Journal of Clinical Neuroscience 22 (2015) 29–34

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Brain tumour-associated status epilepticus

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ARTICLE INFO

Article history:
Received 3 December 2013
Accepted 29 March 2014

Keywords:
Brain tumour
Status epilepticus
Tumour associated epilepsy

ABSTRACT

We have reviewed the scant literature on status epilepticus in patients with brain tumours. Patients with brain tumour-associated epilepsy (TAE) appear less likely to develop status epilepticus (TASE) than patients with epilepsy in the general population (EGP) are to develop status epilepticus (SEGP). TASE is associated with lesions in similar locations as TAE; in particular, the frontal lobes. However, in contrast to TAE, where seizures commence early in the course of the disease or at presentation, TASE is more likely to occur later in the disease course and herald tumour progression. In marked contrast to TAE, where epilepsy risk is inversely proportional to Word Health Organization tumour grade, TASE risk appears to be directly proportional to tumour grade (high grade gliomas appear singularly predisposed). Whilst antiepileptic drug (AED) resistance is more common in TAE than EGP (with resistance directly proportional to tumour grade and frontal location), TASE appears paradoxically more responsive to simple AED regimes than either TAE or SEGP. Although some results suggest that mortality may be higher with TASE than with SEGP, it is likely that (as with SEGP) the major determinant of mortality is the underlying disease process. Because all such data have been derived from retrospective studies, because TASE and SEGP are less common than TAE and EGP, and because TASE and SEGP classification has often been inconsistent, findings can only be considered preliminary: multi-centre, prospective studies are required. Whilst preliminary, our review suggests that TASE has a distinct clinical profile compared to TAE and SEGP.

1. Introduction

Epilepsy in the general population (EGP) is characterised by recurrent seizures of spontaneous onset, associated with hypersynchronous discharges (typically emanating from focal regions of the supratentorial cerebral cortex) and by spontaneous seizure termination (usually within 2 minutes) [1]. Following seizure termination, there is typically a refractory period (which can span minutes to several days) during which it is usually difficult to provoke any further seizure activity.

Status epilepticus in the general population (SEGP) is a potentially life-threatening medical emergency in which seizure activity continues for a prolonged period of time, or where seizures recur before there has been complete recovery from the consequences of the preceding seizure [2]. SEGP is a dynamic condition that, if inadequately treated, may result in permanent changes in clinical condition, responsiveness to treatment and in patient behaviour [2,3]. SEGP may also lead to permanent changes in cerebral histopathology, and in the electroencephalogram (EEG) [2,3]. Despite several advances, the fundamental mechanism by which a single seizure fails to be terminated, or by which the post-seizure refractory period fails to become established (or lapses), remains unknown [4].

We have reviewed and synthesised the scant literature on brain tumour-associated status epilepticus (TASE) as a prelude to further studies. Publications were identified by searching the electronic databases of PUBMED, MEDLINE and CINAHL for the period between January 1955 – June 2013. The medical subject heading (MeSH) terms "brain tumour", "status epilepticus", "non-convulsive status epilepticus", and non-MeSH terms "tumour associated epilepsy" and "antiepileptic drug" were used. Results were restricted to the English language. In addition, a manual search of bibliographies was conducted. The "find similar" function in MEDLINE was used to identify any additional studies. If the electronic version was not available, a hard copy of the article was requested through the local hospital library.

Unfortunately, the study of SEGP and TASE (associated with primary brain tumours and cerebral metastases) has hitherto been confounded by a number of factors:

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http://dx.doi.org/10.1016/j.jocn.2014.03.038
0967-5868/

1. The changing definition of status epilepticus [2,5,6]. SEGP was first defined in the 1962 10th European conference on Epileptology and Clinical Neurophysiology as: "any seizure lasting more than 30 mins, or intermittent seizures over 30 mins from which full consciousness is not regained" [7]. The rationale for 30 minutes derived from animal research which had previously identified this period as a threshold for neuronal injury [2]. In 1991, Bleck defined SEGP as continuous or repeated seizures lasting more than 20 minutes [8], whilst in 1999 Lowenstein et al. defined SEGP as continuous seizures lasting for more than 5 minutes (or two or more discrete seizures without regaining consciousness) [6]. Clearly, studies using older definitions will yield significantly different incidences of TASE than subsequent studies.
2. Studies including variable seizure types [9–12]. The mechanism of each seizure type is distinct, and this may have important implications for SEGP and TASE biology. For example, ictal EEG activity stops abruptly, and without post-ictal sequelae, in absence seizures: yet neither may be the case in generalised or complex partial seizures [1]. Moreover, in another example, the mechanism which prevents the spatial cortical propagation of epilepsia partialis continuans is likely to be different from that which terminates typical seizure activity (and which subsequently initiates the onset of the refractory period). In consequence, series with differing proportions of seizure sub-types may therefore have contributed to inconsistent findings. This may be particularly relevant to primary brain tumours, which may possess a greater propensity to elicit partial TASE than generalised convulsive TASE [13].
3. The retrospective nature of most studies. To our knowledge only four studies have provided significant data on TASE [9,10,14,24]. All of these studies have been retrospective, and suffered from small sample sizes (especially regarding subgroup comparisons and tumour types).
4. The changing incidence of generalised convulsive SEGP. It has been asserted that the incidence of generalised convulsive SEGP has been progressively falling, and that this potentially relates to improvements in emergency management [13,14]. However, with reported incidences for generalised convulsive SEGP as wide as 6–61 per 100,000/year, such assertions might be difficult to substantiate [13,15]. Similar issues beset non-convulsive SEGP, where inconsistencies in definition and classification have been associated with ranges spanning 4–50% [14–16].
5. Epidemiological factors. Age is an important and overlooked issue. For example, the incidence of generalised convulsive SEGP follows a U-type distribution with age: one peak occurring at 0–4 years, the other at 60–75 years [13,14,17,18]. Furthermore, generalised convulsive SEGP has a slight male preponderance (1.3:1) [13].
6. Differences in tumour grade and tumour type between studies. As discussed below, tumour grade and the type of primary brain tumour has a distinctive effect on TASE. In consequence, tumour histology should be considered with all statistical analyses.

Despite the long list of confounding factors, most are in fact surmountable. The principal appellation from this review, therefore, is for the establishment of multi-centre, prospective studies to validate the trends herein implied. Such collaboration may prove fruitful since, based on the current weak evidence, TASE pathophysiology appears to deviate from brain tumour-associated epilepsy (TAE) in several domains.

1.1. Illustrative patient

This 37-year-old woman suffered a single generalised tonic-clonic seizure at work. A CT scan and subsequent MRI showed a non-enhancing lesion in the right posterior frontal region with no calcification and minimal mass effect (Fig. 1). She was neurologically intact. An awake craniotomy was performed and cortical mapping revealed both motor and sensory function within the tumour, thus after discussion with the patient, only a generous biopsy was performed. The histopathological examination of the surgical specimen showed a ganglioglioma, therefore observation only of the tumour was recommended.

The seizures were initially controlled with phenytoin, however a few months after diagnosis crescendo focal seizures occurred over a period of 1 week culminating in focal status epilepticus of the left upper and lower limb requiring admission to the intensive care unit for a midazolam infusion for 1 week. After recovery from the Todd's paresis related to this episode a mild hemiparesis, with spasticity most prominent in the lower limb, was noted. Multiple anti-epileptic drugs (AED) have been trialled over subsequent years with variable seizure control. She has had three subsequent episodes of focal status epilepticus requiring admission to the intensive care unit and after each her lower limb function has worsened, such that while she is able to mobilise independently it is with marked spasticity of the left lower limb.

Serial imaging has shown slow increase in the tumour extent with no change in signal characteristics over 6 years, however due to ongoing seizures, radiotherapy is now planned.

2. Epidemiology

The cumulative incidence of EGP by 74 years is 3.0%, for all unprovoked seizures 4.1%, and for any convulsive disorder 10% [19]. However, epilepsy is vastly more common in patients with

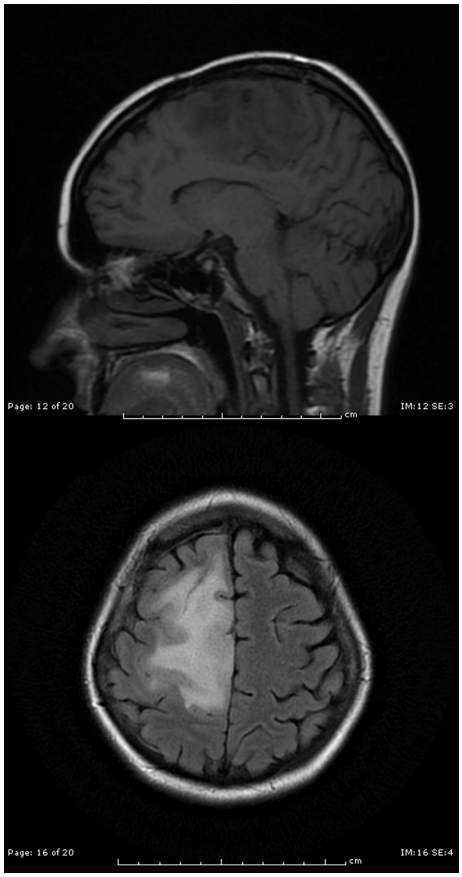

Fig. 1. Sagittal T1-weighted (upper) and axial fluid attenuated inversion recovery (lower) MRI showing a non-enhancing lesion in the right posterior frontal region with no calcification and minimal mass effect.