IGIV in Neurology – Evidence and Recommendations

Vera Bril, Kent Allenby, Gyl Midroni, Paul W. O’Connor and Jiri Vajsar

ABSTRACT: Objective: To summarize the evidence for neurologic uses of immunoglobulin, intravenous (IGIV) in light of present-day clinical usage. This summary guided the development of practice recommendations for the effective and efficient use of IGIV in Neurology. Methods: MEDLINE was searched to identify pertinent English-language review articles and original reports (n = 231) on the use of IGIV in neurology (excluding editorials, letters, and comments) published before March 1998. Evidence on alternative therapies was only included as compared to IGIV. The relevant original reports and review articles and older classic studies (n = 92) were synthesized into an information foundation. Extracted data included laboratory and clinical findings, objective measures, and clinical impressions. Clinical recommendations were based on evidence quality, graded by study design, clinical experiences of IGIV in Neurology Advisory Board members, and the conditions of IGIV use in therapy. Results and Conclusions: In neurology, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. As a result, it is fairly common for best-practice decisions to rest on weaker evidence. The usefulness of IGIV in neurology can be described by a “combined score” based on evidence quality and strength of impact. Combined scores ranged from A+ (strongly recommended) to C (recommended as a last resort). The following clinical recommendations are made: IGIV is strongly recommended for the treatment of Guillain-Barré syndrome (A+); favorably recommended for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy, dermatomyositis, and multifocal motor neuropathy (A); recommended as a second resort for the treatment of multiple sclerosis and myasthenia gravis (B); and recommended as a last resort for the treatment of polymyositis, inclusion-body myositis, intractable epilepsies, and stiff-man syndrome (C).


Contributors: The Bayer-sponsored IGIV in Neurology Advisory Board included 13 physicians, two of whom hold senior positions in Bayer Biologics. Members of the advisory board were: Kent Allenby, MD, FACP; Peter Ashby, MD, FRCP; Vera Bril, MD, FRCP (Chair); Susan EB Fawcett, MD, FRCP; Gordon S Francis, MD, FRCP; Angelika FG Hahn, MD, FRCP (Co-Chair); Robert HA Haslam, MD, FAAP, FRCP (Faculty); Georg Lemm, MD; Gyl Midroni, MD, FRCP (Faculty); Michael W Nicolle, MD, FRCP; Paul W O’Connor, MD, FRCP (Faculty); Jiri Vajsar, MD, FRCP (Faculty); Richard A Wennberg, MD, FRCP (Faculty).

The Advisory Board met in Toronto April 1 and 2, 1998, to discuss and clarify the state of IGIV use in Canadian Neurology practice. Practice conclusions were determined from discussions at the Advisory Board meeting.

Immunoglobulin (Ig) was fractionated out of whole blood more than 50 years ago. By 1979, an intravenous formulation of intact immunoglobulin (immunoglobulin, intravenous [IGIV]) was available. It was found that IGIV therapy was effective in...
IGIV comes in several forms. In general this guide does not distinguish between them, although manufacturing differences have been shown to exist. IGIV discussed in this article include: Sandoglobulin® (Sandoz, Minneapolis, MN); Intralglobulin® (Biotest, Frankfurt, Germany); Venoglobulin® 1 (Alpha Therapeutic, Los Angeles, CA, and Institut Merieux, France); Gamimune® N (Miles-Bayer, West Haven, CT); Gammagard® (Baxter, Glendale, CA); Gammar© IV (Centeon, Kankakee, IL); Ivecgam Immuno® (Immuno Canada, Mississauga, ON); and Polygam® (Baxter, American Red Cross, Washington, DC).

It has been reported that IGIV is used in Canada for more than 90 indications, although far fewer are labeled clinical indications. Several off-label usage recommendations have been published as a result of the overwhelming off-label use of IGIV. Generally, these have relied on the expertise of groups of specialists in tertiary care centers, and a mix of Level I, II and III evidence.

These recommendations have been especially exciting for the field of neurology. In many neurologic disorders, pathophysiology is poorly understood. As a result, it has been difficult to rationalize therapies from a pharmacobiologic basis. This article will clarify today’s state of knowledge about the use of IGIV and directly compare alternatives, in treating neurologic disorders. Note, for legibility, some studies methods have been tabled in Addendum 1, as indicated.

EVIDENCE AND CLINICAL CONSIDERATIONS PERIPHERAL NERVOUS SYSTEM DISORDERS

Guillain-Barré Syndrome

IGIV as Effective as PE

The first randomized-controlled trial (RC-trial) of IGIV treatment in GBS appeared in 1992 (Addendum 1). Improvement by one or more grades within four weeks on a seven-grade scale of motor function was the primary outcome of the trial.

Fifty-three percent of IGIV-users, and 34% of plasma exchange (PE)-treated patients showed functional improvement of one or more grades (19% difference, P = 0.024). The median time to improvement by one grade was 27 and 41 days for IGIV-users and PE-treated patients, respectively (P = 0.05). As well as the favorable secondary outcome results summarized in Table 1, IGIV-users had “significantly” fewer complications and less need for artificial ventilation than PE-treated patients.

It should be noted that these results reflected all patients from the trial’s multinational centers. Differences were found between the PE arms of the studies at these centers, which suggested the IGIV-PE comparison was flawed. On further analysis however, the authors concluded that IGIV was indeed at least as effective as the more complicated PE in treating GBS, and possibly superior.

A later pilot study that compared IGIV and PE in the treatment of GBS patients corroborated these results. Using a similar graded functionality scale, 69% of IGIV-users and 61% of PE-treated patients had improved by one disability grade at one month. Other standard outcome measures, including relapse rates, did not differ between the two groups.

IGIV, PE and IVIG/PE Equivalence

A 1997 randomized-controlled double-blind trial (RC-dB trial) again compared the relative efficacy of PE and IGIV, as well as a combined PE/IGIV therapy, for the treatment of GBS (Addendum 1). At four weeks, patients were assessed for changes on the seven-grade disability scale mentioned above. Whereas primary outcome improvements were significant (Table 1), differences between treatment groups’ primary or secondary outcomes were not. Although not significant, it should be noted there were positive trends in some outcomes with the PE/IGIV combined treatment. It was concluded that PE and IGIV had equivalent efficacy in treating severe GBS within two weeks of neuropathic symptom onset, and that the studied PE/IGIV combination did not confer a significant advantage.

Several recent case-reports of severely compromised GBS patients have corroborated the conclusion that IGIV is an effective treatment, and have suggested that IGIV is an excellent first-line therapy for acutely ill patients. It should also be noted however, that at least one recent non-human GBS model has not shown a positive benefit from IGIV, although results remain ambiguous.

Pediatric GBS

In general, it is accepted that morbidity and mortality outcomes are better in children than in adults, possibly because of a higher tolerance for more intense IGIV dosing. Three open trials have demonstrated that IGIV has an especially rapid impact in

<table>
<thead>
<tr>
<th>Table 1: Significant Improvements.</th>
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<tbody>
<tr>
<td><strong>1992 RC-trial with Open Treatment</strong></td>
</tr>
<tr>
<td><strong>Primary Outcome Criteria:</strong></td>
</tr>
<tr>
<td>19% more IGIV-users achieved ≥ 1 grade improvement, compared to PE-treated patients (P = 0.024)</td>
</tr>
<tr>
<td>IGIV-users (n = 130): 0.8 grades (SD 1.3)</td>
</tr>
<tr>
<td>PE-treated patients (n = 121): 0.9 grades (SD 1.3)</td>
</tr>
<tr>
<td><strong>Secondary Outcome Criteria:</strong></td>
</tr>
<tr>
<td>time until one grade improvement: favoring IGIV - p = 0.05</td>
</tr>
<tr>
<td>time until independent locomotion: favoring IGIV - p = 0.07</td>
</tr>
<tr>
<td>need for assisted ventilation in the second week: favoring IGIV - p ≤ 0.05</td>
</tr>
<tr>
<td>complication rate: favoring IGIV - p ≤ 0.01</td>
</tr>
</tbody>
</table>
Table 2: Greater Dosages over Shorter Periods Support Faster Recovery in Pediatric GBS.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Canadian Patients</th>
<th>Turkish Patients</th>
<th>Non-users Turkish Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. Days to Improve by 1 Grade (Range)</td>
<td>17.4 (5-51)</td>
<td>20.8 (3-60)</td>
<td>62.4 (9-270)</td>
</tr>
<tr>
<td>Change in Disability Grade at 4 Weeks</td>
<td>not recorded</td>
<td>1 grade</td>
<td>0.35 grades</td>
</tr>
</tbody>
</table>

Table 3: Five Factors Promoting the Impact of IGIV in CIDP.

1. Disease duration ≤ 1 year
2. Progression of weakness until treatment
3. Symmetry in arm and leg weakness
4. Arm areflexia
5. Decreased motor nerve conduction velocity of the median nerve

Note: highest chance of improvement after IGIV – those with active CIDP and weakness in arms and legs.

IGIV better than placebo. In an early RC-dB trial, CIDP patients who were positively maintained on IGIV were crossed-over to non-treatment – all patients deteriorated. All patients were then randomized to IGIV (0.4 g/kg/day) or placebo (albumin) for five consecutive days – IGIV-users responded within one week, while placebo-users did not ever. As well, IGIV appeared to leave a residual positive impact; after the trial, all patients were returned to non-treatment – IGIV-users had a mean 6.4 weeks prior to deterioration whereas placebo-users had 1.3.

However, a subsequent RC-dB trial in untreated CIDP patients did not corroborate these findings of significant difference between IGIV and placebo groups. Indeed, in this trial, three placebo-users who showed slow and progressive deterioration before the trial had a dramatic clinical improvement (four of the IGIV-users did as well) – the degree of improvement in both groups was equivalent. Further analysis suggested that IGIV’s shortcomings in this trial reflected a skewed sample – it is possible that only a specific subgroup of CIDP patients respond to IGIV treatment.

Objective demonstration that IGIV helps in CIDP. One six-week RC crossover trial comparing PE with IGIV found that IGIV was comparable to PE in significantly improving endpoints compared to baseline (neurologic disability score [NDS], summed compound muscle action potentials [CMAP], muscle weakness of the NDS – P ≤ 0.001–0.006), (Addendum 1).

More recently, chronic-progressive or relapsing CIDP patients were treated in an RC-dB crossover trial (Addendum 1). Significant differences that favored IGIV were seen in all neurologic function assessments completed in two separate analyses (Table 4). After randomized treatment, placebo patients were crossed-over to IGIV. Nineteen (63%) patients improved in their NDS, clinical grade, and grip strength (P ≤ 0.002). There were no significant differences between chronic-progressive and relapsing patients. Eight of the nine chronic-progressive IGIV responders gradually improved to normal function, and were stabilized with a single five-day course of IGIV, and in five of these eight, small doses of immunosuppressive drugs.

Among the 10 chronic-relapsing IGIV responders, improvements lasted a median six weeks, and were reproducible with open label treatments; a single IGIV dose (≤ 1 g/kg) prior to expected relapses stabilized these patients. A positive response to IGIV was most likely in patients with acute relapse, or with evident CIDP for one year or less.

Table 5 summarizes the results of the discussed RC-dB studies. Several recent case-reports, and long-term case
follow-ups in adults and children have corroborated IGIV's benefical impact in CIDP,21-23 and have suggested that focal upper limb demyelinating neuropathy - a probable CIDP variant - may be particularly responsive to IGIV.24

Long-term Maintenance with IGIV. Over long periods of time, pediatric CIDP patients often have a more rapidly fluctuating illness course than adults, and children show a relapsing course significantly more frequently.22 However, children's recovery from relapse is often complete, more-so than adults. One review found that courses of IGIV were generally effective in treating relapses over the long-term.22

A retrospective study of CIDP patients compared IGIV (n = 22) and PE (n = 33) as long-term therapy.25 Approximately 64% of the IGIV, and 70% of the PE treated patients responded well. Of the IGIV-responders, most required only one course of treatment, while seven received repeated courses for 6-51 months. Importantly, long-term treatment with PE showed transient complications (thrombosis [n = 3], poor venous access [n = 3], hematoma ([n = 1], bleeding diathesis [n = 1], hypocalcemia [n = 1], and sepsis [n = 1]), whereas no "significant" complications were observed in long-term IGIV-users. This study suggested that whereas PE and IGIV were effective long-term treatments for CIDP, PE had more side-effects.

A recent open trial of IGIV in 18 patients with CIDP or multifocal motor neuropathy (MMN) showed a benefit from IGIV even after a long disease duration (~19.5 years).26 Sixteen patients responded very well to treatment of at least six months. Six of these were able to stop treatment, and remain in remission for up to 63 months, while the remaining 10 patients continued to receive IGIV in different dosages. The authors concluded that IGIV was effective and safe as a long-term maintenance therapy for CIDP and MMN.

Using the strongest evidence above, the "usefulness" of IGIV in CIDP was rated at an A, based on an A+20,21,23 evidence quality and its impact (see the Usefulness of IGIV to Treat Neurolologic Disorders section).

Paraprotein-associated Polyneuropathy
Polyneuropathy associated with IgM paraprotein targeted at myelin associated glycoprotein (IgM anti-MAG) is etiologically distinct from idiopathic CIDP. An open trial examined the relative efficacy of IGIV and recombinant interferon-alpha with the IgM anti-MAG CIDP variant (Addendum 1).27 Ten percent of IGIV-users and 80% of IFN-alpha-users showed an NDS improvement greater than 20% at six months (P = 0.005). This response difference was reflected in IGIV-users' lower mean NDS — it decreased by 8%, whereas it improved by 31% in the IFN-alpha-users for at least 12 months. It should be noted that IFN-alpha-users' improvement was primarily sensory (P = 0.02) as the NDS motor component was unchanged (P = 0.39). The authors concluded that IGIV was not effective in these patients, whereas IFN-alpha was.

In contrast, IGIV showed a greater impact in 67 CIDP patients with monoclonal gammopathy of uncertain significance (CIDP-MGUS).28 EMG-assessed conduction block was present in about three-quarters of patients, but only about one-third had a pure demyelinating neuropathy. Sixty-six percent of the patients responded to either IGIV, PE or steroids — Rankin scores (i.e., functional improvement) were greatest with PE. CIDP-MGUS patients showed characteristic symptomatology compared to idiopathic CIDP patients, but responded to PE, IGIV and steroids equivalently.

These two studies suggest that whereas IGIV may not be effective in polyneuropathy associated with IgM anti-MAG paraprotein, it probably is in polyneuropathy associated with IgG, IgA, and IgM non anti-MAG paraproteins.

Multifocal Motor Neuropathy
Early case-reports suggested that patients with MMN improve after cyclophosphamide (CTX) therapy, but not after prednisone or PE.29 Because of the involvement of autoimmune factors in MMN, IGIV was a natural choice for further exploration.

An early RC-dB crossover trial in MMN patients showed that IGIV had a significant beneficial effect in patients who demonstrated complete conduction block, especially in muscle strength.

Table 5: RC-dB trials with CIDP Patients Treated with IGIV.

<table>
<thead>
<tr>
<th></th>
<th>% Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990 - crossover[24]</td>
<td>IGIV* (n = 15) -vs.- placebo (n = 13) 100 significant</td>
</tr>
<tr>
<td>1993 - no crossover[25]</td>
<td>IGIV* (n = 7) -vs.- placebo (n = 7) 27 -not significant</td>
</tr>
<tr>
<td>1996 - crossover[26]</td>
<td>IGIV* (n = 30) -vs.- placebo (n = 30) 63 -significant</td>
</tr>
</tbody>
</table>

*0.4 g/kg/day for 5 consecutive days
The benefits of IGIV have been corroborated by more recent studies - a recent review summarized the comparative benefits of IGIV against steroids, immunosuppressors and PE. It concluded there were strong indications of IGIV's short-term efficacy in MMN, especially as early treatment, although strict proof was not yet available. Similar conclusions have been reported in two other extensive reviews.

A Short-term Benefit from IGIV

One recent open trial looking at the impact of IGIV treatment for long-term MMN showed clinical improvements in 67% of patients (mean isometric strength increase 54.5%) - high titers of IgM anti-GM1 antibodies were predictive of a positive response to IGIV (Addendum 1). Unfortunately, the impact of IGIV did not last.

Maintenance of Short-term Benefit from IGIV

A second open trial with seven MMN patients more precisely explored the durability of IGIV’s impact. It found that treatment with IGIV 0.4 g/kg/day for five consecutive days improved muscle strength until a maximum of 12 weeks.

Thereafter, patients required an IGIV maintenance regimen for 2 - 4 years to remain stable (one dose of 0.4 g/kg/week). The regimen eventually failed in three patients, as measured by muscle strength deterioration in four of the 28 muscle groups that had initially shown an improvement, and in two groups with normal strength at the start of IGIV treatment. Electrophysiological studies of those patients revealed an alleviation of initial conduction blocks paralleled the advent of new blocks and ongoing axonal degeneration.

IGIV/CTx Combination

An open trial explored the long-term effect of an IGIV/oral-CTx combination in MMN patients (Addendum 1). The purpose of the trial was to determine whether oral-CTx use would allow the suspension of IGIV after a fixed treatment period. All patients improved significantly with the combination treatment in terms of the primary outcome variables (median Rankin [P = 0.0335] and mean MRC-scale [P = 0.0561]). Improvement correlated with a reduction in the number of nerves with partial motor conduction block (P = 0.0197), and antiglycolipid antibody titers, in all but one patient.

It was found that IGIV courses were indispensable to maintain improvement, although the interval between courses could be progressively prolonged after 3 - 7 months of oral CTx. Eventually, in three patients, IGIV and CTx were both stopped for up to two years before relapse.

The finding that CTx led to hemorrhagic cystitis in two patients and persistent amenorrhea in one patient, whereas IGIV showed no side-effects, suggests that the risk/benefit balance of IGIV must include a good understanding of IGIV’s benign nature. Indeed, the authors concluded that, whereas oral CTx may help to induce a sustained remission, its side-effects suggest it should be reserved for MMN patients who are unreasonably dependent on frequent IGIV courses to remain in remission.

Using the strongest evidence above, the “usefulness” of IGIV in MMN was rated at an A, based on a +3 evidence quality and its impact (see the Usefulness of IGIV to Treat Neuromuscular Disorders section).

NEUROMUSCULAR JUNCTION DISORDERS

Myasthenia Gravis

IGIV has a long history as a treatment for MG - small weekly IM injections were used beneficially through the 1970s. Three reviews of 13 1980s trials provide data on a total of 132 patients, most of whom had acute MG and a previous thymectomy. Patients received IGIV manufactured by several companies, as 0.4 g/kg/day for five days (n = 110), 0.6 - 0.9 g/kg/day for five days (n = 16), and 10 g/day for five days (n = 6).

In most trials, IGIV was administered as a 3 - 6% solution in normal saline. Anticholinesterases, corticosteroids or azathioprine were almost always being taken prior to, and during IGIV administration. Acute exacerbation or respiratory failure were coincident with about half of patients’ IGIV use. Overall, 74% of patients improved with IGIV. Improvement was noted in 50 - 100% of each trial’s sample, except for in one trial's six patients, who received IGIV 10 g/day for five days, with no improvement.

IGIV/steroid combination was twice as likely as IGIV alone to cause improvement, and caused a longer beneficial impact (64 vs. 34 days).

It should be noted that the conclusion that IGIV was responsible for the results above is confounded by: 1) spontaneous improvement after the first 1 - 3 years in the majority of patients; and 2) improvement accelerations due to other common interventions, such as corticosteroids, cytotoxic immunosuppressant drugs and thymectomy.

Benefit from IGIV/Steroid Combination

In a more complex open trial, muscle strength and vital capacity improvements were seen after 22 of 31 IGIV courses in 11 patients (79%) (Addendum 1). Co-administration with a corticosteroid was twice as likely as IGIV alone to cause improvement, and caused a longer beneficial impact (64 vs. 34 days).

Benefit from IGIV Alone

A 1998 open trial showed that 56% of IGIV courses benefited patients (Addendum 1). In benefiting patients, improvement was demonstrated after a median of three days (range 1 - 12) – the peak benefit occurred after seven days (range 4 - 30).

Patients with a Grade-III University of Virginia's Modification of Osserman's (UVMO) classification did not benefit from IGIV, whereas Grade-V patients improved in five of the seven courses. Acutely-relapsing and subacutely-deteriorating or chronic-static patients responded equally to IGIV (50% vs. 60%). The authors concluded that high-dose IGIV can be an effective therapy in deteriorating generalized-MG patients, with an improvement within a few days of IGIV treatment that peaks by week-2 of therapy.

IGIV vs. PE

Several reviews and controlled trials (C-trails) have shown that IGIV and PE both benefit MG patients. A recent RCT-trial compared the efficacy and tolerance of IGIV to PE in MG exacerbations, using two IGIV dosages (Addendum 1). Myasthenic muscular score (MSS) variations were similar across the PE and IGIV groups (median 18 vs. 15.5, p = 0.65). Eight PE patients reported side-effects, whereas only one IGIV patient did (p = 0.01). Interestingly, the efficacy of the five-day IGIV course was slightly less than the three-day – the authors were unable to analyze this difference significantly with such a small sample size.
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Table 6: RC-trial of IGIV in Dermatomyositis - Primary Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>IGIV (n = 8)</th>
<th>Strong improvement?</th>
<th>Placebo (n = 7)</th>
<th>Placebo, after crossed from IGIV (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength test</td>
<td>yes (n = 8)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Neuromuscular symptom score</td>
<td>yes (n = 8)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Changes in skin rash</td>
<td>yes (n = 8)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Histologic changes in muscle biopsies</td>
<td>yes (n = 8)</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

**PE Followed by IGIV**

The similar efficacy of IGIV and PE has led some researchers to study sequenced use of these therapies. In one C-trial, significant improvement in UVMO classification, clinical involvement and functional activity grades was shown (Addendum 1).44

Improvements began 1 - 6 days following IGIV administration, lasting through the 16-week follow-up period. The authors concluded that the PE/IGIV sequenced combination in exacerbated MG may be synergistic, with each therapy affecting a different immune mechanism.

**Pediatric MG**

A few studies have shown that the impact of IGIV in adult patients can be extrapolated to neonates and children.46,47 However, these data are far from complete, and confirmation of IGIV's use in pediatric MG awaits RC-trials.

Using the strongest evidence above, the "usefulness" of IGIV in MG was rated at a B, based on an A and C evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

**Stiff-person Syndrome**

Two open trials of IGIV use in stiff-person syndrome showed six of six patients improved, although improvement parameters were loosely defined.48,49 Other anecdotal reports and case-reports have reported similar findings.50

Using the strongest evidence above, the "usefulness" of IGIV in stiff-person syndrome was rated at a C, based on a C evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

**IDIOPATHIC INFLAMMATORY MYOPATHIES**

Inclusion-body myositis (IBM), dermatomyositis (DMS), and polymyositis (PM) are distinct idiopathic inflammatory myopathies regarded as autoimmune diseases.51 High-dose steroid therapy is very effective for many patients with DMS and PM, but is encumbered by several difficult management issues:52

1) disease relapse is common as steroid therapy is discontinued;
2) side-effects, such as steroid myopathy, diabetes, avascular necrosis, cataracts, or hypertension are common; and 3) some patients are wholly or partially unresponsive clinically.

Small open trials and case-reports have shown that immunosuppressant medications and treatments can be useful adjuncts in PM and DMS (e.g., azathioprine, methotrexate, cyclosporine, and PE).53-57 These therapies' significant side-effects contrast IGIV's benign nature,52 a strong alternative as a result of the variety of immune mechanisms involved in DMS and PM pathogenesis.

The first reported successful use of IGIV in treating myositis patients was with a PM patient who was resistant to steroid therapy.52 Later, 20 adult patients with refractory DMS or PM, the majority of which had failed adjunctive immunosuppressant treatment, were treated with IGIV.59 Seventy-five percent of patients improved significantly.

Another small open trial (n = 11) showed that monthly IGIV dosages alone, for a mean of four months, beneficially influenced serum creatine phosphokinase (CPK) levels in 73% of patients, but only had a clinical impact in 27% of patients.60

**IBM**

IBM is distinguished from other idiopathic inflammatory myopathies by histopathologic abnormalities,61 although histopathologic exceptions have been reported.62 The molecular basis for the disease remains unknown.63

IBM presents as sporadic-IBM or hereditary-IBM. Sporadic-IBM is the most common progressive muscle disease of older persons. Unfortunately, IBM is generally unresponsive to treatment.

**DMS**

A number of small open trials of IGIV in DMS and PM have shown promising results.64 Indeed, a recent dermatological review listed high-dose IGIV as an acceptable treatment for DMS, along with the autoimmune bullous disorders (epidermolysis bullosa acquisita, pemphigoid, and pemphigus).65

One RC-trial of IGIV in treating 15 patients who had treatment-resistant DMS provides the strongest evidence for the use of IGIV in this variant of idiopathic inflammatory myopathy.66 Primary outcomes are listed in Table 6. As well, decreases in IGIV-users' serum CPK, improvement in skin rash, and eradication of membrane attack complex in biopsies suggested that IGIV interfered with the pathogenic process of the disease.

**Juvenile DMS**

Juvenile DMS patients failing to improve with high-dose steroids and adjunctive immunosuppressants have also been successfully treated with IGIV. In one open trial, DMS-specific rashes and muscle strength showed dramatic improvement within 2 - 4 months of IGIV treatment.66 Importantly in these patients, it was then possible to diminish, or discontinue corticosteroid doses. Other open trials (n = 7, n = 968) have shown similar results, albeit with variations in IGIV regimen.

A more recent open trial (n = 7) of juvenile-DMS patients looked at the impact of monthly IGIV treatments in conjunction with other ongoing therapies.69 The reasons for adding IGIV included: disease exacerbation, continued need for high-dose steroid for maintenance, other drug cytotoxicity, or concern over other therapies' ability to quickly induce remission in patients with severe symptoms.

Only one patient failed to benefit from IGIV. Three showed quick clinical responses, from day-2-3 of treatment — two improved slowly, and could thereafter be maintained on a greatly reduced steroid dose — one responded favorably to the first.
Table 7: RC-dB trial of IGIV in Polymyositis (in IBM Patients).

<table>
<thead>
<tr>
<th></th>
<th>IGIV n = 9</th>
<th>Placebo n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>expanded MRC-scale</td>
<td>+4.2 (-16 to +39.8), (not sig)</td>
<td>+2.7 (-10 to +8), (p ≤ 0.1)</td>
</tr>
<tr>
<td>Maximum Voluntary Isometric Contraction (MVIC)</td>
<td>sig improvement relative to placebo in 39%</td>
<td>N/A</td>
</tr>
<tr>
<td>-in lower limbs</td>
<td>sig decrease in 28%</td>
<td>N/A</td>
</tr>
<tr>
<td>-in other limbs</td>
<td>sig improvement relative to placebo</td>
<td>N/A</td>
</tr>
<tr>
<td>Quantitative swallowing studies</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

three courses only. Unfortunately, four of the patients who benefited from IGIV showed an aggravation of symptoms some time after discontinuing IGIV.

The authors concluded that IGIV is valuable as a quick, potent adjuvant, especially to reduce juvenile-DMS patients' exposure to other immunosuppressive therapies for various reasons. However, they added that their results suggested the durability of IGIV's effect is doubtful.

**PM in IBM Patients**

The impact of IGIV in PM is less clear than in DMS. In an RC-dB crossover trial of IGIV in 19 IBM patients, patients received monthly IGIV infusions of 2 g/kg or placebo for three months, with subsequent crossover. Primary outcomes and results are listed in Table 7.

Modest gains in the IGIV group compared to placebo were evident, but the clinical importance of these gains was unclear. However, for six patients (28%), IGIV had a definite beneficial impact on functionality, greater than 10 MRC-scale points.

Using the strongest evidence above, the "usefulness" of IGIV in DMS was rated at an A, based on an A⁺ evidence quality and its impact. The "usefulness" of IGIV in PM and IBM was rated in the same manner at a C, based on an A⁻ evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

**CENTRAL NERVOUS SYSTEM DISORDERS**

**Demyelination Syndromes: Multiple Sclerosis**

Open trials in the 1980s showed that IGIV reduced acute multiple sclerosis (MS) exacerbations and arrested disease progression,71,72 whereas IM-IgG73 had similar but less consistent results. Other trials in MS have shown that IGIV treatment may be followed by recovery of visual function in patients with chronic optic neuritis who failed to respond to steroids,74 or by improvement in isometric muscle testing,75 although general clinical opinion is that fixed deficits reflecting neuronal degeneration cannot be reversed.

More recently, the results of a C-trial suggested that IGIV suppressed the ongoing pathologic process in MS (Addendum 1).76 Relapsing-remitting MS patients' mean annual exacerbation rate (AER) was almost one-quarter the initial AER after one year of therapy, while remaining unchanged in the controls. This rate continued to decrease during the second and third years of the trial, and the difference between IGIV-treated and control patients remained significant (Table 8). Among the IGIV-users at three years, duration of IGIV treatment correlated with neurologic ability and lower AER. As well, most IGIV-users experienced mild to moderate, whereas controls experienced moderate to severe acute exacerbations.77

Among IGIV-users, mean Kurtzke Expanded Disability Status Scale (EDSS) scores decreased after one year of IGIV treatment, while scores increased in controls - mean changes in EDSS scores at one, two and three years were significant (Table 9).

**Objective Demonstration of Benefit from IGIV**

In the more recent AIMS RC-dB trial (Addendum 1),78,79 IGIV-using relapsing-remitting MS patients' exacerbation rate was about halved (Table 8). The EDSS score decreased in the IGIV-treated patients and increased in the placebo group (Table 9). The decrease in IGIV-users' EDSS score relative to placebo-users was significant, but modest. It was concluded that the early improvement in IGIV-users' EDSS scores suggested the activation of repair mechanisms (e.g., remyelination), whereas fewer exacerbations throughout the trial probably resulted from immunoregulatory effects.

Another 1997 RC-dB trial with relapsing-remitting or progressive MS in 25 patients corroborated these results, although significance was not achieved. The authors concluded that IGIV treatment may help to prevent exacerbations in patients with relapsing MS.80

**Further Confirmation of Benefit from IGIV**

A 1998 RC-dB trial in 40 patients whose MS status was confirmed with magnetic resonance imaging (MRI) also corroborated earlier results (Addendum 1).81 IGIV-treated patients showed a decreased AER, reflecting a 38.6% reduction in relapse rate (Table 8).

The median post-treatment time for IGIV-users until first exacerbation was 233 days, vs. 82 days for placebo-users (p = 0.003). Six IGIV-users had no exacerbations throughout the two-year follow-up, while all placebo-users had exacerbations. IGIV-users' EDSS scores were significantly less than placebo-users' (Table 9), although changes in total lesion scores evaluated by brain MRI did not show a significant difference between groups.

**Magnetic Resonance Imaging – Impact of IGIV in MS**

In general, it is accepted that the beneficial effect of drugs reducing the frequency of MS relapses and neurologic disability can be confirmed by MRI findings.53 In some studies, MRI scores from IGIV or placebo groups have suggested that IGIV treatment arrested disease progression,54 although contradictory results have also been found.55
A 1998 RC-db crossover trial assessed whether IGIV decreased disease activity, as MRIs suggested, in relapsing MS (Addendum 1). Patients showed fewer enhancing lesions per MRI with IGIV (median 0.4, range 0 - 9.3) than with placebo (median 1.3, 0.2 - 25.7, p = 0.03). Fifteen IGIV-period patients and seven placebo-period patients were exacerbation free (p = 0.02), although the difference between the number of exacerbations in the IGIV and placebo periods was not significant (Table 10). Indeed, the difference between the two periods did not reach significance in any of the remaining secondary measures.

Using the strongest evidence above, the "usefulness" of IGIV in MS was rated at a B, based on an A+ evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

### Adult and Pediatric Intractable Epilepsies

A 1994 review of 24 open trials involving a total of 368 patients with intractable epilepsy receiving IGIV (age < 1 - 35 years, mean 7.3 years), found that the mean clinical seizure reduction and the mean EEG improvement due to IGIV was 52% and 45%, respectively. IGIV dosages varied between 0.3 and 6.8 g/kg during a period of 0.15 - 12 months. Complete seizure remission was reported in 23% of patients. Whereas the lack of C-trials (or better) surveyed in this review means that reported results are not conclusive, they strongly suggest that IGIV may be effective in some patients.

An open trial in West or Lennox-Gastaut syndrome patients demonstrated the effectiveness of a biphasic IGIV regimen (Addendum 1). The patient group experienced a 70% reduction in clinical seizures, coincident with a 40% reduction in spike-wave discharges on EEG. All 15 patients showed acceleration of EEG background activity and improved psychomotor development. The authors concluded IGIV should be considered when other treatments have failed.

A C-db trial in refractory epileptic patients showed a positive trend in favor of IGIV - decreasing the daily seizure frequency at six months by at least 50%, albeit this was not significant (P = 0.095) (Addendum 1). As well, no relationship was seen between dose and efficacy (P = 0.31).

Inconclusive results were also reported in an open trial in 19 Rasmussen’s syndrome patients treated with IGIV, and in an uncontrolled manner, steroids. A recent case-report illustrated the dramatic impact of IGIV in an eight-year-old Landau-Kleffner syndrome (LKS) patient refractory to known therapies. LKS is a pediatric condition, characterized by acquired aphasia associated with epileptiform discharges in the form of ESES (electrographic status epilepticus during sleep). After two of three initial treatment courses,
Another case-report of a pediatric LKS patient demonstrated that IGIV had a very dramatic effect in the third of three relapses. The first two relapses were reversed with steroid therapy, with an effect comparable to IGIV in the third relapse.

Using the strongest evidence above, the “usefulness” of IGIV in Cryptogenic West and Lennox-Gastaut syndrome was rated at a C, based on a C92 evidence quality and its impact. In the same manner, the “usefulness” of IGIV in Landau-Kleffner syndrome (E95,96 evidence quality), refractory epilepsies (B95,96 evidence quality), and Rasmussen’s syndrome (C94 evidence quality) were rated at a C (see the Usefulness of IGIV to Treat Neurologic Disorders section).

**Clinical Recommendations**

The evidence from RC-dB trials is the strongest level of clinical evidence available. In well-understood disorders, where a strongly supported therapy is available, evidence of benefit from RC-dB trials is required to switch to a new alternative.

In neurology, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. As a result, it is fairly common for best-practice decisions to rest on somewhat less than RC-dB trial evidence. This article used a grading of evidence quality, loosely based on U.S. Preventive Services Task Force guidelines, to clarify clinical recommendations (Table 11).

**The Usefulness of IGIV to Treat Neurologic Disorders**

In the author’s opinion, best-practice use of IGIV in neurology is two-phased: “initial” and “later.”

**Recommendations for the Initial Phase**

In an initial therapy phase, best-practice begins with treatment based on comparing alternative therapies — first, in terms of the quality of substantiating evidence; and second, when the evidence quality is of equal weight, in terms of demonstrated treatment impact.

Grading the evidence for IGIV in an indication, and rating the shown impact of IGIV treatment allows us to rank IGIV’s “usefulness” in neurology for the purpose of comparison. The “usefulness” of IGIV in neurology can be described by a “combined score” based on evidence quality and strength of impact. Combined scores range from A+ (strongly recommended) to C (recommended as a last resort). Table 12 lists the better evidence for each indication discussed in this article, and the combined scores resulting from this evidence. This ranking compares favorably with another recent set of Canadian recommendations,92 and two reviews.32-31 The reviews listed GBS, CIDP, and MMN as acceptable off-label indications, with dispute around IGIV use in DMS.

**Recommendations for the Later Phase**

In a later therapy phase, best-practice is based on comparing alternative therapies as above (quality of evidence and demonstrated treatment impact), and in terms of the individual patient’s previous response to each possible therapy.

**Conclusion**

In neurology today, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. IGIV has been conclusively shown in some indications to be an effective therapy. In other indications, study results have only hinted at potential benefits, because of lack of study rigor or possible confounding influences.

In one set of Canadian recommendations,92 six non-label neurologic disorders were recommended for current IGIV use, and a further nine recommended for investigation. Several reviews have listed Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN) as acceptable off-label indications,

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Table 12: Evidence and “Combined Scores”.

<table>
<thead>
<tr>
<th>Quality of Evidence of Benefit</th>
<th>Shown Outcomes of Significance in... = Combined Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+6,43</td>
<td>GBS</td>
</tr>
<tr>
<td>A+12,13,20</td>
<td>CIDP</td>
</tr>
<tr>
<td>A65</td>
<td>DMS</td>
</tr>
<tr>
<td>A+30</td>
<td>MMN</td>
</tr>
<tr>
<td>A+12, C42</td>
<td>MG</td>
</tr>
<tr>
<td>A+7,8,9,11</td>
<td>MS</td>
</tr>
<tr>
<td>A+7,9,10</td>
<td>PM and IBM</td>
</tr>
<tr>
<td>C40</td>
<td>Cryptogenic West and Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>E95</td>
<td>Landau-Kleffner syndrome</td>
</tr>
<tr>
<td>B95</td>
<td>Refractory epilepsies</td>
</tr>
<tr>
<td>C94</td>
<td>Rasmussen’s syndrome</td>
</tr>
<tr>
<td>C94</td>
<td>Stiff-person syndrome</td>
</tr>
</tbody>
</table>

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with dispute around IGIV use in dermatomyositis (DMS). The same reviews suggested that randomized-controlled trials (RC-trial) will substantiate today’s suspicions of IGIV’s beneficial effect in DMS and polyneuropathy (PM), myasthenia gravis (MG), and inflammatory neuropathies.

The evidence discussed in this article suggests that IGIV is: strongly recommended for the treatment of CIDP, DMS, and MMN; recommended as a second resort for the treatment of MS and MG; and recommended as a last resort for the treatment of PM, IBM, intractable epilepsies, and stiff-person syndrome.

ACKNOWLEDGEMENTS

The meeting of the “IGIV in Neurology Advisory Board” that generated the clinical advices that formed part of the information basis of this paper was sponsored by Bayer Pharmaceuticals. Publication of this article was also sponsored by Bayer Pharmaceuticals.

REFERENCES


82. Paty DW, Li DKB, for the UBC MS/MRI Study Group and IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 662-667.


### Addendum 1: Selected Studies' Methods

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS4</td>
<td>RC-trial - (IGIV openly compared to PE, follow-up blinded)</td>
<td>n = 147 - GBS diagnosis for less than two weeks (dependent ambulation).</td>
<td>7-grade scale - 0 = healthy, 1 = minor symptoms and fully capable of manual work, 2 = able to walk at least 10 m without assistance, 3 = able to walk at least 10 m with a walker or support, 4 = bedridden or chairbound, 5 = requiring assisted ventilation for at least part of the day, 6 = dead.</td>
<td>$ IGIV treatment (n = 74); 0.4 g/kg/day for 5 consecutive days began on the day of randomization. $ Five PE treatments within 7-14 days (n = 73); 200-250 ml/kg/treatment median delay of one day to begin therapy.</td>
</tr>
<tr>
<td>GBS8</td>
<td>RC-db Trial.</td>
<td>n = 379 - GBS diagnosis for less than two weeks (dependent ambulation).</td>
<td>As above.</td>
<td>$ IGIV (0.4 g/kg/day for 5 days). $ PE (5-50 ml/kg exchanges over 8-13 days). $ PE regimen followed by the IGIV regimen.</td>
</tr>
<tr>
<td>GBS14</td>
<td>Open Trial.</td>
<td>n = 9 - Pediatric GBS diagnosis (2-8;13.5 years old).</td>
<td>Improvement by one or more grades on the scale above - (mean follow-up period, 14.5 months).</td>
<td>IGIV single dose, 2g/kg.</td>
</tr>
<tr>
<td>GBS15</td>
<td>Retrospective Study.</td>
<td>n = 75 - Pediatric GBS diagnosis (Turkish n = 51, Canadian n = 24).</td>
<td>Rate of recovery by functional disability grades - (influence of age or initial disability grade on treatment impact was weak [r = 0.53, p &lt; 0.50]).</td>
<td>IGIV (2g/kg);...</td>
</tr>
<tr>
<td>CIDP15</td>
<td>RC Crossover trial.</td>
<td>n = 20 (13 completed the study) - CIDP diagnosis.</td>
<td>NDS, CMAP, muscle weakness of the NDS.</td>
<td>$ Two PE sessions through three weeks, followed by one session through three following weeks. $ Weekly doses of IGIV 0.4 g/kg in week-1B3, followed by 0.2 g/kg in week-4B6.</td>
</tr>
<tr>
<td>CIDP17</td>
<td>Open Trial.</td>
<td>n = 20 - IgM anti-MAG CIDP variant diagnosis.</td>
<td>$ IGIV 2g/kg loading and then 1 g/kg every three weeks. $ IFN-alpha 3 MU/m2 subcutaneously three times weekly.</td>
<td></td>
</tr>
<tr>
<td>MMN34</td>
<td>RC-db Crossover trial.</td>
<td>n = 12 - MMN diagnosis.</td>
<td>Muscle strength, Norris scale for disability, MCV, immunologic markers.</td>
<td>$ IGIV 0.4 g/kg/day for five consecutive days. $ Placebo of the same regimen.</td>
</tr>
<tr>
<td>MMN36</td>
<td>Open Trial.</td>
<td>n = 6 - Known IGIV responders who had been followed for a mean of 47 months with MMN treatment.</td>
<td>Rankin disability, Medical Research Council strength rating scale (MRC-scale) measures on the 20 most affected muscles.</td>
<td>Oral CTX 1B3 mg/kg/day, and IGIV 0.4 g/kg/day for two days at clinical exacerbations. <strong>cont.</strong></td>
</tr>
</tbody>
</table>
ADDENDUM 1: (CONTINUED)

Reference: MG36
Design: Open Trial.
Patients: n = 14 - MG diagnosis.
Outcomes: $ IGIV 0.4 g/kg daily for five consecutive days.
$ IGIV as above with corticosteroid.

Reference: MG42
Design: Open Trial.
Patients: n = 14 (11 completed the study) - Generalized-MG diagnosis.
Outcomes: A minimum one-grade improvement in The University of Virginia's Modification of Ossemian's (UVMO) classification.
Therapies: 7 courses of IGIV 0.4 g/kg/day for five consecutive days (that included at least one acute exacerbation.

Reference: MG44
Design: RC-trial.
Patients: n = 148 - Relapsing-remitting MS diagnosis - Patients were 15B65 years old and had 1 to 6 EDSS scores.
Outcomes: $ IGIV 0.15B0.2 g/kg once per month, for two years (n = 75).
$ Placebo in the same regimen, (n = 73).

Reference: MS51
Design: RC-dB Trial.
Patients: n = 40 - Relapsing-remitting MS diagnosis confirmed by magnetic resonance imaging (MRI) - 19B60 years old.
Therapies: $ Loading dose of IGIV (0.4 g/kg/day for 5 consecutive days), followed by single booster doses (0.4 g/kg once every 2 months) for two years.
$ Placebo in the same regimen.

Reference: MS55
Design: RC-dB Trial.
Patients: n = 26 (18 completed the study).
Outcomes: Gadolinium enhancing lesions per MRI, exacerbation rate, neurologic rating, MS lesion load on T2-weighted MRI, multimodal evoked potentials.
Therapies: $ IGIV 0.4 g/kg/day for five consecutive days, and then bi-monthly for three months.
$ Placebo in the same regimen.

Reference: Epilepsies57
Design: Open.
Patients: n = 15 - West (n = 3) or Lennox-Gastaut (n = 12) syndrome diagnosis.
Outcomes: $ IGIV 0.4 g/kg/day for two consecutive days, monthly, during two 6-month treatment periods.
$ Placebo in the same regimen.

Reference: Epilepsies58
Design: C-dB trial.
Patients: n = 61 (46 with partial epilepsy) - Patients were refractory.
Therapies: Daily seizure frequency over 6-months.
Therapies: 7 infusions (4 in week-1, 1 in week-2, -3 and -6), of IGIV 0.1, 0.25 or 0.4 mg/kg per infusion respectively.
Digital electroencephalography (EEG) is rapidly replacing paper-based, analog EEG for a number of reasons, e.g., improved convenience, reduced cost (of paper and paper storage or microfilming records) and enhanced flexibility of recording and display. With increasingly widespread use of digital EEG technology from multiple manufacturers, there is a need for minimal standards for such equipment in patient care settings. This document represents a set of minimal standards for such technology and its utilization, as approved by the EEG Section of the Canadian Society of Clinical Neurophysiologists at its annual general meeting in June of 1998. The document meets Canadian standards and those recently developed by the International Federation of Clinical Neurophysiologists. This document addresses some specific concerns relevant to digital technology. The aspects of patient documentation, length and principles of recording and charting are the same as those of previous Canadian documents and are not repeated in this paper.

Optical disk or compact disk read-only-memory (CD-ROM) technology is an acceptable medium for storing digital EEG recordings. It is the user's responsibility to be aware of possible deteriorating legibility or impending technical obsolescence and make suitable arrangements for copying the information onto an updated storage medium or paper to meet storage requirements. Manufacturers should provide for a mechanism, e.g., the conversion of format, that allows electroencephalographers working with different equipment to interpret EEGs for clinical purposes.

To ensure the adequacy of waveform recording, a minimum sampling rate of 200 samples per second for each channel is used, but higher rates are recommended. The sampling rate should be even multiples of 50 or 64 Hz. When sampling at 200 Hz, an anti-aliasing filter of 70 Hz should be used, with a roll-off of at least 12dB/octave. Higher sampling rates require a proportionately higher anti-aliasing filter setting. A low frequency filter of 0.16 Hz should be available; as should a 60 Hz notch filter, for use when required. Digitization at voltage level of 12 bits or greater with the ability to resolve voltage to 0.5μV is recommended. Common mode rejection is 110 dB or greater at each amplifier input. Interchannel cross-talk must be less than 1%, i.e., 40dB down or less.

The available technology is capable of displaying the recording on a video screen as well as on paper. With horizontal scaling, one second of time occupies 25-35 mm and contains at least 120 data points/channel; scaling at 0.5, 2 and 4 times should be feasible. On the vertical display, a minimum spacing of 10 mm between channels for a display of 16 or 18 channels is recommended. Adequate screen resolution is at least 4 pixel resolution per vertical millimetre. It is recommended that the screen have at least 1024 x 768 pixels, preferably 1280 x 1024 pixels. Playback systems should show the montage, filter and sensitivity settings, vertical voltage scale and horizontal time marking scale, technologist comments, event markers (e.g., for hyperventilation) and page number or time. The playback unit should also allow for montage selection changes and post-hoc alterations in sensitivity and filter settings.

Topographic mapping, frequency or power spectral analyses and other quantitative assessments of digital EEG data are not considered an alternative to traditional (standard) EEG display in either digital or analog systems. Interpretation of the quantitative EEG should involve analysis of the simultaneous standard EEG. When used in isolation, a quantitative EEG can yield misleading information.

Developed for the Annual General Meeting of the Canadian Society of Clinical Neurophysiologists held in Montreal in June of 1998.

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REFERENCES