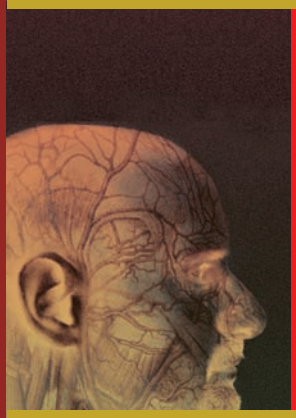
BRINGING CONSENSUS TO THE USE OF IVIG IN NEUROLOGY
STATEMENTS ON THE USE OF **IVIG IN NEUROLOGY**
1ST EDITION
PREPARED BY THE ASIA-PACIFIC IVIG ADVISORY BOARD
November 2004



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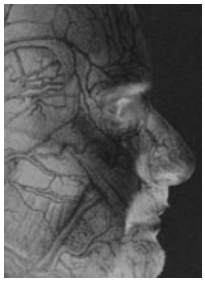

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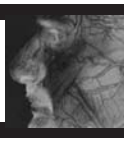
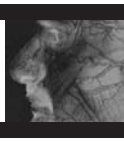




FOREWORD

The purpose of the *BRINGING CONSENSUS TO THE USE OF IVIG IN NEUROLOGY* publication is to support neurologists and clinicians in the use of intravenous immunoglobulin (IVIG) in neurological practice.

In the field of Neurology, IVIG has a dramatic impact in the treatment of autoimmune disorders, with a significant improvement in the quality of life of our patients. The success of IVIG therapy has meant that it is being used in an ever increasing number of disorders, with demand sometimes outstripping supply. The optimal use of IVIG in the treatment of neurological disorders is therefore an important goal.

Over the last few years, there has been an increasing push towards the development of clinical practice guidelines in a variety of medical disciplines. Guidelines have shown to be effective in bringing about change in clinical practices, particularly those that are ineffective. However, they can also reinforce the use of therapies that have the maximum chance of benefit, with minimal risk, and at an acceptable cost. The efficient use of guidelines or consensus statements may therefore lead to better health outcomes, with an improvement in health care. Guidelines are only one element of clinical decision making as patient preferences, clinician experience, and most importantly, the availability of resources and therapies also need to be taken into account.

In the Asia-Pacific region, where half of the world's population live, there is a wide spectrum of clinical expertise and health systems. Guidelines in one country may not be applicable to another country. To this end, an Asia-Pacific IVIG Advisory Board was assembled to specifically look at the synthesis of consensus statements and to review the applicability of the information within each country. The Advisory Board consists of experts in neurological practice together with many world renowned opinion leaders from the Asia-Pacific region.

The process to prepare these consensus statements began at the first Asia-Pacific IVIG Advisory Board Meeting in December 2003. The format of the consensus statements were decided on at that meeting with each statement including:

- background on the relevant disorder
- summary of the diagnostic process and differential diagnosis
- review of the literature for all therapies in the relevant condition
- detailed review of IVIG as a therapy in the relevant condition
- an evidence based approach to the interpretation of all treatment studies

- an expert summary statement of the place of IVIG therapy in the relevant condition with a clinical perspective from a group of experts in their field

Members of the Asia-Pacific IVIG Board were assigned topics and all the available literature was reviewed by members of the Advisory Board. The specific topics reviewed included:

- Guillain-Barré syndrome (GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Amyotrophic lateral sclerosis (ALS)
- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome (LEMS)
- Neuromyotonia (Isaacs' syndrome)
- Dermatomyositis, polymyositis, inclusion body myositis
- Chronic fatigue syndrome
- Paraneoplastic Neurological Disorders
- Stiff-person syndrome
- Epilepsy
- Opsoclonus-myoclonus syndrome-ataxia
- Multiple sclerosis

The conditions chosen for review reflect the disorders commonly treated or considered for treatment with IVIG in neurological practice. In subsequent revisions of the publication other disorders will be added.

The consensus statements were ratified by the committee in late October 2004 and are presented in this publication.

Due to a tight timeline for publication, the "Multiple sclerosis" chapter could not be included in this edition of BRINGING CONSENSUS TO THE USE OF IVIG IN NEUROLOGY. It will be added as an addendum.

Apart from the development of expert consensus statements, the charter of the Asia Pacific IVIG Advisory Board includes the development of an educational program for the Asia Pacific region. The creation of an Asia Pacific IVIG conference is the first part of this program and I am happy to be part of the inaugural INDAPS conference in Singapore taking place in late November 2004. Other elements of the educational program are currently in genesis and will be rolled out progressively over the coming year. The programs being developed will be designed in a region specific manner so that each country will be provided with important educational materials that are relevant to them. This is no small feat but with the ongoing support from CSL Bioplasma and ZLB Behring, I am sure that the programs will be successful.

Publications like this do not happen without a lot of effort, planning and hard work. The Asia-Pacific IVIG Advisory Board has worked tirelessly to make this possible. I thank each and every board member for their strong support and tremendous effort in achieving this major milestone.

A/Prof Andrew J. Kornberg
Chairman, Asia-Pacific IVIG Advisory Board
November 2004

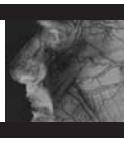
WAIVER OF LIABILITY

The information contained in this document is intended to serve as a guideline only. Neither the contributing authors nor the Asia-Pacific IVIG Advisory Board shall be liable for any actions, claims, damages, costs or obligations that may arise from the inappropriate use or misuse of the material contained in this document.

TERMINOLOGY

Standard Australia and virtually all-national bodies around the world are following the rules set down by the International Standards International Organisation for Standardisation (ISO) for the use of the terms 'shall, and 'should'. The Expert Consensus Statements for the use of IVIG in Neurology have used the definitions of these terms for consistency with current international usage.

- The term '**shall**' indicated a mandatory requirement; however this does not imply mandatory or legal requirement.



- The term '**should**' implies a recommendation where guidance is intended and does not preclude other acceptable practices.
- The term '**may**' is used to indicate an acceptable alternative or addition to the prescribed practice.

These consensus statements are based on evidence base literature research and expert opinion. The continuing development of knowledge, opinion and practice necessitates ongoing revision of practice. It is the intent of the authors that these expert consensus statements be reviewed annually or as the need arises.

Comments and suggestions for revision are welcomed and can be forwarded to:

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COMMENTARY ON THE INTERPRETATION OF PUBLICATIONS REVIEWED

This updated literature review considered all relevant studies and commentaries published in English from 1966 to 2003.

For search strategy please refer to Appendix C

ACRONYMS AND ABBREVIATIONS

AIDP	Acute Inflammatory Demyelinating Polyneuropathy
ALS	Amyotrophic Lateral Sclerosis
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CREAN	Chronic relapsing experimental autoimmune neuritis
DM	Dermatomyositis
EAN	Experimental autoimmune neuritis
EBM	Evidence Based Medicine
GBS	Guillain-Barré syndrome
IBM	Inclusion body myositis
IV	Intravenous
IVIg	Intravenous Immunoglobulin
LEMS	Lambert-Eaton Myasthenic Syndrome
MMN	Multifocal Motor Neuropathy
MRC	Medical Research Council
NHMRC	National Health and Medical Research Council
PE	Plasma exchange
PM	Polymyositis

BIBLIOGRAPHY AND LITERATURE REVIEW

Please see Appendix C

LEVELS OF EVIDENCE RATINGS

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III–i	Evidence obtained from well designed pseudo-randomised controlled trials (alternate location or some other method).
III–ii	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-controlled studies, or interrupted time series with a control group.
IV	Evidence obtained from comparative studies with historical control, two or more single arms, or interrupted time series without a parallel group.
V	Evidence obtained from case series, either post test or pre –test/post - tests.

SOURCE: NHMRC 1999 A Guide to the *Development, Implementation and Evaluation of Clinical Practice Guidelines.* National Health and Medical Research Council, Canberra.

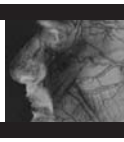
GUILLAIN-BARRÉ SYNDROME

INTRODUCTION

The Guillain-Barré syndrome (GBS) is the commonest cause of acute flaccid paralysis in the West, and probably in other parts of the world where polio is no longer endemic. Reported incidences vary between 1 to 4 per 100,000 (18). The syndrome typically presents with rapidly progressive, relatively symmetrical, ascending limb weakness consistent with a polyradiculoneuropathy, often with associated cranial nerve involvement. Motor signs and symptoms usually predominate over sensory signs and symptoms. Loss of tendon reflexes is almost ubiquitous. Major complications that may occur include respiratory failure, autonomic dysfunction and thromboembolism. The disease is monophasic, reaching its nadir usually within 2 weeks, although arbitrary definition accepts a limit of 4 weeks. A plateau phase of variable duration follows the nadir before gradual recovery. Although recovery is generally good or complete in the majority of patients, persistent disability has been reported to occur in about 20% (24), and death in 4 to 15% of patients (25, 28, 29, 33, 36).

It is now generally recognized that there are several subtypes of the disease (4). The most common form, classic GBS (or acute inflammatory demyelinating polyneuropathy, AIDP), is characterized by segmental demyelination in peripheral nerves. An axonal variant without demyelination (6, 22), either in the form of acute motor axonal neuropathy (AMAN) with pure motor involvement or acute motor and sensory axonal neuropathy (AMSAN) with mixed sensorimotor involvement, has been distinguished from AIDP. The Miller Fisher syndrome variant is defined by the clinical triad of extra-ocular weakness, areflexia and ataxia. Other much less common variants have also been related to GBS, including a pharyngo-cervico-brachial variant, pure sensory GBS and acute pandysautonomia.

Significant advances have been made in understanding the immunopathogenesis of GBS. There is evidence of a primary humoral immune reaction targeted at peripheral nerve components in Schwann cell membrane or myelin, and in the axolemma, with the target sites correlating with AIDP and AMAN respectively (9, 13, 14). High titres of antibodies to gangliosides, which are common components of Schwann cell and neuronal cell membranes, have been associated with subtypes of GBS, eg. anti-GQ1b ganglioside IgG with MFS, and anti-GD1a/anti-GM1 ganglioside IgG with AMAN (38). Specific antecedent infections associated with GBS have been more clearly identified, namely Campylobacter jejuni, mycoplasma pneumoniae, EB



virus and cytomegalovirus (21). In the case of C. jejuni infections, the association of infection with GBS was further correlated with raised anti-GM1b and anti-GalNac-GD1a IgG antibodies. Ganglioside epitopes reactive with anti-GM1 ganglioside antibodies in GBS have been shown to exist in cell wall lipopolysaccharide of C. jejuni. These findings support the hypothesis of "molecular mimicry" as the basis of the immune reaction in GBS, whereby an immune reaction directed at specific antigens of infectious agents cross-react with components of Schwann cell/myelin or axolemma to result in a specific subtype of GBS.

For the common classic AIDP form of GBS, diagnosis rests primarily on a consistent clinical picture that is supported by electrodiagnostic evidence of an acquired, generally multifocal, demyelinating polyneuropathy. Absent demyelinating and prominent axonal electrodiagnostic findings with a consistent clinical picture may suggest the axonal form of GBS. However, the diagnosis of sporadic cases of AMAN or AMSAN, outside of endemic areas, is generally more problematic, requiring exclusion of alternate diagnoses and clinical follow up. The diagnosis of MFS is largely based on consistent signs and symptoms. While anti-ganglioside antibodies generally have limited diagnostic application, specific antibodies can be useful, especially anti-GM1 and anti-GD1a antibodies in AMAN, and anti-GQ1b antibodies in MFS and variants of MFS. CSF examination to look for cytologic-albumin dissociation is useful mainly to exclude alternative diagnoses, especially infections.

TREATMENT IN GBS

Three treatments have been extensively studied in GBS – corticosteroid therapy, plasma exchange and IVIG. Of these, plasma exchange and IVIG have been shown to be effective, while repeated studies have not demonstrated a beneficial effect from steroid therapy. The few studies of immunoabsorption treatment with selective removal of immunoglobulin will not be reviewed, as they generally involve small numbers of patients and are non-blinded and non-randomised.

CORTICOSTEROID THERAPY

The first randomised controlled trial of low dose oral prednisolone showed no significant benefit and suggested that the patients receiving prednisolone fared worse (16). The latest and largest of the studies (10), a double blind and randomised study, compared IV methylprednisolone 500 mg daily +/- PE for 5 days with placebo +/- PE. No significant difference in outcome between the treatment groups was demonstrated in this study. A recent Cochrane review of six randomized trials involving different regimens that included ACTH, methylprednisolone and oral prednisone or prednisolone, and including these two trials, found no significant difference in outcome between the patients receiving corticosteroid and control patients (19).

PLASMA EXCHANGE

Following the encouraging but inconsistent results of several small studies, a large open, randomized North American trial compared PE with supportive care in a large number of GBS patients with onset within 4 weeks and limitation or loss of ambulation (32). The trial showed outcome measures were significantly better in treated patients than in controls. Treated patients also showed significantly faster recovery of function. These findings were substantiated by a large French study which showed similar results (7, 8). Following these reports in the mid-1980's, PE was rapidly adopted as the standard treatment for GBS with significant weakness impairing ambulation, at least until the advent of IVIG trials in GBS. Meta-analysis by a Cochrane systemic review of 6 PE trials showed results consistent with these two leading studies (27). In addition, there was evidence from some of these studies that PE treatment reduced the cost of treatment for GBS compared to supportive care.

IVIG

Case reports that IVIG improved patients with chronic inflammatory demyelinating polyneuropathy led to its application in small series of GBS patients followed by several large randomised trials. Analysis of IVIG trials in GBS is provided by two reviews, one from the Cochrane Review (17) and the other from Quality Standards Subcommittee of the American Academy of Neurology (20).

a. Comparison of IVIG with placebo or supportive treatment

No trials comparing IVIG with placebo were identified.

b. Comparison of IVIG with Plasma Exchange (PE)

As noted above, prior to the conduction of randomised trials of IVIG, PE had been shown to be beneficial in GBS. Thus, in studying the use of IVIG in GBS, it was obligatory to compare IVIG with PE as the established treatment.

Three class I randomised controlled trials compared IVIG with PE (5, 24, 34). Patients entering the trials had similar, though not precisely the same degrees of severity - either with difficulty or loss of ambulation or inability to perform manual work. Patients entered these trials early in the disease, within 2 weeks of onset. The results of all three trials indicated that improvement from IVIG and PE was equal and not significantly different. Meta-analysis of two of the trials (24, 34) showed the weighted mean difference was 0.11 more improvement in the IVIG group than the PE group. The other trial, which was not included in the meta-analysis because of unavailable data, showed a mean of 1.2 grades of improvement in the IVIG group compared with 1.0 grades in the PE group. Thus, all three trials showed a trend in favour of IVIG compared to PE, although the differences were not significant in all. In each trial, there were more adverse events in the PE group than the IVIG group, achieving significant difference in the one (34) and showing a trend in the other two.

c. IVIG in Combination Treatments

i. Comparison of combined PE and IVIG with PE alone and IVIG alone

One blinded randomised trial compared combined PE and IVIG treatment (i.e. PE followed by IVIG) with PE alone and with IVIG alone (24). No significant benefit was demonstrated for the combined treatment group compared to either of the single treatment groups. Although there was a trend towards more improvement in the patients receiving both treatments, the differences were not significant. More complications of treatment were reported in the combined treatment group.

ii. Comparison of combined methylprednisolone and IVIG with IVIG alone

Recently, a trial compared combined IV methylprednisolone and IVIG treatment with IVIG alone in GBS, following a pilot study that suggested it may have a beneficial effect. However, the double-blind, controlled randomised trial did not show a significant difference between the two treatments (35).

d. Further Issues of IVIG treatment in GBS

i. Relapse, lack of response or worsening following IVIG

About 10% of GBS patients treated with IVIG demonstrate secondary worsening after a period of stabilization and improvement. Such relapses appear to be associated with a more prolonged progression of the disease. They respond again to a second similar treatment (37).

About 25% of patients will fail to improve immediately following a first course of IVIG and may even continue to deteriorate. The value of a second course of IVIG or a course of PE in such patients has not been established by controlled studies.

ii. IVIG use in children with GBS

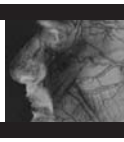
Children were excluded from most trials of therapy in GBS, including those described above under (b) and (c). Several studies with relatively small numbers of children compared IVIG with supportive treatment (11, 30, 31, 39). These studies indicated a beneficial effect of IVIG compared to non-treatment, although significant differences could not be confirmed because of the small number of children studied.

iii. IVIG use in mild GBS IVIG use in GBS lasting longer than two weeks

No randomised trials have been reported on the use of IVIG in mild GBS or in GBS that has lasted more than two weeks.

iv. IVIG use in variants of GBS

The trials described above under (b) and (c) generally used a clinical definition of GBS (2, 3) for case inclusion



that did not specifically distinguish between the common demyelinating form of GBS and its variants, including axonal forms, although classic MFS without significant weakness would have been excluded. No controlled trials are reported that specifically examined the use of IVIG in AMAN, MFS or dysautonomia.

However, in the trial comparing combined PE and IVIG with PE or IVIG alone, patients were classified into sub-groups by nerve conduction criteria (12). Outcome response to the three treatments did not differ among these sub-groups, which included demyelinating, axonal and pure motor variants, and those with inexcitable nerves. This result suggests that the response of axonal variants and AMAN to IVIG may be similar to the common demyelinating form of GBS.

Uncontrolled studies examining IVIG response in small numbers of MFS patients reported beneficial results, although MFS patients in these studies included those with motor involvement (1). As MFS with no motor involvement is generally reported to have a good prognosis, the value of IVIG in such cases remains unresolved.

Anecdotal reports of good response of acute dysautonomia to IVIG are documented (15, 23).

EXPERT CONSENSUS

a. IVIG use in GBS

i. GBS with significant or severe involvement seen within 2 weeks

IVIG use is recommended as therapy for GBS patients with significant involvement. For example, patients who require an aid to walk, those with impaired bulbar or ventilatory function, those who appear to be rapidly deteriorating, or worse. Individuals with difficulties in performing activities of daily living may also be considered for IVIG therapy. Treatment should be initiated early, i.e. within 2 weeks of onset. Considering its relative ease of administration, lower side effects and complications and similar cost when compared to PE, IVIG is often considered the therapy of first choice.

ii. Mild GBS

GBS seen more than 2 weeks after onset

Although no or little evidence is available for IVIG therapy in mild GBS or in GBS seen more than 2 weeks after onset, its use may be considered according to an assessment of potential benefits from treatment versus clinical risks, i.e. cost and adverse effects of IVIG and the subjective clinical assessment of progression and disability. Mild GBS usually recovers well without treatment, although the time to full functional recovery may be an important factor. Treatment with IVIG in GBS beyond two weeks of onset may be considered if deterioration continues or disability is severe, even if response may not be as good. Benefit from IVIG given >4 weeks from onset of symptoms is doubtful.

iii. Childhood GBS

Although effectiveness of IVIG in children with GBS has only been shown in uncontrolled studies and relatively small series of patients, for many pediatric practices, IVIG has become the treatment of choice over PE in childhood GBS, owing particularly to its relative ease of access and administration.

iv. GBS variants

AMAN/AMSAN
Miller Fisher Syndrome
Acute pandysautonomia

While evidence of benefit from controlled trials with IVIG is lacking for all these variants of GBS, treatment with IVIG should be considered in these variants using the same clinical criteria as described above of severe or significant symptoms. In "pure" MFS without motor involvement, the use of IVIG remains unresolved and controversial in view of the generally good prognosis reported.

b. When to use other therapy instead of IVIG in GBS

i. PE

As IVIG and PE have shown equal efficacy, the preference of one treatment over the other is generally based on issues of availability, practicality, convenience, cost and ease or safety of administration.

In practice, the relative ease and safety of IVIG administration compared to PE, has generally made IVIG the preferred treatment. However, there may be situations when PE is preferred or indicated, eg.:

1. Contraindication to IVIG use, eg. low IgA, previous allergy
2. Intolerance or serious side effects of IVIG use
3. Lack of availability of IVIG with PE available

ii. Steroid

Steroids should not be used in GBS and are not recommended.

The combination of methylprednisolone and IVIG is also not recommended.

c. Recommended dose and duration of infusion of IVIG in GBS

The standard total dose for a course of IVIG is 2g/kg. Conventionally, this is given as 0.4 g/kg/day for five days, in accordance with the large controlled trials comparing IVIG with PE. However, many centers now use a course of 1g/kg/day over two days, for faster and more convenient administration. Such a shorter course was used in two of the studies in children (11, 30). In patients at risk from infusion of a large hyperosmolar volume, eg. from cardiac or renal impairment, care should be exercised in using shorter courses of infusion.

A small trial among patients requiring ventilation suggested that a six day IVIG course of 0.4g/kg/day was more effective than three days (26). While this suggests that the dose should not be lower than the conventional 2 gm total dose, it remains unclear if a higher total dose will be more efficacious.

d. Recommended treatment for early relapse or lack of response

A second course of IVIG should be considered in patients who show relapse following initial stabilization or improvement after the first course.

The value of a second IVIG course in patients who fail to respond to the first course is doubtful. A course of PE may be considered in these cases although there is no data that this is beneficial.

e. Combination therapy

Sequential treatment with PE followed by IVIG does not have a superior effect to either treatment given alone and is not recommended.

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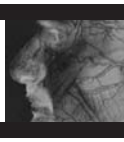


CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

INTRODUCTION

Chronic inflammatory demyelinating neuropathy (CIDP) is an acquired sensorimotor polyneuropathy characterized by a progressive or relapsing/remitting course, evidence for demyelination on electrophysiological or pathological studies, and response to immunomodulating therapies. There is no specific diagnostic test but the characteristic clinical and laboratory findings help distinguish this disorder from other immune mediated neuropathic syndromes.

DIAGNOSIS

Accurate diagnosis is the critical step in management. Since it remains the major treatable neuropathy in the western world CIDP should be considered in all patients presenting with a chronic peripheral neuropathy and in patients presenting with Guillain-Barré syndrome of subacute onset or when recurrent. Diagnostic criteria have been proposed by several groups which describe characteristic clinical, electrophysiological and histological findings and other causes of demyelinating neuropathy that should be excluded.(1-3)

In practice a diagnosis of CIDP may be made when a patient presents with a polyneuropathy or polyradiculoneuropathy which evolves subacutely over more than 4 weeks or chronically over many months and electrophysiological studies show evidence of demyelination. The American Academy of Neurology neurophysiological criteria(2) for demyelination have been recently considered to be overly restrictive and more sensitive but adequately specific criteria are being increasingly employed.(4) In brief the criteria require conduction block or temporal dispersion or nerve conduction values consistent with demyelination in at least one segment of three different nerves(5); moreover demyelinating conduction values must be present in one nerve.

Nerve biopsy is not considered mandatory for diagnosis by most groups(6,7) but it is a useful procedure when doubt concerning diagnosis remains. Since cerebrospinal fluid protein is increased in 80% of patients with CIDP its measurement is another helpful but non mandatory consideration in diagnosis.(8)

The final step in diagnosis is the exclusion of other causes of demyelinating neuropathy.

DIFFERENTIAL DIAGNOSIS

1. Hereditary demyelinating neuropathies when no family history available
2. Neuropathies associated with malignancy including POEMS syndrome

3. IgM related neuropathies
4. Metabolic causes of demyelinating neuropathy (diabetes, uraemia, hypothyroidism, acromegaly). However diabetes and CIDP may coexist.
5. Drug induced demyelinating neuropathies including amiodorone, perhexiline maleate, n-hexane
6. Infective disorders including HIV and Lyme disease
7. Recurrent Guillain-Barré syndrome
8. Multifocal motor neuropathy with conduction block

NATURAL HISTORY

The prevalence of CIDP is between one and two per hundred thousand of population (9,10) CIDP typically presents as a symmetrical sensory and motor disorder, often with proximal and distal weakness which follows a relapsing, progressive or monophasic course. It may present rarely as a purely sensory neuropathy with marked sensory ataxia, a predominantly motor syndrome or with marked asymmetry. CIDP is a relatively rare disease in childhood. As a result, the disease course, response to therapy and prognosis are not well characterized. However, in a number of series, many of the clinical characteristics were similar to those generally found in adults with CIDP.

The clinical course and response to therapy is variable. Few patients have relatively minor disease and in the majority treatment is necessary to prevent severe disability. In large series 4% to 17% of patients have died of the disease usually due to respiratory failure or pulmonary embolism.(11-14)

The prognosis and response to therapy is worse in patients over 65 years.(15)

PATHOGENESIS

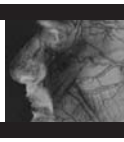
CIDP is widely accepted as an autoimmune disorder, based upon its pathology, similarity to the animal model experimental autoimmune neuritis (EAN) and its chronic counterpart chronic relapsing experimental autoimmune neuritis (CREAN) and response to therapy.(16,16,17) Pathological studies have shown perivascular and endoneurial mononuclear cell infiltrates particularly within spinal nerve roots, ganglia and proximal nerve trunks. These infiltrates are comprised of T cells and macrophages which produce a number of cytokines including interferon gamma, interleukin 2, tumour necrosis factor which together with matrix metalloproteinases presumably up regulate vascular endothelial cell adhesion and disrupt the blood nerve barrier.(18-20) Studies by Yan and colleagues have shown antibodies to the PO protein of myelin in a significant minority of patients with CIDP which cause conduction block and demyelination in rat sciatic nerve. Circulating antibodies against other myelin or axonal proteins including PMP22, P2 and various gangliosides have been reported but their pathogenicity has not been proven (21-23).

TREATMENT

CORTICOSTEROIDS

Beginning with the renowned work of Austin(24) many non randomised studies have shown the efficacy of corticosteroid in the treatment of CIDP(25-29) In these studies 65% to 95% of patients improved with steroid therapy. Dyck and colleagues performed a randomised controlled trial comparing prednisolone commencing at 120mg daily and tapering over 12 weeks with no treatment.(30) This trial showed that corticosteroids significantly reduced impairment and improved measures of nerve conduction. The absence of a true intention to treat analysis in the trial however weakens the strength of the evidence obtained. Recently Hughes et al(31) compared corticosteroid to IVIg and found that in the short term these treatments were of equivalent efficacy. A recent study looking at health-related quality of life found that patients treated with IVIg in comparison to corticosteroids had higher scores but the difference was not statistically significant(32).

A Cochrane review(33) concluded that the randomised controlled study(34) provided weak evidence for the short term efficacy of oral steroids in CIDP. Different regimes for corticosteroid therapy are used. Some centres begin with high does intravenous therapy 1gm daily for 3 to 5 days and then continue IV therapy at increasing intervals of time (weekly & then monthly) or convert to an oral dosage. Others commence with oral prednisone in a dose of 1 to



1.5mg/kg/day for 6 to 8 weeks or until improvement is maintained. The dose is then gradually tapered until an effective maintenance dose is reached, and the maintenance dose is often given on alternate days.(35) These regimes have not been compared in studies.

Although corticosteroids are cheap and convenient to administer the serious complications associated with long term use of these drugs has relegated them to second line therapy in many expert centres. There has been a trend towards using IVIg in CIDP.

PLASMA EXCHANGE

Several uncontrolled studies have reported at least short term benefit from plasma exchange.(36-40) Two controlled trials subsequently confirmed its efficacy. Dyck and colleagues(41) compared twice weekly plasma exchange (PE) or sham exchange for 3 weeks in a double blind trial and showed greater improvement in disability and motor conduction measurements in the plasma exchange treated patients. Hahn and colleagues(42) performed a cross over trial which compared PE with sham exchange; patients were given 4 exchanges in the first week, three in the second, two in the third and one in the fourth. The PE treated patients showed significant improvements in disability grip strength and amplitude of the compound muscle action potential compared to sham exchange. A single case study(43) concluded the immunoabsorption is inferior to PE in CIDP.

Although PE is efficacious it needs to be repeated at regular intervals, usually about 4 weekly. Frequent PE often leads to problems with venous access. Moreover, the procedure is inconvenient, available only in specialized centres, and attended by various complications and is contraindicated in children and patients with cardiovascular instability.

INTRAVENOUS IMMUNOGLOBULIN

Four randomised placebo controlled trials have been performed using IVIg in CIDP of which 3 have shown the efficacy of this treatment.(44-49) A Cochrane review, has confirmed the favourable effect of IVIg(50). Improvement after IVIg usually begins within 2 weeks, but the treatment effect is short lived often lasting only 3-4 weeks so that treatments need to be repeated for maintained improvement. This need for continued therapy contributes a significant problem since IVIg is very expensive. The initial dose of IVIg is 0.4g/kg daily for 5 days and the maintenance dose is between 0.4g and 2.0g/kg given as needed which is usually between 2 and 12 weeks (51-53). There is considerable variation between patients as to how often IVIg needs to be given but most patients need it every 3-4 weeks to maintain the benefit. Cross over trials have shown no significant short term difference between IVIg and plasma exchange(54) or between IVIg and oral prednisone (55).

IMMUNOSUPPRESSIVE AGENTS

No controlled trials have been reported for any immunosuppressive agent in CIDP except for azathioprine, which was reported to show no benefit when added to prednisone in 14 patients.(56) However, that trial lacked the power to detect any but very large treatment effects.

AZATHIOPRINE

Azathioprine is often used together with prednisone to reduce the need for IVIg or PE in CIDP patients but there is very little hard evidence on which to base this practice. A number of anecdotal series report benefit but the numbers in each are small and the studies uncontrolled.(27,57-59)

MYCOPHENOLATE

Several uncontrolled studies of small numbers of patients have examined the effect of Mycophenolate in CIDP. Whereas a beneficial effect was reported by some (60), no benefit was reported by others (61). A controlled trial of adequate power is urgently needed.

CYCLOPHOSPHAMIDE

A series of 15 patients reported by Good and colleagues(62) were given cyclophosphamide by IV pulses of 1g/m^2 monthly for a maximum of six months. Twelve patients were said to improve markedly, three did not

and one worsened. Despite these promising results most neurologists are reluctant to use this drug because of the risk of serious adverse events including marrow suppression, bladder toxicity, cancer, infertility and alopecia.

CYCLOSPORIN A

This drug which acts upon T cell activation and cytokine production has been reported to be effective in treatment resistant CIDP in anecdotal series (63,64). The recommended starting dose is 5mg/kg/day and the maintenance dose 2-3mg/kg. Cyclosporin A levels should be monitored carefully as well as creatinine levels and creatinine clearance measured, if there is any rise in serum creatinine. Nephrotoxicity, the major side effect is dose dependent; less common side effects include hepatotoxity, anorexia, gum hypertrophy, hirsuitism and neurotoxicity.

INTERFERON

An open study of Interferon alpha showed benefit in about 50% of treatment resistant patients in one study (65). Interferon beta was not shown to be effective in a controlled study (66). A large randomized control trial of Interferon beta 1a as add-on therapy to IVIg is currently in progress.

SUGGESTED APPROACH TO MANAGEMENT

INDUCTION OF REMISSION

PE and steroids are equally effective, IVIg has become first line therapy for CIDP in many neuromuscular centres because of its efficacy, lack of serious complications and greater convenience of administration compared to plasma exchange. If IVIg is not effective PE may be tried. Although in experienced hands PE is relatively safe treatment it is available only in major centres and is difficult and expensive to administer. In other centres steroids may be preferred as the first line of treatment because they are much less expensive and convenient, but their use is attended by well know side effects.

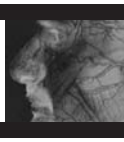
MAINTENANCE TREATMENT

Some groups continue with first line therapy, if effective. An attempt is made to find the lowest effective maintenance dose of IVIg, PE or corticosteroid, as the case may be. Others introduce second line therapies usually a combination of corticosteroid and immunosuppression, in an attempt to lower the dose or frequency of IVIg or PE.

Occasional patients will have a long term benefit from a single treatment course, but most will need repeated therapy usually at an interval from between 2 and 6 weeks to maintain the benefit. If IVIg fails we use PE to lessen the frequency of these expensive and complicated therapies, in those cases when frequent treatments are needed we add corticosteroid and an immunosuppressive agent usually azathioprine or mycophenylate. Steroid is given in a smaller dose say 35mg/day and the dose progressively reduced according to clinical improvement. Some patients can be maintained on low dose steroid and immunosuppression and be gradually weaned off IVIg or PE.

In those patients who do not respond to these therapies, cyclosporin A would then be used. If alone it is ineffective we would add azathioprine and steroid in a transplant like regime.

Most would agree that since IVIg is an expensive and precious resource an attempt should be made in each patient to find the lowest effective maintenance dose by trial reduction of dose and an increase in the interval between treatments. Such rationalisation is already applied to PE and corticosteroid therapy. Moreover it would seem reasonable that for continued access to IVIg, treating physicians provide to the appropriate authority evidence of continued efficacy, based upon objective measures of muscle strength and/or nerve conduction studies. Continued supply of IVIg may be contingent upon the results of monitoring at 6 monthly intervals. Data collection of this type would ensure equitable distribution of IVIg and provide an extremely useful research resource.



EXPERT CONSENSUS

In summary there is class I evidence from randomised controlled studies only for IVIg, PE and corticosteroids. First line therapy in any given area will depend upon issues of economy, availability and safety. However, the evidence concerning the efficacy of these agents is only for the short term. There is no evidence from controlled studies as to which therapy is superior in the long term or as to whether the addition of steroids and immunosuppression can lead to a reduction of the expensive treatments over time. Trials addressing this issue are needed. There is also a need for pharmacoeconomic and safety data to address issues of quality of life and cost effectiveness in the long term.

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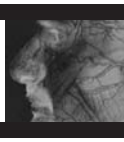

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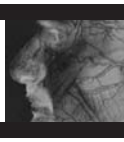

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MULTIFOCAL MOTOR NEUROPATHY

DEFINITION

Multifocal Motor Neuropathy (MMN) is a relatively rare disorder characterized by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting cramps and fasciculations may suggest a diagnosis of Motor Neuron Disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. (Parry & Clark 1988, Parry 1993, Nobile-Orazio et al 2002).

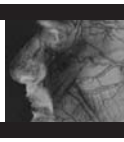
DIAGNOSIS

The hallmark of this condition is persistent localized motor conduction block. Block may occur at any level of the peripheral nerve but proximal segments are often affected (Kaji et al 1993). Conduction velocity through the blocked segment is often markedly slowed and the proximal compound muscle action potential dispersed (Parry 1993, Krarup 1990). Block is persistent for prolonged periods, months or years. Changes of acute or chronic denervation are found on EMG of affected muscles. High levels of IgM anti GM-1 antibodies have been reported in 18 – 84% of patients (Kornberg et al 1994, Bouche et al 1995, Pestronk et al 1991)

Hence the diagnosis is usually made in a patient with the appropriate clinical features and electrophysiological evidence of localized conduction block. The presence of anti GM-1 antibodies provides confirmatory evidence but cannot be considered essential for the diagnosis.

PATHOGENESIS

The pathogenesis of MMN remains unknown. The presence of anti GM-1 antibodies and response to IVIg and immunosuppression is suggestive of an immune aetiology; however the relationship of GM-1 antibodies to the pathogenesis is uncertain. Kiernan and Colleagues (2002) have shown hyperpolorization of nerve distal to the site of conduction block and have postulated depolarization at the site due to inactivation of Na+/K+ pumps possible resulting from GM-1 antibodies. However the application of these antibodies to single nerve fibres has produced both negative and positive results. Conflicting results have also been obtained with intraneural injections. (Hirota et al 1997, Takigawa et al 1995, Santoro et al 1992, Harvey et al 1995). Kiernan et al (2002) have further postulated that extensive depolarization at the site of conduction block will result in the accumulation of Na^+ intracellularly. The combination of depolarization and reduced transmem-



brane Na^+ gradient will lead to intracellular Ca^{2+} accumulation and hence axonal degeneration. These postulates are highly consistent with the pathological findings described by Taylor et al (2004).

NATURAL HISTORY

MMN is a slowly progressive disorder which may ultimately result in severe wasting and disability. Although patients may improve with therapy and this improvement is maintained long term, a majority will ultimately worsen despite increasing IVIg dosage (Terenghi et al 2004). This reduced efficacy of treatment and concomitant deterioration correlates with reduced distal CMAP amplitude presumably because of progressive axonal degeneration (Teranghi et al 2004). In the largest reported group of patients with this disorder none of 46 patients improved spontaneously, however there were no patients who died with the disorder (Taylor et al 2000).

PATHOLOGY

In two earlier studies in which tissue was removed from identified sites of conduction block the changes of thinly myelinated and demyelinated axons and small onion bulbs were found (Auer et al 1989, Kaji et al 1993). However in a recent study of fascicular nerve biopsies in seven patients Taylor and colleagues (2004) found multifocal fibre degeneration and loss with prominent regenerating clusters at the site of block. Although an increase in remelinated fibre profiles was seen axonal pathology predominated. These findings are consistent with the clinical findings of muscle weakness and atrophy.

TREATMENT

INTRAVENOUS IMMUNOGLOBULIN

Four randomised controlled studies and several open studies have shown that IVIg is effective treatment in MMN (Azulay et al 1994, Van den Berg et al 1995, Federico et al 2000, Leger et al 2001, Chaudry et al 1993, Nobile-Orazio et al 1993, Comi et al 1994, Bouche et al 1995). However in the vast majority of patients maintenance therapy is needed (Azulay et al 1997, Meucci et al 1997, Van den Berg et al 1995, van den Berg – Vos et al 2002). Occasional patients receive long lasting benefit from the initial therapy but most patients need repeated maintenance therapy at varying intervals from one to eight weeks (van Doorn and van der Meche 2000, Azulay et al 1997, Meucci et al 1997, van den Berg et al 1998). Most authorities give maintenance treatment at clinical worsening, although others recommend anticipating "end of dose" effect by shortening the interval between infusions to weekly doses in some cases (Terenghi et al 2004, van den Berg – Vos et al 2002). In most long term studies although patients clearly improve following IVIg, some slowly deteriorate despite continued therapy (Azulay et al 1997, Terenghi et al 2004, van der Berg et al 1998, Van den Berg – Vos et al 2002). In the first few years of treatment, the reduced response to IVIg may be restored by increasing IVIg dose, but later this increase in dose is only partially effective (Terenghi et al 2004).

DOSAGE

Treatment is usually initiated by giving 2 g/Kg of IVIg over 1-5 days. Maintenance doses vary and may need to be increased to maintain efficacy over the long term (Terenghi et al 2004). Although one long-term study recommended 0.4 g/Kg weekly, such frequent doses may not be needed and in some areas are not available. As with CIDP an attempt should be made to define the lowest effective maintenance dose of IVIg and to monitor the therapeutic efficacy by objective measures of muscle strength. It is likely that continued access to IVIg will be dependent on documented evidence of efficacy. Clinical improvement has been correlated with improvement of conduction block in neurophysiological studies (Federico et al 2000). However in another long-term study, conduction block improved in some nerves, but became apparent in other nerves during treatment with IVIg (Van den Berg-Voss et al, 2002). The development of axonal loss despite therapy has been reported by other workers (Terenghi et al, 2004). Attempts have been made to reduce the maintenance dose of IVIg by the use of immunosuppressive agents such as Chlorambucil, azathioprine or cyclophosphamide and by

the use of interferon-beta 1a (Nobile-Orazio et al 1993, Meucci et al 1997, Van den Berg – Vos et al 2000, Terenghi et al 2004). However there are no controlled trials of any immunosuppressive agent in MMN alone or in combination with IVIg (Umpathi et al 2002). Because of the well known adverse effects of cyclophosphamide its use in MMN should be considered only in severely affected cases.

IMMUNOSUPPRESSIVE AGENTS

Several uncontrolled studies have reported a beneficial response to cyclophosphamide (Chaudry et al 1993, Feldman et al 1991, Pestronk et al 1998, Tan et al 1994). Cyclophosphamide may be given orally or intravenously alone or following plasma exchange (Pestronk 1994, Meucci et al 1997, Terenghi et al 2004). Although over 70% of patients reported appear to have benefited from cyclophosphamide the lack of controlled studies and its adverse effect profile have limited its use in MMN.

OTHER THERAPIES

Patients with MMN may worsen following treatment with corticosteroids (Donaghy et al 1994) and plasma exchange (Carpo et al 1998) and their use is not indicated. Improvement has been described in small numbers of patients following interferon-beta 1a therapy (Martina et al 1999, van den Berg – Vos et al 2000). Benefit has also been recognised in a small group of patients following the use of the B cell (anti-CD20) monoclonal antibody, Rituximab (Levine & Pestronk 1999, Pestronk et al 2003).

SUMMARY

Because of its proven efficacy and relative safety profile, IVIg is currently first-line therapy for Multifocal Motor Neuropathy. However it will presumably need to be continued lifelong. There is no class 1 evidence for any other therapy either alone or in combination with IVIg or PE. There is no universally accepted dosage regime for IVIg but since it is a scarce and expensive commodity, physicians should attempt to define the minimum effective dose for each patient.

EXPERT CONSENSUS

IVIg is the first-line therapy for multifocal motor neuropathy. Treatment is usually continued over the long term but the minimum effective dose for each patient should be sought.

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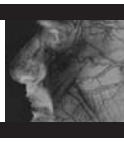

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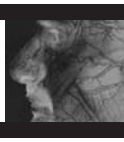

AMYOTROPHIC LATERAL SCLEROSIS

CLINICAL INFORMATION

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder of motor neurons in the spinal cord, brainstem and motor cortex that manifests clinically by muscular weakness, atrophy and corticospinal tract signs. In typical cases, the initial clinical features are of asymmetrical weakness and wasting of hand and forearm muscles, fasciculations of the muscles of the forearms, upper arms and shoulder girdles, spasticity of the legs and generalized hyperreflexia without sensory loss. The muscles of the upper arms and shoulder girdles are usually involved later in the course. The atrophic weakness later spreads to the neck, pharyngeal and laryngeal muscles, trunk, and lower extremities[1]. One of the most characteristic clinical pictures is spastic dysarthria with wasting and fasciculations of the tongue. Involvement of the respiratory muscles results in difficulty in swallowing and breathing which are sinister signs late in the course of the disease.

The pathogenesis is unknown and various etiologies have been proposed for ALS. Excitotoxins (including glutamate)[2], chemicals[3], metals[4,5] and autoimmunity[6,7] have been among the candidates. It is likely that ALS is caused by various causes which share the common mechanism of cell death. An important breakthrough was the finding of mutations within the gene encoding Cu, Zn superoxide dismutase (SOD1) in some of the familial ALS patients[8]. SOD1 is thought to help reduce oxidative stress.

The diagnosis of ALS is made on the basis of clinical criteria and exclusion of conditions which can be mistaken for ALS. The most common disorder that requires exclusion is cervical spondylitic myelopathy. Others include pseudobulbar palsy, multiple system atrophy, myasthenia gravis, and lead intoxication. Multifocal motor neuropathy (MMN) should be excluded in patients with predominantly lower motor neuron features. There is no pathognomonic laboratory test. Nerve conduction study and EMG serve to demonstrate or confirm the presence of abnormalities indicative of a motor neuropathy9 and the absence of conduction block which is seen in MMN. The common findings include small amplitude of compound muscle action potentials with slightly slow motor conduction velocities and normal sensory conduction compatible with either motor axonopathy or neuronopathy. The presence of conduction block and predominantly lower motor neuron type of limb weakness (especially asymmetric) raises the possibility of MMN or other immune-mediated polyneuropathies which may be treatable. High titer

anti-GM1 antibodies are detected in up to 85% of MMN patients[10,11]. However, the presence of these antibodies is supportive of, but not essential for, the diagnosis of MMN[12,13].

ALS is a disease of middle life and the course of this illness is inexorably progressive and invariably fatal[1]. Patients usually develop respiratory failure that may require tracheostomy and mechanical ventilation.

A number of drugs and agents including riluzole have been reported to give marginal benefit for patients with ALS but none have been shown to provide effects that are visible to the patients or physicians[9].

OBJECTIVE

To examine the efficacy of IVIG in ALS.

IVIG AS MAINTENANCE THERAPY

Dalakas et al[14] treated 9 patients with classic ALS who had a rapidly progressive course with IVIG in an open-label study. A patient with multifocal motor neuropathy (MMN) was concurrently treated to document the efficacy of the IVIG in a potentially treatable disease. IVIG was given once a month for 3 months with the dose of 2 g/kg over 2 days. All patients with ALS worsened during the study whereas the patient with MMN responded to the treatment[14].

Meucci et al[15] treated 7 patients with ALS with IVIG at the dose of 0.4 g/kg/day for 5 days followed by monthly 2-day infusions at the same daily dosage and continued with oral cyclophosphamide at 1-2 mg/kg/day for 4-13 months (mean 8.1). All patients continued to deteriorate during treatment15.

SUMMARY

Evidence from open-label studies showed that IVIG has no apparent therapeutic role in improving the symptoms or arresting the pace of progression in patients with ALS.

EXPERT CONSENSUS

IVIG is not indicated in the treatment of patients with ALS.

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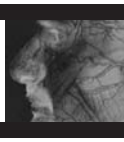

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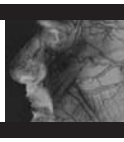
MYASTHENIA GRAVIS

CLINICAL INFORMATION

Myasthenia gravis (MG) is an autoimmune disease associated with the presence of antibodies to the acetylcholine receptors (AChR) at the neuromuscular junction. However, these antibodies cannot be detected in up to 20% of patients with generalized MG[1,2]. Recently, antibodies to muscle-specific tyrosine kinase (MuSK), a surface membrane receptor essential for the development of the neuromuscular junction, were detected in 71% of 24 seronegative MG patients in one series and 37.5% of 32 such patients in another series[3,4]. Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, namely levator palpebrae, extraocular, bulbar, limb and respiratory muscles. Patients usually present with unilateral or bilateral drooping of eyelid (ptosis), double vision (diplopia), difficulty in swallowing (dysphagia) and proximal muscle weakness. Weakness of respiratory muscles can result in respiratory failure in severe cases or in acute severe exacerbations (myasthenic crisis). This is life-threatening and requires mechanical ventilation. Although clinical characteristics of seronegative MG are similar to those of seropositive MG, subsets of seronegative MG patients have predominant oculobulbar weakness and poor response to therapy[5,6].

The factors involved in the initiation or induction of autoimmune MG are unknown. However, MG is associated with other immune system abnormalities particularly prominent being abnormalities in the thymus gland. Approximately 15% of patients have thymoma and another 60% have thymic hyperplasia. There is also a marked increase in other autoantibodies and autoimmune diseases[7]. Congenital myasthenic syndromes (CMS) are inherited disorders of neuromuscular transmission that do not have an underlying autoimmune mechanism. They are a heterogeneous group of disorders caused by a variety of genetic defects and are rare compared with autoimmune forms of myasthenia[8-10]. The gradual evolution of myasthenia has been linked to a number of drugs, especially D-penicillamine.

Diagnosis can usually be made from the characteristic clinical features. This can be confirmed by one or more of the following tests: bed-side injection of edrophonium hydrochloride or neostigmine, repetitive nerve stimulation test (RNST), single-fiber electromyography (SFEMG) and serum AChR antibodies. Five to ten mg of edrophonium, a short-acting cholinesterase inhibitor, is slowly administered intravenously and the effect can be observed within 30 seconds to 1 minute. The most striking response can usually be observed as improve-



ment of eye opening (less weakness of levator palpebrae or less ptosis) and power of proximal muscles lasting up to 5 minutes. If edrophonium is not available, neostigmine, a longer-acting cholinesterase inhibitor, can be given intravenously at a dose of 0.5 mg. Atropine should be given intravenously at the dose of 0.6 mg prior to neostigmine to counter muscarinic side effects. The effect can be observed after several minutes. Since the effect of neostigmine lasts rather long, respiratory function can also be assessed in severe cases. However, this test is neither absolutely sensitive nor specific for MG and patients with weakness from other diseases, e.g., Lambert-Eaton myasthenic syndrome, motor neuron disease, mitochondrial myopathy etc. can also give positive response at times. Therefore, this test alone is not diagnostic of MG. RNST is the most commonly used electrophysiological test being quite sensitive and can be easily performed. It is best recorded in proximal muscles, i.e., anconeus, trapezius, orbicularis oculi (OO) and nasalis with low frequency (3Hz) stimulation on respective nerves. A decrement of 10% or more is considered abnormal and suggestive of abnormal neuromuscular transmission. SFEMG is the most sensitive in the diagnosis of MG[11] but it is more difficult to perform and needs experience of the electromyographer. Extensor digitorum communis is the most commonly used muscle followed by more proximal ones, e.g., frontalis or OO. SFEMG needle electrode is positioned to record from two muscle fibers in one voluntarily or electrically activated motor unit. A variation in the time intervals between pairs of action potentials (AP) from these fibers is called neuromuscular jitter. When neuromuscular transmission is disturbed, the variation in the time intervals (jitter) is increased because it takes longer for the endplate potential to reach the threshold for action potential generation and this time varies[12]. Reference values for jitter measured during voluntary activation have been determined for many muscles[13]. Antibodies to the AChR is generally regarded as the most specific diagnostic marker for MG and are present in about 85% of the cases as measured by the conventional radioimmunoprecipitation assay[14,15]. Normal AChR antibody concentrations do not exclude the diagnosis.

There is evidence that the natural history of MG is characterized by exacerbations and remissions similar to those seen in other autoimmune diseases. The most striking initiating factor of exacerbation has been infection. Respiratory failure is the most common cause of death. Advance technology in artificial ventilation has significantly contributed to the decreased mortality from 40% to 5%[16]. Similarly, improved antibiotics have also reduced mortality from respiratory and other infections in patients with severe exacerbations. The clinical features of drug-induced myasthenic sydrome are similar to idiopathic MG and serum antibodies to AChR may be detected. Gradual recovery is common upon withdrawal of the drug. However, full recovery after drug withdrawal does not occur in all patients and MG may persist with a need for immunosuppressive therapy. In such cases, it may be argued that the drug unmasked a pre-existing immune-mediated disorder of the neuromuscular junction[17].

Available therapies include symptomatic treatment with cholinesterase inhibitors such as pyridostigmine, specific treatment with immunosuppressive drugs particularly corticosteroids and thymectomy. Pyridostigmine is usually effective early in the disease course or for mild cases. There is often a marked improvement at the beginning of the treatment but the effect tends to lessen over time and increasing doses are required for the same result. The more effective treatment is that which directly target the autoimmune response. The strategy of treatment is to first induce a remission and then to maintain the remission (complete or nearly complete absence of symptoms)[18]. This can be achieved by thymectomy and/or immunosuppressive drugs. Thymectomy appears to increase the likelihood of remission and possibly reduces the long-term exposure to immunosuppressive drugs. Its effect is often not apparent until after 1 year and the full effect is not felt for up to 5 years[19,20]. Nevertheless, seronegative MG patients with anti-MuSK antibodies have no benefit from thymectomy[4]. Corticosteroids are the mainstay of immunosuppressive treatment for MG in spite of their side effects. Azathioprine is also useful alone to induce a remission but it has slow onset of action and can take 3-12 months to have any effect. It

was mostly used in conjunction with corticosteroids[21-23]. A randomized double-blind trial has demonstrated that the addition of azathioprine to prednisolone lowered the maintenance dose of prednisolone and was associated with longer remission and with fewer treatment failures[24]. In patients failing to respond to azathioprine or who are intolerant of it may try other drugs. Cyclosporine was shown to be effective in a randomized controlled trial but adverse effects caused one-third of the patients to discontinue the medication[25]. Cyclophosphamide is another useful drug[26,27]. Monthly intravenous pulse cyclophosphamide (CP) was used in a randomized double-blind trial in patients with severe disease responding poorly to corticosteroids. Significant improvement was reported in the CP group and corticosteroid dose could be tapered[28]. Mycophenolate mofetil (MyM), a new immunosuppressive agent, is safe well tolerated and associated with objective evidence of clinical improvement in approximately three-quarters of treated patients[29-31]. In one study, it was effective as an adjunctive and steroid-sparing agent and as the initial or sole form of immunotherapy but it was not as effective in 'refractory' patients of whom fewer than half improved. In this study, patients who improved with MyM treatment had the onset of objective benefit on average 10.7 weeks from the time of treatment initiation ranging from as early as 4 weeks to as late as 40 weeks with maximal benefit occurring at a mean of 26 weeks. The main advantage of MyM appeared to be its tolerability and safety profile[31]. However, randomized controlled clinical trials are needed to confirm its efficacy. In severe disease or acute severe exacerbatioon, plasma exchange (PE) and intravenous immunoglobulin (IVIG) are two treatments with rapid onset of effect. PE and IVIG may be helpful in preparing patients with moderate to severe symptoms for thymectomy. The rationale for PE is that the bulk removal of antibody would reduce the autoimmune attack at the neuromuscular junction. The therapeutic function of IVIG is complex. Its main effects include elimination of pathogens by natural and immune antibodies, provision of anti-idiotypic antibodies which may bind pathogenic autoantibodies thereby preventing binding of them to autoantigens, inhibition of T-cell and B-cell proliferation thereby suppressing autoantibody production, inhibition of the compliment cascade and neutralization of cytokines by anti-cytokine autoantibodies[32]. As regards PE, there are no adequate randomized controlled trials but many case series reported short-term benefit especially in myasthenic crisis[33]. A randomized controlled trial showed PE and IVIG to be of equal benefit[34]. In a retrospective case study of respiratory crisis in MG, PE resulted in a significant better ventilatory outcome than IVIG treament[35]. Another randomized controlled trial comparing the efficacy of PE and IVIG in patients with moderate to severe stable MG, there was no significant difference between the two treatments but the improvement was faster after PE than after IVIG[36]. Occasionally, patients who fail to respond to IVIG may improve after PE[37]. The recommended protocols are to remove one plasma volume daily or on alternate days for 5 treatments or one and a half plasma volume on alternate days for 3 treatments. The standard dose of IVIG is 2g/kg over 2-5 days (usually 0.4 g/kg/d for 5 consecutive days.). Recently, one randomized controlled trial showed that IVIG at the dose of 1g/kg for 1 day and 1g/kg/day for 2 days were equally effective[38].

OBJECTIVES

To examine the efficacy of IVIG in the treatment of MG:

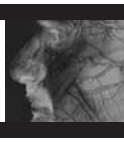
1. Acute exarcerbation (myasthenic crisis)
2. Moderate to severe stable MG

INTRAVENOUS IMMUNOGLOBULIN FOR MG EXACERBATIONS

IVIG VERSUS PE

Efficacy of IVIG has been established for the treatment of myasthenic crisis. There have been two randomized controlled trials (RCT) and many case series.

The first RCT was by Gajdos et al comparing IVIG with PE and comparing 2 doses of IVIG. In the PE group, patients received 3 PE of 1.5 plasma volume every other day. The IVIG group had 2 arms: in one arm, patients received IVIG 0.4 g/kg/day for 3 days and in the other arm, patients received 0.4 g/kg/day for 5 days. If the patients had been on immunosuppressive treatment before randomization, those drugs were contin-



ued without any change in dosage. Eighty-seven participants were included: 41 in the PE group and 46 in the IVIG group (23 each in the 3-day and 5-day groups). There was no difference in the efficacy between PE and IVIG groups nor between the 3-day (total 1.2 g/kg) and 5-day (total 2 g/kg) IVIG groups. In the PE group, 19.5% developed adverse effects consisting of hemolysis, hematoma, catheter-related venous thrombosis, fever, nausea, hypotension and tachycardia. In the IVIG group, one patient (2.2%) had headache. Adverse events led to discontinuation of PE in 2 participants (femoral venous thrombosis and retroperitoneal hematoma)[34].

The second RCT which was also by Gajdos et al compared the efficacy of IVIG 1g/kg for 1 day and 1g/kg/day for 2 days. One hundred and seventy-three patients were randomized. At day 15 after randomization, the increase in mean myasthenic muscular score was not significantly different in both groups[37].

A retrospective multicenter case study by Qureshi et al compared the efficacy of PE and IVIG in 54 episodes of myasthenic crisis. Participants were treated with 5 or 6 PE or with IVIG 0.4 g/kg/d for 5 days. One week after initiation of treatment, there was significant improvement in both groups. Ventilatory status at two weeks and outcome at one month were significantly better in the PE group but total hospital stay was longer in the PE group. Complication rate was higher with PE group (13 VS 5 complications). However, this study was retrospective and there was a hospital bias toward selection of a particular treatment[35].

IVIG VERSUS METHYLPREDNISOLONE

There has been one RCT by Schuchardt (Schuchardt et al, 2002 unpublished data) comparing IVIG to oral methylprednisolone. Participants were randomized to receive either IVIG 30 g/day for 5 days and placebo tablets or methylprednisolone tablets 1 mg/kg/day increased to 1.5 mg/kg/day on day 7 and infusion of 1% human albumin. Thirty-three patients were included with 15 in the IVIG group and 18 in the methylprednisolone group. There was no significant difference of efficacy between these 2 groups. Adverse events in the IVIG group included headache, hypertension, allergic reaction and chill and those in the methylprednisolone group included mild hyperglycemia, hypertension and agitation. The weak point of this RCT is that it did not recruit the number of participants required and so was underpowered in relation to the study objectives.

INTRAVENOUS IMMUNOGLOBULIN FOR MODERATE TO SEVERE STABLE MG

IVIG VERSUS PE

There has been one RCT by Ronager et al[36] comparing the efficacy of IVIG and PE in patients with moderate to severe stable MG in a controlled cross-over study. Participants were randomly assigned to receive either IVIG 0.4 g/kg/d for 5 days and 5 PE every other day 16 weeks later or firstly 5 PE and IVIG 16 weeks later. Twelve participants were included. There was no significant difference between the two treatments after 4 weeks but the improvement had a more rapid onset after PE than after IVIG. Adverse events from PE included hypotension, vomiting, deep venous thrombosis and arterial bleeding. Adverse effects of IVIG were fever, headache, nausea and vomiting[36]. The pitfall of this study is the insufficient number of participants included.

IVIG VERSUS PLACEBO

There has been one RCT by Wolfe et al[38] comparing IVIG with 5% albumin as placebo. Fifteen participants were included, six being in the IVIG arm and nine in the placebo arm. They were randomized to receive either IVIG 1 g/kg or 5% albumin on days one and two. A 1 g/kg IVIG or placebo was repeated on day 22. There was no significant difference in the quantified myasthenia gravis score from day 0 to day 42 between the 2 groups. However, this study was underpowered[39].

IVIG AS MAINTENANCE THERAPY

Two open-label trials by Achiron et al[39] and Hilkevich et al[40] treating 10 and 11 patients with severe generalized MG respectively with IVIG at an initial dose of 2 g/kg over 5 days followed by maintenance doses of 0.4 g/kg

every 4-6 weeks. All patients improved at 1-2 years and doses of prednisolone could be reduced[40,41]. However, it is difficult to deduce from these uncontrolled studies whether there is a drug sparing effect.

SUMMARY

There is good evidence that IVIG is as effective as PE for the treatment of myasthenia gravis exarcerbations. There is no sufficient evidence to determine whether IVIG improves functional outcome or has a sparing effect on steroid dosage in moderate or severe stable MG[42].

Dosage: There are various recommended doses and durations

- 0.4 g/kg/day for 3-5 days (a total dose of 1.2 g/kg is as effective as 2 g/kg)
- 1 g/kg/day for 1-2 days (a total dose of 1 g/kg is as effective as 2 g/kg)

REPORTED ADVERSE EFFECTS: headache, hypertension, allergic reaction, fever, chill, nausea and vomiting, aseptic meningitis, renal tubular acidosis, hemolysis, serum viscosity and thromboembolic events.

EXPERT CONSENSUS

1. IVIG is recommended for myasthenia gravis exacerbations, myasthenic crisis, patients with severe weakness poorly controlled with other agents or in lieu of PE[43].

2. A dose of IVIG of 1g/kg over a single day can be used in the treatment of a MG exacerbation[38].

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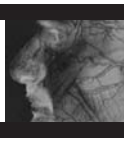


LAMBERT-EATON MYASTHENIC SYNDROME

CLINICAL INFORMATION

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission first recognized clinically in association with lung cancer[1,2] and subsequently in cases in which no neoplasm was detected. Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical picture is characterized by proximal muscle weakness with augmentation of strength after exercise, mild oculomotor signs, depressed deep tendon reflexes and autonomic dysfunction (dry mouth, constipation, erectile failure)[3].

The symptoms are caused by antibodies against presynaptic voltage-gated calcium channels (VGCC) resulting in decreased acetylcholine release[4,5]. LEMS exists in 2 forms: paraneoplastic (P-LEMS) and nonparaneoplastic (NP-LEMS). Carcinoma was detected in one-half of the cases[3]. The most common associated tumor is small cell lung cancer[3] but it is occasionally associated with lymphoproliferative disorders[6]. The onset of LEMS may precede radiological evidence of tumor for many years. The longest interval was 3.8 years in one series[3]. Therefore, it is recommended that patients should be kept under surveillance for up to at least 4 years. The NP-LEMS tends to be younger than P-LEMS. The clinical features of both forms are otherwise indistinguishable[7]. In both groups, serum antibodies to VGCC can be detected in more than 90% of patients[4,5].

LEMS is an uncommon condition and patients with LEMS can be misdiagnosed as suffering from other more common diseases with similar clinical features, e.g., myasthenia gravis. There has to be a high index of suspicion and features favoring the diagnosis of LEMS are the relative absence of ophthalmoparesis and facial weakness, the presence of dysautonomia (especially a dry mouth), muscle pain and decreased or absent deep tendon reflexes which may be increased by exercise (posttetanic potentiation)[3]. There may be mild or moderate ptosis. Diagnosis is confirmed by repetitive nerve stimulation test which shows small compound muscle action potentials that increase by 100% or more following maximum voluntary contraction or during high frequency nerve stimulation and a raised serum titer of VGCC antibodies[7].

Most P-LEMS patients die within 3 years after tumor detection. Those patients who had successful treatment of the tumor lived longer and also had complete remission of LEMS symptoms. Prognosis is good for NP-LEMS and the causes of death were usually conditions other than this disorder[3].

The mainstay of therapy is 3,4-diaminopyridine (10-

20 mg 4 times daily) which can partially or fully control weakness and autonomic dysfunction[8-10]. Intravenous immunoglobulin (IVIG) or plasma exchange (PE) provides short-term improvement[11,12]. In those at risk from P-LEMS (cigarette smokers), an intensive search for lung cancer should be undertaken and specific tumor therapy is likely to improve the neurological deficit[13]. Prednisolone is indicated in those who fail to respond to symptomatic treatment[14]. Azathioprine can be added as corticosteroid sparing medication[12]. Cyclosporine should be considered in patients who fail to respond to azathioprine[7].

OBJECTIVES

To examine the efficacy of IVIG in the treatment of LEMS.

INTRAVENOUS IMMUNOGLOBULIN FOR LEMS

IVIG VERSUS PLACEBO

Bain et al[11] studied 9 patients with NP-LEMS using 2 g/kg of IVIG over 2 days in a randomized double-blind placebo-controlled crossover trial (using 0.3% albumin as placebo). The study showed a significant improvement in strength measures associated with a decline in the serum titer of VGCC antibodies. The maximum change was reached at 2-4 weeks and declined by 8 weeks[11]. This trial studied NP-LEMS in a small number of patients for efficacy in short-term therapy.

IVIG AS MAINTENANCE THERAPY

Muchnik et al reported a case of NP-LEMS with efficacy of monthly IVIG courses at a dose of 0.4 g/kg/day for 5 days up to 24 months[15].

Bird reported a case of NP-LEMS who had been treated with repeated PE with excellent response but this had to be discontinued due to the loss of adequate intravenous access for further PE[16]. She was then treated with IVIG at 0.4 g/kg/day for 5 days with good response. There was a relapse after 10 weeks and repeated treatment with 1 g/kg/day for 2 days resulted in similar improvement. Five additional treatments were given and each resulted in a sustained response of 10-12 weeks[16].

Takano et al[17] reported a case of small-cell lung cancer (SCLC) who was treated with 4 courses of chemotherapy every 5 weeks together with PE just before the 2nd and 3rd courses. He improved (could walk a longer distance) after the 2nd PE and the 3rd chemotherapy. Then IVIG was given just before the 4th chemotherapy with marked improvement. The authors commented that PE had no immediate effect on their patient who showed gradual improvement with chemotherapy and that IVIG was also effective for LEMS with SCLC. His condition remained good 7 months after IVIG (and the 4th course of chemotherapy)[17].

SUMMARY

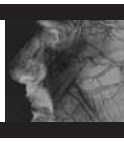
IVIG treatment may be useful short-term therapy particularly in severely affected NP-LEMS patients but there is not sufficient evidence at present to support its use as long-term therapy[7]. For P-LEMS, the role of IVIG is not obvious since chemotherapy alone can result in improvement of the neurological deficit. For long-term use, 3,4-diaminopyridine remains the mainstay of treatment. IVIG may be applied as supplementary or bridging therapy together with other therapies such as prednisolone and other immunosuppressants. Pyridostigmine may be considered if 3,4-diaminopyridine is not available although its benefit is likely to be less. There have been no trials comparing IVIG with PE or other treatments.

DOSAGE: The sole RCT trial used 2 gm/kg over 2 days but due to the high frequency of headache, the authors stated that this might have been reduced by administering over 5 days rather than 2 days.

ADVERSE EFFECTS: (from the RCT) headache, aseptic meningitis.

EXPERT CONSENSUS

1. Treat the underlying tumor in P-LEMS
2. 3,4 diaminopyridine (DAP) is effective but not always available.
3. Pyridostigmine is of some benefit although not as effective as DAP



4. If DAP and pyridostigmine are not effective, immunosuppressants can be added. Prednisolone and azathioprine are the most frequently used immunosuppressants[18].
5. IVIG or PE produces temporary improvement. Therefore, each has a role as second line therapy.
6. There is a theoretical concern that immunosuppression may reduce the immunologic suppression of tumor growth. Therefore, in NP-LEMS aggressive immunotherapy may be more justified[18].

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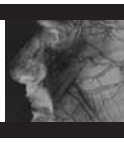

NEUROMYOTONIA (ISAACS' SYNDROME)

CLINICAL INFORMATION

Neuromyotonia or Isaacs' syndrome is characterized by the occurrence of spontaneous and continuous muscle fiber activity that manifests clinically by muscle cramps, pseudomyotonia (slow relaxation of the muscle) and undulating myokymia (continuous rippling of the muscle surface), muscle stiffness, weakness and excessive sweating. Less constant features are distal muscle wasting, decreased deep tendon reflexes and distal decrease in sensation[1-3]. Neuromyotonia may occur in association with dysautonomia and encephalopathy characterized by confusion, insomnia, hallucination and agitation known as Morvan's syndrome[4,5].

The spontaneous activity is characterized electromyographically by doublets, triplets or multiple single motor unit discharges that have high (40-200/s) intraburst frequency. This activity continued during sleep and general anesthesia. The activity arises from peripheral nerves since it is abolished by curare blockade of neuromuscular transmission but continues during complete proximal nerve block. Neuromyotonia has been seen in patients with chronic inflammatory demyelinating polyneuropathy and incomplete recovery from Guillain-Barré syndrome. Other cases had electrophysiological or morphological evidence of a mild neuropathy[2]. The exact cause of the disease is unknown. It can occur as a paraneoplastic disorder associated with small-cell lung cancer[6-8] or thymoma[9-11]. A pulmonary carcinoma was disclosed at autopsy in a patient with Morvan's syndrome[5]. Recent studies suggest an autoimmune mechanism in which presynaptic voltage-gated potassium channels may be targeted by autoantibodies in at least a subset of patients including patients with Morvan's syndrome[2,5,12,13].

The diagnosis of neuromyotonia is made on the basis of clinical features. Nerve conduction study may show evidence of polyneuropathy. Electromyogram shows spontaneous and continuous motor unit potentials consisting of high frequency multiple single unit discharges.

The natural history has not been clearly documented. Remission may occur spontaneously as is also sometimes observed in other autoimmune disorders[2,14]

Most patients symptomatically improve with anticonvulsant drugs that block sodium channels, e.g., carbamazepine and phenytoin. Immunosuppressants, e.g., corticosteroids or azathioprine have been used with variable success. In some cases, plasma exchange proved to be beneficial[10,11,15]. Limited case reports show a variable response with IVIG.

OBJECTIVE

To examine the efficacy of IVIG in the treatment of neuromyotonia.

INTRAVENOUS IMMUNOGLOBULIN FOR NEUROMYOTONIA

IVIG AS MAINTENANCE THERAPY

Alessi et al[16] reported a patient with neuromyotonia who had failed to respond to anticonvulsants, benzodiazepine and plasma exchange. Corticosteroid and azathioprine were not tolerated. IVIG was given at a dose 0.4 g/kg/day for 5 days. The symptoms improved after the 4th day up to 3 weeks. IVIG was administered at 6-weekly intervals, with substantial improvement after 6 months of therapy[16].

van den Berg et al[10] reported a patient with two paraneoplastic syndromes, acquired neuromyotonia and nephrotic syndrome in association with a thymoma. A few weeks after removal of the thymoma, the patient's clinical condition deteriorated. A 5-day treatment with IVIG at 0.4 g/kg/day had no effect on the clinical manifestations. Three weeks later, plasma exchange (5 times a week 2.4 l for 2 weeks) resulted in a dramatic improvement. Subsequent immunosuppressive treatment (prednisolone and azathioprine) was associated with disappearance of all clinical signs and symptoms[10].

Ishii et al[15] evaluated the effects of PE and IVIG in a patient with neuromyotonia who showed an insufficient response to pharmacological treatment. After PE, the symptoms almost disappeared for 2-3 weeks and the recorded continuous muscle action potentials were considerably decreased. In contrast, symptoms worsened after IVIG at a dose 0.2 g/kg/day for 5 days with an increase in continuous muscle activity in EMG and these improved after another course of PE[15].

SUMMARY

The limited information available on IVIG use in neuromyotonia shows variable efficacy. Case reports indicate that plasma exchange was more beneficial than IVIG in 2 patients and IVIG was beneficial with sustained improvement on maintenance therapy in another patient.

EXPERT CONSENSUS

There is little evidence of benefit of IVIG in neuromyotonia.

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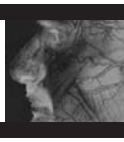

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INFLAMMATORY MYOPATHIES

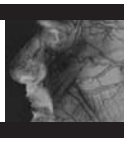
BACKGOUND

The inflammatory myopathies are a set of three discrete disorders of skeletal muscle – dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). These disorders are acquired, and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle.

A key set of characteristics distinguishes the three disorders (Table 1). The clinical and pathological features of DM, PM and IBM have been previously reviewed[1, 2].

Table 1: Key distinguishing features of DM, PM and IBM

	Dermatomyositis	Polymyositis	Inclusion body myositis
Mean age at onset symptoms	<50 years	<50 years	>50 years
Mode of onset symptoms	Subacute (weeks to months)	Subacute (weeks to months)	Slow (years)
Sex differences	F>M	F>M	M>F
Occurrence in childhood	Yes	Yes (very rare)	No
Distribution of weakness	Proximal > distal	Proximal > distal	Proximal & distal
Rash	Yes	No	No
Association with malignancy	Yes	Yes (weak)	No
Creatine kinase	Usually ↑ or ↑↑	Usually ↑ or ↑↑	Usually ↑
Autoimmune aetiology	Yes	Yes	Unclear
T cell-mediated myocytotoxicity	No	Yes	Yes
Prominent rimmed vacuoles	No	No	Yes
Complement-mediated depletion of capillaries	Yes (early)	No	No
Perifascicular atrophy	Yes (inconstant)	No	No
Good response to corticosteroids	Yes (usually)	Yes (usually)	No



The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists and relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography, and muscle biopsy. Endocrine or toxic myopathies, some types of muscular dystrophy[3] and occasionally myophosphorylase deficiency[4] can mimic PM. IBM should not be confused with hereditary inclusion body myopathy due to mutations in the gene encoding UDP-N-acetylglucosamine-2-epimerase / N-acetylmannosamine kinase[5].

The natural history of DM and PM is unclear, as patients are almost always treated with corticosteroids. However, spontaneous remission in DM and PM is uncommon. Patients with IBM, for whom there is no particularly effective therapy, gradually deteriorate over years. They eventually lose ability to form a fist and to extend the knee against gravity, but loss of ambulation is unusual. More than half eventually develop dysphagia[6, 7].

TREATMENT OF DM AND PM

A) DRUG TREATMENT

The drug treatment of DM and PM are usually considered together. Corticosteroids form the mainstay of treatment, although no controlled trials have ever been performed. Resistance to corticosteroid therapy should prompt a review of the diagnosis[8]. Azathioprine is an effective second-line immunosuppressive agent, but at least 3 months is required for a significant effect[9, 10]. Oral methotrexate, another commonly used second-line agent, is probably effective in DM and PM, although evidence from randomised trials with suitable controls is lacking[11-13]. Plasma exchange is ineffective in DM and PM[14].

B) IVIG TREATMENT

Level II Evidence: A single double-blind, randomised, controlled trial (RCT) has studied use of IVIG for treatment-resistant DM[15]. With cross-overs, a total of 12 patients received three, monthly infusions of IVIG (each infusion 2g/kg, given in 2 doses). Nine of these 12 patients showed major improvement, three mild improvement, and one no change. Three of 11 placebo-treated patients showed mild improvement. The improvement with IVIG was noticeable about 15 days after the first infusion but was definite only after the third infusion. Patients subsequently required maintenance infusions of IVIG approximately every 6 weeks (dose not stated).

Uncontrolled open label studies or retrospective reviews provide additional support for the efficacy of IVIG treatment in DM and PM. Monthly infusions of IVIG were successful as add-on treatment in five of five patients with juvenile DM who had persistent weakness despite corticosteroid therapy[16]; the dose of corticosteroid was subsequently reduced in all 5 patients. Twenty four of 35 patients with DM (10) or PM (25), resistant to prednisone and second-line agents, improved with monthly courses of IVIG given for a mean of 4 months[17]. Improvement was usually noted within the first two infusions and reached a maximum at the fourth infusion. Most of the patients who responded required maintenance IVIG therapy, usually monthly or bimonthly. Similar results were reported when this series of patients was extended[18, 19]. Nine of nine patients with treatment-resistant juvenile DM and corticosteroid side-effects showed improvement with IVIG[20]. Six of seven patients with juvenile DM, some of whom were treatment-resistant, improved with IVIG infusions[21]. Eight of 11 patients with treatment-resistant DM, PM or an overlap syndrome responed to monthly infusions of IVIG[22]. Twelve of 18 patients with treatment-resistant juvenile DM showed clinical improvement and tolerated reduction of corticosteroid dose[23]. Seven of 19 patients with DM responded to IVIG[24]; non-responders in this study had severe muscle and skin disease. The addition of IVIG to prednisone and cyclosporine in 13 patients with DM or PM increased the chances of complete remission at 4 years compared to patients given prednisone and cyclosporine alone[25]. Initial monotherapy with IVIG produced significant clinical improvement in only three of 11 patients with DM or PM[26], suggesting that IVIG is probably not suitable as first-line therapy in these disorders.

Case reports further describe benefit from IVIG treatment in PM[27-32] and DM[29, 30, 33-38].

TREATMENT OF IBM

A) DRUG TREATMENT

Corticosteroids and second-line immunosuppressive drugs may produce, at most, modest benefit in some patients with IBM[6, 39, 40]. Monotherapy with oral methotrexate did not seem effective in a RCT[41].

B) IVIG TREATMENT

Three RCT have assessed the value of IVIG in the treatment of IBM.

1. In a double-blind crossover RCT, 19 patients with IBM received IVIG (2g/kg) or placebo at monthly intervals for 3 months, followed by the alternative treatment[42]. No significant differences were found in skeletal muscle strength based on the the Medical Research Council (MRC) scale, the primary outcome measure. Retrospective limb-by-limb analysis showed patchy improvement of strength in the leg muscles of some patients. Significant improvements with IVIG were found in objective measures of swallowing, but the clinical significance of this improvement was not discussed. Overall, 13 of the patients indicated some degree of improvement on IVIG, and nine pursued IVIG therapy after the trial was completed.

2. In a double-blind crossover RCT, 19 patients with IBM received IVIG (2G/kg monthly) or placebo for 6 months, followed by the alternative treatment[43]. Mild significant improvement (11%) was found in the Neuromuscular Symptom Sore, but not in several other outcome measures. The authors concluded that treatment with IVIG may be mildly effective in IBM by preventing disease progression or inducing mild improvement.

3. In a further double-blind RCT, 36 patients with IBM were randomised to receive prednisone + IVIG (2G/kg monthly for 3 months) or prednisone + placebo[44]. In the 19 who received IVIG, no significant improvements were noted in muscle strength scores or swallowing. The number of necrotic fibers and the amount of endomysial inflammation were reduced in repeat muscle biopsies, but the clinical significance of this was thought doubtful.

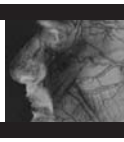
Uncontrolled open label trials and case reports have provided weak and conflicting evidence that IVIG can improve some patients with IBM. In a pilot study, the strength 'improved or normalised' in three of four patients with IBM treated with two, monthly infusions of IVIG[45]. In another study, none of nine patients with IBM improved on objective manual muscle testing or functional disability scores[46]. An extended course of IVIG increased knee strength in one patient[47]. None of five patients with IBM showed functional improvement with monthly IVIG infusions, although myometry scores improved in some muscles in one patient[22]. IVIG given each 2 weeks for 24 weeks produced enduring benefit in one patient48. Monthly courses of IVIG for 6-8 months produced sustained improvement of dysphagia in four patients[49].

SUMMARY

1. DM and PM

There is evidence from open label studies (Level III-3 evidence), case reports (Level IV evidence), and one RCT (Level II evidence) that monthly infusion of IVIG is effective add-on therapy for patients with DM who have not responded adequately to corticosteroids and second-line immunosuppressive agents. There is weaker evidence from open label studies (Level III-3 evidence) and case reports (Level IV evidence) that monthly infusion of IVIG is effective add-on therapy for patients with PM who have not responded adequately to corticosteroids and second-line immunosuppressive agents. There is general consensus in the literature that patients with DM or PM require 2-3, monthly infusions of IVIG in order to assess responsiveness; and that most responders subsequently need maintenance infusions at intervals of approximately 4-8 weeks.

The high cost of the treatment and the need for intravenous administration must be considered when deciding to use IVIG in patients with DM or PM. As the majority of patients with DM or PM will respond to treatment with corticosteroids and second-line immunosuppressive agents, IVIG cannot be recommended as the first-line or sole therapy.



2. IBM

There is evidence from three RCT (Level II evidence) that monthly infusions of IVIG fail to produce overall significant benefit in patients with IBM. The weight of evidence from open label trials (Level III-3 evidence) and case reports (Level IV evidence) supports this conclusion. There is conflicting evidence among the three RCT on the efficacy of IVIG for treating the dysphagia associated with IBM; additional weaker evidence from case reports (Level IV evidence) suggests that IVIG may be effective for this indication.

EXPERT CONSENSUS

IVIG can be trialled as add-on treatment for patients with DM or PM who have not responded adequately to corticosteroids and second-line immunosuppressive agents. Patients should receive 2-3 courses (2g/kg) of IVIG at monthly intervals in order to assess responsiveness. Responders will often require maintenance therapy at intervals of approximately 4-8 weeks. IVIG cannot be recommended at this time to treat the limb weakness of IBM. Weak evidence suggests that it may benefit patients with severe dysphagia associated with IBM.

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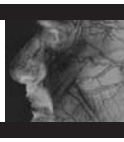

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CHRONIC FATIGUE SYNDROME

BACKGROUND

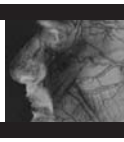
Chronic fatigue syndrome (CFS) is a disorder of unexplained cause with no specific biomedical marker. It is characterized primarily by disabling and persistent fatigue, usually associated with other ill defined symptoms. Diagnosis of CFS is, therefore, based on clinical case definition and the exclusion of disorders of known cause showing similar features (7, 8, 11, 19). The US Centre for Disease Control, which gave the name to this disorder, developed a case definition which is now widely used, even though it was developed primarily for research (7). This case definition requires at least 6 months of persistent fatigue that substantially reduces activity, accompanied by four or more of the following symptoms – impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multi-joint pain, new headaches, non-refreshing sleep and post-exertional pain.

The onset of CFS is usually acute, often with a flu-like illness. Fatigue exacerbated by exertion is pre-eminent, but besides the associated symptoms included in the case definition, patients with CFS also complain of a variety of other somatic symptoms, including anorexia, nausea, night sweats, dizziness and drug and alcohol intolerance. As is evident from this definition, there will be overlap of CFS with similar syndromic disorders that include fibromyalgia, epidemic myalgic encephalomyelitis, chronic mononucleosis syndrome, post viral fatigue syndrome, neurasthenia, multiple chemical sensitivities, irritable bowel syndrome and temporomandibular joint disorder. (1, 6, 13, 16,)

Studies from Western countries suggest that CFS may not be uncommon and reported in more than 0.4% of the adult population (9), although prevalence rates have varied widely, depending on the definition used and the population studied. A study from the US suggested a significant economic cost with an estimate of $20,000 loss per year per case (17)

ETIOLOGY, PATHOPHYSIOLOGY AND LABORATORY OBSERVATIONS

The etiology of CFS remains unknown and unclear despite many years of study. However, there are numerous reports of the association of CFS with abnormalities or dysfunction of disparate organ systems, including neuroendocrine, psychiatric, sleep and immunological systems, and with infections. These associations are mostly derived from isolated or unsubstantiated reports, while the interrelationships between these associations are unclear. This has given rise to the concept that CFS is a complex disorder with multifactorial etiology. (1, 6, 13,)



Neuropsychiatric symptoms of impaired memory or concentration, depression and anxiety often manifest in CFS. However, studies have suggested that neuropsychiatric disorders, such as depression, are not the primary process because of the absence of neuroendocrine changes usually associated with depression, such as hypercortisolism. There are reports of subtle MRI, single photon emission CT and fMRI changes in the brain in CFS, suggesting structural or functional changes (3). Several diverse neuroendocrine abnormalities have been reported, including hypofunction of the HPA axis and disturbances in serotoninergic and noradrenergic pathways (2). The high frequency of overlap of fibromyalgia and CFS symptoms of musculoskeletal pains suggested a common etiologic factor, although the etiology of fibromyalgia is equally contentious and unresolved. CFS patients have been reported to have disturbed and poorer sleep. CFS patients have also been reported to have reduced physical activity, with suggestions that this could exacerbate or prolong fatigue.

Of particular interest with respect to the use of IVIG in CFS are reports of immunological changes and infections being associated with CFS. Infections reported to cause or trigger CFS include Epstein-Barr virus and infectious mononucleosis, Borrelia burgdorferi and Lyme disease, Q fever, human herpes virus type 6, mycoplasma, parvovirus B19, group B Coxsackie virus, human T-cell lymphotrophic virus II, hepatitis C, enteroviruses and retroviruses, and others (1, 6, 13, 20). These reports have mostly been isolated, and conversely, only small percentages of patients with these infections (with some exceptions) are known to proceed to symptoms associated with CFS. Thus, it has been suggested that the host response to infection may be more relevant to pathophysiology in CFS.

There are certainly several reports of immunological change associated with CFS. These include reports of impaired cell mediated immunity, increased CD8+ T cells, decreased NK cells, elevated TGF-beta, raised antinuclear antibodies, elevated immune complexes and decreased C3 and C4 levels. There are also conflicting reports of elevated, reduced or unchanged IL-1alpha, IL-2, IL-6, interferon-alpha, tumour necrosis factor-alpha and beta, immune complexes and C3 and C4 levels (1, 6, 13, 14, 20). While overall, some of these findings may point towards chronic low level immune activation, the evidence is fragmentary and inconsistent, and their association with CFS remains unclear. From the above review, it would be fair to conclude that evidence of a specific infection or a specific host response as the cause of CFS is lacking in most, if not all, CFS cases.

Recently there has been a proposal to subclassify CFS into categories according to the related symptoms of the four organ systems in the case definition (20). Such sub-classification could lead to studies of more homogenous subsets of patients, which may clarify whether CFS is one illness with several etiopathogenic factors.

THERAPY IN CFS

While symptomatic therapy is frequently applied in CFS, a specific treatment directed at the underlying etiology cannot be identified as the underlying etiology and pathophysiology remain unclear. However, several diverse therapies have been proposed and studied. In addition to IVIG, these include other immunological or anti-infectious therapies such steroids, anti-inflammatory and anti-viral agents, antidepressants, hormones, as well as behavioural interventions and exercise programs (5), and alternative and complementary medicine. No further comments will be made about this wide variety of therapies (1, 6, 13, 16, 22).

IVIG IN CFS

There are four randomised clinical trials comparing IVIG with placebo in CFS, reviewed below in chronological order of appearance (12, 15, 18, 21). The use of IVIG in these trials was based on the hypothesis that a chronic viral infection or an immunoregulatory defect is involved in CFS. Based on these hypotheses, IVIG could provide neutralizing antibodies against persistent viral antigen, and may correct the immunoregulatory defect in CFS, by analogy to its effectiveness in a variety of diseases with disordered immunoregulation. As reviewed in the

section above, while there are many reports of associated virus infections and changes in a variety of immune indices, these hypotheses of immune or infectious etiology of CFS remain unproven.

The first trial (15) involving 30 CFS patients compared monthly IVIG (1gm/kg) with placebo given for 6 months. Response was measured by self assessment of symptoms, functional status and health perceptions. At the end of the study, no significant therapeutic benefit from IVIG treatment was detected in symptoms or functional status.

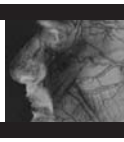
The second trial (12) involving 49 CFS patients compared monthly IVIG (2g/kg) with placebo given for 3 months, with the subjects evaluated at 6 months. Subjects were evaluated by physician interview and by self assessment, using subjective symptom and disability measures. At the 6 months time-point, the physician rated assessment determined that 43% of the IVIG treated subjects had substantial improvement in symptoms and disability, compared to 12% of placebo recipients, indicating that IVIG is effective in a significant number of patients.

The third trial (18) differed from the others in being conducted on a group of 71 adolescents aged 11 to 18 years. It compared IVIG (1g/kg) given monthly for three months with placebo. Response was measured by the investigators using functional scores of school, social and physical activity. A significant difference between the IVIG and placebo treated groups was reported for the mean functional outcome, i.e the mean of ratings for all activities. However, both the IVIG and placebo groups showed significant improvements from baseline measurements up till the final 6 months time-point.

The fourth trial (21) was conducted by the same investigators who led the Lloyd et al trial (12) and was intended to resolve the conflicting results of the first two trials reviewed above, while recognizing the differences between them, including differences in dosage. Hence, in this trial, 99 CFS patients were allocated randomly to receive one of three different doses of IVIG (0.5, 1 and 2 g/kg) or to receive placebo, all given monthly for 3 months. The subjects were evaluated 3 months after the final infusion, i.e. at the 6 months time-point. As in the earlier study by these investigators, response was assessed by the investigators using a performance score, and by the subject using a self report score. At the 6 months time-point, irrespective of the treatment, all patients showed a similar improvement in the investigator assessed functional capacity, with no significant difference between the groups. Similar results were derived from the self reported scores. Hence, this double-blind, placebo-controlled trial failed to demonstrate any significant benefit from IVIG at all three doses of 0.5 g/kg, 1 g/kg and 2 g/kg.

Thus, the four reports reviewed above showed contradictory outcomes, with two reporting a beneficial outcome, and two reporting no difference. One general limitation of all four studies is the necessary reliance on functional and symptom scores, often subjective, by investigators and/or the subject to measure response. Some limitations of the two trials reporting beneficial outcome may be mentioned. In the report of Lloyd et al (12), the method of physician assessment was potentially too subjective. In the Rowe report (18), both IVIG and placebo groups showed significant improvement in scores compared to base-line, suggesting a natural history of improvement or an effect of the treatment environment, both of which may be variables that could also influence the outcomes. The adolescent subjects ranging from 11 to 18 years may be too heterogenous, another variable that may have an impact on the outcome. On the other hand, the study of Vollmer-Conna et al (21) attempted to re-evaluate the earlier study reporting beneficial outcome by the same study group (12) and the report of Petersen et al (15), with a larger study population, an improved method of evaluation and a comparison of different IVIG dosages. There is, therefore, more to recommend this study than the two studies with reporting beneficial outcomes.

There is some data to suggest that subsets of CFS patients may respond to immunotherapies such as IVIG (10). Acute parvovirus B19 infection has been reported to be followed by rheumatic symptoms and CFS. IVIG is considered specific therapy as it likely contains neutralising antibodies to the virus. In this case report (10), three patients with CFS following acute par-



vovirus B19 infections given IVIG showed clearance of parvovirus B19 viremia, resolution of cytokine changes, and resolution of CFS symptoms with improvement in physical and functional ability. Additionally, the literature includes an older report of a randomised controlled trial of intramuscular gamma globulin in 22 "chronic mononucleosis syndrome" patients with antibodies to EB virus (4), in which 53% of treated patients were improved compared to 32% of patients given placebo injections.

a) In summary, it is concluded that there is contradictory and insufficient evidence of a beneficial effect from IVIG use in CFS.

b) The question whether subsets of CFS may respond to IVIG, namely those that have evidence of association with specific infections or disordered immune regulation, remains unresolved and merit further investigation.

EXPERT CONSENSUS

a) IVIG AS TREATMENT IN CLINICAL MANAGEMENT OF CFS

IVIG cannot be recommended as routine therapy for CFS.

b) IVIG AS AN INVESTIGATIONAL THERAPY:\

If IVIG is to be applied as investigational therapy in CFS, this should be considered as part of a properly constructed clinical study in a well defined subset of CFS patients with confirmed specific infections or specific immunologic abnormalities.

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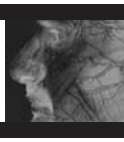


PARANEOPLASTIC NEUROLOGICAL DISORDERS

INTRODUCTION

Paraneoplastic neurological disorders (PND) are a rare group of neurological disorders believed to be due to immune-mediated damage of the central and/or peripheral nervous system (CNS and/or PNS) as a result of immune response triggered by a remote neoplasm[1,2]. The identification of paraneoplastic autoantibodies and subsequent characterization of the autoantigens bound by these antibodies have provided insight into understanding of basic neuroscience and neuropathogenesis of PNDs.[3] These antigens are ascribed as onconeural proteins as they are expressed by both the neoplasm and neural tissues. Immune response triggered by the neoplasm aim to eliminate the tumour cells, with neural elements damaged simultaneously by the immune response targetting at the onconeural proteins.

PND are diagnostically difficult and a high index of suspicion is required. A variety of neurological manifestations can be the presenting features. Table 1 lists the paraneoplastic anti-neuronal autoantibodies with associated oncological and neurological features. Detection of these autoantibodies facilitates the early diagnosis of PND. PND are important to diagnose as in more than half of the patients, neurological manifestations precede the detection of the tumour. Hence early diagnosis of PND help to initiate prompt and aggressive search for underlying malignancy, which is usually occult.[4] Early tumour therapy helps to optimize the patient's survival and neurological prognosis, with or without specific immunomodulatory therapy for the PND.

CLINICAL FEATURES

PND can affect any site of the neuroaxis and can have multifocal involvement in a single patient, increasing its diagnostic difficulty.[3,6,14] For instance, a patient with paraneoplastic encephalomyelitis associated with small cell lung carcinoma (SCLC) with anti-Hu antibody (also called anti-neuronal nuclear antibody type 1, ANNA-1) can also have Lambert-Eaton myasthenic syndrome (LEMS) with voltage-gated calcium channel antibodies (VGCC antibodies).

ENCEPHALITIS

Cortical encephalitis, limbic encephalitis and brainstem encephalitis have been described in PND.[7-9] Confusion, impairment of higher mental functions such as aphasia, apraxia, agnosia, labile mood and other psychiatric symptoms are common features for cortical encephalitis. Paraneoplastic limbic encephalitis is characterized by subacute progressive course presenting with short-

term memory impairment, seizures, confusion, depression, hallucinations, personality change, bulbar dysfunction, hypothalamic dysfunction such as abnormal appetite, cognitive dysfunction. Tumours associated with limbic encephalitis include SCLC, testicular tumours, breast tumours and Hodgkin's lymphoma.[9,10] Magnetic resonance imaging, cerebrospinal fluid (CSF) and electroencephalogram (EEG) may show abnormalities. Paraneoplastic autoantibodies associated include anti-Hu [4], anti-Ta/Ma [11], ANNA-3 [6], and autoantibodies against collapsin response mediated protein 5 (CRMP-5 antibody).[5]

Gaze palsy, diplopia and central sleep apnoea causing respiratory failure have been reported in patients presenting as a brainstem encephalitis with SCLC with anti-Hu,12 anti-Ma2 and anti-Ri (also called ANNA-2) antibodies.[16]

MYELITIS

Usually associated with or followed by progression to encephalitis and neuropathy. The pyramidal tract and anterior horn cells can be involved together as grey matter is mostly affected pathologically.[1] The patient presents classically with spastic weakness and sensory level, but combined spastic and flaccid paralysis can occur.[13] CSF analysis reveals an inflammatory response. This presentation is mostly commonly associated with SCLC with anti-Hu antibody, but has also been reported in associated with PCA-2 [14], anti-CRMP5 [5] and ANNA-3 [6] antibodies.

OPSOCLONUS-MYOCLONUS-ATAXIA

Opsoclonus is characterized by chaotic involuntary eye movements (dancing eyes). The syndrome was initially recognized in children with neuroblastoma[15]. Subsequently, adults with this "dancing eye, dancing feet" syndrome were described. Among 24 patients in whom 14 were paraneoplastic, the most commonly found cancer was lung (10 patients) followed by breast (2 patients). Testicular tumour was also reported. Paraneoplastic autoantibodies associated include anti-Hu, anti-Ri and anti-Ta/Ma.[16]

CEREBELLAR ATAXIA

Patients present with a subacute cerebellar ataxia. Those with anti-Hu antibody (associated with SCLC and neuroblastoma) tend to progress rapidly having a median survival of 9-12 months. In patients with anti-Yo antibody, stabilization is common and the median survival is 100 months with breast cancer, and 22 months for those with other gynecological cancers.[17,18] Other paraneoplastic autoantibodies associated include anti-Ri,[16] anti-Tr (associated with Hodgkin's lymphoma), anti-Ma/Ta,[11] PCA2,[14] anti-CRMP5 [5] and ANNA-3 [6].

SENSORY AND SENSORIMOTOR NEUROPATHY

Prominent sensory ataxia due to sensory neuronopathy is the classic presentation of PND associated with SCLC and anti-Hu antibody[4]. Pseudoathetosis due to severe loss of proprioception are the hallmark. Neuropathies with an indolent course and resembling acute inflammatory demyelinating polyneuropathy (AIDP) have been reported in anti-Hu associated PND. Other autoantibodies associated with sensory neuropathy are anti-amphiphysin antibody,[19] anti-CRMP5 [5] and ANNA-3.[6]

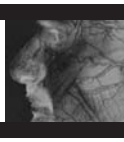
Sensorimotor polyneuropathy is a common presentation of PND. Associated tumours include haematological malignancy such as myeloma and Waldenstrom macroglobulinemia with monoclonal gammopathy, SCLC, thymoma and breast cancer. Associated paraneoplastic autoantibodies are anti-Hu,[4] anti-amphiphysin[19] and CRMP-5 antibodies.[5]

AUTONOMIC NEUROPATHY

It is important to consider PND in patients with autonomic dysfunction. Presenting symptoms include postural dizziness, abdominal pain, diarrhoea, impotence, urinary retention and intestinal motility disorders such as pseudo-obstruction, dysphagia and gastroparesis.[4,20] Paraneoplastic autoantibodies associated include anti-Hu and CRMP-5 antibodies.

RETINOPATHY

Patients present with visual symptoms including impaired visual acuity, photosensitivity, abnormal color



vision, ring scotomas and prolonged dark adaptation. The retinopathy usually runs a progressive course for several months. Underlying cancers are mostly SCLC, others include melanoma, breast, gynecological and endocrine cancers.[21] The most common associated autoantibody is recoverin, a 23 kDa photoreceptor protein.[22] Autoantibodies against other antigens such as enolase alpha have been reported.[23]

MYASTHENIA GRAVIS (MG) AND LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

The well known association of autoimmune MG with thymoma and LEMS with SCLC have been discussed in other parts of the consensus statements.

INFLAMMATORY MYOPATHY

Dermatomyositis is associated with a variety of cancers. Polymyositis is less frequently associated with an underlying malignancy. These disorders have been discussed in detail in another consensus statement.

PATHOGENESIS

The discovery of anti-neuronal antibodies in PND that also bind to the associated tumours suggest an underlying autoimmune pathogenesis. The paraneoplastic autoantibodies probably do not cause the inflammatory response and neuronal damage directly,[24], although anti-recoverin antibody may be the exception.[25] Both Hu-specific CD4 T helper 1 cells and CD8 cytotoxic T cells have been detected in patients serum.[26,27] Importantly, CD8 cytotoxic T cells are abundant in the interstitial infiltrate histologically while CD4 T helper cells are found in perivascular infiltrate of neural tissues.[28] Current evidence supports the view that cytotoxic T cells specific for onconeural proteins cause direct damage to the neurons and neural elements, when MHC class 1 is upregulated in the proinflammatory environment produced by activated CD4 T helper cells specific for onconeural proteins. These specific T helper cells cross the blood-brain barrier and mediate the production of paraneoplastic anti-neuronal autoantibodies by B cells. As the PND's only occur in a minority of patients with tumours, mechanisms underlying presentation of antigen (onconeural proteins) such as MHC moleculers [29] to activate T cells are probably important in the initiation of PND.

TREATMENTS FOR PARANEOPLASTIC NEUROLOGICAL DISORDERS

GENERAL MEASURES – a strong index of suspicion is essential for early diagnosis by serological testing for paraneoplastic autoantibodies, and prompt aggressive search for underlying malignancy, especially if occult. Symptomatic therapies aim to reduce disability and discomfort from the neurological deficits of PND. A multidisciplinary approach is most beneficial.

TUMOR THERAPY – the mainstay of treatment for PND. As most PND's affect the central nervous system, therapy is often difficult. Early anti-tumor therapy is recommended. Neurological presentations such as sensory neuronopathy and limbic encephalitis tend to respond better than others such as cerebellar degeneration.[18] There is evidence suggesting that complete response to anti-tumor therapy is a favorable prognostic factor for PND.[30]

IMMUNOMODULATORY THERAPY – therapies that have been used include plasma exchange (PE), IVIg, corticosteroids, immunoadsorption, and cyclophosphamide. It is generally accepted that earlier immunotherapy is associated with a better neurological prognosis.

Graus et al. studied 11 patients with PND with anti-Hu or anti-Yo antibodies and concluded that the efficacy of PE with other immunosuppressants in the stabilization of neurological deficits of PND was uncertain.[31]

Stark et al. reported improvement of neurological deficits in 2 patients with paraneoplastic cerebellar degeneration treated with cyclophosphamide.[32] Keime-Guibert et al. studied 17 patients with PND with anti-Hu or anti-Yo antibodies given a regime consisting of IVIg, cyclophosphamide and methylprednisolone. Of the 16 patients evaluated, none improved and 3 patients who were ambulatory before treatment were stabilized. The authors conclude that vigorous immunomodulatory

therapy in severely disabled PND was not useful, and in a minority of patients (mainly with sensory neuropathy) without severe disability at onset of therapy, a transient stabilization was possible.[33]

Blaes et al. reported efficacy of IVIg in 2 patients with PND when therapy was started within 3 weeks of onset of neurological deficits, while 2 other patients had no improvement with IVIg given 3-6 months after onset of neurological deficits.[34] All 4 patients harboured either anti-Hu or anti-Yo antibodies. Uchuya et al. treated 22 patients with PND with anti-Hu or anti-Yo antibodies with IVIG. Of the 21 patients evaluated, 1 improved for at least 15 months, 10 remained stable and 10 deteriorated. It was suggested that improvement and stabilization were more frequent in patients with isolated involvement of the PNS (62%) than those with CNS damage (37%).[35]

In children with neuroblastoma and paraneoplastic opsoclonus-myoclonus-ataxia, IVIg improves motor coordination and speech function rapidly.

SUMMARY

CNS INVOLVEMENT: no immunomodulatory agents have been shown to be effective. Reports of marked improvement have only been seen in single patients or small case series, particularly when therapy is started early.

PNS INVOLVEMENT: response to immunomodulatory therapy is probably better in patients with isolated PNS involvement, especially if therapy started early.

Voltz suggests to start with one course of methylprednisolone (five 500mg pulses) and observe for effects for 1 to 2 weeks. If there is no improvement, one course of IVIg (2gm/kg over 5 days), and if there is still no response, to try cyclophosphamide or plasma exchange tailored to the individual patient's clinical characteristics.[36]

Patients with PND who fulfil clinical and electrophysiological criteria of Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneu-

Table 1. Paraneoplastic anti-neuronal autoantibodies and their associated oncological and neurological features in PND.

Paraneoplastic anti-neuronal Autoantibodies	Neurological features	Common tumours associated
ANNA-1 (anti-Hu)	CA/PEM/LE/SN/SMN/OMA OMA (children)	SCLC (adult) neuroblastoma (children)
ANNA-2 (anti-Ri)	CA/OMA	breast cancer
ANNA-3	CA/PEM/LE/SN/SMN	SCLC, lung adenocarcinoma
PCA-1 (anti-Yo)	CA	breast, ovarian cancers, Cancers
PCA-2	CA/PEM/LE/AD	lung cancer
Anti-CRMP5	CA/PEM/LE/SN/CN/EPS	SCLC, thymoma
Anti-Tr	CA	Hodgkin's lymphoma
Anti-Ma/Ta	CA/BE/LE	Testicular cancers,Others
Anti-amphiphys	SMS/SN/SMN/OMA	SCLC, ovarian cancer

CA=cerebellar ataxia, PEM=paraneoplastic encephalomyelitis, SN=sensory neuronopathy, SMN=sensorimotor neuropathy, AD= autonomic dysfunction, CN=cranial neuropathy, BE-brainstem encephalitis, LE=limbic encephalitis, EPS=extrapyramidal symptoms, SMS=stiff man syndrome, SCLC=small cell lung carcinoma

ropathy (CIDP) should be treated according to standard regimens. Patients with LEMS tend to response well to IVIg and PE, but immunosuppressants such as azathioprine should only be used in the non-paraneoplastic form. For MG with thymoma, IVIg and PE are efficacious for rapid short-term improvements, while thymectomy and immunosuppressants (steroids and azathioprine) bring long-term benefits in most cases. IVIg and PE may be beneficial in neuromyotonia associated with thymoma or lung cancer, and IVIg was proven to be efficacious in stiff-man syndrome in a controlled cross-over study.

EXPERT CONSENSUS

IVIg is useful in children with opsoclonus-myoclonus-ataxia associated with neuroblastoma. For patients with involvement of the CNS (encephalitis, myelitis) and severe neurological disability, IVIg has not shown to be effective. IVIg with or without other immunosuppressants and corticosteroids given before development of severe disability may lead to transient stabilization, especially for patients with involvement restricted to the PNS (sensory neuronopathy and sensorimotor neuropathy).

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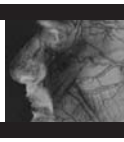

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STIFF-PERSON SYNDROME

BACKGROUND

Stiff person syndrome (SPS) is a disorder first described in 1956 by Moersh and Woltman (1). It occurs mainly in adult life and can be paraneoplastic in 20-30% (2). It presents with symptoms related to muscular rigidity and superimposed episodic spasms (3). The rigidity insidiously spreads involving axial muscles primarily abdominal and thoracolumbar as well as proximal limb muscles. Occasionally it is asymmetric and involves one leg preferentially (so – called stiff – limb syndrome). Typically, co-contraction of truncal agonist and antagonistic muscles leads to a board-like appearance with hyperlordosis. Less frequently, respiratory muscle involvement leads to breathing difficulty and facial muscle involvement to a mask-like face (3).

Initially the rigidity fluctuates but later becomes fixed and results in difficult ambulation with significant disability. Frequent falls are brought on by episodic spasms induced by tactile, auditory and other stimuli as well as by emotional stress leading to a fear of ambulating independently. About 2/3 develop significant difficulty in carrying out activities of daily living and many eventually become bedridden (4).

Examination reveals rigid axial muscles, hyperlordosis, difficulty in bending forward and a surprisingly normal neurologic examination.

About 5-10% of patients will have nocturnal seizures.

Thee differential diagnosis includes chronic tetanus, extrapyramidal syndromes with dystonia and rigidity, neuromyotonia and psychogenic disorders (3).

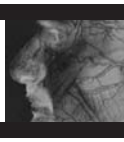
NEUROPHYSIOLOGY

The EMG hallmark of SPS is continuous motor unit activity occurring at rest in both agonist and antagonist muscles (3).

Electrophysiology has established this as a disorder due to a disturbance of GABAergic inhibitory circuits. This results in hyperexcitability of the motor cortex caused by a loss of intra-cortical inhibition by GABAergic neurons (3). Although spinal GABAergic circuits may also be involved there is no clear evidence supporting this at present.

AUTO-ANTIBODIES AND IMMUNOPATHOGENESIS

In 1988 it was found that about 65% of SPS patients have auto-antibodies to GAD–65 or GAD–67 the rate-limiting enzyme for GABA synthesis (5). The titers in SPS are characteristically very high as compared to the relatively lower titres in type 1 diabetes mellitus. About 30% of SPS also have diabetes mellitus. Other condi-



tions with low titers of GAD antibodies include myasthenia gravis, hyperthyroidism, and polymyositis (3).

It is postulated that these antibodies reduce GABA synthesis and cause a functional rather than a structural disturbance. This is supported by low CSF GABA concentrations and reduced GABA peaks on MRS (3). The serum and CSF of SPS patients inhibit GAD activity affecting GABA synthesis in vitro (3).
MRI is usually normal confirming the absence of histopathological changes in the few autopsies available. Recent reports have detailed non-specific changes in the limbic regions.

The paraneoplastic form of SPS is associated with antibodies towards a 128 kd neuronal protein, amphiphysin (2). These patients usually have breast carcinoma.

Some patients with SPS have no associated malignancy or anti-GAD antibodies.

THERAPIES

Considering the pathogenesis of SPS two main therapies have been in use.

1) Drugs enhancing GABA activity. High doses of diazepam up to 100 mg/ day are most widely used. Although no controlled trials are available, this drug is most often used initially. A dramatic response to diazepam is considered a criterion for diagnosis. Adverse effects limit the use of this drug however. Other drugs used are valproate, vigabatrin, baclofen and tiagabine – all with variable effects (3).

2) Immunomodulatory treatments. The initial focus was on prednisone with anecdotal evidence supporting its use. Plasmapharesis and IVIG are the other modalities in use (3).

This review now focuses on the evidence supporting IVIG use.

IVIG IN SPS

Early trials of IVIG in a rare syndrome like SPS suffered drawbacks of small sample size and publication bias. Other problems included difficulties in evaluating disease activity where subjective feelings of improvement may easily overshadow objective gains.

Initial reports in the early 1990s focused on open label trials in either single patients or on a small series of patients (6,7,8). Most focused on patients refractory to standard medications and showed a fairly consistent response to IVIG sometimes within a couple of weeks (6,7) and sometimes delayed till after 3 months (8). This was often transient lasting a few weeks to several months and the response to a subsequent course of IVIG was maintained. A well designed study of 3 patients (6) using objective scales of gait (time to walk 30 feet) as well as blinded video analysis, showed dramatic subjective and objective improvement within a few weeks of infusion. The lordotic angle also reduced on radiographs in one patient. At about the same time Karlson (7) reported three bedridden patients who became ambulatory after IVIG. Prednisone was slowly tapered in one of them without any ill effects. Similar benefits were shown in the childhood-onset form as well (9).

This set the stage for the first randomized double–blind, placebo controlled crossover study using either high dose IVIG once monthly for 3 months or half normal saline and then after a washout period a crossover to the alternate therapy (4). Sixteen patients were recruited and 14 were finally analyzed. Monthly evaluation used specially designed objective scales - distribution-of-stiffness index (DSI) and heightened–sensitivity scale (HSS) along with patients' subjective assessments. There was a statistically significant decrease in the DSI during the IVIG period lasting a month after the last infusion. The HSS scores were similar but not significantly different during IVIG or placebo. The time taken to walk 9.1 m reduced significantly after the IVIG and lasted even after the washout period. 12/14 patients identified the IVIG period correctly and many continued the IVIG after the trial was over. The anti-GAD antibody titers decreased signifi-

cantly after IVIG and rebounded significantly after it was stopped. This strongly supported the importance of these antibodies in the pathogenesis of this disease. The authors concluded that IVIG was a safe and effective therapy for persons with SPS and improved quality of life (QOL) as well. The effect appears to be short-lived in some patients though it lasts up to a year in others. In a subsequent open label study of QOL in 6 patients this benefit was confirmed (10)

SUMMARY

There is level 2 evidence supporting the use of IVIG in SPS. Periodic infusions may need to be given for optimal benefit. No clear-cut data are available for paraneoplastic forms of SPS; however the probable autoimmune nature of this syndrome suggests that IVIG should be used here as well.

EXPERT CONSENSUS

Considering the disabling progressive course of the stiff person syndrome, IVIG should be offered as the first line treatment. Though periodic infusions would be required in the majority, further studies are needed to determine optimal dosage and duration.

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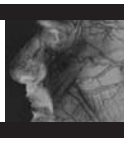


EPILEPSY

BACKGROUND

The epilepsies are a heterogeneous group of diseases characterized by two or more unprovoked seizures more than 24 hours apart. The etiology, natural history, response to interventions, co-existence of disabilities and the final outcome is vastly different amongst this group. The classification into more specific epilepsy syndromes is an attempt to put together disorders with similar characteristics. These are essentially divided into the idiopathic epilepsies (presumably genetic), the symptomatic epilepsies (due to underlying diseases / lesions) and the cryptogenic epilepsies (where a lesion or an underlying disorder is presumed but not demonstrated) epilepsies.

INTRACTABLE EPILEPSIES

About 10-20% of the epilepsies are refractory to the AEDs and this is more commonly encountered in the symptomatic and the cryptogenic epilepsies and in certain syndromes like the West syndrome (WS), Lennox-Gastaut syndrome (LGS) etc. This state disrupts normal activities of living and has a significant deleterious effect on cognition, memory and learning. Newer AEDs have made some inroads in management but there remains a substantial number who remain uncontrolled. It is in this group that alternative treatments like resective surgery, the ketogenic diet, vagal nerve stimulation, etc are often used and are now accepted as valid treatment options.

WEST SYNDROME (WS)

This epileptic syndrome is usually limited to infancy but can occasionally start later and sometimes persist into the teenage years – the so-called juvenile spasms (1). Most patients are symptomatic and the rest cryptogenic. Symptomatic WS has a poorer prognosis both in developmental and seizure outcome (2). ACTH (3,4), vigabatrin (5), nitrazepam (6) and valproate (7) have been shown to be effective in randomized comparative trials. Topiramate is recently been shown to be useful as an add-on in open label studies (8,9). The ketogenic diet (10) and resective surgery (11) in selected patients are other treatment options in refractory spasms.

LENNOX-GASTAUT SYNDROME (LGS)

This is one of the most refractory of all childhood epilepsies. About 2/3 are symptomatic and about 40% evolve from the WS. Mental retardation is the ultimate outcome in virtually all uncontrolled LGS patients and symptomatic cases have a worse prognosis for devel-

opmental outcomes. About 6% of symptomatic and 25% of cryptogenic LGS cases finally recover from their seizures (2).

Since the early 1990's a few new AEDs like felbamate (12), lamotrigine (13) and topiramate (14) have been shown to be partially effective in controlling the major seizures of LGS and improving the quality of life in randomized controlled trials. The effect appears to be maintained over the long term in felbamate (15) and topiramate (16). The ketogenic diet, corpus callosotomy and vagal nerve stimulation are other alternative procedures used in this disorder (17).

RASMUSSEN'S ENCEPHALITIS (RE)

Rasmussen's encephalitis (RE) is a rare condition occurring usually in children and adolescence, characterized by progressive unilateral hemispheric dysfunction, intractable focal epilepsy including epilepsia partialis continua, cognitive and behavioural changes, and inflammatory histopathology. There is an adult form of RE as well though this appears to have a more variable course with slower progression (18). The etiology appears to favour a dysimmune process since the role of autoantibodies against the GluR3 receptor was highlighted (19). This however may not be specific for RE as these antibodies are seen in other focal epilepsies with high seizure frequency (20).

The natural history seems to be divided into prodromal, acute and residual stages (21). The prodromal stage has an intermediate frequency of seizures and no or little hemiparesis; the acute stage lasts for a median of 8 months and has a high frequency of focal seizures, progressive hemiparesis and hemispheric atrophy on MRI. This stage is finally followed by a residual stage with a marked decrease in seizure frequency. Hence the maximum intensity of the disease is in the first year of onset and this would have a bearing on the disease's management.

Hemispherectomy seems to be the only definitive treatment halting further progress of the disease (22); however it is difficult to recommend early before the development of a permanent hemiparesis. Other immunomodulatory treatments include steroids, IVIg, cyclpophosphamide, therapeutic plasma exchange and protein A immunoglobulin G immunoadsorption (22,23). These are usually used in the initial stages when there is no hemiparesis and hemispherectomy is therefore a difficult option. Antivirals have been used in the past with variable effect.

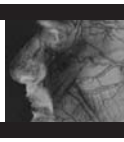
LANDAU KLEFFNER SYNDROME (LKS)

The Landau Kleffner syndrome (LKS) and electrical status in slow wave sleep (ESES) are now classified as epileptic encephalopathies. The severe paroxysmal EEG disturbances disrupt already acquired language function and other cognitive / behavioural processes (24). Clinical seizures may or may not be a part of the syndrome and usually have a benign prognosis (25). Language deficits are usually long lasting (25) especially in those with young age at onset and a prolonged period of severe EEG abnormality (24, 25, 26). However recovery of normal language may occur in a small minority (26).

Treatment with AEDs results in control of the epilepsy but not necessarily improves language function. There is some evidence that LKS may have an autoimmune basis. A positive autoimmune reaction to peripheral and central myelin has been demonstrated. Recently, LKS patients were shown to have IgG antibodies to brain endothelial cells (27). Steroids, both oral and high dose parenteral seem to be the most effective so far (28). There has been recent interest in IVIG in this condition. In resistant cases multiple subpial transactions (MSTs) may be useful (29).

BASIS FOR USING IMMUNOMODULATION

There are several lines of evidence suggesting immune dysfunction in at least some of the epilepsies (30). Viral infections and vaccinations often have a negative or sometimes a positive effect on seizure frequency. Certain immunodeficiencies like IgG2 and IgA are fairly commonly encountered in epilepsies (31). Studies on animal models have shown that seizure activity could be induced by specific antisera to brain proteins which persisted after withdrawal of the antisera.



Rasmussen's encephalitis is possibly due to autoantibodies and immunomodulatory treatments have been at least partially effective (30).

IVIG IN EPILEPSY

There has been an interest in IVIG in epilepsy since Prichard demonstrated a benefit of intramuscular immunoglobulins in eight of ten patients in 1977 (32). Most of the literature focuses on the intractable epilepsies including WS, LGS, and Rasmussen's encephalitis. Other syndromes where IVIG has been used includes LKS and the intractable partial epilepsies.

The evaluation of efficacy has been difficult due to the heterogeneity of the available studies with high variability in the study designs, patient selection, treatment modalities, IVIG dosage and regimens and outcome parameters. Most studies are not double blind and placebo controlled probably because of the limitation related to the route of IVIG administrations. A publication bias must be also considered because the results of small series of non-responders may not be published.

Since the initial reports in the seventies, several case reports and small series were published highlighting the use of IVIG in IE. Most of these were uncontrolled, unblinded and often retrospective. Up until 1996, a total of 29 studies had used IVIG in 373 patients with a benefit in 174 patients (30). In a critical review (31) Van Engelen reported an improvement in seizures in 52% with complete remission in 23%. EEG improvements were noted in 45% with behavioural improvements in 63% of patients. The dosage used varied from 0.3 gm/kg upto 6.8gm /kg over periods of 5 days to 12 months. Adverse effects were minimal. The authors concluded, "IVIG is likely to be effective in some patients with IE and may be considered as a safe add-on medication in it".

In the only large multi-center double blind randomized placebo controlled study using three different dosage regimens of IVIG in 61 patients, Van Rijekevossel (33) showed a reduction in seizure frequency in 52.5% patients as compared to 27.78% in those given placebo. Though these results suggested a trend they were not significant. In a subgroup analysis of 46 patients with partial epilepsy there was a significant difference between patients and controls. Also there was a highly significant global improvement noted in these patients by the family or caregivers. An important point to note was that it took more than 4 months to elicit a favourable response. Also there was no difference in low, medium or high dosage regimens. The only caveat was the short follow up of only 6 months.

IVIG IN WS

IVIG was used first by Arizumi (11) in a systematic open label study in 11 infants with WS. Remarkably all 6 with cryptogenic WS responded, 4 within 1 month. The EEG and development also improved concurrently. There were poor results in the symptomatic group with only 1/5 responding. Low dose recurrent infusions were used. Echenne in 1991 (34) conducted the first prospective study in 23 patients using standard doses of 2g/kg given periodically every few weeks. Only 5 children responded dramatically with seizure freedom and 2 of these had normal or near normal development on follow up. Cryptogenic WS were under-represented (4/23) which may had a bearing on the results. Rescue ACTH was used after a short observation period of only a week, which may have resulted in underestimating the responder rates. The IVIG used in this study was enzymatically treated which may have reduced its efficacy.

Van Engelen conducted a well-designed add-on study in 15 patients where 3 had WS and demonstrated efficacy in only one of these (35). A more recent retrospective study in the very refractory "juvenile" spasms (41) demonstrated clinical improvement in 4/5 patients with 1 becoming seizure free. However 2 of these patients also had other interventions carried out at the same time. An important weakness in these studies is that video EEG was not used to confirm spasm disappearance and only clinical reports were relied upon.

IVIG IN LGS

Initial reports in the 1980s suggesting benefit led to two well designed open label studies (35,36) with add-

on IVIG in LGS patients and one single blind placebo randomized controlled study (37). Though different dosage and regimens were used both found significant benefit. Van Engelen (35) reported > 75% improvements in seizure frequency in 9/12 patients over the short term while Gross-Tsur (17) reported improvements in 7/9 (8 had LGS) with long term remission in 3 over 22 months. The response took upto 6 weeks. Ilium (37) compared IVIG infusions to placebo in 10 patients with a crossover design at 2 week intervals and demonstrated substantial benefit in 5 with complete seizure freedom in 2. Significant EEG improvements and improved neurobehavioural outcomes were reported in responders in all 3 studies.

The only caveat is that when IVIG was used other effective treatments for LGS like the newer AEDs were not in use. A comparative randomized controlled multicenter study with use both in recently diagnosed and refractory cases would be useful.

IVIG IN RE

Hart initially reported a multi-center prospective open label study of steroids or IVIG or both in mostly biopsy proven RE (23). The treatment protocol was variable and hence statistical analysis was not possible. There was a benefit in 7/9 patients treated with IVIG (2 were also on steroids). However this was transient in 3. The two adult RE's did not improve contrary to later reports (vide below). Steroids were also beneficial in 8/19 patients.

Granata (22) in a more recent paper reports their experience of different immunomodulatory therapies in 15 patients of RE. Steroids were temporarily beneficial in 6/11 patients but were associated with worsening of seizures if they were withdrawn. Eight patients were treated with periodic infusions of IVIG. The response in 7 children was disappointing with 'slight improvement' in only 2. The single adult patient had a fairly dramatic response with >75% improvement in seizure frequency and a reduction in neurologic deficits. This robust response in adult RE was re-emphasized by Villani (18) and Leach (38). Periodic full dose IVIG in 3 adults several years into disease with disabling deficits resulted in a dramatic improvement over a few months with clear reductions not only in seizure frequency but also in deficits and disability.

Double blind placebo controlled studies in RE will be difficult as it is a rare disease necessitating patient recruitment from multiple centers; placebo control in a progressive disease with a variable fluctuating course is poses problems.

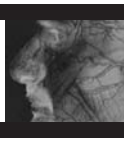
IVIG IN LKS

Initially three case reports (27,39,40) suggested a role of IVIG in LKS. In all patients a dramatic response in language functions as well as near normalization of the EEG occurred within 3-7 days of starting the infusions. One of the patients was steroid unresponsive (39), the other was steroid dependent (40) and in the third IVIG was used as initial montherapy (27). The dosage used was the standard 2g/kg over a few days. Importantly 2/3 children relapsed and needed repeated doses every few weeks / months for optimal response. An open label well designed prospective study of five patients from Beirut (41) confirmed a significant difference in language and EEG scores after a 2g/kg infusion of IVIG within 1 month. Two of these five patients had already been reported (27,40) and did extraordinarily well with normal language scores 18m –5 years after their last dose of IVIG. These appeared to be the 'pure' LKS while the other three were symptomatic of prior brain insults. The CSF IgG index was elevated in the two patients who responded dramatically suggesting an immune basis for their symptoms. The other three patients improved only mildly.

SUMMARY

Intractable epilepsy is heterogeneous and the bulk of the evidence supporting IVIG use is level 2 or 3.

There is a single RCT supporting its use in partial epilepsy. In WS, there is level 3 evidence supporting IVIG use and a small subset of refractory patients may have a dramatic response to it. The dosage, duration of treatment and long term results have been variable and need further study. Similarly there is level 2 or 3 evidence for its use in LGS. However these studies were done before the newer AEDs and VNS and before the ketogenic diet became popular. It could be used prior



to considering corpus callosotomy. In RE there appears to be good level 3 evidence of IVIG efficacy in the rare adult onset RE and periodic infusions are probably needed even several years after onset. The data in children appears less promising and it cannot be recommended. In LKS there seems to be level 3 evidence of a promising role of IVIG in at least a subset of patients with this syndrome and a large multi-center randomized controlled trial is needed before it is recommended over steroids. It should be used in steroid failures and before the surgical option.

EXPERT CONSENSUS

1) The evidence for the use of IVIG as a standard treatment in the majority of the intractable epilepsy syndromes is not adequate at this stage. Other treatment options are comparatively more effective. IVIG could be considered after the other options have failed.

2) In adult Rasmussen's syndrome there seems to be a role for periodic IVIG therapy before surgical treatment is considered, especially in the patient without deficits.

3) In the Landau-Kleffner syndrome, IVIG might be considered especially in steroid failures.

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OPSOCLONUS–MYOCLONUS–ATAXIA

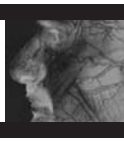
BACKGROUND

Opsoclonus-myoclonus-ataxia (OMA) is an immune mediated monophasic or multiphasic disorder affecting both children and adults. It is a rare and is either paraneoplastic or idiopathic, presumably parainfectious. In children it complicates 2-3% of all neuroblastomas while in adult life it is seen in association with several cancers most commonly small cell lung and breast carcinomas. Characteristically it has an acute to subacute onset of opsoclonus (conjugate chaotic eye movements), action arrhythmic myoclonus affecting limbs, trunk and head and ataxia. About two-thirds of patients have the complete syndrome. Initial imaging is usually normal. In later chronic and ongoing disease, cerebellar, especially vermian atrophy is often seen on imaging (1).

The pathogenesis of OMA was thought to be antibody mediated. Anti-Ri, anti- Hu and other antineuronal antibodies are sometimes found in adult onset paraneoplastic OMA (2). In childhood anti-Purkinje cell and anti-neurofilament antibodies have been reported (1,3). However these are not consistent and a recent study suggests that most do not have any persistent antibodies (4). Recent work on CSF lymphocyte subsets have shown higher percentage of B cells and other T cell abnormalities with correlation to disease severity, suggesting that this may be a primary B cell mediated disorder (5). In childhood paraneoplastic OMA the onset is typically after the first year with a mean age of around 22 months (6). Neuroblastoma is the most common tumor associated with this syndrome in childhood. There is a lack of tumour myc- oncogene amplification suggesting a better tumour prognosis. There is often no increased excretion of VMA (6). The tumor is often not abdominal and is most often does not metastatize (6). The OMA often precedes the diagnosis of tumor.

The course of the disease is often punctuated by relapses precipitated by intercurrent illness. The idiopathic form, especially in adults is often monophasic (2). It must be highlighted that neuroblastomas in infancy may spontaneously regress and this may occur before the OMA becomes apparent raising the possibility that many 'idiopathic' OMAs are actually paraneoplastic.

Long term follow up in childhhod paraneoplastic OMA suggest that the prognosis of the neuroblastoma is generally good with > 90% surviving 3 yrs (6). However the neurologic and developmental outcome is far from satisfactory. Earlier short-term follow up identified significant delays, cognitive, behavioural and motor deficits in the majority of such children (6,7,8). Longer follow - ups have suggested continued improve-



ment with about half the children achieving average intelligence (1).

CONVENTIONAL MANAGEMENT

The first line treatment of the immune syndrome has been ACTH / oral steroids (6) with or without pulse methylprednisolone therapy (9). Other immunomodulatory treatments like plasma exchange (10) and immunoadsorption (11) may also be successful though the evidence is in single case reports or in small series. Chemotherapy given for the associated cancer seems to be effective for the OMA symptoms as well (6) presumably due to its immunosuppressive effects. It forms the backbone of therapy in adult-onset paraneoplastic OMA (2). Recently promising results have been obtained with the use of Rituximab – a monoclonal antibody to B cells (12)

IVIG IN OMA

It is difficult to conduct randomized controlled trials in such a rare disorder. The evidence of the efficacy of IVIG is limited to case reports since it's first use in an infant by Sugie in 1992 (13). Pless used IVIG in an adult with parainfectious OMA who had failed ACTH & thiamine (14). A rapid improvement was noted within a week after the IVIG infusion. A similar adult patient of parainfectious OMA and an abnormal CSF responded within 2 days after having failed treatment with methyllperednisolone and valproate (15). The problem with these two studies was the short follow up and the possibility that the steroids and other medications may have had a delayed effect. Prantizelli reported the most convincing case study (16). This 41 year follow up was on a patient who presented first in infancy with post-vaccinial OMA with a good initial response to ACTH. The first remission lasted 10 years. At 22 years he had a disabling pan-cerebellar syndrome responsive to ACTH. He however kept relapsing over the next few years. At 36 years intermittent IVIG resulted in a sustained response for 5 years and the patient has gone back to his activities of daily living. This case illustrates that OMAs can relapse over several decades but still retain their responsiveness to immunotherapy. The study clearly shows the long-term benefits with IVIG therapy.

In paraneoplastic adult OMAs, what appears clear is that unless the primary tumour is in remission all immunotherapies are unhelpful. In childhood paraneoplastic OMAs associated with neuroblastoma, two long-term case studies suggest clear benefit to immunotherapy. Petruzzi reported its use in an 18 month old girl with a non-resectable ganglioneuroblastoma who responded significantly to IVIG 48 hours before chemotherapy was begun (3). She has been symptom free for 2 years on long term IVIG maintenance given for 15 months. It was noted that symptoms would relapse a few days before the next IVIG infusion was due suggesting a clear cause–effect relationship. Eiris noted similar results in a 15 month girl (17) with paraneoplastic OMA who had only transient response to ACTH. She has been symptom free after only a single low dose of IVIG (150 mg/kg over 3 days) though this response was gradual and may suggest a natural remission. Borgna–Pignatti however report less favourable results in a 22 month old infant girl with paraneoplastic OMA (18) where periodic IVIG infusions were continued for 10 months. The tumour was diagnosed fairly late and the dosage used was very low (400 mg/kg), which may have been some of the factors responsible for this therapeutic failure. (We have a similar case of paraneoplastic OMA who after a brief initial response to IVIG failed to respond to two prolonged high dose IVIG course given for 6 months each time).

SUMMARY

1) There is Level IIIb evidence supporting the use of IVIG in OMA. It seems to be useful in both idiopathic OMA and in childhood paraneoplastic OMA associated neuroblastoma. The response is often only transient in some and long- term maintenance therapy may be needed for continued response. Some children however do fail to respond and there may be a paucity of reports of such therapeutic failures in the literature due to a publication bias.

2) It is possibly less useful in adult paraneoplastic OMA where tumor control seems more crucial.

3) Most successes were continuing other therapies like ACTH / chemotherapy and this may have influenced the results.

4) The dosage of IVIG used has been variable from very low doses given once to high doses given for several years. The dosage / duration would need to be addressed in any long term RCT in the future.

5) Side effects were transient and did not limit the use of this treatment option.

EXPERT CONSENSUS

IVIG might be considered as one of the therapies for this difficult and devastating syndrome. Further studies are needed to validate efficacy and decide on optimal dosage and duration of therapy.

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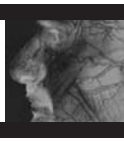

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APPENDICES

APPENDIX A

Terms of reference and membership of the Scientific Committee

TERMS OF REFERENCE

The Asia Pacific IVIG Advisory Board was launched at the 5th International Symposium on IVIG conference in September 2003.

The Advisory Board is an autonomous body of neurologists drawn from across the Asia Pacific region. There are 17 members who are experts in their field; they represent Australia, New Zealand, Hong Kong, Singapore, China, Thailand, India, Taiwan, Malaysia and the USA. The membership of this board represents around half the world's population.

The charter of the Asia Pacific IVIG Advisory Board includes the development of expert consensus statements, using evidence based medicine approach for the use of IVIG in neurological practice, the development of an educational program for the Asia Pacific region and the creation of an Asia Pacific IVIG conference.

APPENDIX B

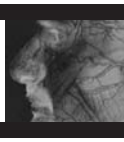
Relevant articles were summarized by the Advisory Board over a 2 day meeting in Singapore in December 2003. A decision on the format of the statements was decided at that meeting. The decision was to provide a background on the relevant disorder, with a summary of the diagnostic process and differential diagnosis. The statement was to include a review of the literature for all treatments and a detailed review of IVIG in the relevant condition. Members of the Asia-Pacific IVIG Board were assigned topics for review.

The statements were prepared by Board Members and circulated for comment to all members of the Board. Comments were received and revisions of the statements then proceeded. A teleconference in February 2004 and then a formal meeting in June 2004 were scheduled. At the June 2004 meeting, the statements were reviewed in an open forum and revisions were made. An expert consensus statement was then formulated for each review. The consensus statements were circulated for comment again and a final teleconference in late October 2004 ratified the statements.

APPENDIX C

Literature Review on the use of IVIG in Neurology
Search Strategy and Results

Asia-Pacific IVIG Advisory Board members of INDAPS who undertook the literature review on which the Consensus Statements are based.



2.1 SEARCH STRATEGY

The OVID interface was used to search the following electronic databases:

◊ PREMEDLINE
◊ MEDLINE –1966-2003
◊ Cochrane Database
◊ Review of article citations and Cochrane Reviews for relevant additional citations

- EMBASE-1993-2003
- Elsevier Science B.V, 2003

2.2 SEARCH TERMS

40016 abstracts obtained with search terms.
Terms used to identify relevant citations included:
Immunoglobulins - Intravenous
Immunoglobulin
Immunoglobulin - Drug Administration
Immunoglobulin - Adverse Drug Reaction
Immunoglobulin - Clinical Trial
Immunoglobulin - Drug Dose
Immunoglobulin - Intravenous Drug Administration
Demyeliating Autoimmune Diseases, CNS or Dymelinating Disease
Lambert Eaton Myasthenic Syndrome or Eaton Lambert Syndrome
Leukoencephalitis, Acute Haemmorrhagic or Eaton Lambert Syndrome
Leukoencephalitis, Acute Haemorrhagic or Encephalomyelitis
Myasthenia Gravis
Polyradiculoneuropathy
Stiff-Person Syndrome
Stiff Man Syndrome
Brain Disease
Brain Diseases
Central Nervous System Infections
Central Nervous Infection
Encephalomyelitis
Spinal Cord Diseases
Spinal Cord Disease
Paraneoplastic Syndromes
Nervous System
Paraneoplastic Syndrome
Fatigue Syndrome
Chronic
Chronic Fatigue Syndrome
Motor Neurone Disease
Neuromuscular Junction Disease
Neuromuscular Junction Disorder
Peripheral Nervous System Disease
Peripheral Neuropathy
Isaacs Syndrome
Myokymia
Vasculitis
Central Nervous System
Brain Vasculitis
Uveomeningoencephalitic Syndrome
Meningoencephalitis
Autoimmune Disease
Immunoglobulins

2.3 SEARCH FINDINGS

Citations were screened and selected using the process outlined in Appendix C. The search retrieved 40016 citations of which 900 citations were utilised to perform the literature analysis.

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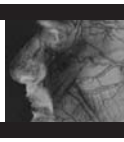
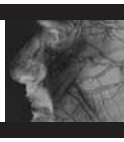


COMMENTARY ON INTERPRETATION OF PUBLICATIONS REVIEWED

The literature review considered all relevant studies and commentaries published in English from 1966 onwards. The integration of Evidenced based Medicine (EBM) into clinical practice includes the integration of individual clinical expertise, best available external clinical evidence from systemic review and patients values and expectations. EBM alone is never sufficient to make a clinical decision. Decisions must always trade the benefits and risks and inconvenience, and costs associated with alternative, management strategies, and in doing so consider the patients values.



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- CSL Bioplasma and ZLB Behring for supporting the development of the Asia-Pacific IVIG Advisory Board and ensuring that it remains autonomous and independent

- Ms. Eileen Conway from CSL Bioplasma for her administrative and production expertise and support. It is due to Ms. Conway's hard, and often "behind the scenes", work, that we were able to get this far in such a short time

- Dr. Elizabeth Campbell and Mr. Chris Church from CSL Bioplasma and ZLB Behring respectively for having the confidence, foresight and drive for supporting this initiative. This enabled us to begin the journey of realising our goals. Our first goal of completing consensus statements in the use of IVIG in neurological disorders has been achieved. Their ongoing support will allow us to create a formalised education program for the Asia-Pacific region

- Our families for giving each of us their unfailing understanding and patience during the course of the last year. The writing of these statements and the planning of the inaugural INDAPS conference in November 2004 in Singapore is testament to their support

WAIVER OF LIABILITY

The information contained in this document is intended to serve as a guideline only. Neither the contributing authors, the Asia-Pacific IVIG Advisory Board, CSL Bioplasma or ZLB Behring shall be liable for any actions, claims, damages, costs or obligations that may arise from the inappropriate use or misuse of the material contained in this document.