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Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders (Review)

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[Intervention Review]

Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders

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ABSTRACT

Background

Fisher syndrome is one of the regional variants of Guillain-Barré syndrome, characterised by impairment of eye movements (ophthalmoplegia), incoordination (ataxia) and loss of tendon reflexes (areflexia). It can occur in more limited forms, and may overlap with Guillain-Barré syndrome. A further variant is associated with upper motor neuron signs and disturbance of consciousness (Bickerstaff's brainstem encephalitis). All of these variants are associated with anti-GQ1b IgG antibodies. Intravenous immunoglobulin (IVIg) and plasma exchange are often used as treatments in this patient group. This review was undertaken to systematically assess any available randomised controlled data on acute immunomodulatory therapies in Fisher Syndrome or its variants.

Objectives

To provide the best available evidence from randomised controlled trials on the role of acute immunomodulatory therapy in the treatment of Fisher Syndrome and related disorders.

Search methods

We searched the Cochrane Neuromuscular Disease Trials Specialized Register (February 2009), MEDLINE (January 1966 to February 2009), EMBASE (January 1980 to February 2009), CINAHL (January 1982 to February 2009) and LILACS (January 1982 to February 2009) for randomised controlled trials and quasi-randomised trials.

Selection criteria

All randomised and quasi-randomised controlled clinical trials (in which allocation was not random but was intended to be unbiased, e.g. alternate allocation, and non-randomised controlled studies were to have been selected. Since no such clinical trials were discovered, all retrospective case series containing five or more patients were assessed and summarised in the discussion section.

Data collection and analysis

All studies of Fisher Syndrome and its clinical variants were scrutinised for data on patients treated with any form of acute immunotherapy. Information on the outcome was then collated and summarised.

Main results

We found no randomised or non-randomised prospective controlled trials of immunotherapy in Fisher Syndrome or related disorders. We summarised the results of retrospective series containing five or more patients in the discussion section.

Authors' conclusions

There are no randomised controlled trials of immunomodulatory therapy in Fisher Syndrome or related disorders on which to base practice.

PLAIN LANGUAGE SUMMARY

Treatment for Fisher syndrome, Bickerstaff's brain stem encephalitis and related disorders

Fisher syndrome is an uncommon paralysing illness, usually caused by autoimmune inflammation of nerves following an infection. Fisher syndrome is characterised by impairment of eye movements, abnormal co-ordination and loss of tendon reflexes. It is a variant of Guillain-Barré syndrome. Unlike Guillain-Barré syndrome, it does not cause limb or respiratory muscle weakness. In Western countries Fisher syndrome represents between 5% and 10% of Guillain-Barré syndrome cases, but it is more common in Eastern Asia, for example 25% of cases in Japan. Bickerstaff's brain stem encephalitis shares many clinical features but also includes altered consciousness and signs of central nervous system inflammation. Treatment strategies tried have been immunotherapies such as plasma exchange or intravenous immunoglobulin which are used in Guillain-Barré syndrome. This systematic review found no randomised controlled trials of treatments for Fisher syndrome, Bickerstaff's brain stem encephalitis or their variants. Observational studies suggest that Fisher syndrome always and Bickerstaff's brain stem encephalitis usually recovers completely. Randomised controlled trials are needed to establish the value of immunotherapies or other treatments.

BACKGROUND

Fisher syndrome (FS) is a clinical variant of Guillain-Barré syndrome (GBS), an acute post infectious paralytic illness caused by inflammatory disruption of peripheral nerve integrity and function (Hughes 1997). Fisher syndrome is characterised by impairment of eye movements (ophthalmoplegia), incoordination (ataxia) and loss of tendon reflexes (areflexia) (Fisher 1956). The incidence of GBS has been reported as 1 to 2 per 100,000 per year (Hughes 1997), with FS representing between 5% and 10% of cases in Western countries. While the incidence of GBS is broadly the same throughout the world, the incidence of FS *as a proportion of GBS* has been reported to be considerably higher in Eastern Asia - 19% in Taiwan (Lyu 1997) and 25% in Japan (Mori 2001).

Pupillary abnormalities, ptosis (drooping of the eyelid), bulbar and facial palsy are accepted as components of the clinical presentation of FS. These features often occur in addition to the characteristic clinical triad that defines the syndrome (Mori 2001). Fisher syndrome can occur in a more limited form, involving only components of the triad (for example, a regional motor variant characterised by only ophthalmoplegia (Yuki 2001a)). Bulbar or facial palsy may also occur as an isolated presentation.

Although the aetiology of the two conditions may be similar, the separation of FS from GBS *clinically* is straightforward, and is important in terms of prognosis and treatment. Guillain-Barré syndrome is defined according to internationally accepted diagnostic criteria as acute polyradiculoneuropathy causing progressive weakness of two or more limbs, with an onset phase not more than four weeks, reduced or absent tendon reflexes, and lacking alternative causes (Asbury 1990). Although there are pure sensory variants, GBS usually progresses to generalised weakness, and often involves respiratory function. Fisher syndrome may overlap with GBS, causing limb or respiratory muscle weakness or both, in addition to some or all of the features of the FS triad, and such cases are rightly classified as GBS with ophthalmoplegia (Chiba 1993). 'Ataxic GBS' is commonly associated with the serological marker for FS (anti GQ1b IgG antibodies - see below) (Yuki 2000), emphasising that while classification systems may vary (and sometimes appear confusing), these conditions all form part of the same spectrum of disorders.

Though FS is uncommon, its immunological basis has provided impetus to the continuing search for anti-glycolipid antibodies in acute autoimmune neuropathies. Gangliosides are surface antigens preferentially localised in the nervous system. Antiganglioside antibodies are frequently observed in acute phase sera from GBS patients. In 1992 it was reported that six patients with FS had anti-GQ1b IgG antibodies during the acute phase of their illness (Chiba 1992). Anti-GQ1b antibodies in FS almost invariably cross react with the structurally similar ganglioside GT1a (Chiba 1993; Susuki 2001). Anti-GQ1b IgG antibodies are sensitive and specific tests for FS and its variants (Willison 1993; Yuki 1993a). Antibody titres peak at clinical presentation, decay rapidly with the course of the clinical recovery, and become undetectable as early as one month after onset (Odaka 2003a).

In common with GBS, FS is usually preceded by infection, and the temporal pattern of clinical onset and spontaneous recovery that occurs in FS strongly suggests an acute phase primary immune response. Particular attention has been paid to its association with *Campylobacter jejuni* enteritis, and considerable support for the theory of molecular mimicry between GQ1b/GT1a and *C. jejuni* lipo-oligosaccharides now exists (Yuki 2001; Yuki 2005). A comprehensive study of the pathogens showed that 31% of 201 patients with GBS, and 18% of 65 patients with FS, were seropositive for recent *C. jejuni* infection (Koga 1998). *C. jejuni* and *Haemophilus influenzae* are related to FS development, and production of anti-GQ1b autoantibody is mediated by the GQ1b-mimicking lipo-oligosaccharides on those bacteria, but the causative agent remains unclear in the majority of patients with FS (Koga 2005). In a case series involving 50 participants, respiratory symptoms were the most common infectious symptoms in the month before onset (occurring in 76% of cases), with gastrointestinal symptoms occurring in only 4% (Mori 2001). Elevation of cerebrospinal fluid protein, in the absence of a cellular response (albumino-cytological dissociation), is observed in most cases (Nishimoto 2004).

Fisher syndrome is generally regarded as a self-limiting, benign condition, and the limited epidemiological evidence available supports this view. All of 28 untreated FS patients returned to normal activities six months after neurologic onset (Mori 2001). The respective median (range) periods in days between neurologic onset and the disappearance of ataxia and ophthalmoplegia were 32 (8 to 271) and 88 (29 to 165). In contrast, GBS has an overall mortality of between 3.5% and 12% during the acute phase (Hughes 2006b; Italian Guillain-Barré Study Group 1996), and causes considerable long-term disability. Twelve per cent of patients still require an aid to walk a year after onset (Rees 1998).

Bickerstaff's brainstem encephalitis (BBE) (Bickerstaff 1957) is a closely related condition, in which alteration of consciousness or long tract signs or both are seen in addition to ophthalmoplegia and ataxia. The relationship of BBE to FS and GBS remains controversial. While ophthalmoplegia and ataxia are present in all cases, some authors regard BBE as a separate clinical entity, the key distinguishing features being drowsiness, coma, hyperreflexia, and extensor plantar responses. Others classify BBE as an FS variant, citing the presence of an antecedent infection (in 92%), presence of raised protein in the cerebrospinal fluid (in 59%) and presence of anti-GQ1b antibody (in 66%) as features common to both disorders (Odaka 2003; Yuki 1993). Brain magnetic resonance imaging abnormalities are present in 30% of patients with BBE (Odaka 2003). The situation is further complicated by 'GBS overlap' syndromes in which the clinical features of BBE are seen in conjunction with limb weakness (Odaka 2003). Treatment strategies used (see below) are similar to those that have been used for FS. The largest published series included both BBE without limb weakness and BBE with limb weakness ('BBE with overlapping GBS'), and recorded complete remission of symptoms at six months in 66% of patients, most of whom had received various combinations of immunotherapy (Odaka 2003). Co-authors of this review published a large recent series examining the clinical details of patients referred to a diagnostic laboratory and proposed the eponym 'Fisher-Bickerstaff syndrome' after reviewing the clinical and investigational similarities between FS and BBE (Ito 2008).

The rationale behind the use of plasma exchange (PE) and intravenous immunoglobulin (IVIg) in acute demyelinating neuropathies is discussed in Cochrane reviews examining their use in GBS (Hughes 2006b; Raphaël 2002). Plasma exchange is superior to supportive care in mild, moderate and severe GBS, and benefit is seen up to 30 days after disease onset (Raphaël

2002). Intravenous immunoglobulin is similar in efficacy to PE, but no adequate trials have compared it to placebo (Hughes 2006b). A Cochrane review of the effects of methylprednisolone on outcome in GBS has reported no benefit (Hughes 2006a). In a randomised trial of patients with GBS in 2004, the addition of intravenous methylprednisolone to standard therapy with IVIg did not confer any additional effect on recovery from disability at four weeks, when compared to IVIg therapy alone (van Koningsveld 2004). Numerous case reports and series of patients with FS who have been treated with immunotherapy (generally PE, IVIg or a combination including one of these) have been published. Often such cases have been associated with central neurologic disturbance (Odaka 2003; Yeh 1999), severe bulbar weakness leading to a requirement for ventilation, or have been complicated by 'GBS' features (limb or respiratory involvement).

To the authors' knowledge no randomised trials of immunomodulatory treatments in FS had been published when the protocol for this review was written, and no other systematic reviews of therapy exist. This review attempts to systematically consider the available evidence. It is hoped that it will identify the need for clinical trials or prospective data collection in FS, and will serve as a basis for maintaining an up-to-date record.

OBJECTIVES

Our objective was to systematically review the randomised and non-randomised literature on treatment for FS and related disorders.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomised controlled trials (RCTs) of acute immunomodulatory therapy in FS and related disorders. It was anticipated that this type of evidence would be unavailable, and so non-randomised studies were also sought. We planned to report quasi-randomised trials (those trials in which treatment allocation was intended to be random but might have been biased, for example alternate allocation or allocation according to the day of the week), historically controlled trials and trials with concurrent controls in the meta-analysis, provided adequate diagnostic criteria were applied (see below), and adequate descriptions of interventions and clinical course were stated. These controlled (but not randomised) trials were to be considered and reported separately from any RCTs. Each of these study designs carries inherent bias, which was to be reflected in their interpretation.

Given the anticipated lack of studies that included pre-planned data collection and eligibility criteria, and in an attempt to summarise the available clinical data, other types of studies were reviewed and summarised in the discussion section. Prospective and retrospective comparative cohort studies, case-control studies and case series containing five or more patients were included in this assessment. Both untreated (natural history) patients and patients treated with immunomodulatory therapy were assessed, provided that sufficient clinical features were available to classify the syndrome (as below), adequate descriptions of interventions were given, and enough information was available to determine clinical outcome. All languages were considered.

Types of participants

It is recognised that while a specific triad of clinical features denotes 'classical' FS, contemporary classifications have broadened as a result of the anti-GQ1b antibody test. This review included four groups of patients.

(1) Typical FS: Patients with each of the components of Fisher's triad (ophthalmoplegia, arreflexia and ataxia). The clinical severity of each component may vary, and accordingly hyporeflexia (rather than areflexia) is acceptable. Additional features such as pupillary abnormalities, ptosis, bulbar and facial palsy may be present.

(2) Bickerstaff's brainstem encephalitis (BBE): Patients with ophthalmoplegia and ataxia, who also present with altered consciousness or pyramidal signs (hyperreflexia or extensor plantar responses) or both.

(3) Limited FS: Patients with one or two components of the triad, and positive serology. These patients may have ophthalmoplegia, ataxia or a mixed picture. Positive serology is defined as the presence of serum anti-GQ1b/GT1a IgG antibody. Additional features such as pupillary abnormalities, ptosis, bulbar and facial palsy may be present.

(4) Other limited syndromes: Patients with positive serology (presence of anti-GQ1b/GT1a IgG antibody in serum) and isolated cranial motor syndromes that do not include ophthalmoplegia. In practice the clinical features of this group will be oropharyngeal or facial weakness or both.

For patients in each group, investigations should have excluded alternative explanations for the clinical picture.

Types of interventions

All interventions were considered. It was anticipated that most studies would focus on the use of plasma exchange, IVIg, steroids or a combination of these agents. We considered studies that compared any treatment with placebo or no treatment, or compared one treatment against another.

Series containing five or more participants that have reported outcome in patients not receiving any immunomodulatory therapy were also assessed. Patients receiving supportive treatments, physiotherapy or ventilation for bulbar palsy or altered consciousness were considered as 'untreated'.

Types of outcome measures

Primary outcomes

This review considered a variety of clinical presentations. There is no accepted scoring scale for ophthalmoplegia severity, and the severity of premorbid ataxia is poorly documented in accessible literature. No randomised trials have set a precedent by defining a reproducible and standardised outcome measure that can be used to assess outcome in FS. Therefore, the primary outcome measure was taken as the proportion of patients who were symptom free and had returned to normal function (in the trial authors' opinion) by six months. Depending on initial presentation, this may equate with time to complete resolution of ataxia or to complete resolution of ophthalmoplegia or other motor weakness. If necessary the results from studies using different time periods were converted to their six-month equivalent values assuming constant monthly rates

of recovery, in order to provide approximate estimates using all the available studies.

In the context of an illness that is usually self-limiting, treatments may affect the speed of improvement, and so symptom resolution by one month was assessed as a secondary outcome measure.

Secondary outcomes

(1) Proportion of patients with complete resolution of symptoms at one month.
(2) Proportion of patients requiring ventilation within one month of clinical onset.
(3) Proportion of patients dead at six months.
(4) Proportion of patients who experienced a treatment related fluctuation (defined as a period of worsening lasting at least seven days following a period of improvement lasting at least seven days) during the 12 weeks after the onset of treatment or a relapse (worsening for more than seven days starting more than 12 weeks but within one year after the onset of treatment).
(5) Proportion of patients with the following adverse events, whether attributable to treatment or the disease itself, during, or within one week after stopping, treatment:
(a) new infection treated with antibiotics;
(b) haemorrhage requiring blood transfusion;
(c) occurrence of cardiac arrhythmia requiring treatment with cardiac rate modifying drugs or pacemaker;
(d) autonomic instability consisting of either daily variations of systolic blood pressure larger than 40 mm Hg or sudden bradycardia involving a reduction of heart rate by more than 20 beats per minute;
(e) hypertension requiring drug treatment;
(f) development of renal failure with serum creatinine > 200 mmol/l (when this occurred, possible pre-existing factors, including age, pre-treatment serum creatinine, hypovolaemia, and brand of immunoglobulin, were to be noted);
(g) headache;
(h) skin rash, for example palmar eczema;
(i) abnormal liver function (appearance of elevation of serum liver enzymes by more than three standard deviations above the normal mean within four weeks after randomisation, taking into account the presence of abnormal liver function before randomisation).

Again, these outcomes were assessed in the available non-randomised studies.

Search methods for identification of studies

We updated the search of the Cochrane Neuromuscular Disease Trials Specialized Register in February 2009 using 'Miller Fisher syndrome', 'Miller-Fisher syndrome' and its synonyms 'Fisher syndrome', 'Fisher's syndrome', 'anti-GQ1b antibody syndrome', 'acute ataxic neuropathy', 'acute ophthalmoplegia', 'acute ophthalmoparesis', 'acute oropharyngeal palsy', 'Bickerstaff's brain stem encephalitis' and 'Bickerstaff's encephalitis' as the search terms. The strategy was adapted to search MEDLINE (January 1966 to February 2009), EMBASE (January 1980 to February 2009), CINAHL Plus (January 1937 to February 2009) and LILACS (January 1982 to February 2009). We contacted the authors of any trials identified and other disease experts seeking other published and unpublished trials.

Electronic search strategies

See Appendix 1; Appendix 2; Appendix 3 and Appendix 4.

Data collection and analysis

Selection of studies

A considerable proportion of the literature available on FS and anti-GQ1b IgG antibody syndromes was in Japanese or Chinese journals. The review team comprised both native English speakers (JRO, HJW), native Japanese speakers (NY, MO) and a Chinese speaker (STH). For English and Japanese articles two authors (JRO and HJW for English language, NY and MO for Japanese languages) independently checked the titles and abstracts of the articles identified by the search. They then extracted data using a specially designed form, assessed the methodological quality of the selected articles and decided upon inclusion independently. If there was disagreement, they reached agreement by discussion, with adjudication if necessary by a third author. Chinese articles were assessed in the same way by STH, with any uncertainties being resolved by discussion with a second author.

Assessment of risk of bias in included studies

If any RCTs or pre-planned controlled clinical trials had been found, we would have assessed the risk of bias for any included studies according to the methods described in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Prospective and retrospective comparative cohort studies, case-control studies and series (containing five or more patients) were assessed to ensure that the types of patients included fulfilled the explicit diagnostic criteria stated above, that interventions were clearly stated, and that clinical course and outcome were clearly documented.

Data synthesis

When there was more than one trial with a specific agent or class of agents we planned to calculate a weighted treatment effect (using a fixed-effect model, or a random-effects model if heterogeneity was present) across trials using the Cochrane statistical package Review Manager 5. Relative risks and risk differences with 95% confidence intervals were to be used for the dichotomous primary and secondary outcome measures. We planned to test for heterogeneity using the Chi-squared test, and to investigate any reasons for it. Sensitivity analysis was planned on the basis of methodological quality when appropriate. In the event that our preferred outcome measures were not available but others were available for more than one trial we also planned to use those to calculate a weighted treatment effect across trials.

Subgroup analysis and investigation of heterogeneity

If the data allowed we planned to test the effect of immunomodulatory interventions in the following subgroups.

(1) Four different groups of patients described in Types of participants:
(a) typical FS;
(b) BBE;
(c) limited FS;
(d) other limited syndromes.
(2) Children (up to 15 years).
(3) Patients requiring ventilation, because of loss of consciousness or bulbar palsy.

(4) Patients treated within 7 days of onset of neuropathy, patients treated between 7 and 14 days after onset of neuropathy, and patients treated 14 days after onset of neuropathy.

We planned to consider both adverse events and cost effectiveness when the non-randomised evidence was reviewed.

RESULTS

Description of studies

We found no randomised, quasi-randomised, historically controlled trials, or trials with concurrent controls that met the selection criteria. Case series containing five or more patients in which sufficient clinical features were available to classify the syndrome, reasonable descriptions of interventions were given, and enough information was available to assess one or more of our pre-defined clinical outcomes, were summarised in the discussion section.

Risk of bias in included studies

Not applicable.

Effects of interventions

We found no (randomised) controlled trials of any treatment in FS or in related disorders, nor did we find any prospective cohort series or case control studies. A number of retrospective series met our criteria for discussion, and are summarised below.

DISCUSSION

The literature on FS and its related disorders is populated by a large number of case reports and small retrospective case series. Additional complexity is created by the fact that the disorder can occur in more limited forms, can be accompanied by upper motor neuron features or disturbance of consciousness (BBE), and can either overlap with or develop into GBS. Since all these disorders are thought to share common pathological triggers and features, it might be argued that randomised controlled data from trials in GBS should simply be extrapolated to FS and its variants, with the aim of speeding recovery. However, while FS related disorders can cause disabling ataxia and ophthalmoplegia for months, and also severe bulbar palsy requiring intubation, it may be that a disorder rightly regarded as self-limiting (see below) should be treated conservatively, rather than subjecting patients to potentially toxic therapies. Unfortunately no randomised controlled data are available, and observational data are retrospective and provide very limited information for therapeutic decision making, due to numerous sources of bias.

We have summarised the data on our pre-defined outcome measures from published series of five or more patients (treated or untreated) that were identified during the search process in Table 1 (typical FS), Table 2 (BBE) and Table 3 (limited FS).Only studies in which sufficient clinical features were available to classify the presenting syndrome, adequate descriptions of interventions were given, and enough information was available to assess one or more of our pre-defined clinical outcomes were included. All studies were retrospective, and whether cases were consecutive was variably stated. No comparative cohort or case control studies were identified. Attempts were made to contact the authors of the larger published studies for data if the published trial report contained information that was unsuitable for the assessment of our outcome measures (for example if median time to recovery was published rather than proportion recovered by six months). Unfortunately only one small case series was available for 'limited FS' and no suitable data were available for 'other limited syndromes', but published case reports and case series in these groups suggest a similar natural history to typical FS.

Fisher Syndrome

The series of typical Fisher syndrome patients were: Al Din 1982; Barontini 1983; Cheng 2003; Kobayashi 1983; Mizoguchi 1998; Mori 2001; Mori 2002; Mori 2007; Mukai 1978; Shuaib 1987; Yin 1985; Yip 1991; Yuki 1996. Such information should be interpreted with caution, but some tentative conclusions can be drawn. Table 1 demonstrates high rates of complete clinical recovery from typical FS in untreated patients at six months (range 60% to 100%). Only one group (Mori 2001; Mori 2002; Mori 2007) has published five or more patients treated with IVIg, and 89% of their 28 patients were symptom-free at six months. The proportion of symptom-free patients at six months in the various series of plasma exchange treated patients ranged from 66% to 96%. There are very few typical FS patient series treated with steroids, and other outcome measures are difficult to assess with any clarity. Many patients are not symptom free at one month, but there is no evidence to suggest that this proportion can be increased by immunotherapy. Reported adverse events with IVIg and plasma exchange are infrequent.

The largest series of typical FS patients was reported initially in 2001 (Mori 2001), with further information summarising the lack of difference between plasma exchange treated and untreated patients being published in letter form in 2002 (Mori 2002). The same group recently reported their most up to date analysis of the same cohort in 2007 (Mori 2007). Clinical recovery was reviewed in a consecutive series of 92 patients with typical FS. The time-course of recovery was compared between patients treated with IVIg (n = 28), PE (n = 23), or supportive treatment only (n = 41), with complete remission of ophthalmoplegia and ataxia as the study endpoint. The median periods for disappearance of ophthalmoplegia (82 days) and ataxia (39 days) in the IVIg group showed no statistical difference from the values in the plasma exchange group (ophthalmoplegia 92 days, ataxia 21 days) and the control group (ophthalmoplegia 76 days, ataxia 31 days). One year after onset, 89 (96%) of the 92 patients had complete remission of ophthalmoplegia and ataxia. The authors reported that the periods between neurological onset and the 'beginning of amelioration' of ophthalmoplegia and ataxia were slightly shorter for the IVIg group than the control group (ophthalmoplegia, median 12·0 days versus 13·5 days; P value = 0·04; ataxia; 8·0 days versus 10·0 days; P value = 0·027), but were similar between the PE and the control groups. The authors concluded that in FS IVIg slightly hastens the amelioration of ophthalmoplegia and ataxia, but does not affect the final outcome, presumably because of a good natural recovery.

Bickerstaff's Brainstem Encephalitis

In BBE (Table 2) the series were: Al Din 1982; Kuntzer 1987; Odaka 2003; Yaqub 1990. The two largest published series included patients with limb weakness ('BBE with overlapping GBS') and these patients have been included in our analysis. Most of the data on BBE come from a single large retrospective series (Odaka 2003 - see below). In our analysis fewer (a mean of 65%) BBE patients were symptom-free at six months than FS patients, and a higher

proportion (a mean of 16%) required ventilation. No advantage of any particular treatment can be inferred from the data available.

In 2003, Odaka et al. (co-authors on this review) reported the largest series of patients with BBE, which has greatly clarified the characteristics of the disorder (Odaka 2003). Detailed clinical profiles and laboratory findings were reviewed for 62 cases of BBE diagnosed by the strict criteria of progressive (peaking within four weeks), relatively symmetrical external ophthalmoplegia and ataxia, and disturbance of consciousness or hyperreflexia. Flaccid symmetrical tetraparesis was seen in 60% of the patients, and these patients were considered to have 'BBE with overlapping GBS'. We have included these patients in our analysis. Ninety-two per cent of the affected cases had an antecedent illness. Disturbance of consciousness was frequent (74%), and Babinski's sign was present in 40%. Facial diplegia was present in 45%, and pupillary abnormalities and bulbar palsy were found in 34%. Deep tendon reflexes were absent or decreased in 58%, normal in 8%, and brisk in 34%. Serum anti-GQ1b IgG antibody was positive in 66%, and MRI showed high intensity abnormalities in the posterior fossa, white matter or thalami in 30% of the patients.

Almost all the patients in this study had a monophasic remitting course and, in keeping with previous reports, generally had a good outcome with complete remission of symptoms at six months in 66% of patients. Combinations of steroids and plasma exchange (PE, double-filtration plasmapheresis, or immunoadsorption therapy) were given to 16 (26%) patients, plasma exchange only to 14 (23%), steroids only to 13 (21%), combinations of steroids and IVIg to 5 (8%), combinations of steroids and plasmapheresis followed by IVIg to 3 (5%), plasma exchange followed by IVIg and IVIg only to 2 (3%), and no specific immunotherapy to 7 (11%). Assisted ventilation was required for 10 (16%) of the 62 BBE patients during the acute phase. Dysaesthesiae or limb weakness persisted in 8 (14%), and diplopia or gait disturbance in 5 (9%). Three patients had residual symptoms, (one each of psychic change, dementia, and dysphagia). Three patients died respectively of respiratory obstruction, sudden cardiopulmonary arrest and of a haemorrhagic infarction complication in the right cerebrum caused by candida meningitis.

Limited Fisher Syndrome

A small case series was published in 2008 describing the clinical features of acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody (Lee 2008). Eleven patients were reported, but follow-up data were available in only eight, and these are summarised in Table 3. Data on which treatment each patient received were not published, but were sought from the authors for the purposes of this review. External ophthalmoparesis was present in all the patients and included mixed horizontal-vertical (n = 7), pure horizontal (n = 3) and pure vertical gaze palsy (n = 1). Binocular involvement was common, but unilateral ophthalmoparesis was observed in 27%. Other findings included ptosis (in 46%) and internal ophthalmoplegia (in 55%). Prognosis was uniformly excellent, with symptoms in three of the four immunoglobulin treated patients and the untreated patient fully resolving by three months, and those in all patients fully resolving by six months.

General Conclusions

Experimental studies support the use and development of the approaches considered in this review. Studies in an ex-vivo mouse neuromuscular junction model have shown that human IVIg, as used in clinical therapy, inhibits the binding of anti-GQ1b antibodies to GQ1b, thereby preventing antibody binding to neural GQ1b, complement activation and subsequent pathophysiological effects (Jacobs 2003). This finding provides an experimental rationale for the use of IVIg in the treatment of FS. Considerable technical issues remain unresolved in the elimination of anti-ganglioside antibodies from the circulation through specific immunoadsorption therapy. Nevertheless, as more proof emerges that anti-GQ1b antibodies, and anti-ganglioside antibodies in general, are central pathogenic mediators of disease, the possibility that they could be removed by selective PE becomes more worthy of exploration (Willison 2004). Calpain inhibitors may be useful therapeutically in limiting nerve terminal and axonal injury in autoimmune peripheral neuropathies in which calcium influx is a key component of the pathogenic pathway (O'Hanlon 2003). Recently eculizumab (a humanised monoclonal antibody which inhibits terminal complement activation at the C5 protein) has been shown to protect against complement mediated damage in murine FS (Halstead 2008).

Clinical studies of all of these approaches will need to concentrate on speed of recovery from FS, or the more severe BBE variant of FS that often overlaps with GBS, and more often requires intubation and ventilation. Complete resolution of ataxia by one month and complete resolution of ophthalmoplegia by three months would be appropriate outcome measures based on the observational data available.

Despite the absence of evidence from randomised trials, the review authors consider it clinically logical to extrapolate GBS data to the population of FS patients with complicated disease (profound ataxia, severe bulbar palsy, or those with respiratory or limb weakness in GBS overlap syndromes). Patients with less severe syndromes are likely to improve completely with a conservative approach. Whether the speed of this recovery can be hastened with currently available therapies is unknown.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials of immunomodulatory therapy in FS or related disorders on which to base practice.

Implications for research

Randomised controlled trials are needed to establish the value of immunomodulatory therapy in FS and related disorders. Typical FS is self-limiting, and has a benign prognosis, and so the clinical aim of any therapeutic intervention is limited to speeding recovery.

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ADDITIONAL TABLES

Table 1. Typical FS. Data from series of 5 or more patients.

Study ID / name	Treatment	N	n(%)asympto-matic 6m	n(%)asymp-tomatic 1m	n(%)venti-lated 1m	n(%)dead 6m	n(%)fluct / relapse	? Adverse event
Cheng 2003	PE	3	2 (66%)	2 (66%)	0	1 (33%)	0	1 pneumo-nia (day 12)
	Natural history	4	3 (75%)	3 (75%)	0	1 (25%)	0	1 cardiac ar-rest (day 22)
Mori 2001, 2002, 2006	PE	23	22 (96%)	-	-	0	-	-
	IVIg	28	25 (89%)	-	-	0	-	-
	Natural history	41	39 (95%)	-	-	0	-	-
Mizoguchi 1998	PE	10	-	1 (10%)	-	-	-	-
	Natural history	6	-	0	-	-	-	-
Kobayashi 1983	Natural history	5	3 (60%)	2 (40%)	5 (100%)	0	0	0
Yuki 1996	Tryptophan gel column	11	11 (100%)	0	-	0	-	-
J49 Mukai 1978	Prednisolone	1	1 (100%)	-	1 (100%)	0	0	0
	Natural history	6	6 (100%)	-	6 (100%)	0	0	0
Shuaib 1986	Natural history	7	7 (100%)	-	0	0	0	0
Barontini 1983	Prednisolone	1	1 (100%)	0	0	0	0	0
	Natural history	5	5 (100%)	2 (40%)	1 (25%)	0	0	0
Al-Din 1982	Prednisolone	1	1 (100%)	0	0	0	0	0
	Natural history	4	4 (100%)	0	1 (25%)	0	0	0
Yin 1985	Methylprednisolone	2	-	-	0	0	0	-
	Natural history	5	-	-	0	0	0	-

Table 1. Typical FS. Data from series of 5 or more patients. *(Continued)*

Yip1991	Prednisolone	3	3 (100%)	0	0	2	0
	Natural history	6	6 (100%)	0	0	0	0

Table 2. BBE. Data from series of 5 or more patients.

Study ID / Name	Treatment	N	n(%)Asymptomatic 6m	n(%)Asymptomatic 1m	n(%)Ventilated 1m	n(%)Dead 6m	n(%)Fluct / relapse	? Adverse event
Odaka 2003	PE	14	8 (57%)	-	2 (14%)	1 (7%)	1 (7%)	1 cardiac arrest
	Steroids	13	11 (85%)	-	0	0	0	0
	IVIg	2	2 (100%)	-	0	0	0	0
	PE + steroids	16	6 (38%)	-	4 (25%)	0	0	0
	IVIg + steroids	5	3 (60%)	-	0	0	0	0
	PE + IVIg	2	0	-	2 (100%)	0	0	0
	PE + IVIg + steroids	3	1 (33%)	-	1 (33%)	1 (33%)	0	1 respiratory obstruction
	Natural history	7	1 (14%)	-	1 (14%)	1 (14%)	0	1 meningitis
Yaqub 1989	Natural history	6	6 (100%)	1 (17%)	1 (17%)	0	0	0
Kuntzer 1987	Steroids (1), acyclovir (1)	2	2 (100%)	0	0	0	-	-
	Natural history	5	5 (100%)	1 (20%)	1 (20%)	0	-	1 pneumonia
Al-Din 1982	ACTH or prednisolone	3	2 (67%)	1 (33%)	0	0	0	0
	Natural history	10	7 (70%)	0	1 (10%)	1 (10%)	0	1 chest infection + pulmonary embolism

Table 3. 3 Limited FS. Data from series of 5 or more patients

Study ID / Name	Treatment	N	n(%)Asymptomatic 6m	n(%)Asymptomatic 1m	n(%)Ventilated 1m	n(%)Dead 6m	n(%)Fluct / relapse	? Adverse event
Lee 2008	IVIg	4	4 (100%)	-	0	0	-	-
	IVIg + steroids	1	1 (100%)	-	0	0	-	-
	Steroids	2	2 (100%)	-	0	0	-	-
	Natural history	1	1 (100%)	-	0	0	-	-

APPENDICES

Appendix 1. MEDLINE (OvidSP) strategy

1. Miller Fisher syndrome.mp. or Miller Fisher Syndrome/
2. (Miller adj3 Fisher).mp.
3. Fisher$ syndrome.mp.
4. acute opthalmoparesis.mp.
5. acute ataxic neuropath$.mp.
6. acute opthalmoplegia.mp.
7. acute oropharyngeal pals$.mp.
8. (bickerstaff$ adj5 encephalitis).mp.
9. Ophthalmoplegia/co [Complications]
10. ATAXIA/co [Complications]
11. Acute Disease/
12. 10 and 11
13. 9 and 11
14. or/1-8
15. 12 or 13 or 14
16. limit 15 to human

Appendix 2. LILACS strategy

Tw Miller Fisher syndrome or Mh Miller Fisher Syndrome or Tw Miller Fisher or Tw Fisher syndrome or Tw MillerFisher or Tw Miller Fischer or Tw acute opthalmoparesis or Tw acute ataxic neuropathy or Tw acute opthalmoplegia or Tw acute oropharyngeal palsy or Tw bickerstaff encephalitis or Tw bickerstaff brain stem encephalitis or (Mh Ophthalmopathy AND Mh Acute Disease) or (Mh ATAXIA and Mh Acute Disease) AND Ct human

Appendix 3. EMBASE (OvidSP) strategy

1. Miller Fisher Syndrome.mp.
2. Miller Fisher Syndrome.tw.
3. Miller-Fisher syndrome.mp.
4. Miller-Fisher syndrome.tw.
5. Fisher syndrome.mp.
6. Fisher syndrome.tw.
7. Fisher's syndrome.mp.
8. Fisher's syndrome.tw.
9. anti-GQ1b antibody syndrome.mp.
10. anti-GQ1b antibody syndrome.tw.
11. acute ataxic neuropathy.mp.
12. acute ataxic neuropathy.tw.
13. acute ophthalmoplegia.mp.
14. acute ophthalmoplegia.tw.
15. acute ophthalmoparesis.mp.
16. acute ophthalmoparesis.tw.
17. acute oropharyngeal palsy.mp.
18. acute oropharyngeal palsy.tw.
19. Bickerstaff's brain stem encephalitis.mp.
20. Bickerstaff's brain stem encephalitis.tw.
21. Bickerstaff's encephalitis.mp.
22. Bickerstaff's encephalitis.tw.
23. bickerstaff brainstem encephalitis/ or Bickerstaff.mp.
24. Bickerstaff.tw.
25. Bickerstaff brain stem encephalitis.tw.
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. limit 26 to human

Appendix 4. CINAHL Plus (EBSCOhost) strategy

S29- S18 AND S28
S28- S27 or S26 or S25 or S24 or S23 or S22 or S21 or S20 or S19
S27- Bickerstaff

S26- Bickerstaff's encephalitis
S25- acute ophthalmoplegia
S24- acute ataxic neuropathy
S23- Fisher's syndrome
S22- Fisher syndrome
S21- Miller Fisher
S20- Miller-Fisher syndrome
S19- Miller Fisher syndrome
S18- S17 or S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S17- TI random* or AB random*
S16- (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy))
S15- (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*))
S14- (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*))
S13- (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*))
S12- ABAB design*
S11- PT clinical trial or PT systematic review
S10- (MH "Factorial Design")
S9- (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")
S8- (MH "Meta Analysis")
S7- (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")
S6- (MH "Quasi-Experimental Studies")
S5- (MH "Placebos")
S4- (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")
S3- (MH "Clinical Trials+")
S2- (MH "Crossover Design")
S1- (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

WHAT'S NEW

Date	Event	Description
2 August 2009	New search has been performed	Update conducted on 2 August 2009, after new search on 16 February 2009 using previous criteria, and additional minor amendments.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 1, 2007

Date	Event	Description
28 July 2008	New search has been performed	Converted to new review format.
28 September 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JRO and HJW prepared the protocol and review, and amended it after peer review. They assessed all English language papers.They prepared the updated version in 2009. NY and MO assessed all Japanese language studies and STH assessed all Chinese language studies. NY, MO and STH made comments and amendments at each stage.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods section has been updated in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

INDEX TERMS

Medical Subject Headings (MeSH)

*Brain Stem; *Immunotherapy; Consciousness Disorders [etiology] [therapy]; Encephalitis [*therapy]; Miller Fisher Syndrome [*therapy]

MeSH check words

Humans