Molecular Autism

LETTER TO THE EDITOR

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A proof-of-concept study of growth hormone in children with Phelan–McDermid syndrome

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Abstract

Background: Phelan–McDermid syndrome (PMS) is caused by 22q13 deletions including *SHANK3* or pathogenic sequence variants in *SHANK3* and is among the more common rare genetic findings in autism spectrum disorder (ASD). *SHANK3* is critical for synaptic function, and preclinical and clinical studies suggest that insulin-like growth factor-1 (IGF-1) can reverse a range of deficits in PMS. IGF-1 release is stimulated by growth hormone secretion from the anterior pituitary gland, and this study sought to assess the feasibility of increasing IGF-1 levels through recombinant human growth hormone (rhGH) treatment, in addition to establishing safety and exploring efficacy of rhGH in children with PMS.

Methods: rhGH was administered once daily for 12 weeks to six children with PMS using an open-label design. IGF-1 levels, safety, and efficacy assessments were measured every 4 weeks throughout the study.

Results: rhGH administration increased levels of IGF-1 by at least 2 standard deviations and was well tolerated without serious adverse events. rhGH treatment was also associated with clinical improvement in social withdrawal, hyperactivity, and sensory symptoms.

Limitations: Results should be interpreted with caution given the small sample size and lack of a placebo control.

Conclusions: Overall, findings are promising and indicate the need for larger studies with rhGH in PMS.

Trial registration NCT04003207. Registered July 1, 2019, https://clinicaltrials.gov/ct2/show/NCT04003207.

Keywords: Phelan–McDermid syndrome, PMS, Shank3, Autism spectrum disorder, ASD, Growth hormone, Insulin-like growth factor-1, IGF-1

Introduction

Phelan–McDermid syndrome (PMS) is caused by deletions in the long arm of chromosome 22 which include the *SHANK3* gene (MIM: 606230), or by pathogenic sequence variants in *SHANK3* [1–4]. PMS is associated with developmental delays, intellectual disability, and autism spectrum disorder (ASD), in addition to renal, cardiac, and gastrointestinal abnormalities, hypotonia, and dysmorphic features [5]. *SHANK3* has been established as the critical gene in PMS [1–4, 6] and appears to account for ~0.5% of ASD [7]. *SHANK3* encodes for a master scaffolding protein in the post-synaptic density of excitatory synapses and is responsible for the formation and maintenance of synapses [8]. As such, *SHANK3* and associated pathways represent important targets for intervention.

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Evidence from both preclinical and clinical studies suggests that insulin-like growth factor-1 (IGF-1) can reverse deficits in synaptic plasticity and motor learning in mouse and human neuronal models of PMS [9, 10]. A clinical trial with IGF-1 in children with PMS also showed improvement in social withdrawal and restricted behaviors, both core features of ASD [11]. Additional evidence of the utility of IGF-1 comes from animal, human, and human neuronal studies of Rett syndrome, another rare genetic disorder associated with ASD, where IGF-1 was effective in reversing phenotypic features [12–16].

IGF-1 is released mainly by the liver upon growth hormone stimulation and enters the brain from the circulation to promote brain vessel growth [17], neurogenesis, and synaptogenesis [18]. Once IGF-1 binds to the IGF-1 receptor, activation of the PI3K/mTOR/AKT1 and MAPK/ERK pathways induces its downstream effects [19]. Treatment with IGF-1 is generally administered twice daily via subcutaneous injection and requires careful monitoring due to numerous risks, including hypoglycemia. Further, IGF-1 is challenging to manufacture and while commercially approved for short stature due to primary IGF-1 deficiency, it is costly and not readily available. However, IGF-1 levels can be increased intrinsically by growth hormone [20] without the risk of hypoglycemia. Recombinant human growth hormone (rhGH) has an excellent safety profile and approved indications in pediatric and adult populations. One recent case report also supports the use of rhGH in PMS [21]. For these reasons, rhGH was chosen for this trial with the primary aims of demonstrating the feasibility of increasing IGF-1 levels in the blood and establishing safety in PMS. Furthermore, we sought to explore signals of efficacy using a battery of clinical outcome assessments, including the Aberrant Behavior Checklist—Social Withdrawal subscale (ABC-SW) [22] as the primary clinical outcome. The ABC-SW subscale was chosen based on results from the previous clinical trial with IGF-1 in PMS [11].

Methods

This study was approved by the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai, and all caregivers provided written informed consent.

Inclusion/exclusion criteria

Participants were required to have a confirmed genetic diagnosis of PMS and be between 2 and 12 years of age. Participants were excluded if they had closed epiphyses, active or suspected neoplasia, intracranial hypertension, hepatic insufficiency, renal insufficiency, cardiomegaly/valvulopathy, or allergy to growth hormone or any component of the formulation.

Drug administration

rhGH was administered in its commercially available form as somatropin (Zomacton). Caregivers were trained by a pediatric endocrinologist (Sethuram, S) to administer rhGH subcutaneously, through demonstration and written material. rhGH was given once daily for 12 weeks using an open-label design. Doses were based on standard clinical practice for children who are not growth hormone deficient with a target dose of 0.3 mg/kg/week. All participants were initiated on half the target dose (0.14–0.16 mg/kg/week) for two weeks as a safety precaution and then increased to a full dose for the remaining 10 weeks. IGF-1 levels were measured every 4 weeks, and IGF-1 Z scores were used to guide titration of rhGH dose using two standard deviations (SD) above the population mean as the target.

Safety measures and laboratories

Medical and psychiatric history was collected prior to the onset of the trial. Safety laboratories, physical examinations, and IGF-1 values were collected at the baseline visit and at each follow-up visit: weeks 4, 8, and 12. Adverse events were collected at every visit using the Systematic Longitudinal Adverse Events Scale (SLAES).

Clinical measures

The primary clinical outcome was the ABC-SW subscale (ABC-SW) [22]. Additional clinical outcome assessments were used to capture a range of ASD-related symptoms, including the Repetitive Behavior

Table 2 Adverse events

Adverse event	Number of participants
Increase in appetite	3
Gastroenteritis	3
Polyuria/nocturia	3
Crying spells	3
Runny nose/cough/sneezing	3
Decrease in appetite	1
Fever	3
Worsening repetitive behavior	2
Eye/ear infection	2
Diarrhea	1
Worsening hyperactivity	2
Sleep disturbance	1
Disruptive behavior	1
Bruising at injection site	1
Sweating of hands/feet	1
Limping/gait changes	1

Table 1 rhGH dose in mg/kg/week and IGF-1 *Z* scores

Participant		Baseline	Week 2	Week 4	Week 8	Week 12
1	IGF-1 *Z* score	0.8	–	2.6	4.8	2.2
	rhGH dose	0.15	0.3	0.28	0.24[a]	–
2	IGF-1 *Z* score	1.0	–	6.0	5.0	3.9
	rhGH dose	0.15	0.28	0.24[a]	0.16[a]	–
3	IGF-1 *Z* score	1.1	–	2.8	4.7	1.7
	rhGH dose	0.14	0.3	0.29	0.24[a]	–
4	IGF-1 *Z* score	0.9	–	4.5	1.8	2.9
	rhGH dose	0.16	0.29	0.21[a]	0.19[b]	–
5	IGF-1 *Z* score	2.3	–	4.9	4.2	1.3
	rhGH dose	0.14	0.27	0.22[a]	0.13[a]	–
6	IGF-1 *Z* score	− 1.2	–	1.1	1.3	0.9
	rhGH dose	0.15	0.31	0.33	0.32	–

[a] Dose reduced due to high IGF-1 levels

[b] Dose reduced due to crying spells

Scales—Revised (RBS-R) [23], the Sensory Profile (SP) [24], other ABC subscales (Table 2), and the Clinical Global Impression—Improvement scale (CGI-I) [25].

Statistical analyses

Nonparametric Wilcoxon signed-rank tests were used to evaluate differences in clinical outcomes between baseline and week 12. All tests of statistical hypotheses were done on the two-sided 5% level of significance. We

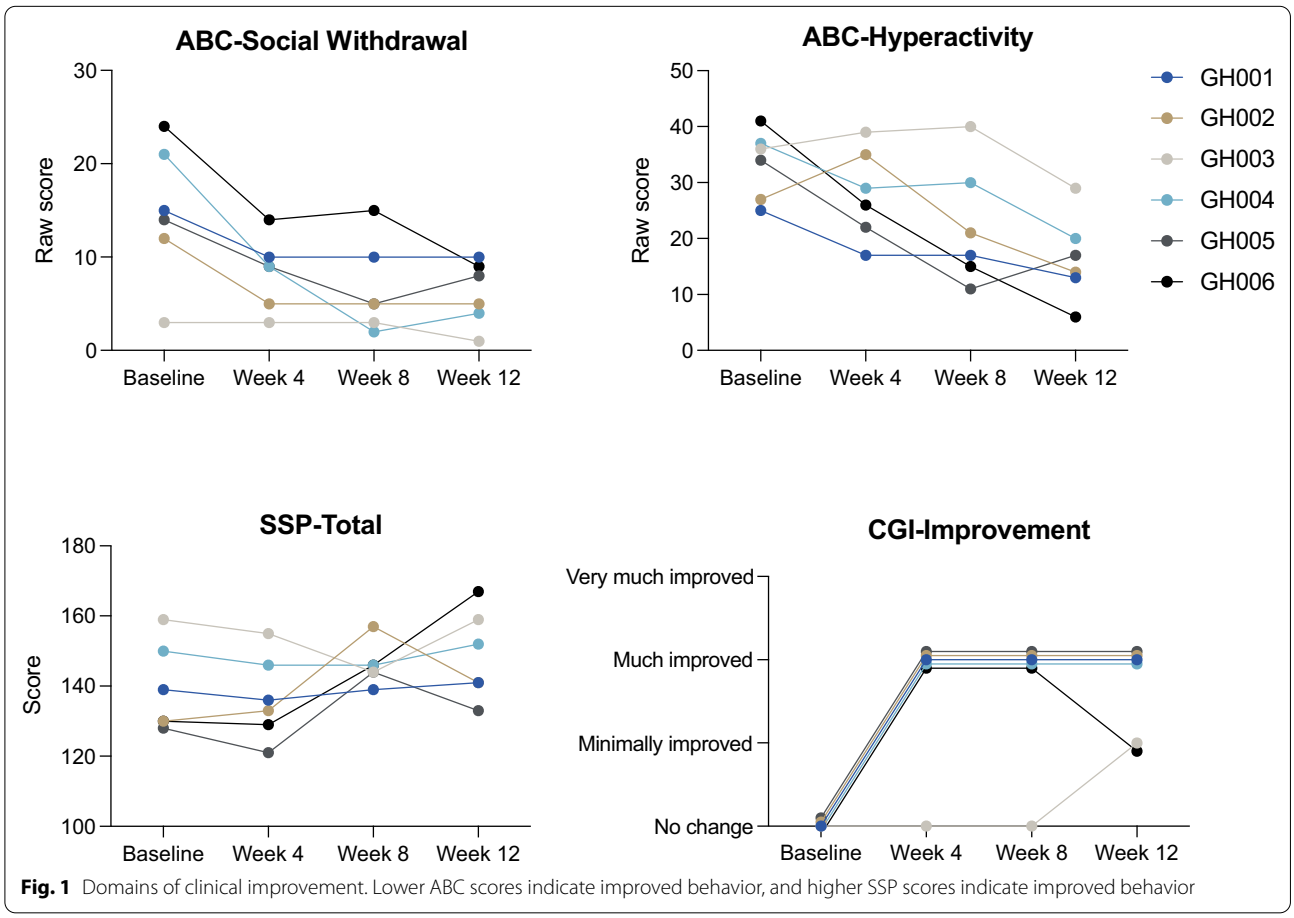

Fig. 1 Domains of clinical improvement. Lower ABC scores indicate improved behavior, and higher SSP scores indicate improved behavior

Table 3 Summary statistics for clinical outcomes

Measure[a]	Variable	Baseline Mean (SD)	Week 12 Mean (SD)	*p* value	Wilcoxon *r* effect
ABC	Irritability	10.31 (7.6)	4.6 (2.3)	0.225	0.50
	Social withdrawal	14.8 (7.4)	6.2 (3.4)	0.028	0.90
	Stereotypy	8.8 (6.9)	5.1 (1.8)	0.249	0.47
	Hyperactivity	33.3 (6.2)	16.5 (7.7)	0.027	0.90
	Inappropriate speech	3.3 (4.3)	2.3 (3.8)	0.285	0.44
RBS-R	Stereotyped behavior	4.3 (1.7)	4.0 (2.4)	0.577	0.23
	Self-injurious behavior	0.7 (0.8)	1.3 (1.8)	0.157	0.58
	Compulsive behavior	2.8 (3.2)	1.3 (1.6)	0.083	0.71
	Ritualistic behavior	1.2 (1.2)	0.8 (1.2)	0.414	0.33
	Sameness behavior	2.3 (2.4)	2.0 (1.7)	0.680	0.17
	Restricted behavior	2.0 (2.2)	1.2 (1.5)	0.129	0.62
	Total	13.3 (6.1)	10.7 (3.1)	0.248	0.47
SSP	Tactile	31.5 (2.1)	31.7 (2.0)	1.00	0.00
	Taste/smell	18.2 (3.6)	19.4 (1.3)	0.317	0.41
	Movement	13.3 (1.6)	13.7 (1.8)	0.157	0.58
	Sensation	17.5 (4.8)	20.0 (2.4)	0.416	0.33
	Auditory	20.0 (1.9)	22.0 (2.4)	0.144	0.60
	Low energy/weak	16.5 (6.9)	20.5 (5.2)	0.141	0.60
	Visual/auditory	22.3 (2.3)	22.7 (1.5)	0.414	0.33
	Total	139.3	148.8	0.042	0.83
CGI	Improvement score	–	1.7 (0.5)	0.023	0.93

ABC Aberrant Behavior Checklist, *CGI* Clinical Global Impressions scale, *RBS-R* Repetitive Behavior Scales—Revised, *SSP* Short Sensory Profile

[a] For the ABC and RBS-R, lower scores indicate better performance; for the SSP and CGI-Improvement scale, higher scores indicate better performance

selected a single primary efficacy variable (ABC-SW) a priori and did not adjust for multiplicity of statistical tests. All raw *p* values are presented to allow an adjustment post hoc (Table 3). In the case of missing data, we used the last observation carried forward. The sample size was not based on statistical criteria and was determined by feasiblity for this pilot study.

Results

Participants

This trial was conducted from September 2019 to June 2020 and terminated early due to COVID-19; the original recruitment target was 10 participants. Six participants were screened, and all met inclusion criteria and were enrolled. Participants (2 males; 4 females) were between 3.2 and 11.4 years of age (7.5 ± 3.2). All participants except one female were pre-pubertal. The one child who was pubertal on physical and biochemical evaluation did not reach menarche. At baseline, all children were of average weight (-0.85 ± 1.15 SD), height (-1.38 ± 0.75 SD), and body mass index (-0.82 ± 1.27). All bone ages were within the normal range. Baseline IGF-1 *Z* scores varied between -1.2 and 2.3 (Table 1).

Safety

Recombinant human growth hormone was generally well tolerated, and there were no serious adverse events (Table 2). On average, participants experienced approximately five treatment emergent adverse events. One participant experienced gait changes, and rhGH was terminated early at week 11 out of an abundance of caution due to the risk of slipped capital femoral epiphysis. The participant was evaluated by their pediatrician, and no additional workup was deemed necessary; gait normalized within 2 days after stopping rhGH and without further sequelae. Another participant required dose reduction due to crying spells. Crying spells in all three participants were attributed to increased emotional lability. There were no clinically significant abnormalities on laboratory blood work.

Efficacy

There was an improvement in our primary clinical outcome, the ABC-SW subscale, between baseline and week 12 ($p = 0.028$) (Fig. 1). There was also an improvement in hyperactivity using the ABC hyperactivity subscale ($p = 0.027$), and in overall sensory symptoms as measured by the short sensory profile total score ($p = 0.042$).

Overall, there was global improvement as measured by the CGI-I ($p=0.023$). There were no significant changes in other clinical domains (Table 3).

Discussion

The results of this pilot open-label clinical trial demonstrate that standard clinical doses of rhGH increased levels of IGF-1 in children with PMS by at least 2SD from baseline for all participants; final levels of greater than or equal to 2SD were reached in all except one participant. Further, we show that rhGH was well tolerated without serious adverse events. As rhGH is already FDA-approved and established as safe in children with growth-related problems and in adults with growth hormone deficiency, these results provide preliminary evidence of safety in a new patient population without specific growth issues. rhGH treatment was also associated with clinical improvement that parallels the effects of IGF-1 on social withdrawal in this population. In addition, rhGH was associated with benefits in hyperactivity and sensory symptoms, all leading to global improvement based on the CGI-I. Studies of rhGH in PMS are ongoing using a randomized, placebo-controlled, crossover design. In addition, it will be critical to discover biomarkers to predict treatment response to rhGH in PMS, and potentially, within subgroups of ASD more broadly.

Limitations

Results should be interpreted with caution given the small sample size and open-label design of the study.

Conclusions

Taken together, these findings support the development of rhGH as treatment for children with PMS. Future studies of the effects of rhGH in PMS using an adequately powered placebo-controlled design are warranted.

Abbreviations

ABC: Aberrant Behavior Checklist; AEs: Adverse events; ASD: Autism spectrum disorder; CGI-I: Clinical Global Impression—Improvement Scale; IGF-1: Insulin-like growth factor-1; PMS: Phelan–McDermid syndrome; RBS-R: Repetitive Behavior Scale—Revised; rhGH: Recombinant human growth hormone; SD: Standard deviation; SLAES: Systematic longitudinal adverse events scale; SSP: Short sensory profile.

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Authors' contributions

TL and S Sandin contributed to data analysis and manuscript writing; S Sethuram, DH, PS, RR, and AK contributed to study design, data collection, and manuscript writing; HW collected and entered data for analysis; JFF and JDB contributed to manuscript writing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Mount Sinai Program for the Protection of Human Subjects, and all caregivers signed informed consent.

Consent for publication

Not applicable.

Competing interests

AK receives research support from AMO Pharma and consults to Acadia, Alkermes, Jaguar, Neuren, GW Pharma, and Ovid Therapeutics. JDB has a shared patent with Mount Sinai for IGF-1 in Phelan–McDermid syndrome. No other authors have competing interests to disclose.

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