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Can Growth Hormone Lead to a Faster Recovery from Guillain-Barré Syndrome? Case Report of the First Therapeutic Use in One Patient

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Keywords
Growth hormone · Insulin-like growth factor 1 · Guillain-Barré syndrome · Therapy · Strength gain

Abstract
Although the prognosis in Guillain-Barré syndrome (GBS) is generally good, protracted and incomplete courses of recovery can be a heavy burden. Animal studies suggest growth hormone (GH) treatment could stimulate myelin repair and thus accelerate functional recovery in acute polyneuropathy. We report on the first use of GH in GBS. Our objective was to monitor safety and tolerability as well as to evaluate the effect of an off-label GH therapy during recovery from GBS in 1 patient. A 28-year-old male with flaccid tetraparesis caused by pure motor GBS was treated off-label with GH (1 mg/day) for 10 weeks. Muscle strength was measured regularly before, during, and after the treatment over a total span of 330 days. Serum levels of IGF-I were assessed before, during, and after GH treatment. Changes in strength gain were used as the main parameter of efficacy. No side effects of GH treatment were observed. Serum IGF-I increased from 177 ng/mL at baseline to an average of 342 ng/mL (normal range 78–270 ng/mL) during treatment. Prior to GH administration, strength (R^2 = 0.99, p < 0.01) was associated with time, representing the natural course of recovery. During GH treatment, the slope of strength gain increased (Glass' Δ = 1.08, p < 0.01). The association between alterations of strength gain and IGF-I serum levels reached

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trend level (R^2 = 0.36, p = 0.09). In this single case, GH treatment seemed to be associated with faster muscular strength gain. Controlled studies are needed in order to establish GH as a potential therapeutic approach in motor GBS.

Introduction

Guillain-Barré syndrome (GBS) is an acute polyneuropathy, usually caused by postinfectious autoimmune inflammation. It can lead to severe autonomic, sensory, or motor disorders including complete flaccid paralysis. The long-term prognosis for patients surviving the acute phase is generally rather good; however, about 20% remain unable to walk 6 months [1] after onset of the disease. Even years later, patients report a severe negative impact on social life and daily activities [1] and the economic costs of disability due to GBS are considerable [2]. Hence, more effective treatments of GBS and post-GBS recovery remain desirable.

The current standard treatment of GBS consists of intravenous immunoglobulin application or plasmapheresis. Both treatment options are effective in improving neurological outcomes through immune modulation when administered at an early stage of disease [3]. However, no pharmacological treatment enhancing regeneration is available yet.

In the most common GBS subtype, the acute inflammatory demyelinating polyneuropathy, demyelination of peripheral nerves is the leading pathophysiological mechanism. Therefore, myelin repair in affected nerves is crucial for recovery [4]. Among multiple other factors, growth hormone (GH) and insulin-like growth factor 1 (IGF-I) both play an important role in neural stem cell proliferation, differentiation, and survival as well as nerve regeneration and myelination [5]. Several small studies have examined the effect of GH therapy in central nervous system disorders (e.g., traumatic brain injury, amyotrophic lateral sclerosis, and Alzheimer's disease). Interestingly, no clinical studies with GH have yet been conducted in peripheral neuropathy although animal studies have shown promising results. For instance, GH was shown to enhance the recovery nerves in rats [6]. It does so by stimulating axonal regeneration, muscle reinnervation, and the survival of Schwann cells after peripheral nerve injuries [7]. Likewise, IGF-I promotes myelination and proliferation in Schwann cells [8] which is essential for functional recovery of nerves. Local administration of IGF-I was shown to accelerate nerve regeneration in rats [6] and rabbits [9]. In summary, various studies conducted in animals suggest that GH administration could contribute to better recovery in peripheral neuropathy [6]. However, no case reports or clinical studies in humans have been published so far.

The willingness to conduct such trials diminished since one study [10] observed a higher mortality in ICU patients treated with GH in 1999. However, extremely high doses (up to the 20-fold of physiological doses) were used. When dosed correctly and monitored carefully, pharmacological GH treatment for approved indications is generally considered as safe [11]. Therefore, the Growth Hormone Research Society explicitly encourages new studies of GH in conditions which may potentially benefit from GH treatment [11]. Here, we report on the first therapeutic use of GH in 1 GBS patient.

Case Report

Patient

The patient was a 28-year-old male who was diagnosed with GBS 1 week after an infection with *Campylobacter jejuni*. He had presented with lower extremity weakness. Physical examination revealed flaccid tetraparesis with decreased or absent muscle reflexes.

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There were no sensory deficits. Cerebrospinal fluid analysis was unremarkable, serum anti-GM2 IgM antibodies were highly positive, and anti-GM1 IgM antibodies were borderline positive. Nerve conduction studies were consistent with acute inflammatory demyelinating polyneuropathy (cf. appendix). Treatment with intravenous immunoglobulins (140 g over 5 days) was started when inability to walk occurred on day 2 after onset of symptoms. Clinical nadir was reached on day 3, and the patient regained independent walking within 1 week.

Intervention

The patient received recombinant human GH (Nutropin®) 1 mg/day via subcutaneous injection for 10 weeks during recovery from GBS.

Safety Considerations

Treatment with GH was conducted as an off-label use following the patient's request. It was considered appropriate in this individual case and its clinical circumstances. Notably, the treatment was not administered in the context of a clinical trial. The patient was appropriately informed about the lack of evidence and potential risks of the treatment. Detailed treatment and surveillance protocols were established and agreed upon. A completed CARE checklist can be found as an online supplementary file (for all online suppl. material, see https://doi.org/10.1159/000530065).

Safety Parameters

Safety visits were scheduled regularly during the treatment period. Physical examination and fasting blood glucose tests were performed. Serum IGF-I concentration was measured using the IDS iSYS IGF-I assay to monitor compliance and prevent severe overdosing. Furthermore, the patient was advised to measure his blood pressure daily and report the values along with potential side effects.

Outcome Parameters

Isometric strength of hand grip, elbow extension (at 90°), elbow flexion (at 90°), knee extension (at 90°), knee flexion (at 90°), as well as body mass were regularly assessed. Strength was assessed using a Deyard EH 101 dynamometer (Deyard Corp., France), and in case of elbow and knee joint strength testing, cables were used to transduce produced forces.

Time Course

The treatment and surveillance protocols were divided into three sections: an observation phase to monitor the natural course of recovery, the treatment period, and further observation upon completion of treatment. The observation phase started 1 week after the onset of GBS (day 0) and was followed by the GH treatment period from days 158 to 224 (week 22–32). Overall, a total time span of 330 days (47 weeks) was covered.

Throughout the entire time (excluding two inpatient stays at a neurorehabilitation facility), the patient received three sessions of outpatient physiotherapy per week with a home exercise program focused on muscular strength gain. This training program was interrupted during two periods of 3 weeks each: (a) before GH treatment due to medical problems independent of GBS and (b) after GH treatment due to a mildly symptomatic SARS-CoV-2 infection.

Objective

The objective was to monitor safety and tolerability as well as to evaluate the effect of an off-label GH therapy during recovery from GBS in 1 patient.

Statistical Approach

A 2nd degree polynomial regression (named $REG_{pre\text{-}GH}$) was calculated for all strength measurements prior to treatment to get an approximation of the natural course of strength gain (shown in Fig. 1 as a dotted line) and a second one for strength measurements during GH treatment (named REG_{GH}, shown in Fig. 1 as a continuous line). The slopes of the two regression lines were compared to examine the effect of GH on strength gain.

Using $REG_{pre\text{-}GH}$, alterations in strength gain were examined by calculating its first derivate (named RESIDUAL). Statistical significance of the alterations due to rehabilitation and GH treatment was tested by *t* tests. For this purpose, single-day measurement points were interpolated using a moving average of 21 days (−10 to +10 days).

In order to estimate the time to effect of the GH therapy, a Pearson cross-correlation was computed between RESIDUAL and IGF-I in dependence of time lags from 0 to +27 days. For this purpose, both rehabilitation phases were excluded by setting RESIDUAL to 0 during the pretreatment period (shown in Fig. 2 as a gray line). α was set to 0.05. Effect sizes are given in R^2 and Glass' Δ.

Two intercepts were corrected to compensate for the setbacks in strength due to the abovementioned training interruptions: (a) training interruption due to medical problems right before the beginning of GH therapy and (b) COVID-19 (shown in Fig. 1). Therefore, all points past the onset of GH therapy were shifted by $REG_{pre\text{-}GH\ at\ day\ 158} - Day_{158}$, and all points past the onset of COVID-19 were shifted by $REG_{pre\text{-}GH\ at\ day\ 270} - Day_{270}$ (shown in Fig. 1 as gray circles). This correction did not influence the comparison between strength gains before and during GH therapy.

Results

Throughout the treatment period, blood glucose as well as blood pressure remained in the normal range. No side effects were observed. Pre- and post-treatment IGF-I levels were 177 and 183 ng/mL, respectively, which equals the 50th percentile of the age- and sex-adjusted reference interval (normal range 78–270 ng/mL) (21). Under GH treatment, mean IGF-I level was 342 ng/mL (range 271–416 ng/mL) which is above the 97.5th percentile.

Body mass initially decreased by 12 kg after onset of GBS and subsequently increased by 10 kg during observed recovery. Counting from the time of lowest body mass, mean weight gain was 61 g/days during the pretreatment period and 30 g/days under GH treatment.

When excluding all measurement points during GH treatment, the patient showed a significant association of body mass and time ($R^2 = 0.85$, $p < 0.01$, $n = 10$) and between relative strength and time ($R^2 = 0.99$, $p < 0.01$, $n = 12$, shown in Fig. 1). During GH treatment, linear regression revealed an increased slope of strength gain (REG_{GH}) of 3.66%/days ($R^2 = 0.95$, $p = 0.025$); for this time interval, the expected linear slope of $REG_{pre\text{-}GH}$ would have been 1.91%/day.

The alterations of relative strength gain (RESIDUAL) are displayed in Figure 2. There were three significant alterations of RESIDUAL: both inpatient stays at a neurorehabilitation facility and the GH application (Glass' $\Delta_{Rehab1} = -1.50$, $p < 0.01$, Glass' $\Delta_{Rehab2} = 0.57$, $p < 0.04$, Glass' $\Delta_{GH} = 1.08$, $p < 0.01$). Cross-correlation between RESIDUAL and IGF-I revealed the highest correlation coefficient for a time lag of zero days (shown in Fig. 3b), but the association only reached trend level with an R^2 of 0.36 ($p = 0.09$, shown in Fig. 3a).

Discussion

We report the first off-label use of GH in 1 patient with pure motor GBS. The data presented here were collected under real-life circumstances for the purpose of treatment monitoring and not within the framework of a clinical study. They were influenced by

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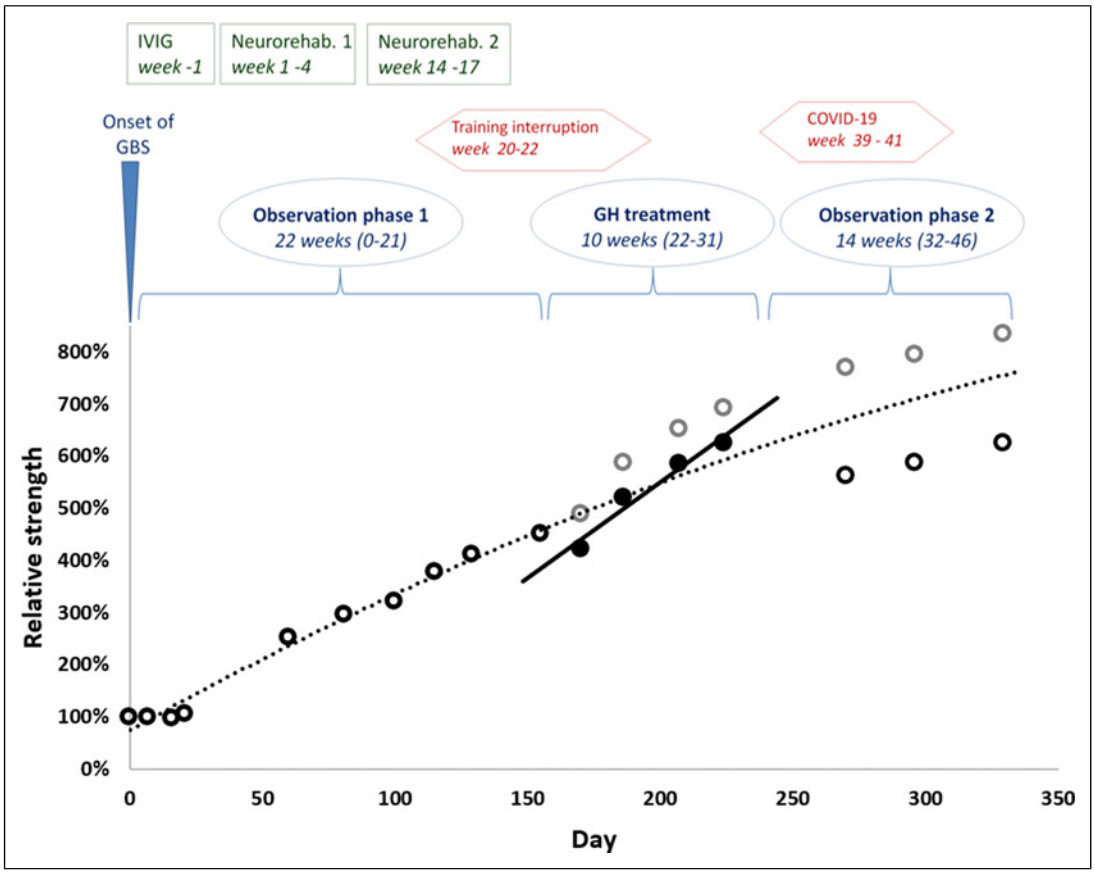

Fig. 1. Time course of relative strength during the observation period of 330 days. Each circle illustrates a strength measurement, and filled circles are measurements during the GH treatment period. The dotted 2nd degree polynomial regression line ($REG_{pre\text{-}GH}$) is based on the first 10 pre-GH treatment measurement points. The continuous regression line during GH treatment (REG_{GH}) revealed an increased slope. Gray circles are offset-corrected relative strength values after both training interruptions (in red rhombi).

confounding factors such as a training interruption and a SARS-CoV-2 infection (both resulting in a negative intercept; shown in Fig. 1) and do not allow for any conclusions regarding the efficacy and safety of GH therapy in GBS. However, we were still able to observe some interesting and statistically significant phenomena that indicate a beneficial effect of GH.

We used gain in muscle strength to assess the effect of GH therapy. Muscle strength was confirmed as a valid parameter to monitor disease progression and recovery in GBS in several studies [12]. Regarding the dosage of GH, we considered that it needed to be in the supraphysiological range; otherwise, it would potentially just replace the endogenous GH secretion and no effect could be expected. On the other hand, very high doses are more likely to cause side effects (hyperglycemia, hypertension, fluid retention) and might thus be detrimental. Furthermore, GH's dose-dependent effects are influenced by age, sex, and concomitant oral contraceptive therapy [13]. We opted for starting with 1 mg/day as it was the protocol in a study examining GH therapy in traumatic brain injury [14]. This dose led to an approximate doubling of IGF-I levels which was considered safe for the time interval of 10 weeks.

During the pretreatment phase, gain in body mass and muscle strength were significantly associated with time (shown in Fig. 1) which represents the anticipated natural course of recovery. In comparison, the slope of strength gain was increased during GH treatment. Both

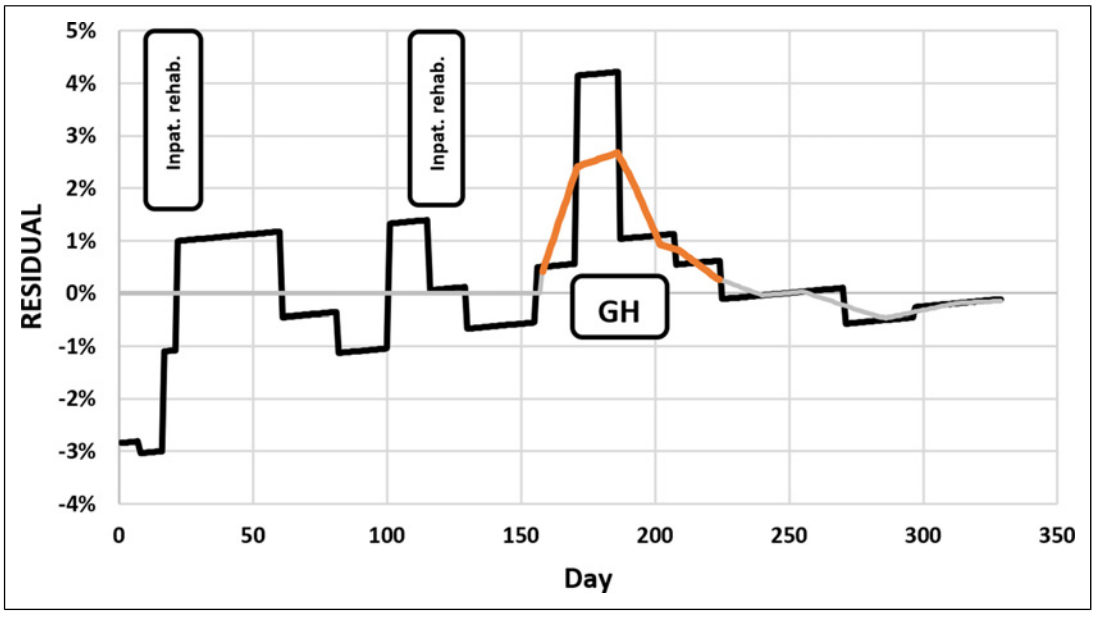

Fig. 2. Alterations of relative strength gains (RESIDUAL). First and second inpatient neurorehabilitation stays and GH treatment are indicated by boxes. The gray-orange line is a moving average of ±10 days, and pre-GH treatment values were set to zero for cross-correlational analyses.

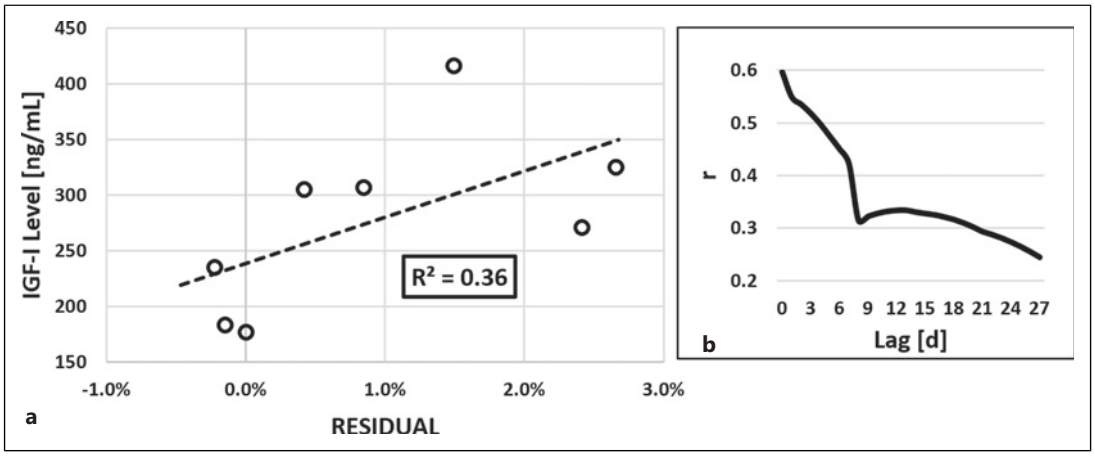

Fig. 3. a Regression of RESIDUAL (dashed line) and IGF-I serum level. The association only reached trend level (R^2 = 0.36, p = 0.09). **b** Course of correlation coefficient between IGF-I levels and RESIDUAL in dependence of time lag. The highest correlation is found with a time lag of 0 days, suggesting a rapid effect of GH treatment.

inpatient neurorehabilitation stays and GH treatment led to significant alterations in relative strength gain. The first, very early, inpatient rehabilitation seems to have had a negative effect (Glass' Δ = −1.50) for unclear reasons. Possibly, the inflammatory process of GBS was still active and counteracted the anticipated effects of physiotherapy or the initial loss of muscle mass was delayed to some extent. The second inpatient rehabilitation, in contrast, had a moderate positive effect (Glass' Δ_{rehab} = 0.57). The greatest positive alteration, however, was observed under GH treatment (Glass' Δ_{GH} = 1.08, p < 0.01).

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Notably, strength gain declines during the natural course of GBS recovery [13]. We are therefore confident that the faster gain observed under GH therapy compared to the prior observation period actually represents faster recovery due to GH. Although GH is well known for its anabolic effect on muscle mass, gain in body mass did not increase under GH therapy. This is in accordance with literature on healthy subjects [15]. Hence, myelin regeneration and not muscle growth might have played the major role in the observed effect on recovery. Studies using electrophysiologic assessments could provide further clarification.

The level of evidence is still low, and our findings cannot be generalized. For instance, the impact of GBS subtype, biological sex, and age remain unclear. Certainly, the approach should be understood as a complementary measure helping patients recover as natural recovery with supplementary physiotherapy proved to be very effective in our case as well.

Conclusion

We reported on the first GH therapy in 1 GBS patient. GH therapy seemed to be associated with a faster gain in muscle strength and hence a faster recovery from GBS symptoms. No side effects were observed. Given the safety of short-term GH treatment, our findings emphasize the need for clinical trials examining this promising therapeutic approach. Such trials should include electrophysiological measures and examine the impacts of GBS subtype, biological sex, and age on the effect of GH administration.

Acknowledgment

Recombinant human growth hormone (Nutropin®) was provided to the patient by Ipsen Pharma GmbH on the patient's individual request ("compassionate use").

Statement of Ethics

Treatment with GH was conducted as an off-label therapy following the patient's request. All the data displayed in this manuscript were initially gathered to ensure the patient's safety and to monitor the potential positive or negative effect on his recovery. Ethical approval was not required for this study in accordance with national guidelines, as this was not a prospective trial. Written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images. The treatment and monitoring were conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

F.A. received travel grants from Ipsen Pharma GmbH and Ascendis Pharma. M.B. has received lecture fees and/or consultancy honoraria from Consilient Health, Crinetics, Diasorin, GeneScience, IDS, IPSEN, Novartis, Novo Nordisk, Pfizer, Recordati, and Sandoz. S.S. has received consulting fees from Crinetics and Recordati Rare Diseases (RRD) as well as honoraria for lectures and conference chairing by RRD. Besides these recent subsidies, S.S. declares having received honoraria, personal fees, and grants from Novartis, Ipsen, Hexal/Sandoz, and Pfizer and having served as advisory board member for Novartis in the further

past. K.S. has received lecture fees and/or consultancy honoraria from Consilient Health, Pfizer, Recordati, Ipsen, and Sandoz. P.R. received lecture fees from Biogen, Janssen, Merck, Roche, EMD Serono, and Sanofi. P.G. received a travel grant from Biogen. J.S. reports grants and personal fees from Novartis, Ipsen, Pfizer, and Recordati, as well as grants from Crinetics, OPKO, Chiasma, and Camurus. M.F. has no conflicts of interest to declare.

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Author Contributions

F.A., P.G., S.S., and J.S. set up the treatment and monitoring protocol. K.S. and M.B. performed measurement of IGF-I and other laboratory measurements and provided consultation on the treatment including dosage and surveillance measures. P.R. provided neurological consultation. M.F. performed strength measurements und provided physiotherapeutic consultation. P.G. performed the statistical analyses. F.A., S.S., and P.G. wrote the manuscript. All authors contributed to and reviewed the final form of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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