS ≥4 at follow-up.

DISCUSSION

This meta-analysis demonstrates that a good recovery is possible in selected patients with closed head injuries and BFDPs after aggressive surgical management. The most important factor affecting outcome appeared to be pathology, with patients with extradural haematoma showing better outcomes than patients with traumatic subdural haematoma. Indeed, of the patients with traumatic extradural haematoma who underwent surgery, more than two-thirds survived, and the majority went on to make a good recovery. We believe that 54% of patients with extradural haematoma with BFDPs having a good outcome is an underappreciated prognosis, and the perceived poor prognosis of BFDPs (from all causes) has influenced decision making deeming surgery inappropriately futile in some cases. This finding reflects the unique pathophysiology of the disease. In many cases, extradural haematoma is associated with little or no parenchymal injury; therefore, early surgical intervention can greatly reduce the risk of morbidity and mortality.[21] The surgical management of extradural haematoma may be regarded as one of the most cost-effective neurosurgical interventions available.[4]

The evidence that patients with BFDPs and traumatic subdural haematoma benefit from surgical intervention is less convincing. While 33.6% of patients did survive after aggressive surgical management, only 6.6% made a good recovery, with

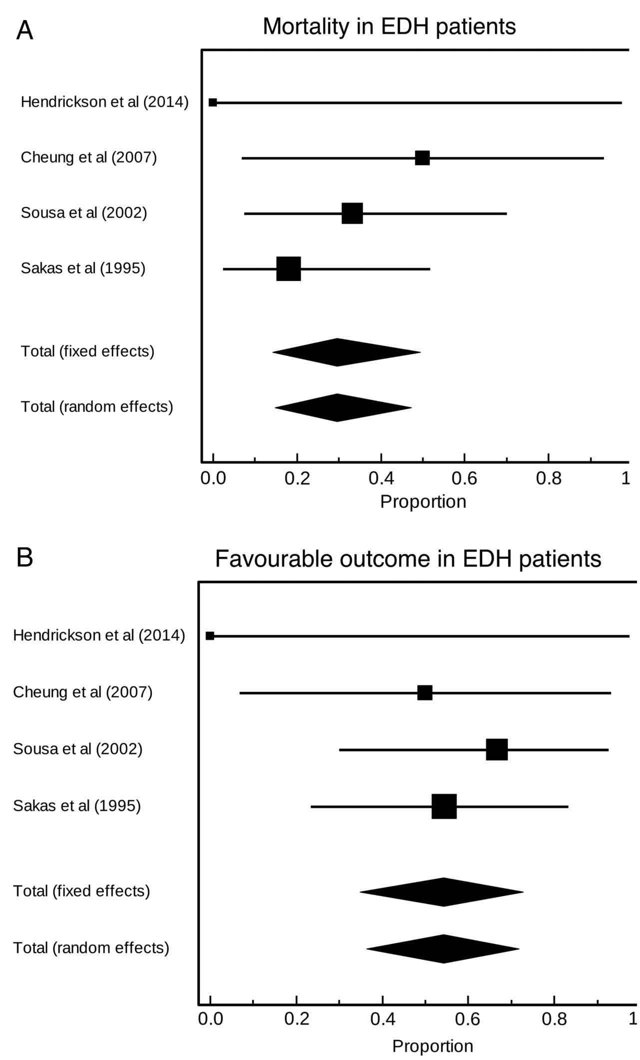

Figure 2 Forest plot showing the rates of (A) mortality and (B) favourable outcome in patients with bilateral fixed and dilated pupils who underwent surgical evacuation of acute extradural haematoma.

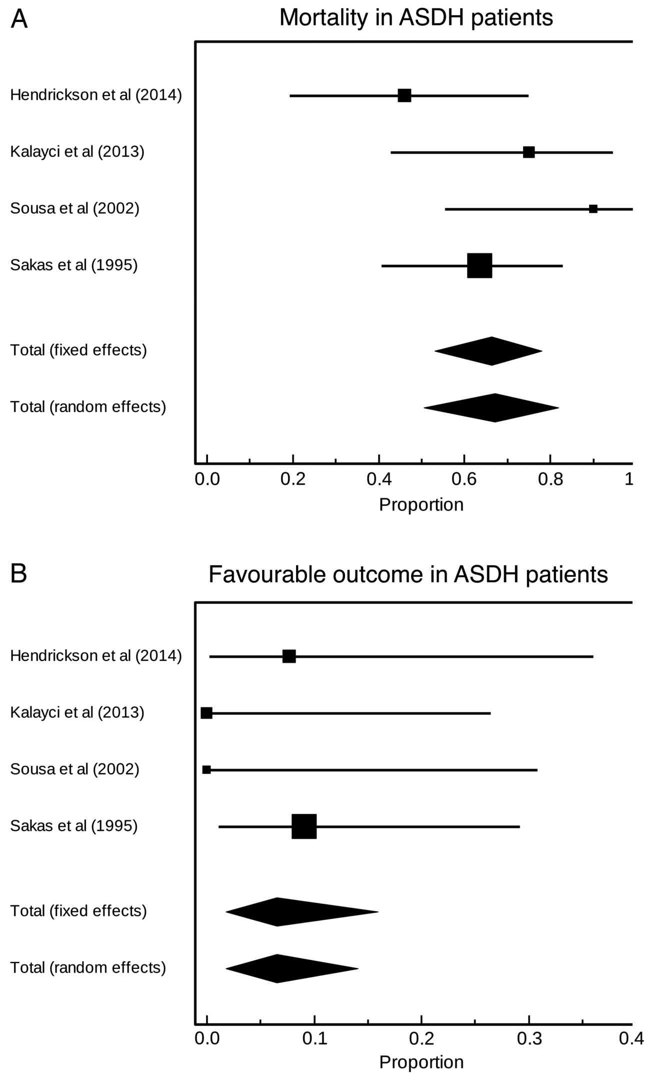

Figure 3 Forest plot showing the rates of (A) mortality and (B) favourable outcome in patients with bilateral fixed and dilated pupils who underwent surgical evacuation of acute subdural haematoma.

the remaining survivors either severely disabled or in a persistent vegetative state. The relatively poor outcome of patients with subdural compared with extradural haematoma is in part likely to be due to the presence of concurrent primary brain injury.[22] We cannot exclude selection bias because of the small cohort size of the included studies, and therefore we cannot draw any firm conclusions about the difference in survival between these two injury types. Nonetheless, the fact that a few patients with traumatic subdural haematoma did make a good recovery suggests that there is still a role for surgery in selected cases.

Confounders such as patient age and delay to surgery almost certainly influence the prognosis of patients with BFDPs undergoing evacuation of traumatic extradural or subdural haematoma. Patients with traumatic extradural haematoma, for example, are likely to be younger than patients with acute subdural haematoma, which may have contributed to their contrasting outcomes. Unfortunately it was not possible to extract primary data on age in this analysis. Previous studies have demonstrated a strong association between advanced age and adverse outcome in patients with traumatic brain injury. In a large statewide study, Susman *et al*[23] reported on the outcome of nearly 12 000 patients with head injury and demonstrated that older people (age >64 years) had a worse mortality and functional outcome than younger adults (age >15 and <65 years), despite their injuries seemingly being less severe. A subsequent study has argued that the observed association between advanced age and poor outcome in patients with traumatic brain injury is likely be in part due to their worse management; older patients are likely to be managed by more junior doctors, encounter greater delay in undergoing CT head imaging, and are less likely to be transferred to a centre providing acute neurosurgical facilities.[24]

Delay to surgery is also known to influence patient outcome in patients with traumatic intracranial haemorrhage.[25 26] Although it was not possible to extract primary data on delay to surgery, several of the included studies did comment on their findings. Sakas *et al*[14] reported that most patients with traumatic extradural or subdural haematoma undergoing surgery within 3 h of their pupils becoming fixed and dilated survived. Interestingly, the studies by Kalayci *et al*[20] and Cheung *et al*[19] failed to demonstrate a significant association between delay to surgery and outcome, although it must be noted that they reported delay from the time of injury and admission to emergency department, respectively (rather than time of pupils becoming fixed and dilated). With the establishment of robust major trauma networks in the UK, such patients should be able to undergo surgery within an hour of arrival, which may improve patient outcomes in the future.

Limitations

A major limitation of this meta-analysis is that all of the included articles were relatively small retrospective cohort studies (although the Sakas *et al*[14] paper did include some prospectively collected data). These studies are therefore liable to several biases. Importantly, the available evidence may be skewed towards favourable outcomes with surgeons avoiding operating on patients in whom intervention was deemed futile.[14] With this potential selection bias as well as the absence of a control group, it is not possible to conclude that the outcomes of the patients studied are representative of patients presenting with closed head injury and BFDPs, nor is it possible to conclude which subset of these patients would benefit most from an aggressive surgical approach.

Another limitation of this meta-analysis is its comparatively stringent inclusion criteria. While many studies describe the outcome of patients with closed head injury and BFDPs, only four studies provided data for the subset of patients who underwent surgery for traumatic extradural or subdural haematoma (with a further study later included after further information was provided by the corresponding author). Other studies were excluded from this analysis because they included either patients for whom the evidence of benefit of surgical intervention remains equivocal (such as diffuse or intraparenchymal brain injury)[5–7] or patients who had extradural or subdural haematoma but who were managed conservatively (because interventions were considered futile). We were specifically concerned with the prognosis of patients who had BFDPs and traumatic extradural or subdural haematoma who underwent surgery, the clinical corollary being whether aggressive management in such patients is justified.

CONCLUSIONS

This meta-analysis demonstrates that good recovery is possible in selected patients with BFDPs after aggressive surgical management. Patients with extradural haematoma appeared to show the best outcomes: almost two-thirds of patients with extradural haematoma survived after surgery, with over half having a good outcome. This rate of recovery compares favourably with other heroic surgical interventions such as prehospital thoracotomy for cardiac arrest in penetrating trauma, which is associated with a 15% rate of good outcome.[27] To this end, we recommend a low threshold for surgery for patients with BFDPs and an extradural haematoma.

In patients with BFDPs and traumatic acute subdural haematoma, the evidence for benefit of aggressive surgical management is less convincing, which may reflect associated primary brain injury. Nonetheless, the fact that some of the patients included in this study did make a good recovery supports intervention in selected cases. Further larger prospective studies are warranted to investigate the impact of confounding variables such as advanced age and delay to surgery. In the meantime, our current practice is generally to manage such patients aggressively in the first instance, and to rapidly withdraw therapy if there is no or minimal improvement in neurological status.

Contributors JS: literature search, data extraction, analysis, manuscript authorship. SH: data collection and analysis, manuscript revisions. HJM: literature search, data extraction, analysis, manuscript authorship, manuscript revisions. MHW: concept, supervision and manuscript corrections, manuscript revisions.

Competing interests None.

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