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# Long-term effects of intravenous immunoglobulin in CIDP

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**Abstract**

*Objective:* Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired demyelinating disease of the peripheral nervous system characterized by muscle weakness, areflexia or hyporeflexia, and sensory disturbances. Although short-term efficacy of intravenous immunoglobulin (IVIg) has been demonstrated in randomized-controlled trials, the data pertaining to long-term outcome in CIDP are limited. Consequently, the aim of the present study was to assess the long-term effects of IVIg on neurophysiological parameters in CIDP.

*Methods:* Neurophysiological records from 11 CIDP patients, treated with IVIg for $\geqslant 12$ months, were reviewed. Nerve conduction studies were assessed at baseline, 1-year, and last follow-up.

*Results:* There was a significant reduction in the frequency of conduction blocks (pre-treatment nerve segments affected 61%; last follow-up 39%, $P < 0.01$) and a reduction in ongoing axonal loss (pre-treatment regions with spontaneous activity, 47%; post-treatment 29%, $P < 0.01$) with IVIg treatment. Further, there was significant improvement in sensory nerve conduction studies with IVIg treatment (sensory amplitudes reduced pre-treatment, 90% nerves tested; post-treatment, 62%, $P < 0.01$).

*Conclusions:* The present study suggests that long-term IVIg maintenance therapy improves neurophysiological parameters in CIDP. However, CIDP patients remain IVIg dependent and new conduction blocks may develop.

*Significance:* The present study suggests that long-term IVIg maintenance therapy improves neurophysiological parameters in CIDP, possibly by reducing the immune response and thereby fostering nerve healing.



*Keywords:* CIDP; IVIg; Conduction block

## 1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired demyelinating disease of the peripheral nervous system, characterized by generalized muscle weakness, areflexia or hyporeflexia, and sensory disturbances (Dyck et al., 1975; Barohn et al., 1989). The diagnostic neurophysiologic features of CIDP include a combination of prolonged distal motor and F-wave latencies, conduction block/temporal dispersion, and slowed motor conduction velocities (Cornblath et al., 1991; Saperstein et al., 2001; Nicolas et al., 2002). Albuminocytological dissociation is supportive of a diagnosis of CIDP in 90% of cases (Saperstein et al., 2001). Although the etiology of CIDP remains elusive, an autoimmune-mediated response directed against peripheral nerve myelin has been proposed as a likely pathophysiological mechanism (Toyka and Gold, 2003), forming the basis of therapeutic interventions.

The clinical benefits of intravenous immunoglobulin (IVIg) therapy in CIDP have been demonstrated in

*Abbreviations*: ANOVA, analysis of variance; CB, conduction block; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound muscle action potential; CV, conduction velocity; DML, distal motor latency; EMG, electromyography; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; MRD, modified Rankin disability score; NCS, nerve conduction study; SA, spontaneous activity; SNAP, sensory nerve action potential.

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randomized-controlled trials (van Doorn et al., 1990a,b; Dyck et al., 1994; Hahn et al., 1996; Hughes et al., 2001; Mendell et al., 2001). These studies by design were short-term, and demonstrated improvement in strength measurements, functional scales and neurophysiological outcomes. The occurrence of side effects (Burks et al., 1986; Dalakas and Clark, 2003; Caress et al., 2003; Okuda et al., 2003; Vucic et al., 2004), cost of IVIg maintenance therapy (Dalakas and Clark, 2003), and limited IVIg supply warrant further studies to establish the long-term effectiveness and safety of IVIg in CIDP (Hughes et al., 2006).

The long-term effectiveness of IVIg in CIDP has been infrequently assessed (Choudhary and Hughes, 1995; Hahn et al., 1996; Kuwabara et al., 2006; Rajabally et al., 2006). Although these studies reported clinical improvement and a possible reduction in IVIg dosage (Rajabally et al., 2006), concurrent adjuvant immunosuppressive therapy was administered during the follow-up period and data regarding the long-term effects of IVIg on neurophysiological parameters, such as conduction block, were limited. Consequently, the aim of the present study was to assess the long-term effectiveness of IVIg on neurophysiological parameters in CIDP. This approach should allow insights into the long-term outcome of the underlying pathophysiological factors causing weakness in CIDP patients treated with IVIg.

## 2. Methods

Medical records of 11 CIDP patients, five males and six females (mean age 53 years, range 35–75), were reviewed retrospectively for neurophysiological data. Nine patients presented with symmetrical subacute-onset sensorimotor deficits with hyporeflexia and two patients (Patients #4 and #7, see Table 1) presented with ataxia and hyporeflexia. All patients were electrically diagnosed with CIDP according to the neurophysiological INCAT criteria (Hughes et al., 2001). Inclusion criteria for the study included; (i) initial and continuing clinical response to IVIg treatment, (ii) on maintenance IVIg treatment for at least 12 months, and (iii) no concurrent treatment with steroids, plasmapheresis, or other immunosuppressive medications. Any patient requiring adjuvant immunosuppressive therapy was excluded from analysis, as in such an instance definite conclusions about the long-term effectiveness of IVIg could not be ascertained.

### 2.1. IVIg therapy

All patients were initially treated with IVIg (2 g/kg) administered over five consecutive days for three consecutive months (Venoglobulin-3, 5% albumin, Alpha therapeutics or Gammagard/Polygam, 5%, Baxter/Hyland/Immuno). IVIg dosage was subsequently tailored according to the clinical response by the managing neurologists. Specifically, the dose of IVIg was increased by 0.4 mg/kg/day if the patient reported recurrence of symptoms, such as weakness, prior to the next dose. Once a maintenance dose was achieved the monthly IVIg dose remained unchanged and no patient developed weakness prior to the next dose.

### 2.2. Neurophysiology

Nerve conduction studies (NCS) were performed at the Massachusetts General Hospital Neurophysiology Laboratories, using the Oxford Synergy electromyography machines (Oxford Instruments, Old Woking, Surrey, England). The temperature of the upper extremities was maintained at 32 °C and of the lower extremities at 30 °C (Denys, 1991). Surface disk electrodes were used for recording the compound muscle action potentials (CMAP). Motor nerves were evaluated to Erb's point in the upper limbs and popliteal fossa in the lower limbs. In the upper limbs, the median, ulnar and radial nerves were studied, while in the lower limbs the tibial and common peroneal nerves were assessed. Ten consecutive F-waves were obtained by supramaximal stimulation for each nerve. Sensory nerve action potentials (SNAP) were recorded orthodromically from the median, ulnar, and sural nerves bilaterally. Evidence of primary nerve demyelination was defined in accordance with the INCAT criteria (Hughes et al., 2001). Specifically, conduction block (CB) was defined as >20% reduction in negative peak–peak.

Needle electromyography (EMG) was performed using a disposable 20-gauge concentric needle. The following muscles were studied: deltoid, triceps and biceps brachii; abductor pollicis brevis and first dorsal interossei; vastus laterallis, gluteus medius, and maximus; tibialis anterior and medial gastrocnemius. Evidence of spontaneous activity (SA) indicative of ongoing denervation (fibrillation potentials and positive sharp waves) was determined for each muscle and graded as follows: 0, no activity; 1+, SA

Table 1
Clinical features in 11 CIDP patients treated with long-term maintenance intravenous immunoglobulin (IVIg)

| | Pt 1 | Pt 2 | Pt 3 | Pt 4[a] | Pt 5 | Pt 6 | Pt 7[a] | Pt 8 | Pt 9 | Pt 10 | Pt 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | F | F | M | M | F | M | F | F | F | M | M |
| Current age | 83 | 59 | 48 | 55 | 60 | 67 | 77 | 74 | 65 | 18 | 59 |
| Age onset | 75 | 49 | 37 | 49 | 58 | 63 | 70 | 61 | 63 | 11 | 50 |
| IVIg dose (g/kg/4 weeks) | 1.6 | 1.2 | 2.0 | 1.2 | 2.0 | 0.4 | 1.6 | 1.2 | 2.0 | 1.0 | 1.2 |
| Duration of treatment and follow-up (years) | 5 | 6 | 3 | 4 | 3 | 3 | 1.5 | 4 | 4 | 3 | 3 |

[a] Patients 4 and 7 presented with ataxia and unsteadiness, but fulfilled the INCAT neurophysiological criteria for CIDP.

in two sampled areas; 2+, SA in more than two sampled areas and of moderate degree; 3+, profuse SA filling the screen monitor; 4+, profuse SA filling the screen monitor and no voluntary motor unit action potential recruitment.

### 2.3. Statistics

Mean summated distal and proximal CMAP amplitudes, distal motor latencies, F-wave latencies and SNAP amplitudes were compared between baseline, at 1-year and last follow-up using analysis of variance (ANOVA). One-sample test of proportions was used to compare differences in the remaining neurophysiological parameters, including the presence of CB, prolonged DML, reduced motor CV, prolonged or absent F-wave minimum latency, reduced or absent SNAP amplitudes, and EMG evidence of spontaneous activity, at baseline, at 1-year after commencement of IVIg treatment, and at last follow-up, i.e. last NCS available to the neurologist assessing outcome (1-month after the last IVIg dose). A probability ($P$) value of $<0.05$ was considered statistically significant.

## 3. Results

The clinical features for 11 CIDP patients are summarized in Table 1. Mean duration of follow-up and treatment in the 11 CIDP patients was 3.6 years (1.5–6), with the mean monthly maintenance IVIg dose of 1.4 g/kg every 4 weeks. The mean time between symptom onset and treatment was $4.0 \pm 2.8$ (1–9) years.

### 3.1. Neurophysiology

The neurophysiological findings are summarized in Table 2.

#### 3.1.1. Conduction block

At baseline, CB was noted in 22 of 36 (61%) nerve segments. At 1-year, CB was evident in 14 of 36 (39%) nerves segments ($P < 0.01$). Four of the 14 (29%) CBs noted at 1-year were new. At last follow-up, CB was evident in 14 of 36 (39%) nerve segments ($P < 0.01$, compared to pre-treatment). Four of the 14 (29%) CBs at last follow-up were new. Mean summated pre-treatment proximal CMAP amplitude was $2.16 \pm 1.8$ mV versus $3.66 \pm 2.6$ at 1-year ($P < 0.01$) and $4.02 \pm 2.7$ mV at last follow-up, representing an increase of 86% over the follow up period ($P < 0.001$). The mean summated proximal to distal CMAP amplitude ratio at baseline was 0.52, 0.69 at 1-year and 0.72 at last follow-up representing an increase of 38.5% over the follow-up period ($P < 0.01$).

#### 3.1.2. CMAP amplitude and EMG

Overall, the mean summated pre-treatment distal CMAP amplitude at baseline was $4.13 \pm 3.3$ mV versus $5.29 \pm 3.0$ mV at 1-year ($P = 0.09$) and $5.51 \pm 2.7$ mV at last follow-up ($P = 0.09$), representing an increase of $33 \pm 18\%$.

For nerves exhibiting CB, mean summated pre-treatment distal CMAP amplitudes were $4.57 \pm 3.6$ mV versus $6.03 \pm 3.6$ mV at 1-year ($P < 0.01$) and $6.17 \pm 3.6$ mV at last follow-up ($P < 0.01$), representing an increase of 46.6%. Sixteen of 36 nerves had low distal CMAP amplitudes. The mean summated distal pre-treatment CMAP amplitudes for these nerves were $1.56 \pm 1.3$ mV versus $3.58 \pm 2.8$ mV at 1-year and $3.98 \pm 3.4$ mV at last follow-up, representing an increase of 155% over the follow-up period ($P < 0.05$). The changes in CMAP amplitudes were accompanied by improvement in EMG findings. Specifically, at baseline, needle EMG revealed SA in 24 of 51 (47%) muscles, while at last follow-up, 15 of 51 (29%) muscles had evidence of SA ($P < 0.01$).

### 3.2. Other neurophysiological findings

#### 3.2.1. Conduction velocity

At baseline, CV was reduced in 14 of 35 (40%) nerve segments. At 1-year, 10 of 35 (29%) nerve segments had reduced CV ($P = 0.15$). At last follow-up, 13 of 35 (37%) nerve segments had reduced CV ($P = 0.71$, compared to pre-treatment). The mean summated motor conduction velocity increased from $36.9 \pm 8.7$ m/s (representing a 7% reduction compared to normal controls) at baseline, to $46.2 \pm 9.0$ m/s at 1-year, and $49.0 \pm 7.1$ m/s at last follow-up, representing an increase of 33% over the follow-up period, which was not significant ($P = 0.6$).

#### 3.2.2. Distal motor latency

At baseline, DML was prolonged in 12 of 49 (24%) nerves. At 1-year, 10 of 49 (20%) nerves had prolonged

Table 2
Summary of neurophysiological data

| Parameter | Pre-treatment $N$ (%) | 1-year $N$ (%) | Last follow-up $N$ (%) |
|---|---|---|---|
| Conduction block | 22 (61) | 14 (39)[†] | 14 (39)[†] |
| Spontaneous activity | 24 (47) | – | 15 (29)[†] |
| Reduced CV (m/s) | 14 (40) | 10 (29) | 13 (37) |
| Prolonged DML (ms) | 12 (24) | 10 (20) | 8 (16) |
| Prolonged F-wave latency (ms) | 25 (64) | 23 (59) | 21 (54) |
| Reduced or absent SNAP | 26 (90) | 18 (62)[†] | 18 (62)[†] |

CV, conduction velocity; DML, distal motor latency, SNAP, sensory nerve action potential; N, number of abnormal nerve segments; %, percentage of abnormal nerve segments.
[†] Significant $P \leqslant 0.01$.

DML ($P = 0.48$). At last follow-up, 8 of 49 (16%) nerves had prolonged DML ($P = 0.12$, compared to pre-treatment). At baseline, the mean summated DML was $5.7 \pm 0.7$ ms, $5.5 \pm 0.8$ ms at 1-year, and $5.2 \pm 0.6$ ms at last follow-up, representing an improvement of 8.8% over the follow-up period which was not significant ($P = 0.28$).

*3.2.3. F-wave responses*

At baseline, F-wave responses were absent or of prolonged latency in 25 of 39 (64%) nerves. At 1-year, 23 of 39 (59%) nerves exhibited either absent or prolonged F responses ($P = 0.52$). At last follow-up, 21 of 39 nerves tested (47%) were either absent or prolonged ($P = 0.2$, compared to pre-treatment). At baseline the summated minimum F-wave latency was $42.2 \pm 2.0$ ms, $41.8 \pm 2.4$ ms at 1-year, and $39.8 \pm 2.1$ ms at last follow-up, representing a reduction of 5.7% over the follow-up period which was not significant ($P = 0.40$).

*3.2.4. Sensory NCSs*

At baseline, SNAPs were reduced in amplitude or unobtainable in 26 of 29 (90%) nerves. At 1-year, 18 of 29 (62%) nerves had reduced or absent SNAP amplitudes ($P < 0.01$). At last follow-up, 18 of 29 (62%) nerves exhibited absent or reduced SNAP amplitudes ($P < 0.01$, compared to pre-treatment). At baseline, the mean summated SNAP amplitude was $1.6 \pm 0.6$ μV, $2.5 \pm 0.7$ μV at 1-year and $3.4 \pm 0.9$ μV at last follow-up representing an increase of 125% over the treatment period ($P < 0.05$).

## 4. Discussion

The present study establishes effectiveness of long-term IVIg maintenance therapy on neurophysiological parameters in 11 CIDP patients followed for an average duration of 3.6 years. Specifically, long-term IVIg treatment resulted in reversal of CB, improvement in distal CMAP and SNAP amplitudes, and a reduction in spontaneous activity at last follow-up, suggesting that IVIg fosters both remyelination and reinnervation in CIDP patients. Although there was significant improvement in neurophysiological parameters, all patients remained IVIg dependent and new conduction blocks developed.

There have been no systematic studies addressing the issue of long-term effectiveness of IVIg on neurophysiological parameters in CIDP, therefore precluding establishment of treatment based guidelines (Hughes et al., 2006). One study reported an increase in summated proximal CMAP amplitudes 6 weeks after commencement of IVIg treatment, thereby suggesting that IVIg results in a reversal in CB and ultimately clinical improvement (Hahn et al., 1996). However, long-term effectiveness of IVIg maintenance on other neurophysiological parameters was not reported on and most patients received concomitant adjuvant therapy, in the form of prednisone, azathioprine, and/or cyclosporine. In the present study, there was a significant improvement in CB at 1-year. The reversal in CB may in part be explained by IVIg-mediated remyelination through immunomodulatory effects at the humoral and cellular levels (van Doorn et al., 1990a,b; Frank et al., 1992; Saoudi et al., 1993;. van Engelen et al., 1994; Miyagi et al., 1997) and direct effects on the myelin sheath (Dalakas, 2002). Interestingly, new CBs developed despite maintenance therapy, suggesting that either the maintenance dose was inadequate or that CBs resolve and appear independent from IVIg treatment.

Of further clinical relevance, long-term IVIg maintenance resulted in a significant increase in the distal CMAP amplitudes, which was greater in nerves with baseline low distal CMAP amplitudes, and a reduction in the number of muscle regions exhibiting spontaneous activity. These findings could be explained by either reversal of distal CB and/or re-innervation. A potential mechanism underlying re-innervation may relate to accumulation of $Na^+$ ions at sites of CB (Kiernan et al., 2002), that would also result in reverse operations of the $Na^+/Ca^+$ exchanger with intra-axonal accumulation of calcium and ultimately axonal degeneration through activation of calcium-dependent enzyme pathways (Stys et al., 1991). Axonal remyelination may result in normalization of intra-axonal $Na^+$ concentration and activity of the $Na^+$–$Ca^{2+}$ exchanger thereby fostering reinnervation.

Although IVIg is a safe form of long-term immunomodulating treatment in CIDP, adverse effects have been reported at a frequency of 10% (Dalakas, 2002). The most frequent side effects include minor self-limiting reactions, such as headache, fever, myalgia, low back pain, and chest pain. More serious side effects such as aseptic meningitis, anaphylactic reactions in IgA deficient patients, acute tubular necrosis, and thromboembolic complications have also been reported with IVIg treatment (Asham, 1998; Dalakas and Clark, 2003; Caress et al., 2003; Okuda et al., 2003; Vucic et al., 2004). In the present study, IVIg proved to be a safe treatment.

In conclusion, the present study has demonstrated that IVIg maintenance results in reversal of conduction blocks, improvement in distal CMAP and sensory amplitudes along with reduction in spontaneous activity suggesting that long-term IVIg reduces the immune response, thereby enabling nerve healing and resulting in remyelination and reinnervation in CIDP patients. However, new CB developed suggesting that the dose of IVIg may have been inadequate in some patients. Randomized-controlled studies are required to assess the optimum IVIg required to maintain both clinical and neurophysiological remission.

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