Online Supplement 1: Full Research Report

An n-of-one RCT for intravenous immunoglobulin G for inflammation in hereditary neuropathy with liability to pressure palsy (HNPP)

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Abstract

Background

There is evidence that hereditary neuropathies may coexist with inflammatory neuropathies, which are associated with pain and increased muscle weakness. It is debated whether immunomodulation is an effective treatment in these cases. We present data from a patient with genetically confirmed hereditary neuropathy with liability to pressure palsies (HNPP) and symptoms of a painful inflammatory neuropathy, which seemed responsive to intravenous immunoglobulin (IVIg).

Objectives

To assess the effects of IVIg on pain and muscle strength, and the need for continued treatment with IVIg, using an n-of-one randomised controlled trial.

Methods

We conducted a multiple crossover n-of-one trial in which IVIg and placebo infusions were administered in random order. Pain and self-reported muscle strength were assessed using a patient diary. We used Bayesian evaluation of informative hypotheses to compare the effect of IVIg and placebo on pain and muscle strength, and to assess the course of pain and muscle strength following IVIg infusions. Conventionally, a Bayes factor (BF) larger than 10 is considered strong support for a hypothesis.

Results

Four IVIg and three placebo infusions were administered. There was strong evidence that IVIg was superior to placebo in reducing pain to a clinically meaningful extent (BF=63.74). Similarly, there was strong evidence that IVIg was superior to placebo in increasing muscle strength to a clinically meaningful extent (BF=61.51). In addition, we showed that there was a continued need for IVIg infusions every three weeks to treat pain (BF=13.78) and muscle weakness (BF=15.67). No adverse events occurred.

Conclusions

IVIg was beneficial in alleviating pain and muscle weakness in a patient with a genetically confirmed hereditary neuropathy (HNPP).

BACKGROUND

Hereditary neuropathy with liability to pressure palsy (HNPP; tomaculous neuropathy) is an autosomal dominant disorder caused by a loss of function of the gene for peripheral myelin protein 22 (*PMP22*; OMIM #601097) on chromosome 17.p12. HNPP is a rare disorder, with an estimated prevalence of two to five per 100,000.[1] Symptoms usually start in the second or third decade of life and consist of recurrent painless episodes of focal sensory loss and muscle weakness (palsy) in the distribution of a peripheral nerve. Episodes are often provoked by compression of the nerve and resolve spontaneously within days to months.[2-4] There is no curative treatment; management consists of supportive measures to prevent nerve compression, and bracing to alleviate muscle weakness.

In this report, we describe the case of a female patient with HNPP who initally presented with symptoms of a painful neuropathy which were successfully treated with intravenous immunoglobulin (IVIg), as well as the results of a subsequent placebo-controlled n-of-one randomised controlled trial (RCT) that was conducted to formally assess the effects of IVIg on pain and muscle strength and the need for continued treatment with IVIg.

Case report

In 2002, a 35-year-old female patient presented to the Leiden University Medical Centre Neurology Clinic with a 15-month history of neuropathic pain in the right gluteal region that radiated via the back of the leg to the right foot. Four months before presentation, she had experienced weakness and sensory loss in the lower left leg after a prolonged car journey, but this resolved spontaneously after several weeks. Two months later, she experienced more severe weakness and sensory loss: she was unable to lift her left leg when lying prone and also experienced numbness in her left hand. No triggering events were reported for this episode. Her medical history was unremarkable, and there were no family members with similar symptoms.

Her physical examination at the time of presentation showed mild proximal weakness of the left leg (MRC 4) and severe weakness (MRC 0-2) of the left foot extensor muscles. Hypoalgesia was found in the ulnar side of the left hand and the left lower leg. She had reduced tendon reflexes; Achilles tendon reflexes were completely absent. The following examinations were normal or negative: lumbar MRI, cerebrospinal fluid analysis, serum anti-GM1, and serology for cytomegalovirus, Epstein-Barr virus, mycoplasma, and Borrelia burgdorferi. Faecal

tests for Salmonella, Shigella and Campylobacter were also negative. A nerve biopsy was not performed.

Electromyographic studies showed bilateral demyelinating conduction blocks at compression sites of the ulnar nerves, prolonged distal motor latencies of the right and left-sided ulnar, tibial, peroneal , and left median nerves, and absent F-waves in both peroneal and the right tibial nerves, consistent with HNPP, but also with definite electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) according to the EFNS/PNS CIDP guidelines.[5] Based on these results, a preliminary diagnosis of CIDP was made and a DNA test for suspected HNPP was ordered.

She was treated with IVIg (0.4 mg/kg per day) for five days, which resulted in marked improvement: after three weeks she was able to do domestic chores again for the first time in a year. She continued to receive a maintenance dose of IVIg every three weeks, and her muscle strength continued to improve. The pain disappeared completely and she only suffered residual mild weakness of left foot dorsiflexion (MRC4). However, DNA analysis subsequently revealed a deletion of 17p11.2 including the PMP22 gene, and a definite diagnosis of HNPP was made.

Rationale for n-of-one trial

It remains debated whether genetic neuropathies can give rise to superimposed immune-mediated neuropathies,[6] and the diagnosis of HNPP raised doubts whether continued IVIg was needed, especially given its high cost and limited availability.[7] In light of this ambiguity, the patient consented to a formal assessment of the effects of IVIg in an n-of-one trial. This is a multiple crossover trial in a single patient in which intervention and control treatment periods are randomised over time (e.g. AB-BA-BA). It is suitable to evaluate the effects of relatively fast-acting, symptomatic treatment for chronic and relatively stable disease symptoms in individual patients.[8, 9]

By means of the n-of-one trial, we aimed to evaluate the effects of IVIg on pain (primary outcome) and muscle strength (secondary outcome) in this patient with HNPP and an associated CIDP-like inflammatory neuropathy. The following hypotheses were tested: a) IVIg infusions reduce pain more than placebo infusions and this reduction is clinically meaningful; b) IVIg infusions increase subjective muscle strength more than placebo infusions and this increase is clinically meaningful. To assess the need for continued use of IVIg, we also tested the following

hypotheses: c) following IVIg, pain levels first decrease and then increase again; and finally, d) following IVIg, subjective muscle strength first increases and then decreases again.

METHODS

Trial design

We conducted a double-blind, multiple crossover n-of-one trial of four trial infusions that were given in hospital on an outpatient basis and in a randomised order at three week intervals. The intervention treatment consisted of intravenous immunoglobulin (0.4 mg/kg) and was compared to an inactive placebo infusion of 0.9% saline. A placebo infusion was chosen as comparator, because there is currently no pharmacotherapy for HNPP. The patient consented to participate in this study as a way to optimise her personal long-term clinical treatment.

A week after each trial infusion, an optional "rescue" infusion with the opposite treatment was offered (i.e. placebo if IVIg had been administered most recently and vice versa). The patient could accept or refuse this rescue infusion depending on her subjective assessment of the effects of the trial infusion (see Figure 1). The rescue infusion was offered to ensure that the most beneficial treatment was not withheld for more than a week after it was due according to her pre-trial 3-weekly treatment schedule. An open run-in period had shown that a 1-week delay in administering IVIg was not associated with unacceptable muscle weakness or pain. If the patient opted to have the rescue infusion, she returned to the randomisation schedule 3 weeks later.

Simple randomisation was carried out by the dispensing hospital pharmacy, which was also responsible for blinding of treatment by delivering all infusion packs to the hospital infusion room wrapped in opaque tin foil. This ensured that the patient and clinician remained blind to the order of the trial infusions, although both were aware that the rescue infusion was always the opposite one to the trial infusion given the week before.

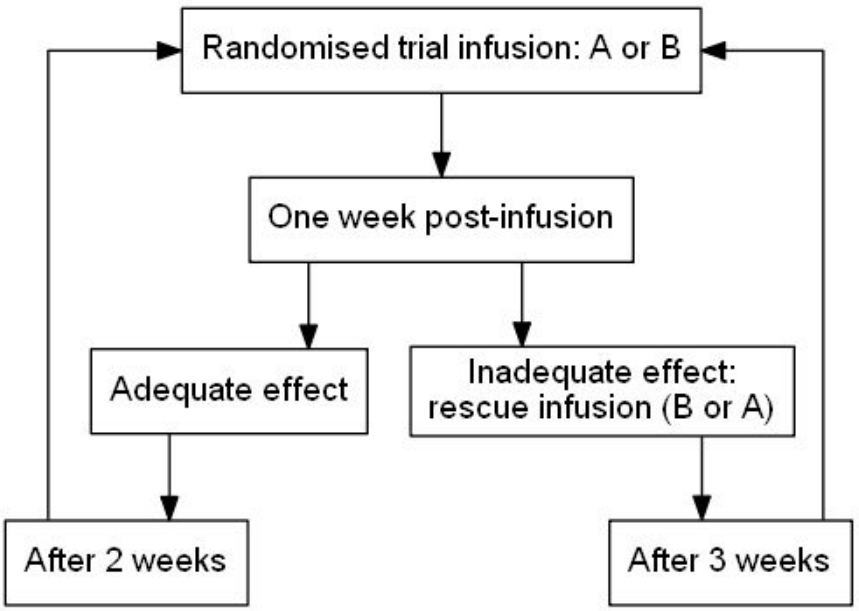

Figure 1. Flow diagram of one cycle of the n-of-one trial with optional rescue infusion one week after each trial infusion. Note that the interval between the last infusion (i.e. 'trial' if deemed adequate 1 week post-infusion, or 'rescue' if trial infusion is deemed inadequate 1 week post-infusion) and the next trial infusion is held constant at 3 weeks.

Outcomes and data collection

Pain was chosen as primary outcome measure and muscle strength as secondary outcome measure. Pain scores for the right leg, which had always been most affected by pain, were recorded by the patient three times per week in a patient diary at home. Pain was scored on a 14 cm visual analogue scale (VAS) ranging from 0 (indicating complete absence of pain) to 14 (worst possible pain imaginable). Ratings were converted into scores in millimetres, from which the percentage change from baseline was calculated. A clinically meaningful reduction in pain was defined as a 30% reduction compared to the baseline level of pain at the time of the last infusion. A reduction of this magnitude was previously found to correspond to 'some' to 'much' change in pain, and is associated with not needing rescue medication for chronic pain.[10]

Analogous to pain, subjective muscle strength was recorded three times a week on a 14 cm VAS scale (0 = complete paralysis to 14 = normal strength for this patient). This was done for the left leg, which was most affected by weakness. Ratings were converted into scores in millimetres, from which the percentage change from baseline was calculated. No reference values were available from the literature and we chose to define a clinically meaningful

difference in muscle strength as an *increase* of at least 30% compared to baseline. Finally, at the time of each infusion, the patient was asked to report any side effects since the last infusion.

Data analysis

The effect of IVIg on pain and subjective muscle strength was assessed for the first 7 days after each infusion only (not longer because rescue infusions were offered 7 days after each randomised infusion). To assess the need for continued administration of IVIg every 3 weeks, the course of pain and subjective muscle strength was evaluated over the course of three weeks following IVIg. Coefficients were first estimated using SPSS version 20.0, followed by Bayesian evaluation of informative hypotheses using BIG.[11] Bayesian hypothesis testing allowed us to evaluate the inequality constrained hypotheses we had formulated regarding the magnitude of the increase/decrease following IVIg and placebo.[11] We compared the inequality constrained hypotheses that IVIg was superior to placebo to an unconstrained hypothesis which did not specify a relationship between the magnitude of the effect following IVIg and placebo infusions. For each comparison, a Bayes factor was calculated, which is a measure of support for two competing hypotheses. A Bayes factor of 1 indicates that the data support both hypotheses equally. In the present study, a Bayes factor of more than 1 indicates that our (inequality constrained) hypotheses are more supported by the data than the unconstrained hypothesis, while a Bayes factor of less than one indicates the reverse. Conventionally, Bayes factors larger than 10 would denote strong support for the inequality constrained hypothesis.[12] A detailed description of the analyses is provided in Online Supplement 2, and the data archive is provided in Online Supplement 3.

RESULTS

The total number of infusions given during the trial was eight, but there were reasons to exclude data from one infusion for the analyses[1]. Four infusions were given according to the randomisation schedule: one IVIg and three placebo infusions. After each placebo infusion, the

1 The reason for excluding data from one infusion is that the trial partly took place over the summer and the patient requested to receive one non-randomised and non-blinded IVIg infusion before her summer holiday. The results of this infusion were not used in the analyses; data for this infusion are not shown in tables or graphs.

patient opted for a rescue infusion with the alternative treatment one week later; she did not ask for a rescue infusion after the randomised IVIg infusion. The total duration of the trial was 15 weeks. The timeline of the trial and VAS scores for pain and self-reported muscle strength are shown in Figure 2. The data archive for the results presented below can be found in Online Supplement 2: data archive.

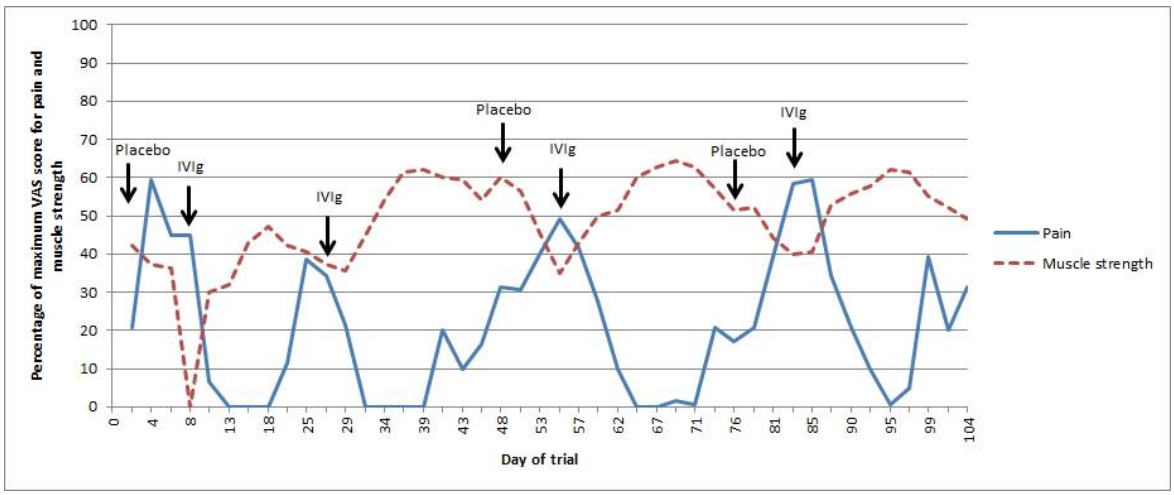

Figure 2. Trial timeline, administered infusions, and VAS scores for pain and subjective muscle strength.

Pain

We first tested the expectation that the decrease in pain in the first 7 days after IVIg is greater than after placebo. We obtained a Bayes factor of 33.22 when we compared this hypothesis to the unconstrained hypothesis, providing strong evidence that IVIg reduces pain more than placebo. We obtained a Bayes factor of 13.40 when we compared the hypothesis that IVIg produces a clinically relevant reduction in pain (≥ 30%) to the unconstrained hypothesis, which implies that there is strong support for the hypothesis that IVIg reduces pain.

When these hypotheses were combined in a single hypothesis, i.e. pain decreases more rapidly after IVIg than after placebo in the first week after infusion, and it decreases to a clinically relevant level, and evaluated against the unconstrained hypothesis, we obtained a Bayes factor of 63.74. This strongly supported the hypothesis that IVIg has a clinically meaningful effect on pain, compared to placebo. Estimates and variances of the coefficients are shown in Table 1.

Table 1. Estimates and variances of the coefficients. L1t and l2t denote the relevant levels for the decrease of pain and increase of muscle strength, respectively, in the first week after IVIg.

	Pain					Muscle strength				
		n*	estimates	variance	l_{1t}		n*	estimates	variance	l_{2t}
placebo	β_{11}	4	0.416	0.187		β_{21}	4	-0.734	0.142	
	β_{12}	4	0.253	2.79E-2		β_{22}	4	-0.319	3.17E-2	
	β_{13}	4	0.824	2.76E-2		β_{23}	4	-0.234	5.04E-3	
IVIg (1 week)	β_{14}	4	-0.907	0.106	-0.27	β_{24}	4	0.823	3.39E-2	0
	β_{15}	4	-0.412	3.61E-2	-0.126	β_{25}	4	0.508	8.41E-4	0.216
	β_{16}	4	-0.753	1.04E-2	-0.294	β_{26}	4	0.321	4.10E-3	0.210
	β_{17}	4	-0.984	4.62E-3	-0.354	β_{27}	4	0.340	5.93E-3	0.246
IVIg (3 weeks)	γ_{11}	8	0.063	1.96E-4		γ_{21}	8	-0.041	4.9E-5	
	γ_{12}	9	0.016	1.69E-4		γ_{22}	9	-0.029	9.0E-6	
	γ_{13}	10	0.044	3.60E-5		γ_{23}	10	-0.022	9.0E-6	
	γ_{14}	9	0.056	2.89E-4		γ_{24}	9	-0.024	9.0E-6	

*This denotes the number of measurements upon which the estimates are based.

Subjective muscle strength

We assessed the effects on subjective muscle strength in a similar fashion. We obtained a Bayes factor of 36.24 when we compared the hypothesis that the subjective increase in muscle strength in the first 7 days after IVIg infusion would be greater than after placebo to the unconstrained hypothesis. This implies that there is strong evidence that IVIg increases muscle strength more than placebo. We then assessed whether the increase in subjective muscle strength could be considered meaningful, as expressed by a 30% increase in subjective muscle strength compared to the baseline muscle strength score for each infusion. We obtained a Bayes factor of 15.05 for the hypothesis that IVIg produces a clinically relevant increase in muscle strength (≥ 30%) when compared to the unconstrained hypothesis. This implies that there is strong evidence that IVIg increases muscle strength.

When these hypotheses were combined, i.e. muscle strength increases more rapidly and to a clinically relevant level in the first week after IVIg than after placebo, and evaluated against the unconstrained hypothesis, we obtained a Bayes factor of 61.51. This strongly supported the

hypothesis that IVIg has a clinically meaningful effect on subjective muscle strength, compared to placebo.

Course of pain and muscle strength

Finally, to assess the need for regular IVIg infusions, we used quadratic models to test the hypotheses that pain first decreases and then increases again, and that muscle strength first increases and then decreases, in the three weeks following IVIg. The Bayes factor for the hypothesis about pain was 13.78, and the Bayes factor for the hypothesis about muscle strength was 15.67. These findings strongly support the notion that IVIg needs to be administered regularly to control pain and improve muscle strength. No adverse effects were reported during the trial.

Follow-up

We have now followed up this patient for 11 years. After the trial, she first continued to receive IVIg infusions every three to four weeks for two years, without any adverse effects. The interval was then successfully increased to five weeks. After a period of symptom stability, we attempted to give infusions every six weeks. However, this was followed by an increase in muscle weakness and pain, and the interval was reduced again to five weeks. Multiple EMGs during follow-up (2003-2014) initially showed signs of demyelination (prolonged distal motor latencies and decreased nerve conduction times), but over the years became more consistent with stable axonal damage. The patient's quality of life has remained stable: her muscle strength is stable, and she continues to work in the same job.

DISCUSSION

The results of this trial suggest that IVIg had a clinically meaningful effect on pain and weakness in this patient with HNPP. The positive effects of IVIg diminished after several weeks, necessitating continued treatment with regular IVIg infusions every few weeks for a sustained clinical response.

Our findings lend support to the growing number of case reports suggesting that some patients with hereditary neuropathies such as HNPP, Charcot-Marie-Tooth disease, and hereditary brachial plexus neuropathy may also be affected by inflammation.[4, 13-23] Like our

patient, most of these patients initially presented with clinical and electrophysiological findings suggestive of an acute or chronic inflammatory demyelinating polyneuropathy (AIDP or CIDP), but were later diagnosed with an hereditary neuropathy. Some also responded favourably to immunomodulatory treatment with steroids or intravenous immunoglobulin (IVIg).[13, 14, 18, 19, 22] Although the co-occurrence of inflammatory and hereditary neuropathies may be purely coincidental, some have suggested that the tissue damage caused by hereditary neuropathies could evoke an immune response leading to superimposed inflammatory neuropathies.[13, 14]

Regardless of whether their CIDP is idiopathic or not, a diagnosis of inflammation in patients with an hereditary neuropathy may be difficult. Clinical signs and symptoms may overlap, and evaluations such as electrophysiology or nerve biopsies are not helpful to establish a diagnosis of inflammatory demyelinating disease when demyelination is already present due to hereditary disease. Moreover, current diagnostic criteria for CIPD list hereditary demyelinating neuropathies as a diagnostic exclusion criterion [5], meaning that inflammatory neuropathies may go unrecognised and untreated in patients with an established diagnosis of an hereditary neuropathy.

However, it is important to recognise possible inflammation in patients with hereditary neuropathies, because of its therapeutic implications: where hereditary neuropathies can usually only be managed with lifestyle changes, bracing, and physical therapy, inflammation may be amenable to pharmacological treatment. The use of IVIG in CIPD, for example, is well established [24], and there is a growing body of evidence on the use of IVIg in chronic pain syndromes.[25] Hereditary neuropathies are usually painless, so the presence of pain, like in our patient, may indicate inflammation. Inflammation should also be considered in patients who show signs of a long-term, progressive neuropathy rather than the regular episodic weakness seen in HNPP. An n-of-one trial to test the effect of treatment for this potentially coexisting inflammatory neuropathy, such as the one described for our patient, could be considered in these patients.

Clinical n-of-one trials, such as the one presented here, are a tool that can be used to guide appropriate treatment in rare diseases.[9] N-of-one trials have been used in the past to optimise treatment for individual patients, reduce unnecessary prescribing, and increase treatment compliance.[26, 27] Formal "trials of therapy", such as the one described in this study, can be valuable in guiding clinical practice when there is no evidence available from group-randomised clinical trials (RCTs), when the results of such trials do not necessarily

generalise to one's patient in the consultation room, or when there are other pertinent reasons to optimise treatment, for example, because of the high cost of a medicinal product.[9] IVIg to treat inflammation associated with HNPP fulfils these criteria: there are no clinical treatment guidelines, there is no evidence from earlier trials available, and IVIg is costly to produce and its availability is limited. Moreover, many diseases for which IVIg is prescribed require long-term treatment [28, 29], including when it is used to treat CIDP. The majority of patients require infusions every two to six weeks for a sustained response [7], and a review suggests that it can be withdrawn in less than 15% without causing a relapse.[30] In our patient, increasing the interval between infusions from five to six weeks led to an unacceptable clinical deterioration. N-of-one trials such as the current one may help to establish whether a particular patient has a true need for this type of treatment, and may thus aid appropriate prescription.

To our knowledge, this is the first randomised controlled trial (RCT) of IVIg to treat symptoms of inflammation in patients with HNPP; thus far, only anecdotal evidence suggested that IVIg may be effective in such patients.[4, 13, 14] The lack of RCTs may partly be due to the challenges associated with conducting RCTs in such small patient populations.[31] The n-of-one trial design could greatly facilitate the process of conducting RCTs in this type of patient population, since data from several n-of-one trials can be aggregated to obtain population effect estimates.[32, 33] Furthermore, Bayesian analysis methods, which can make use of prior knowledge, allow for continued updating of treatment effect estimates as new data become available.[33] Thus, results from future trials in similar patients can be meaningfully combined with the results from the current trial to obtain an increasingly robust estimate of the population effect of IVIg to treat inflammation in patients with HNPP. Such personalised and adaptive approaches may also be useful in other situations where only very few patients are available for research.[31]

Because this study was done in only one patient, its results may not necessarily generalise to other patients. Other limitations of the design include the need for multiple crossovers between the active and control intervention, which means that the participant burden in n-of-one trials is generally higher than in most other intervention research. Efforts should be made to reduce this burden and to prevent dropout during the trial. We chose to use a patient diary with two separate VAS scales to measure our outcomes and minimise the number of hospital visits for the patient. Although the VAS scale for pain has been extensively validated,[10] this was not the case with the VAS for subjective muscle strength. Furthermore,

subjective scores of pain and strength may co-vary. For example, when a limb is painful, it may also be self-reported as being weak, even if bedside strength assessment is normal. Future studies could benefit from using only validated outcome measures and from including more objective outcome measures alongside subjective ones, if this is possible without increasing the participant burden to an unacceptable level. Because of the frequent crossovers between IVIg and placebo, we were unable to assess whether the effect of IVIg is cumulative over several doses. Unblinding of the patient may also be a problem in multiple crossover trials, and may occur more easily when there are clear treatment or adverse effects. Our patient experienced such a clear effect of treatment (but no adverse effects). Although she was blinded to the infusion type at the time of each trial infusion, the clear treatment effect of IVIg meant that she was able to guess the nature of the infusion after several hours to days. This may have introduced some bias in the outcome measures, although Figure 1 still displays considerable variation and trend changes in both outcomes over time and regardless of the type of trial infusion. In future studies, bias may be reduced by using objective outcome measures and blinding of the outcome assessor. Finally, readers may not be familiar with Bayesian testing of informative hypotheses, a method which is more common in psychological research than clinical medicine. Therefore, it is noted that conventional statistical analysis of this n-of-1 RCT could not have accommodated consideration of multiple, clinically relevant hypotheses. Furthermore, conventional analyses would have suffered from low power. Despite the limitations of the trial, the results were useful to guide treatment of this patient.

In conclusion, we presented a trial of a patient with HNPP and concomitant symptoms of pain and muscle weakness which improved after continued treatment with IVIg. This suggests that some patients with hereditary neuropathies may have co-existing inflammation, which is important to recognise because adequate treatment can improve their symptoms and quality of life. We also demonstrated the value of n-of-one trials for conducting research in rare conditions.

AUTHORS' CONTRIBUTIONS

JJGMV, JW and MDF conceived the study and carried out the data collection. JJGMV, CV, SSW, HH, and XG formulated the informative hypotheses, which were evaluated by HH and XG.

JJGMV and CV drafted the manuscript, with assistance from MHS. All authors commented on the manuscript and consented to submission of the final draft.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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FUNDING

No funding was obtained to conduct this trial.

SUPPLEMENTARY MATERIAL

1. Online Supplement 2: Description of analyses
2. Online Supplement 3: Data archive

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